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Kazuhiko Yanai
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The Functional Roles of Histamine Receptors

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The Functional Roles of Histamine Receptors

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Preface

Research in the field of histamine receptors over the past 100 years went hand-in-hand with the development of modern pharmacology. Advances in histamine research led by outstanding scientists were so incisive that the clinical approach to treat allergies and gastrointestinal ailments was revolutionized. Maybe no other field of pharmacology was honoured by four Nobel laureates, namely Adolf Windaus for the chemical synthesis of histamine, Sir Henry H. Dale who described the physiology of histamine, Daniel Bovet for his discovery of H_1 receptor antagonists and Sir James W. Black for his discovery of the H_2 receptor and synthesis of selective antagonists.

In the following decades, histamine pharmacology witnessed a rapid growth of H_1 and H_2 receptor antagonists with an improved profile for the treatment of conditions such as allergic rhinitis, conjunctivitis, urticaria and peptic ulcer. The pharmacological treatment of peptic ulcer and gastro-oesophageal reflux was indeed a revolution as it ended the surgical intervention.

Several of the older antihistamines are still marketed for skin applications or desired for their sedative effects. It was indeed the sedative action of these compounds that intrigued the scientists and lead them to suggest, as early as the 1970, that histamine was present in the brain. Indeed, it was. Neuroanatomical and classical pharmacological studies confirmed that histaminergic neurons form a small cluster in the posterior hypothalamus and have extensive projections in the brain. A new receptor in the CNS was also identified within the same years: the H_3 receptor. These findings ignited an explosion of interest on the function of brain histamine, both by the academia and the industry.

Several selective ligands for the H_3 receptor have been synthesised and have helped elucidate the role of histamine in the healthy and diseased brain. Clinical trials abounded in the early 2000 exploiting H_3 receptor antagonists for their procognitive effects in Alzheimer's, Parkinson's, ADHD patients. The clinical trials failed though, which decreed the downfall of H_3 receptor pharmacology. Only one

H_3 receptor antagonist for the treatment of narcolepsy was approved by the European Medicine Agency in 2016 and FDA in 2019 and reached both markets.

Interest in histamine pharmacology was in the meantime resurrected by the discovery of another histamine receptor, number 4, using genomics-based reverse pharmacological approaches for screening orphan GPCRs. This receptor is preferentially expressed by immune cells and its discovery raised hopes for its translational exploitation as a new therapeutic target for unmet medical needs ranging from asthma to cancer. However, several drawbacks emerged and dramatically slowed down research in the field.

All along the history of histamine pharmacology, clinical and preclinical studies progressed hand-in-hand. Despite the raises and falls, histamine research is all but dead. For instance, a better understanding of receptor intra- and interspecies heterogeneity will certainly improve and accelerate the translation of experimental data into clinical practice. Also, the plethora of data on brain histamine is hinting at a fundamental role of this system as a hub that receives internal and peripheral stimuli to allocate the necessary excitation to specific brain circuits that preside the appropriate behavioural responses.

The development of new histaminergic ligands is an on-going process that constantly provides new preclinical tools (e.g. photoswitchable compounds to modulate histamine function with calibrated wavelengths) to elucidate the functional complexity of histamine networks in human (patho)physiology.

In our book, we will try to cover the salient aspects of histamine receptors function and pharmacology IN THE CENTRAL NERVOUS SYSTEM, hopefully giving a full account of the preclinical and clinical progress in the last decades and the exciting perspective for the future. We will try to cover the clinical areas that are in major need of new therapeutic approaches and that may take advantage of new histaminergic compounds for a personalised medicine.

Sendai, Japan Kazuhiko Yanai
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Part I
Pharmacology and Medicinal Chemistry

New Chemical Biology Tools for the Histamine Receptor Family

Yang Zheng, Gábor Wágner, Niels Hauwert, Xiaoyuan Ma, Henry F. Vischer, and Rob Leurs

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Abstract The histamine research community has in the last decade been very active and generated a number of exciting new chemical biology tools for the study of histamine receptors, their ligands, and their pharmacology. In this paper we describe the development of histamine receptor structural biology, the use of receptor conformational biosensors, and the development of new ligands for covalent or fluorescent labeling or for photopharmacological approaches (photocaging and photoswitching). These new tools allow new approaches to study histamine receptors and hopefully will lead to better insights in the molecular aspects of histamine receptors and their ligands.

Keywords Biosensors · Covalent ligands · Fluorescent ligands · Histamine receptor structural biology · Photocaging · Photopharmacology · Photoswitching

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1 Introduction

As the target of more than 30% of FDA approved drugs, G protein-coupled receptors (GPCRs) are an important family for drug discovery (Santos et al. 2016). As an important family A GPCR subfamily, four histamine receptors (H_1R, H_2R, H_3R, H_4R) have been discovered and are known to regulate many crucial physiological processes (Gantz et al. 1991; Yamashita et al. 1991; Lovenberg et al. 1999; Nakamura et al. 2000; Passani et al. 2004; Simons and Simons 2011; Panula et al. 2015; Provensi et al. 2016, 2020; Panula 2021).

In view of the early recognized (patho)physiological role of histamine and histamine receptors (Panula et al. 2015), also the medicinal chemistry of histamine receptor ligands is well developed (Figueroa and Shankley 2010; Panula et al. 2015; Corrêa and dos Santos Fernandes 2015; Kiss and Keserű 2016). Consequently, for each of the 4 histamine receptor subtypes selective agonists and antagonists are available, allowing pharmacologists to further explore the role of histamine in (patho)physiology. The availability of selective ligands has recently been extensively reviewed (Panula et al. 2015) and can also be consulted at the IUPHAR website (https://www.guidetopharmacology.org/GRAC) (Chazot et al. 2019). As widely known in the community, histamine H_1-, H_2-, and H_3-antagonists are currently used clinically (Panula et al. 2015), whereas the H_4R also still holds promise for the development of new therapeutically useful approaches in allergic and inflammatory diseases (Panula 2021). In this paper, we will therefore not review the commonly used agonists and antagonists/inverse agonists of the various histamine receptors, but will highlight recent developments of new chemical biology tools to study histamine receptors and their ligands. In the following paragraphs, we will, e.g., highlight new bioengineering strategies that allow the first glimpses of histamine H_1R structures and how the H_1R is modulated by histamine and histamine H_1R antagonists. Moreover, for both H_1R and H_3R various conformational biosensors have been developed, allowing the real-time detection of conformational dynamics upon ligand binding. Next to the new approaches to study ligand–receptor interactions, also new ligands have been developed for various histamine receptors in the last decades.

2 New Histamine Receptor Tools

2.1 Structural Biology of Histamine Receptors

In general, the field of GPCR drug discovery and pharmacology has recently been strongly supported by the overwhelming success of GPCR structural biology (García-Nafría and Tate 2021). From the latest update of GPCRdb (Dec 23rd, 2021 at https://gpcrdb.org) (Kooistra et al. 2021), one can perceive that there are currently 637 experimental GPCR structures available, solved by either X-ray

crystallography or cryo-EM studies. For the family of histamine receptors, structural biology has also made an impact and structural data for the H_1R in both the inactive and active state have been reported (Shimamura et al. 2011). In 2011 Shimamura et al. reported the inactive structure of the H_1R in complex with the tricyclic antagonist doxepin that binds with high affinity to the H_1R (Shimamura et al. 2011). To arrive at this seminal discovery, the H_1R protein was modified in order to arrive at crystallization. To this end, the enzyme T4-lysosyme(T4L) was inserted into the third intracellular loop of the H_1R and the *N*-terminus of the H_1R was partly truncated (residue 1–19). The H_1R–T4L fusion protein behaves in radioligand binding studies like the wild-type H_1R and was overexpressed in *Pichia pastoris* yeast cells to allow purification and subsequent lipidic cubic phase crystallization. Supported by the high tendency of T4L to crystallize, crystals of the H_1R–T4L fusion protein in the presence of doxepin were successfully obtained and resolved at a 3.1 Å resolution (PDB: 3RZE). The H_1R is structurally similar to its close family members, the aminergic receptors (i.e., histamine, serotonin, dopamine, muscarinic acetylcholine, and adrenergic receptors) and shows the characteristic 7 transmembrane alpha-helical folds that form a transmembrane pocket to bind the H_1R antagonist doxepin (Fig. 1). The H_1R shares common motifs with other GPCRs, like the DRY motif at the end of helix III, CWxP motif in helix VI, and NPxxY motif in helix VII, as well as a disulfide bond connecting extracellular loop 2 with the extracellular end of helix III and the helix VIII, that most likely is located perpendicularly to the membrane (Fig. 1). As earlier suggested by both site-directed mutagenesis and computational modeling (Ohta et al. 1994; Wieland et al. 1999), the binding site for the H_1R antagonist is found relatively deep between transmembrane domain 3, 5, and 6. The ligand interacts first of all with D^{107} in TM3, a residue that is highly conserved in aminergic GPCRs. The ligand also makes a number of hydrophobic contacts with mainly aromatic residues in TMs 5 and 6 (e.g., with Trp^{428} and Phe^{432}). The Trp^{428} residue has also been implicated in interaction with doxepin by recent NMR spectroscopy measurements with purified stable-isotope labeled H_1R (Mulry et al. 2021). The elucidation of the inactive structure has had a direct impact on histamine drug discovery efforts, allowing, e.g., de Graaf et al. to identify in the same year several new high-affinity hits (up to nM) via a virtual screening approach, using the H_1R X-ray structure (de Graaf et al. 2011).

It took a decade for a new histamine receptor structure to appear, but after the development of cryo-EM techniques and their implementation in GPCR structural biology (García-Nafría and Tate 2021), in 2021 Xia et al. reported on the cryo-EM structure of the active human H_1R in complex with its main G-protein, the G_q protein (Xia et al. 2021). In order to arrive at this structure with 3.63 Å resolution (PDB:7DFL), the H_1R again needed modification (IL3 deletion, C-terminal fusion to LgBiT) to allow purification from Sf9 insect cells and complex formation in the presence of histamine via NanoBiT complementation with a HiBiT-modified G_β subunit, that was incorporated in purified heterotrimeric G_q proteins. In this large ternary complex (Fig. 1), histamine is bound to the 7TM pocket mainly via the ionic interaction of its ethylamine sidechain with the acidic D^{107} in TM3, next to, e.g., residue N^{198} in TM5. As for doxepin, also these residues have before been

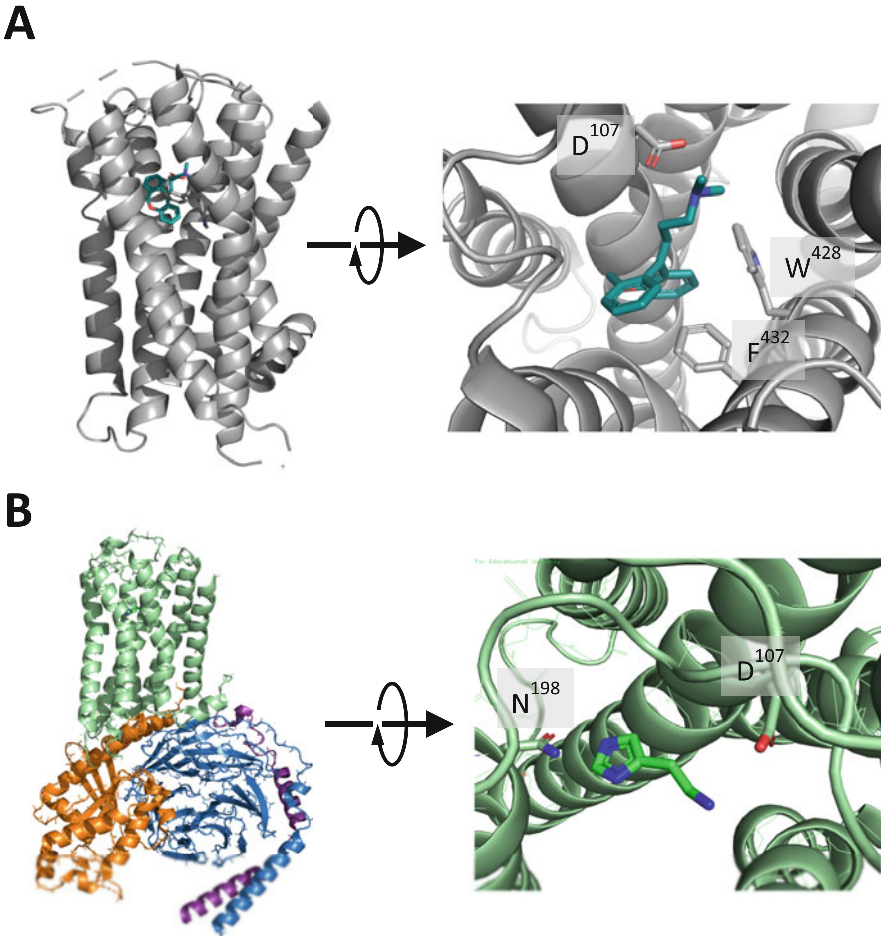

Fig. 1 (**a**) Side view and top view of the inactive state of the human H_1R in complex with the antagonist doxepin, as seen in the X-ray structure of a T4-lysozyme fusion protein (PDB: code 3RZE). The top view highlights some residues shown to be involved in the binding of the antagonist. (**b**) Side view and top view of the active state of the human H_1R in complex with the agonist histamine, as seen in the cryo-EM structure of H_1R in complex with a trimeric G_q protein (orange: α-subunit, bleu: β-subunit, purple: γ-subunit (PDB: code 7DFL). The top view highlights some residues shown to be involved in the binding of the antagonist

highlighted as interaction points for histamine by site-directed mutagenesis (Leurs et al. 1994; Ohta et al. 1994). Comparisons of the active and inactive states of the H_1R indicate that agonist binding leads to a reduction of the solvent-accessible volume of the transmembrane binding pocket, as also seen e.g. for β_2-adrenergic receptors (Rosenbaum et al. 2011). Following the contraction of the extracellular part via an inward movement of TM6, the intracellular part of TM6 is consequently

moving dramatically outward, allowing the GPCR to bind the G-protein (Xia et al. 2021).

The described recent developments in the structural biology of histamine receptors will most likely continue to develop and will most certainly help the field to better understand receptor structure-function relationships, next to the discovery and design of new histamine receptor ligands.

2.2 Biosensors to Detect Conformational Changes of Histamine Receptors

To investigate what happens after ligand binding, a number of groups have developed biosensor tools to measure conformational changes upon ligand–receptor interactions. Currently, for both the H_1R and the H_3R conformational biosensors have been reported (Liu et al. 2018; Erdogmus et al. 2019; Schihada et al. 2020).

Building upon the work with a number of family A GPCRs (Kauk and Hoffmann 2018), Erdogmus et al. were the first to report on a fluorescence resonance energy transfer (FRET)-based conformational sensor for the H_1R (Erdogmus et al. 2019). To this end, a C-terminal tail H_1R fusion protein with the Cyan Fluorescent Protein (CFP) variant cerulean (FRET donor) was combined with the introduction of a small binding motif (amino acid insertion CCPGCC) for the fluorescein arsenical hairpin binder FlAsH (as FRET acceptor) in the third intracellular loop or between TM7 and helix 8. Using FRET microscopy with living cells, the kinetics change in receptor conformation change upon histamine activation was reported to have a half-life of 148 ms (Erdogmus et al. 2019). This FRET biosensor was thereafter used to show that the H_1R can act as endothelial mechanosensors of fluid shear stress and contribute to flow-induced vasodilation (Erdogmus et al. 2019).

For the H_3R, a similar approach was followed by Liu et al. FRET donor CFP was fused in-frame to the H_3R C-terminus and the majority of the third intracellular loop (icl3) was replaced with the FRET acceptor YFP, which was inserted between residues T^{229} and F^{348} (Liu et al. 2018). Also this FRET approach allowed the measurement of changes in the intramolecular interaction between the FRET acceptor and donor following agonist-induced conformational changes of this Δicl3-$H_3R_{CFP\text{-}YFP}$ biosensor. Capitalizing on the successful developments of a number of FRET-based GPCR conformational biosensors, Schihada et al. recently engineered a BRET-based H_3R conformational biosensor by fusing the BRET donor Nanoluciferase (NanoLuc) to the C-terminus of H_3R and inserting the self-labeling HaloTag between T^{229} and F^{348} in the third intracellular loop (Schihada et al. 2021). After labeling of the Halotag with the fluorescent Halotag dye 618 and administration of NLuc substrate furimazine to cells expressing this Δicl3-$H_3R_{Nluc/Halo(618)}$ biosensor, ligand-induced BRET responses in living cells can be followed in a microplate reader, in both 96- and 384-well formats (Schihada et al. 2020). Hence, this BRET-based biosensor allows the high-throughput measurement of the H_3R

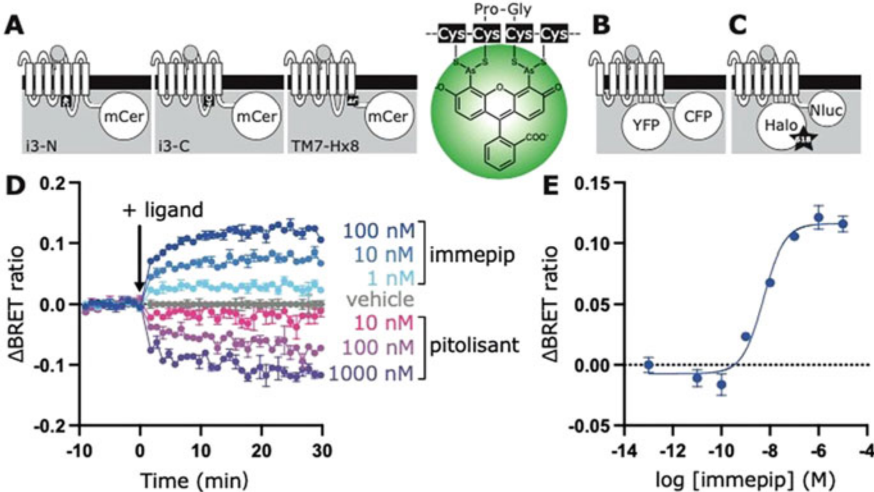

Fig. 2 Schematic representation of FRET- and BRET-based histamine receptor H_3R conformational sensors and their use. (**a**) FRET-based FlaSH sensors, where the FRET acceptor is located at the N- or C-terminal part of the i3 loop (i3-N or i3-C) or at the end of TM7, close to helix 8 (TM7-Hx8). The FlaSH-labeled amino acid sequence is shown. (**b**) FRET-based sensor based on the YFP-CFP pair. C) A BRET-based sensor based on the insertion of a Halo-tag in the i3 loop. Light emitted by nanoluciferase (Nluc) will result in a BRET signal from the 618 dye, used to label the Halo-tag (**d**) Typical kinetic tracings of changes in the BRET signal of the BRET-based H_3R sensor (**c**), stably expressed in HEK293A cells, upon stimulation of different concentrations H_3R agonist (immepip) or inverse agonist (pitolisant). The data at 30 min can also be displayed as a concentration-response curve, as exemplified for the H_3R agonist immepip (**e**)

conformational effects of both agonist and inverse agonists (Fig. 2b), both in a kinetic and end-point modus (Fig. 2b, c). Using this sensor, it is possible to detect the direct (opposite) conformational effects of agonists and antagonists (Fig. 2b), although the sensor does not allow the kinetic measurements of H_3R conformational changes at the msec scale, like the FlaSH-based FRET sensor (Erdogmus et al. 2019).

3 New Histamine Receptor Ligands

As mentioned before, in this review we will confine ourselves to conceptually new developments in the field of the histamine receptor ligands, and not review again the availability of selective agonists and antagonists. Here, we will pay attention to developments in the field of covalent ligands, fluorescently labeled ligands and photoswitchable ligands for the family of histamine receptors.

3.1 Covalent Ligands for the Histamine Receptors

Covalent drugs, which form irreversible bonds with their target have often been ignored in drug research in order to avoid the risk of side effects such as off-target reactivity, reactive intermediates, idiosyncratic drug-related toxicity (Potashman and Duggan 2009; Singh et al. 2011; Bauer 2015). Nevertheless, several covalent ligands show excellent therapeutic effect and have become blockbuster drugs (e.g., aspirin, penicillin, omeprazole, clopidogrel). These covalent inhibitors usually were discovered as serendipity, rather than rational drug design and often their covalent mechanisms of action were discovered considerably later than their initial discovery (Potashman and Duggan 2009; Singh et al. 2011; Bauer 2015).

With increased knowledge on protein target structures (Potashman and Duggan 2009; Singh et al. 2011; Bauer 2015) in the twenty-first century, the rational design of covalent ligands, named "targeted covalent inhibitors" (TCIs), has taken off (Hauser et al. 2017). To obtain TCIs high-affinity reversible ligands are most of the time substituted with a weak electrophilic covalent group, which is able to form a covalent bond with a non-catalytic nucleophilic amino acid residue, mostly cysteine, within the active site of the target protein (Singh et al. 2011). The emerging wave of the TCIs in, e.g., the kinase inhibitor field resulted in a new generation of approved covalent drugs, for instance the Bruton's tyrosine kinase inhibitor Ibrutinib (Pan et al. 2007) or the epidermal growth factor receptor inhibitor Dacomitinib (Reed and Smaill 2016).

As GPCRs form the most significant class of drug targets (Hauser et al. 2017) and GPCR-target residence time is of major importance for the clinical efficacy of new GPCR ligands (Sansuk 2010), including, e.g., the histamine H_1R (Bosma et al. 2018), covalent modulation of GPCRs is also considered to be advantageous in several cases.

Due to the advances in GPCR structural biology (García-Nafría and Tate 2021), the covalent targeting of orthosteric and allosteric binding sites of GPCRs has also become an emerging strategy for the targeting of GPCRs (Bian et al. 2020). The discovery of covalent histamine receptor ligands also started with a serendipitous discovery. The α-adenoreceptors blocking agents β-haloalkylamines were identified as the first covalent ligands of histamine receptors. Phenoxybenzylamine (**1**), SY-14 (**2**, known also as GD121) and ECB (**3**) (Fig. 3) block, e.g., non-competitively histamine-induced contractions of guinea pig ileum (Nickerson 1956; Cook 1971; Kenakin and Cook 1976). The irreversible binding of phenoxybenzylamine to H_1R was proven by binding assay (Sansuk 2010) and β-arrestin2 recruitment assay (Bosma et al. 2016). Moreover, MALDI-ToF MS analysis of the purified ligand-H_1R complex showed that phenoxybenzylamine was covalently bound to Cys^{302} residue, located on the third intracellular loop, suggesting that phenoxybenzylamine binds to an intracellular binding pocket, just like a number of newly discovered GPCR ligands (Sansuk 2010; Chan et al. 2019).

A general strategy for the design of covalent agonist derivatives of monoamine neurotransmitters was reported to aid the production of suitable ligand-GPCR

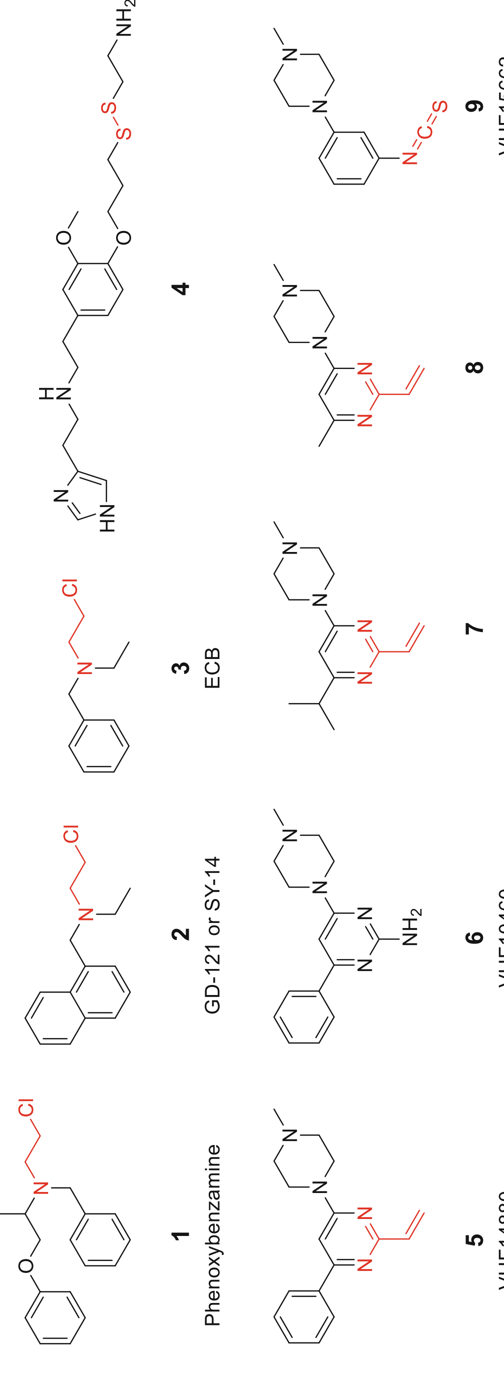

Fig. 3 Histaminergic ligands used to covalently target various histamine receptors. The reactive moieties are indicated in red

complexes for structural studies toward GPCR activation. To this end, a nucleophilic cysteine residue was introduced into the same position in TM2 in several aminergic GPCRs, namely β_2-adrenoreceptor (β_2AR), dopamine D_2 receptor (D_2R), Serotonin 2A (5-HT_{2A}), and H_1R (Weichert et al. 2014). This cysteine residue was subsequently targeted with a disulfide moiety, connected to the primary amino group of the respective aminergic neurotransmitters (noradrenaline, dopamine, serotonin, histamine) via a flexible linker. This covalent histamine analogue (**4**, Fig. 3) can fully activate (EC_{50}: 740 nM) the wild-type H_1R as measured by an inositolphosphate accumulation assay (Weichert et al. 2014). Moreover, the covalent binding of compound **4** to the mutant H_1R-Y^{87}C was inferred by the inability of the H_1R antagonist diphenhydramine to block its agonist action on this mutant receptor (Weichert et al. 2014).

The partial agonist VUF14480 (**5**, Fig. 3) was the first designed covalent ligand for the H_4R (Nijmeijer et al. 2013). The design was based on the computational modeling of ligand–protein interactions between VUF10460 (**6**, Fig. 3) and H_4R (Schultes et al. 2013). The model predicted that the position 2 of the pyrimidine ring would be oriented favorably toward the cysteine C^{98} of H_4R. Subsequently, an ethenyl group was introduced as reactive moiety (Michael acceptor) to this position, leading to VUF14480 (**5**). Initial studies showed sufficient reactivity of VUF14480 with glutathione or cysteine ethyl ester and VUF14480 shows submicromolar affinity for H_4R (pK_i = 6.3), next to partial agonism in a H_4R GTPγS binding assay (pEC_{50}: 6.0, maximum response: 60% of full agonist histamine) (Nijmeijer et al. 2013). The covalent interaction with C^{98} as an anchor point was investigated by mutating the C^{98} residue into a serine residue (C^{98}S mutant). Pre-incubation with VUF14480 followed by extensive washing steps decreased histamine binding to wild-type H_4R but not to the mutated H_4R-C^{98}S, confirming the formation of a covalent bond between VUF14480 and the C^{98} residue (Nijmeijer et al. 2013).

The H_4R and H_3R binding pockets show high similarity (~80%) and the C^{98} residue of the H_4R is also conserved in the H_3R (Kooistra et al. 2013). Therefore, the H_4R covalent agonist VUF14480 served as a starting point for the design of a series of covalent H_3R ligands targeting the conserved C^{118} residue. The design cycles resulted in three ligands that can bind irreversibly to H_3R (**7–9**, Fig. 3).

While the 2-ethynyl-pyrimidine derivatives **7** and **8** show micromolar affinity (**7** pK_i: 5.5; **8** pK_i: 5.4), the phenyl-isothyocyanate derivative VUF15662 (**9**) shows submicromolar affinity for H_3R (pK_i: 6.5), combined with inverse agonistic activity (Wágner et al. 2019). VUF15662 shows appropriate stability in water, bound rapidly to gluthatione and selectively forms covalent bonds with the cysteine residue of a nonapeptide containing various nucleophilic residues (lysine, tyrosine, histidine, and cysteine). The irreversible interaction of inverse agonist VUF15662 with H_3R was further validated by washout experiments (Wágner et al. 2019).

Compared to the earlier mentioned covalent kinase inhibitors, the covalent targeting of histamine receptors is still in its infancy and the few reported compounds were developed for support of protein crystallography or as pharmacological tool compounds. The increasing interest in covalent GPCR ligands might ultimately lead to the therapeutic exploitation of covalent modulators of GPCRs, including the

histamine receptors. The increasing knowledge on emerging TCI warheads and targeted amino acid residues (Gehringer and Laufer 2019), combined with the recent expansion of the reactive moieties (Lonsdale et al. 2017; Ábrányi-Balogh et al. 2018) and the covalent fragment libraries (Keeley et al. 2019, 2020; Resnick et al. 2019) might become the driving force for future covalent GPCR drug discovery.

3.2 *Fluorescent Ligands for the Histamine Receptors*

Fluorescent ligands offer great opportunities to visualize and understand the modulation of GPCRs, including histamine receptors (Kuder and Kieć-Kononowicz 2014; Stoddart et al. 2015; Soave et al. 2020). Compared to the conventionally used radiolabeled ligands, assays with fluorescence ligands are safe and inexpensive and can be performed with living cells, fixed tissues, or even whole animals (Kim et al. 2017). Careful matching of the photo-properties of the many available fluorophores can significantly reduce the risk of interference with other biological readouts, allowing in principle multiplexed assays. The field of fluorescent GPCR ligands has substantially been growing in the last decade (Kuder and Kieć-Kononowicz 2014; Stoddart et al. 2015; Soave et al. 2020) and also a fair number of fluorescent ligands for the histamine receptor family have been developed.

Harris et al. were the first to report on a fluorescent histaminergic compound (**10**, Fig. 4) by directly connecting histamine to fluorescein separated by a thiourea moiety (Harris and Hutchinson 1994). Whereas nothing is reported about the specificity of **10** for the various histamine receptor, this fluorescent ligand was

Fig. 4 Fluorescent H_1R ligands. Photochemical details shown in Table 1

used to identify H_1R and H_2R on immune cells. Together with a series of monoclonal antibodies, they performed dual staining of rat lymph node cells for two-color flow cytometric analysis. This experiment identified lymphocytes and macrophages as two distinct populations. With the assistance of inhibition studies with mepyramine and cimetidine (H_1R and H_2R antagonist, respectively), they could use **10** to measure the expression of H_1R in lymphocytes and H_2R expression in macrophages (Harris and Hutchinson 1994). Currently, also a BODIPY-conjugated histamine is commercially available (Fischer Scientific n.d.). This ligand has been used to label histamine receptors (Mocking et al. 2018), but since the actual chemistry has not been described in primary literature, this ligand is not further considered in this work. Similarly, fluorescent H_2R and H_3R ligands of unknown chemical nature are available from Abcam, but will also not be considered here, despite their successful use in some cases (Mocking et al. 2018).

Based on mepyramine, Buschauer and coworkers synthesized a series of fluorescent H_1R ligands by conjugating the tertiary amine of mepyramine with different fluorescent units (Li et al. 2003a). The excitation wavelength (λ_{max} Ex) of these fluorescent ligands varies from 321 to 555 nm, which is similar to the photochemical properties of the employed fluorescent units. Interestingly, some of the fluorescent H_1R probes are more potent H_1R antagonists compared to their non-labeled H_1R antagonists, which might be due to additional interactions between the fluorescent units and the extracellular loop regions of H_1R. The most potent compound (**11**, Fig. 4) with a nitrobenzoxadiazole moiety exhibited a pA_2 value of 8.71 and pK_B value of 9.05 as measured against histamine-induced contraction of the guinea pig ileum or in a U373MG cell-based assay, respectively (Li et al. 2003a).

In 2012, Hill and coworkers reported on another series of fluorescent H_1R antagonists (**12**, Fig. 4) based on mepyramine in combination with the fluorescent moiety BODIPY630-650 (Rose et al. 2012). In the intracellular calcium mobilization assay using a CHO cell line stably expressing the H_1R, this compound showed a pK_B value of 8.9, which is similar to mepyramine (pK_B 8.6). Using CHO-K1 cells transiently expressing H_1R fused to YFP, single cell fluorescent microscopy allowed visualization of largely co-localized binding of **12** by means of YFP fluorescence. The observed fluorescence could be inhibited by pre-incubation with H_1R antagonist cetirizine. Also Fluorescence Correlation Spectroscopy (FCS) was employed to follow the specific H_1R binding and diffusional properties of **12** to the endogenously expressed H_1R in HeLa cells (Rose et al. 2012). In a follow-up study, the groups of Kellam and Hill further improved the overall properties and replaced the long aliphatic linker of **12** (increases lipophilicity) with a peptide linker (Stoddart et al. 2018). With this new linking strategy the H_1R antagonist mepyramine and VUF13816 were conjugated with BODIPY630-650 and these less lipophilic ligands were tested for improved specific binding to H_1R in the membrane. The binding kinetic properties of the most promising ligand (**13**, $pK_i = 7.6$) were used to develop a homogeneous, real-time kinetic NanoBRET binding assay in intact cells and membrane preparations (Stoddart et al. 2018). The binding of fluorescent **13** to H_1R, which is *N*-terminally tagged with the extremely bright Nanoluciferase, can be detected both by microscopy or microplate reader as BRET and has allowed the

Table 1 Photochemical properties of fluorescent histamine receptor ligands

Compound	λ_{max} Ex (nm)	λ_{max} Em (nm)	Stokes shift (nm)	Compound	λ_{max} Ex (nm)	λ_{max} Em (nm)	Stokes shift (nm)
10 [a]	488	–	–	**26**	547	573	26
11 [b]	633	650	17	**27** [c]	344	366	22
12 [d]	483	536	53	**28** [c]	342	357	15
13 [e]	633	650	17	**29** [c]	467	526	59
14 [d]	483	539	56	**30** [f]	397	527	130
15 [a]	340	440	100	**31** [c]	481	531	50
16 [a]	340	400	60	**32**	480	530	50
17 [a]	330	370	40	**33** [a]	644	668	24
18	–	–	–	**34**	–	–	–
19 [a]	648	666	18	**35** [a]	455	705	250
20 [a]	675	703	28	**36** [f]	405	584	179
21 [a]	450	695	245	**37** [f]	468	670	202
22	–	–	–	**38** [f]	405	567	162
23	465	535	70	**39** [f]	468	563	95
24	430	552	122	**40** [g]	481	646	165
25	546	579	33	**41**	–	–	–

[a] PBS
[b] HEPES buffered saline solution (HBSS; 10 mM HEPES, 10 mM D-glucose, 146 mM NaCl, 5 mM KCl, 1 mM $MgSO_4$, 1.5 mM $NaHCO_3$, 2 mM sodium pyruvate, 1.3 mM $CaCl_2$; pH 7.45)
[c] 10^{-5} M in absolute spectroscopic EtOH
[d] Buffer (NaCl 120 mM, KCl 5 mM, $MgCl_2$ 2 mM, $CaCl_2$ 1.5 mM, HEPES 25 mM, glucose 10 mM, pH 7.4 with NaOH)
[e] HBSS
[f] 10 mM in a buffer (12.5 mM $MgCl_2$, 100 mM NaCl, and 75 mM Tris/HCl, pH 7.4)
[g] PBS with 1% BSA

large-scale studies of ligand binding kinetics of H_1R antagonists (Bosma et al. 2019). Another homogeneous HTRF-based binding assay is commercially available from Perkin Elmer/Cisbio using a SNAP-tagged H_1R, but in fact the fluorescent ligand used is unknown (Cisbio n.d.).

The first fluorescent H_2R ligands were reported by Li et al. in 2003 (Li et al. 2003b). Based on the structure of *N*-cyano-*N*′-[3-(3-piperidin-1-ylmethylphenoxy) propyl]guanidines, they conjugated this common H_2R scaffold with different fluorescent units (e.g., NBD and fluorescein) via various lengths of methylene chains. The λ_{max} Em of this series ranges from 360 to 483 nm (Table 1). Their antagonistic activity was evaluated on isolated spontaneously beating guinea pig right atrium and displayed more than three log units difference. The most potent compound (**14**, Fig. 5) shows a pA_2 of 7.96 in this assay together with the highest λ_{max} Em (539 nm).

As a follow-up, Malan et al. reported similar fluorescent H_2R ligands based on the aforementioned guanidine scaffold and 2-(5-methyl-4-imidazolyl)-methylthioethylamine in 2004 (Malan et al. 2004). A shorter aliphatic methylene linker and several new fluorescent units were introduced, e.g., cyanoindolizine, cyanoisoindole, and BODIPY. Affinities of this series were measured in a

Fig. 5 Fluorescent H_2R ligands. Photochemical details are shown in Table 1

[^{125}I]-iodoaminopotentidine binding assay. Several new cyanoguanidine derivatives exhibited pK_i values of 5.99–8.84 for the rat H_2R. Fluorescent variants with a combination of the guanidine moiety and BODIPY showed desirable fluorescent properties. However, only moderate H_2R affinities were obtained (pK_i of 6.3–6.9). Compounds **15**, **16**, **17** (Fig. 5) exhibited high H_2R affinity but combined this unfortunately with low to moderate fluorescence and small Stokes shifts (the difference between λ_{max} Ex and λ_{max} Em), except for compound **15** (100 nm). A large Stokes shift is beneficial for biological imaging.

Since the affinity of most fluorescent H_2R ligands from Buschauer's first series was not high enough for spectroscopic applications, a second series of ligands with fluorophores showing emission wavelengths over 650 nm was reported in 2006 (Xie et al. 2006). To this end, they coupled *N*-cyano-*N'*-[3-(3-piperidin-1-ylmethylphenoxy)propyl]guanidines with BODIPY 650/665-X and S0536. In a G-protein GTPase assay, **18** (Fig. 5) proved to be a potent human H_2R ($K_B = 47$ nM) and gpH_2R ($K_B = 58$ nM) inverse agonist with high selectivity over H_1R.

Due to unsatisfactory signal-to-noise ratios in flow cytometry or confocal microscopy caused by the emission interference of cellular autofluorescence, red-emitting dyes have proved their applicability in the design of fluorescent labeled ligands (Schneider et al. 2006, 2007). In the PhD thesis of Erdmann, a series of red-emitting dyes was incorporated into the structure of BMY 25368 to design new fluorescent

H_2R ligands (Erdmann 2010). Among them, compounds **19–21** (Fig. 5) stood out due to their high affinity and preferred photochemical properties. For ligands **20** and **21**, emission wavelengths were observed at around 700 nm. All three ligands exhibited high H_2R antagonism activity (H_2R-Gα_s K_b, 22–162 nM) in the GTPase assay with high selectivity over H_1R/H_4R and moderate selectivity over H_3R. More importantly, high signal-to-noise ratios were observed in confocal microscopy.

With a similar scaffold as **21**, Grätz et al. reported on fluorescent H_2R ligand **22** (UR-KAT478) in 2020 (Grätz et al. 2020). Next to its chemical stability in buffer, **22** showed in combination with H_2R, *N*-terminally tagged with nanoluciferase, a pK_d value of 7.35 in a NanoBRET saturation binding assay with good signal intensity. Full association was established within 30 min and a slow disassociation rate in kinetic assays warrants this compound as a valuable fluorescence-based alternative to canonical radioactive binding assays. The obtained pK_i values from several reference compounds in the BRET-based competition binding assay with **22** are in agreement with radioligand binding data.

In 2006, the first fluorescent H_3R ligand series was reported by Cowart et al. (2006) based on previous SAR studies, they incorporated different fluorophores at the 5-position of the benzofuran moiety in ABT-239. Among them, all ligands exhibited high potency at H_3R (K_i value range from 0.10 to 5.89 nM). However, **23** and **24** (Fig. 6) are only weakly fluorescent, which limits their further application. Gratifyingly, **25** and **26** (Fig. 6) are potent H_3R inverse agonists with intense fluorescence, which indicates that bulky groups are tolerated in the receptor (Cowart et al. 2006).

In the same year, Amon et al. reported fluorescent non-imidazole-based H_3R ligands (Amon et al. 2006). They introduced two fluorophores (isoindolenitrile and nitrobenzofurazan) to the structure of 5-(piperidin-1-yl)pentan-1-amine with different linker lengths. All analogues exhibited moderate to high affinity (K_i value: 11–351 nM) for H_3R. Among them, **27** and **28** (Fig. 6) both showed a K_i value of 31 nM with similar photochemical properties. Ligand **29** was three times more potent compared with **27** and **28** (K_i value of 11 nM) with more red-shifted λ_{max} Ex (467 nm) and λ_{max} Em (526 nm) wavelengths (Table 1). One year later, Amon et al. reported their second series of fluorescent non-imidazole-based H_3R ligands based on the 1-(3-phenoxypropyl)piperidine structure with more fluorophores (Amon et al. 2007). All compounds showed high affinity (K_i values of 0.048–13.4 nM). Among them, **30** and **31** (Fig. 6) exhibited the highest H_3R affinity (K_i value of 48 pM and 66 pM, respectively) with acceptable Stokes shifts (130 and 50 nm). In 2010, Kuder et al. reported a close analogue of **31** by introducing a methyl group at the 3-position of the piperidine ring (Kuder et al. 2010). The obtained analogue **32** (Fig. 6) exhibited similar photochemical properties and affinity (K_i value of 0.11 nM) compared with **31**.

In order to obtain potent fluorescent H_3R ligands with emission wavelength over 600 nm to avoid cell autofluorescence, Erdmann replaced the phenoxyalkyl-substituted piperidine ring in JNJ5207852 with different fluorophores as described for H_2R ligands in her PhD thesis (Erdmann 2010). Most of the compounds exhibited high potency with H_3R antagonistic activities in the GTPase assay (K_b:

Fig. 6 Fluorescent H_3R ligands. Photochemical details shown in Table 1

5.8–1,976 nM). Among them, **33–35** (Fig. 6) also showed high selectivity over the other histamine receptors. Compound **34** was further employed in confocal microscopy, and clear specific binding could be detected.

For similar reasons (high emission wavelengths), Wolfgang et al. reported their chalcone-based fluorescent H_3R ligands in 2012 (Wolfgang et al. 2012). A series of

chalcone ligands based on the structure of ciproxifan and UCL-2190 showed affinities comparable to the parent compound ciproxifan (K_i values of 41–101 nM), and all showed high selectivity over H_1R and H_4R with big Stokes shifts (>130 nm). Among them, yellow fluorescent **36**, **38,** and red fluorescent **37** (Fig. 6) were further characterized in confocal microscopy and showed negligible autofluorescence with clear labeling of the membrane of HEK-293 cells expressing H_3R. Tomasch et al. also reported another fluorescent ciproxifan analog, H_3R ligand **39,** that incorporates a BODIPY moiety (Fig. 6) (Tomasch et al. 2013). This compound, bodilisant (K_i value of 6.6 nM), is around seven times more potent than ciproxifan (K_i value of 46 nM) and also showed high selectivity over H_1R and H_4R. A good signal-to-noise ratio was observed in confocal microscopy experiments using HEK-293 cells expressing H_3R. Remarkably, experiments with human globus pallidus slices proved **39** as a useful tool for receptor imaging in human tissue at endogenous H_3R expression levels (Tomasch et al. 2013).

In an effort of searching for fluorescent ligands for H_4R binding studies and imaging, Bartole et al. reported their first fluorescent H_3R/H_4R dual ligand (Bartole et al. 2020) (Fig. 6). In this work, they coupled histamine and several homologs with the pyrylium dye Py5, which yielded **40** as a potent H_3R/H_4R ligand (pK_i 8.60 and 7.85, respectively) with good selectivity over H_1R/H_2R. Functional assays proved this compound to act as a H_3R partial agonist ($\alpha = 0.61$) and H_4R inverse agonist ($\alpha = -0.34$). In confocal microscopy, **40** enabled time-dependent localization studies of H_4R in HEK293T cells. Moreover, this ligand can be efficiently used in NanoBRET-based binding studies with both *N*-terminally nanoluciferase tagged H_3R and H_4R (Bartole et al. 2020).

Very recently, Rosier et al. reported the novel fluorescent H_3R ligand **41** (UR-NR226, Fig. 6) (Rosier et al. 2021). Based on the structure of JNJ-5207852 and previously published SARs, they introduced 5-TAMRA as a fluorescent dye at the 4-position of the piperidine through a PEG linker. NanoBRET saturation binding experiments using H_3R, *N*-terminally tagged with nanoluciferase, provided a pK_d of 9.80 and very low nonspecific binding. Moreover, an outstanding selectivity profile (at least 100,000-fold) was observed toward human H_1R, H_2R, and H_4R. This compound acts as a neutral agonist in the BRET-based G_{i2} biosensor functional assay. Notably, it is also the first fluorescent ligand to enable single molecule imaging of H_3R confirmed by confocal microscopy experiments.

3.3 Histamine Receptor Photopharmacology

Biomedical sciences have in recent years been heavily impacted by optogenetic approaches. Especially the field of neuroscience has embraced the optical control of isolated cells by the use of light-sensitive proteins to dissect the complexity of neuronal systems. The development of red-shifted opsins has reached wavelengths such that neuronal activation is even possible through the intact skull (>660 nm), allowing spatial and temporal control of neurotransmission with light (Chuong et al.

Fig. 7 Structures of caged histamine ligands. Photochemical details are shown in Table 2

2014). Optogenetics has already been employed to study histaminergic neuronal systems. Using optogenetics, it has, e.g., been established that arousal is controlled in the ventrolateral preoptic nucleus by H_1R and in the tuberomammillary nucleus by H_3R in an autoregulatory fashion (Williams et al. 2014).

For similar spatial and temporal control of specific GPCR signal transduction pathways, the promise of optical control of GPCR–ligand interactions has stimulated the field of photopharmacology, i.e. the development of photocaged and photoswitchable ligands. The concept of "photocaging" dates back to the 1970s when Engels and Hoffman reported the nitrobenzyl caged cyclic adenosine monophosphate (cAMP) triester (Engels and Schlaeger 1977) and adenosine triphosphate (ATP) (Kaplan et al. 1978). Thereafter, photocaging was used for the optical modulation of neurotransmitter release, including histamine (vide infra*).* Focus in recent years has been shifted to the so-called red-shifted photocages, since light of higher wavelengths (in the red spectrum) can penetrate deeper into tissues and inflicts less tissue damage. As a result, several new photocages based on the structure of coumarin, BODIPY, and cyanine have been published (Bardhan and Deiters 2019). Among them, the BODIPY photocage has attracted interests recently, because of its high absorption wavelength (λ_{max} 490–650 nm), high molar absorption coefficient (ε 30,000–80,000 L mol^{-1} cm^{-1}), and chemical stability.

The first BODIPY-caged histamine was reported by Urano after a serendipitous discovery of the release of an aryloxy group upon irradiation of **42a** (Fig. 7) with a blue-green visible light source (~500 nm) (Umeda et al. 2014). For the design of photocaged histamine, the terminal amine group of histamine was attached to the 4-phenoxy-BODIPY via a carbonyl linker (**42b**). This photocage **42b** could release free histamine with CO_2 and quinone methide as by-products under irradiation of 460–500 nm. To improve its water solubility and thus application in biological matrix, two carboxylic acid groups were introduced to yield the photocage **42c**. Biological evaluation showed no H_1R antagonist activity at 5 μM and very weak

Table 2 Spectroscopic and photochemical properties of different forms of caged histamine

	λ_{max} abs (nm)	λ_{max} Em (nm)	Stokes shift (nm)
42b	498 [a]	511 [a]	13
42c	510 [a]	524 [a]	14
43	543 [b]	–	–
44	549 [c]	567 [c]	18

[a] Measured in 0.1 M sodium phosphate buffer pH 7.4
[b] 100 mM in PBS pH 7.4 with 5% MeCN
[c] Measured in MeCN/water (7/3)

histamine H_1R agonist activity, while irradiation via argon lasers successfully evoked a Ca^{2+} response in H_1R expressing cells, due to a 40% yield of histamine upon uncaging.

Instead of connecting histamine with the boron atom via an aryloxy group in the structure of BODIPY, Rubenstein et al. designed *meso*-methylhydroxy-BODIPY to cage histamine with a carbonyl linker (Rubinstein et al. 2015). Compound **43** exhibits similar photochemical properties as **42b/c** but higher λ_{abs} (Table 2). To test the photoactivation of **43** in living cells, changes in Ca^{2+} response were measured in HeLa cells endogenously expressing H_1R using fura-2 fluorescence. Compared with 89% of cells responding to 5 μM of histamine, **43** (5 μM) led to 27% of cells responding under irradiation of 540 nm green light. Control experiments showed no Ca^{2+} response with **43** before light illumination.

As a general drawback of these BODIPY cages, their water solubility limits their applications in aqueous solutions. To tackle this problem, Miller and Weinstain focused on the methyl group in the BODIPY structure, resulting in mono/di-MESNA-BODIPY (Kand et al. 2020). By introducing sulfonic acid groups, the solubility and cell membrane permeability of such BODIPY photocages can be controlled; i.e. di-MESNA-BODIPY caged ligands are completely cell impermeable. Yet, the mono-MESNA-BODIPY caged histamine (**44**, 5 μM) could induce a Ca^{2+} response in H_1R expressing cells upon light-induced uncaging (542 nm).

Despite the successful BODIPY photocaging of histamine, so far such tools have only been evaluated as an on-demand source of histamine to induce H_1R-induced Ca^{2+} responses. Other histamine receptors or histaminergic neurotransmission have not been investigated yet, using such tools.

Next to the irreversible photo-release of histamine from photocaged histamine, recently also reversible photoswitches for the H_1R and H_3R have been reported. Since 2014, GPCR photoswitchable ligands have been described as new and interesting tools to dynamically modulate GPCR function using light (Ricart-Ortega et al. 2019). In this approach, a photoswitchable moiety, like an azobenzene group, is incorporated in GPCR ligands (Fig. 8). Such an azobenzene moiety can be isomerized by light from its thermodynamically stable *trans* isomer, which is elongated and flat, to a more condensed and bulkier *cis* isomer (Fig. 8). In view of the intricate complementarity of GPCRs and their ligands, it is easy to understand that incorporation of a photoswitchable unit at an allowed position in a GPCR ligand can

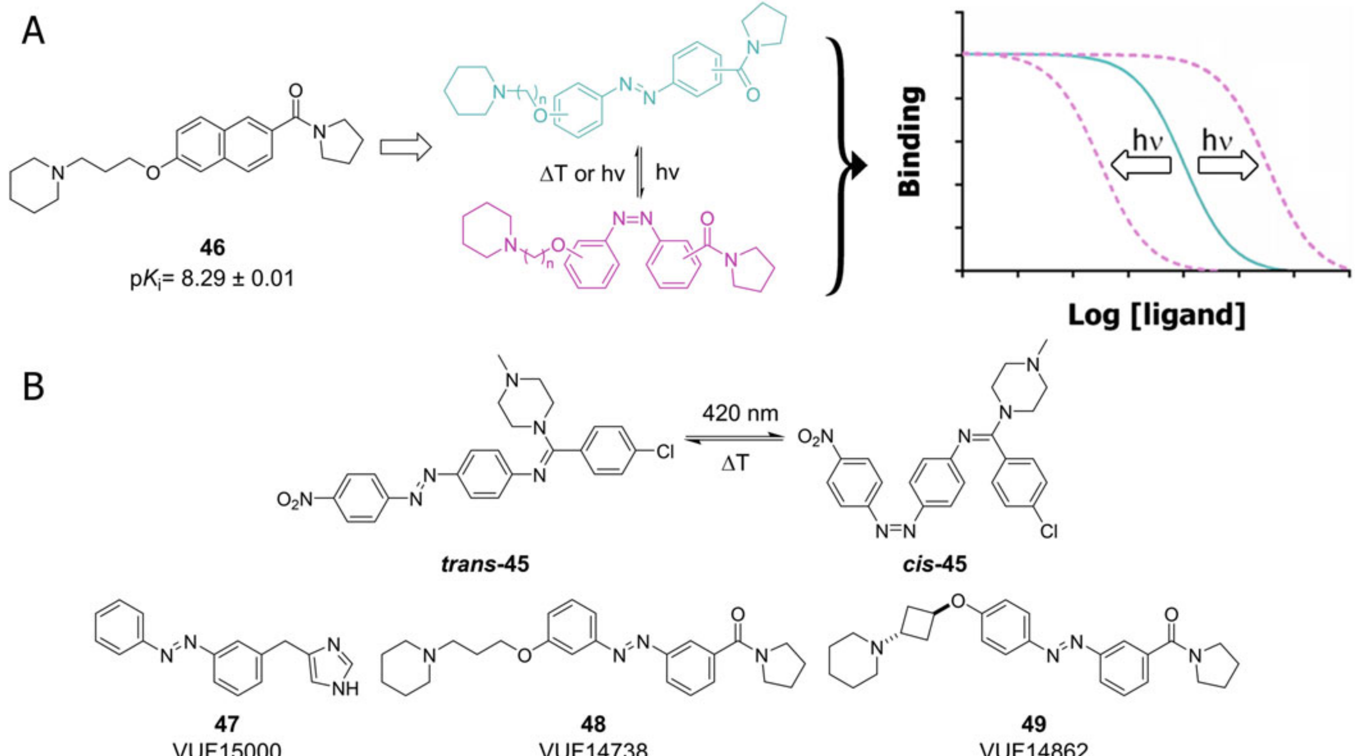

Fig. 8 (**a**) General design and concept of photoswitchable ligands. The azobenzene moiety is incorporated in the core of compound 1 (a potent H_3R antagonist) to give a series of differently substituted trans isomers (cyan). Illumination leads to their corresponding cis isomers (magenta) that can, e.g., have an increased or decreased GPCR affinity. (**b**) Currently available photoswitches for H_1R (**45**) and H_3R (**47–49**)

dramatically increase or decrease its affinity and/or efficacy for the respective target upon isomerization.

For the H_1R, a first account has been published with a potential photoswitchable H_1R antagonist targeting the guinea pig ortholog of the H_1R (Rustler et al. 2019). In the best molecule, the azobenzene photoswitch was replacing a phenyl ring of a classical H_1R structure. The resulting ligand **45** (Fig. 8) shows the most favorable pharmacological profile in the series, albeit showing a pA_2 of only 6.16 for its *trans* isomer (guinea-pig ileum contraction). Upon illumination of *trans*-**45** with visible light of 420 nm, the pA_2 decreases to around 4.50, although the actual value could not be determined properly by Schild plot analysis. Yet, the presumed shift represents a 46-fold decrease in H_1R affinity upon illumination. Currently, no data for the human H_1R is known and unfortunately the absolute affinity of the ligands is rather low and prevents widespread use in biological studies. But, the concept clearly can be applied to H_1R ligands and future work will hopefully lead to high-affinity H_1R photoswitchable ligands.

A bi-directional photochemical toolbox for dynamic agonism and antagonism of the H_3R has been successfully developed by Hauwert et al. (2018, 2019). To arrive at the photoswitchable agonist VUF15000 (**47**, Fig. 8), 16 azobenzene-substituted histamine analogs were evaluated. The photoswitchable H_3R agonists changed their affinity and consequently potency upon *trans-cis* isomerization following illumination with 360 nm (Hauwert et al. 2019), indicating a successful azologization strategy (Schoenberger et al. 2014; Broichhagen et al. 2015; Morstein et al. 2019). All photoswitches also possess long thermal relaxation half-lives at room temperature making them useful for a variety of pharmacological studies. VUF15000 (**47**) was selected as a key compound on the basis of synthetic tractability and the highest absolute H_3R affinity. Upon illumination **47** displays a high potency and 20-fold potency shift while maintaining full intrinsic activity in G_i protein activation making it especially attractive as a tool compound. Electrophysiology experiments demonstrated successful dynamic optical modulation of H_3R activation by **47** in real time.

A core-centered approach replacing a naphthalene moiety in a known H_3R antagonist (**46**) scaffold by a substituted azobenzene unit was followed by a SAR exploration of 16 compounds that show a shift in H_3R binding affinity upon photoisomerization (Hauwert et al. 2018). Two key compounds, **48** and **49**, were selected based on their 13.5-fold increase or 11.2-fold decrease in H_3R binding affinity upon photoisomerization, respectively. Both photoswitchable H_3R antagonists possess long thermal relaxation half-lives for spontaneous *cis-trans* isomerization and resistance to fatigue (i.e., can be switched $>1,000$ times). Photoswitching directly translated to dynamic, light-modulated antagonism of histamine-induced H_3R activity in real-time electrophysiology experiments using *Xenopus* oocytes co-expressing H_3R and G protein-coupled inwardly-rectifying potassium (GIRK) channel.

In view of the widespread distribution of the H_3R in the central and peripheral nervous system, photopharmacology approaches with tools such as **47**, **48**, and **49** offer new means (complementary to optogenetic approaches) to investigate the

spatial and temporal details of H_3R modulation of important processes like arousal, cognition, and neuropathic pain (Panula et al. 2015), setting the stage for further unraveling of the downstream signaling of H_3R with great spatiotemporal precision.

4 Concluding Remarks

Recent developments in the field of histamine receptors and their ligands have opened up new avenues to understand histamine receptor function both at the molecular level and at the system level. Structural biology approaches have appeared successful for the H_1R and similar developments are awaited for the other three receptors. Moreover, conformational biosensors now allow to study the details of ligand–receptor interactions and provide new options for drug screening. Foreseen use of newly developed chemical biology tools, e.g., highly sensitive fluorescent ligands for imaging of endogenously expressed histamine receptors or histamine receptor photoswitchable ligands for spatial and temporal pharmacology approaches, will further increase the fields' insights in the role of histamine and its receptors in (patho)physiology.

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Chemical Probes for Histamine Receptor Subtypes

Markus Falkenstein, Milica Elek, and Holger Stark

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Abstract Ligands with different properties and different selectivity are highly needed for in vitro and in vivo studies on the (patho)physiological influence of the chemical mediator histamine and its receptor subtypes. A selection of well-described ligands for the different receptor subtypes and different studies is shown with a particular focus on affinity and selectivity. In addition, compounds with radioactive or fluorescence elements will be presented with their beneficial use for other species or different investigations.

Keywords Fluorescence · Histamine · Histamine H_1 receptor · Histamine H_2 receptor · Histamine H_3 receptor · Histamine H_4 receptor · PET · Radioligands

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Abbreviations

2-TEA	2-Thiazoleamine
5HT	Serotonin
AC	Adenylyl cyclase
ACh	Acetylcholine
AD	Alzheimer's disease
ADHD	Attention deficit hyperactivity disorder
BBB	Blood-brain barrier
BRET	Bioluminescence resonance energy transfer
cAMP	Cyclic adenosine monophosphate
CNS	Central nervous system
CREB	cAMP-responsive element-binding protein
DA	Dopamine
DAG	Diacetyl glycine
DAO	Diamine oxidase
DiO	Diet-induced obese
EMA	European Medicines Agency
FCS	Fluorescence correlation spectroscopy
FDA	Food and Drug Administration
FRET	Förster resonance energy transfer
GABA	γ-Aminobutyric acid
GPCR	G-protein coupled receptor
GIT	Gastrointestinal tract
Gly	Glutamate
HCV	Hepatitis C virus
HDC	Histidine decarboxylase
hERG	Ether-a-go-go related gene for voltage-dependent potassium ion channel
HHV	Human herpes virus
HNMT	Histamine-*N*-methyltransferase
HTMT	Histamine-trifluoromethyl-toluidide
HR	Histamine receptors (H_1-$_4R$)
PAINS	Pan-assay interference compounds
IP3	Inositol-1,4,5-trisphosphate
MAO B	Monoamine oxidase B
MTCP	Multi-target directed chemicals probes
MTDL	Multi-target directed ligands
NA	Norepinephrine
NO	Nitric oxide
PD	Parkinson's disease
PKA	Protein kinase A
PKC	Protein kinase C
PLC	Phospholipase C
PPI	Proton pump inhibitors

SARS	Severe acute respiratory syndrome
SHR	Spontaneously hypertensive rat
SCM	Scanning confocal microscopy
VMAT	Vesicular monoamine-transporter
wt	Wild type

1 Introduction

1.1 Chemical Probes

Chemical probes (small-molecule tools) are well-characterized substances regarding their influence on a biological target or action mechanism. Depending on the target of interest, the assay setup, and the read-out mechanisms, different chemical probes or combinations of probes can be used due to their beneficial biochemical or pharmacological properties (Stark 2020). According to the clearly defined criteria, the chemical probe should have an affinity below 100 nM, >10-fold selectivity against off-targets, potency in concentration ranges below 10 μM in cell-based assays, and no pan-assay interference compounds (PAINS) elements (Arrowsmith et al. 2015). Chemical probes are powerful research tools that can lead to verification of the proposed mechanism of action as well as the development of novel drug-like candidates. Besides, chemical probes are necessary for drug-discovery processes as they serve for assay system validation. Without a valid assay system, results are not comparable or reliable and cannot be transferred for further evaluation (Bunnage et al. 2013).

In the case of the histamine receptor subtypes, these innovative tools can be used for different purposes, as in vitro examination of receptor affinities, in vivo estimation of receptor localization, and distribution or clinical trials for drug approval. Histamine receptors belong to the group of G-protein coupled receptors (GPCRs), and therefore chemical probes are defined as ligands. A ligand quality as a chemical probe depends on various characteristics as affinity, efficacy, binding properties (covalent or non-covalent), solubility, permeability, and especially the type of assay system (Bunnage et al. 2013). A general classification of the quality of a chemical cannot be made due to high assay versatility but rather an allocation of well-characterized ligands for particular assays (Frye 2010). Despite the numerous possibilities to modify histaminergic transmission by genetic or enzymatic intervention, this review focuses on ligand-based modification only.

1.2 Physiology of Histamine

Sir Henry Dale et al. described 2-(1*H*-imidazole-4-yl)ethanamine (histamine) in 1910. This biogenic amine was firstly extracted from human tissue in 1927 (Dale and Laidlaw 1910; Best et al. 1927). Histamine is ubiquitously distributed in the body of numerous species and involved in regulating various physiological functions of smooth muscles, gastrointestinal, cardiovascular, immune system, central and peripheral neurons. As a local mediator, histamine leads to increased acid production in the stomach, triggers local vasodilation in the skin and lungs, and acts as an inflammatory mediator of the immune system. As a neurotransmitter in the CNS, histamine influences temperature regulation, the sleep-wake rhythm, and learning and memory processes (Obara et al. 2019; Panula et al. 2015).

1.2.1 Biosynthesis and Metabolism

Due to the aromatic imidazole moiety, histamine has two tautomeric structures where either the nitrogen at 1-position (N^1-H) or 3-position (N^3-H) carries the hydrogen. Several studies in gas, liquid, and solid-state indicate that N^1-H is the predominant tautomer (Ramírez et al. 2003). For a precise description of histamine and metabolites, Black and Ganellin introduced a specific nomenclature (Fig. 1) (Black and Ganellin 1974).

The aliphatic amine is referred to as N^{α} and the N^1 of the imidazole ring is described as N^{π} and N^3 as N^{τ}. With the aliphatic and aromatic amines, histamine contains two basic centers. The N^{α} has a p*K*a value of 9.4, and the imidazole nitrogen N^{τ} is less basic with a p*K*a value of 5.8. Under physiological conditions (p*H*: 7.4), histamine is in the form of mono cation, protonated at the N^{α}-position.

The histamine biosynthesis is a one-step process, where L-histidine undergoes an oxidative decarboxylation, mainly catalyzed by the histidine decarboxylase (HDC) (Obara et al. 2019; Parsons and Ganellin 2006). Histamine is stored in vesicles by the vesicular monoamine-transporter VMAT-2 (Hu and Chen 2017). Various stimuli lead to a release of histamine through exocytosis. Once released, histamine does not undergo reuptake by specific transporters or channels like other neurotransmitters. Organic cation transporters (OCT-1, OCT-2, OCT-3, VMAT-1) are discussed for transport mechanisms (Slamet Soetanto et al. 2019; Ogasawara et al. 2006). Histamine is metabolized to inactive N^{τ}-methylhistamine via *N*-methyltransferase (HNMT) or diamine oxidase (DAO) to inactive imidazolyl acetic acid. N^{τ}-methylhistamine is further metabolized through monoamine oxidase B (MAO B) to N^{τ}-methylimidazoylacetic acid (Shahid et al. 2009; Akdis and Blaser 2003).

Histamine exerts its action through four receptor subtypes, histamine 1-4 receptors ($H_{1\text{-}4}R$). All receptor subtypes belong to the class A G-protein coupled receptors (GPCRs) (Shahid et al. 2009).

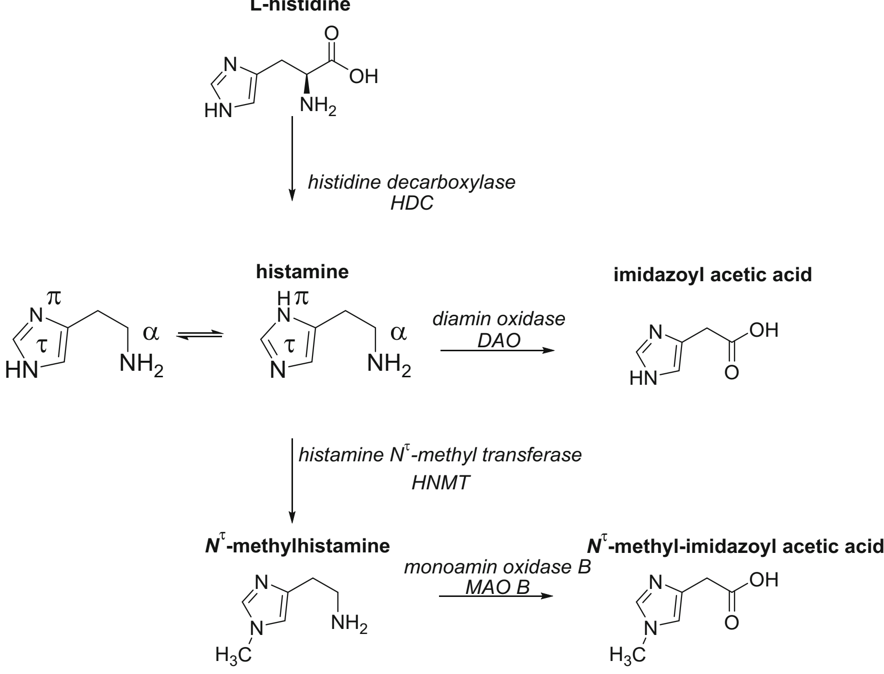

Fig. 1 Formation, tautomerism, and metabolism of histamine

1.2.2 Histamine Receptors

Histamine H_1 Receptor

The histamine H_1 receptor (H_1R) is a Gq-coupled GPCR and is expressed ubiquitously in the body. Activation on histamine H_1R stimulates phospholipase C (PLC) activation and further results in the inositol-1,4,5-trisphosphate (IP_3) and diacetyl glycine (DAG) formation, increased intracellular Ca^{2+} concentration, and activation of protein kinase C (PKC), respectively. The increased Ca^{2+} concentration leads to vasoconstriction in lung smooth muscle cells and large blood vessels. On the other hand, in the small blood vessels, dilatation occurs due to the stimulation of nitric oxide (NO) formation. These processes lead to H_1R-mediated allergic reactions, characterized by heavy breathing, skin redness, itching, and swelling of the nasal mucous membranes (Leurs et al. 2002). In addition to peripheral tissues such as the lungs, skin, cardiovascular system, and gastrointestinal tract (GIT), the receptor is also broadly distributed in the CNS (Panula et al. 2015; Shahid et al. 2009).

The H_1R with high density in different brain areas influences attention, wakefulness, sleep-wake rhythm, and cognition in the hypothalamus, the thalamus, the amygdala, and the cortex (Sadek et al. 2016a). Activation of the H_1R leads to reduced food intake (Díaz et al. 2019). Blockade of the H_1R in the CNS can lead

to significant weight gain, often observed as a side effect of antipsychotics or first generation of antiallergic H_1R antagonists (Kaar et al. 2019).

In 2011, the first X-ray crystal structure of a stabilized H_1R with the antagonist doxepin was reported (Shimamura et al. 2011).

Currently, only H_1R antagonists are used as pharmacological treatment options. The involvement of the H_1R in allergic reactions qualifies H_1R antihistamines as an essential substance class in their treatment. H_1R antagonists are divided into two generations based on their central nervous side effect profiles. In treating allergic reactions, representatives of the first generation are less often used, as they penetrate the blood-brain barrier (BBB). This further results in side effects but can be used for drug repurposing. For instance, the sedative effect is exploited in sleep disorders, and H_1R blockade in CNS leads to the use in the treatment of nausea and vomiting (Simons and Simons 2011).

The second generation of H_1R antihistamines penetrates the BBB to a smaller extent and expresses fewer sedative effects. Active second-generation metabolites and newly designed compounds with higher selectivity rates and simultaneously reduced BBB penetration can therefore be used as a safer and more potent therapeutic antiallergic alternative.

Histamine H_2 Receptor

The histamine H_2 receptor (H_2R) is a Gs-coupled receptor. Signalling through Gs leads to activation of the adenylate cyclase (AC), an increased cyclic adenosine monophosphate (cAMP) concentration, protein kinase A activation (PKA) followed by downstream processes (e.g., cAMP-responsive element-binding protein (CREB) cascade) (Obara et al. 2019; Panula et al. 2015; Sadek et al. 2016a).

The influence on gastric acid production is the well-described process associated with H_2R. H_2R stimulation leads to an increase in cAMP concentration and further in gastric acid secretion. Pharmacologically, gastric secretion is suppressed by H_2R antagonists, which enabled the treatment of reflux diseases, dyspepsia, and gastric ulcers. However, this class was replaced by more efficient and safer proton pump inhibitors (PPIs) as omeprazole, esomeprazole, and pantoprazole (Panula et al. 2015).

H_2R is expressed in the CNS and seems to influence cognitive processes as well as the sleep-wake rhythm (Haas et al. 2008), even though the exact relationship is still unclear. Besides, the H_2R is involved in the glucose metabolism of food-intake control (Schneider et al. 2014). Also, the H_2R is expressed in numerous types of cells, including smooth muscle cells, endothelial and epithelial cells, chondrocytes, neutrophils, eosinophils, monocytes, macrophages, dendritic cells, T and B cells (Jutel et al. 2009).

Histamine H_3 Receptor

The Histamine H_3 receptor (H_3R) is the third histamine receptor subtype, discovered toward the end of the last century and first cloned in 1999 (Panula et al. 2015). The H_3R is predominantly expressed in the CNS; however, expression in the periphery has also been detected and is increasingly being discussed on therapeutic aspects (Sander et al. 2008). High receptor density is found in the CNS in the cortex, the striatum, the nucleus accumbens, the amygdala, the palladium, and the hippocampus (Sadek et al. 2016a; Sander et al. 2008; Nieto-Alamilla et al. 2016). The H_3R is predominantly expressed as a presynaptic receptor and acts as an autoreceptor controlling histamine synthesis and release via a negative feedback mechanism. As a heteroreceptor on non-histaminergic synapses, the H_3R also regulates the release of dopamine (DA), acetylcholine (ACh), norepinephrine (NA), glutamate (Glu), serotonin (5-HT), γ-aminobutyric acid (GABA), substance P and other neurotransmitters (Sander et al. 2008; Nieto-Alamilla et al. 2016). Postsynaptic H_3Rs were recently described (Ghamari et al. 2019). Presynaptic H_3R is a $G_{i/o}$ coupled GPCR (Sadek et al. 2016a; Nieto-Alamilla et al. 2016). The $G_{\alpha i}$ subunit inhibits the AC and thereby leads to a decreased cAMP concentration and reduced PKA activity. The reduced cAMP level reduces CREB-mediated gene transcription and lowers protein biosynthesis. HDC activity and histamine synthesis are reduced (Sander et al. 2008; Nieto-Alamilla et al. 2016; Obara et al. 2019).

The $G_{\beta\gamma}$ subunit binds to and inhibits the P- and Q-type of voltage-gated calcium channels. The inhibition of these channels reduces Ca^{2+} influx into the presynapse and diminishes the depolarization. Activation of GIRK potassium channels leads to increased K^+ efflux and hyperpolarization. Decreased Ca^{2+} influx and increased K^+ efflux result in decreased neurotransmitter exocytosis (Nieto-Alamilla et al. 2016).

H_3R antagonists suppress the H_3R mediated inhibitory effect and consequently increase the histamine biosynthesis and release. Through H_3R heteroreceptors, other neurotransmitters and mediators like ACh, NA, DA, 5-HT, Glu, and GABA are modulated (Nieto-Alamilla et al. 2016; Ghamari et al. 2019; Obara et al. 2019).

As GPCR with high constitutive activity, antagonists of the H_3R can act as neutral antagonists or inverse agonists. Inverse agonists can decrease the basal activity of the receptor by stabilizing the inactive state (Latorraca et al. 2017; Berg and Clarke 2018).

An influence of H_3R inverse agonists on the waking state, through increased histamine concentrations and postsynaptic H1R activation, led to the development of pitolisant, the first and so far, only H_3R inverse agonist approved by the FDA (Food and Drug Administration) and the EMA (European Medicines Agency). Pitolisant (Wakix®) is indicated for treating narcolepsy with and without cataplexy (Ghamari et al. 2019; Romigi et al. 2018) and excessive daytime sleepiness in obstructive sleep apnea (Ozawade®) (Wang et al. 2021).

As described, the H_3R mediates several neurotransmitter levels and targets diseases associated with CNS disorders. These include schizophrenia, epilepsy, attention deficit hyperactivity disorder (ADHD), autism, altered sleep-wake rhythms, Prader-Willi syndrome, and neurodegenerative diseases such as

Alzheimer's disease and Parkinson's disease (Ghamari et al. 2019; Reiner et al. 2020; Sadek and Stark 2016).

Histamine H_4 Receptor

The histamine H_4 receptor (H_4R) is a G_i-coupled GPCR identified in 2000 as the last histamine receptor subtype. H_4Rs are structurally related to H_3Rs. However, the expression patterns of the receptors differ significantly, so that the H_4R shows increased peripheral expression (Panula et al. 2015; Schneider and Seifert 2016).

The H_4R is mainly expressed on hematopoietic cells, especially on eosinophilic granulocytes (Buckland et al. 2003). Besides, mast cells, natural killer cells as well as monocytes also express the H_4R (Gschwandtner et al. 2013; Capelo et al. 2016). Strong evidence suggested H_4R association with various functional inflammatory responses mediated by histamine, including chemotaxis and cell recruitment upregulation of adhesion molecule expression, and modulation of cytokine and chemokine release (Neumann et al. 2014; Hartwig et al. 2015). Preclinical and emerging clinical data supporting the association of H_4R with pruritus and atopic skin inflammation (Werfel et al. 2016). For example, H_4R agonists have been described to upregulate the T_H2-associated and itch-inducing cytokine IL-31 (Gutzmer et al. 2009).

Other diseases discussed in context with the therapeutic H_4R blockade include bronchial asthma and non-specific inflammatory reactions (Panula et al. 2015). Up to date, no H_4R ligand has been approved by drug agencies.

2 In Vitro Assays

In the case of GPCRs, in vitro assays display test systems to evaluate ligand affinity, functionality, and efficacy in a cell-based system. In receptor binding assay, a ligand can be characterized by its affinity at the receptor of interest (on-target) and its selectivity over undesired receptors (off-targets).

Intrinsic activity and efficacy are determined in functional assays, and at least two types of chemical probes can be beneficial for in vitro assays conduction. Unlabelled or reference ligands display a large group of compounds. With well-defined receptor profiles and high on-target affinities, they are needed to standardize the results. In a validated assay, the reference ligand is the critical element to compare and transfer to other results and studies. Reference ligands are used in both binding studies and functional assays.

The second group is labelled ligands, subdivided into radioactive (radio-) and fluorescent-labelled ligands. These labelled ligands are used as measurable/countable values to determine affinities and receptor distributions. The labelled ligand should show high selectivity, especially for receptor distribution assays and assays with native or primary cells (containing more than one receptor).

2.1 Reference Ligands

Histamine is the endogenic ligand of histamine receptors (HR) that shows moderate to high affinities at all four receptor subtypes. Interestingly, the affinity at H_1R and H_2R is more than 1,000-fold lower compared to those at H_3R and H_4R. As an endogenous ligand, histamine displays unfavorable properties as a chemical probe. At H_1R and H_2R, the affinity is not high enough, and for H_3R and H_4R, the missing selectivity is an essential drawback. However, histamine is used as a reference in functional assays to calculate the intrinsic activity and efficacy compared to the endogenous ligand.

2.1.1 Histamine H_1 Receptor

Agonists

First attempts to synthesize H_1R agonists lead to imidazole-containing analogues as 2-thiazoylhistamine (2-TEA). Like histamine, the affinity and selectivity of 2-TEA are not suitable for use as a chemical probe. With an intrinsic activity of 27% compared to histamine, 2-TEA is a partial agonist with moderate efficacy (EC_{50}: 440 nM) (Seifert et al. 2003). The introduction of a 3,3-diphenylpropyl group in position 2 of imidazole leads to a substance class named histaprodifens. Histaprodifens display partial agonists with an intrinsic activity of up to 77% (methylhistaprodifen) and 84% (suprahistaprodifen) (Elz et al. 2000). H_1R affinity of methylhistaprodifen is moderate. However, it is still mostly used as an H_1R agonist, with an acceptable selectivity over H_2R (~100×) and H_3R (~10×). Although histaprodifen and derivatives were synthesized already 20 years ago (Elz et al. 2000), meanwhile no remarkable progress was made in the field of H_1R agonists. A full agonist with high and selective H_1R affinity remained to be designed.

Antagonists

In contrast to agonists, a variety of H_1R antagonists with high affinities were synthetized. A well-characterized representative of H_1R antagonists is mepyramine. It belongs to the group of first-generation antihistamines, as it penetrates the blood-brain barrier. Due to its high affinity (pK_i: 8.4) and selectivity over other HRs (~100×), mepyramine was used to synthesize radio and fluorescent-labelled analogues/derivatives (Rose et al. 2012). Doxepin, another first-generation antihistamine, showed increased affinity at H_1R with a pK_i value of 9.5. While the other HR's selectivity is high, some off-target interaction to serotonin receptors (5-HTR) is reported (Mansbach 2008; Zhou et al. 2018). With a resolved doxepin-H_1R crystal structure, doxepin is a promising chemical probe for clarifying structure activation

relationships (Shimamura et al. 2011). Side effects of first-generation antihistamines due to central H_1R blockade resulted in developing second generation of H_1R antagonists. Well-described members of this group are the frequently used antiallergic drugs cetirizine and loratadine (Sadek and Stark 2016). Their highest benefit of chemical probes is the transferability from in vitro data to clinical outcomes. Desloratadine, an active metabolite of loratadine, was introduced to the market and showed increased affinity to H_1R. Desloratadine as well as loratadine show affinities at 5-HT_2R, in a comparable range like doxepin (pK_i: 6.5–7.5). This should be kept in mind when analyzing the results of native cell experiments. Cetirizine points out the stereoselective binding at H_1R; the racemic Cetirizine shows a pK_i value of 8.2, where the pure *R*-enantiomer called levocetirizine has an affinity of pK_i: 8.5, and the *S*-enantiomer has a lower affinity with a pK_i value of 7.1 (Hair and Scot 2006). Due to its higher affinity, levocetirizine was brought to the market as a pure enantiomeric drug (Fig. 2). Histamine H_1R ligands are summarized in Table 1.

2.1.2 Histamine H_2 Receptor

Agonists

Compared with H_1R agonists, the search for selective H_2R agonists started with the imidazole ring variation. As a result, 4-methylhistamine was synthesized and is nowadays used as an H_4R agonist with around 100-fold selectivity at H_4R over H_2R. The replacement of imidazole with aminothiazole leads to amthamine (Fig. 3). Even though amthamine acts as a full agonist at H_2R, it shows a low affinity (pK_i: 5.2) and no selectivity to other receptor subtypes. The partial agonist impromidine (intrinsic activity 79%) has an improved affinity to H_2R (pK_i:7.2) and selectivity over H_1R (~100×) but retains its lack of selectivity over H_3R (pK_i:7.2) and H_4R (pK_i:7.9). According to the stereoselectivity of histamine receptors, sopromidine shows interesting behavior. Comparable to cetirizine at the H_1R, the two stereoisomers of sopromidine show different binding affinities to H_2R. Moreover, *R*-sopromidine acts as a full agonist, where *S*-sopromidine acts as a moderate antagonist (Elz et al. 1989). It is noteworthy that guanidine-based impromidine derivatives show affinity at H_3R and H_4R and were used as lead structures for selective H_3R and H_4R ligands (Venable and Thurmond 2012; Gbahou et al. 2012).

UR KAT471 is a potent partial agonist of the H_2R and shows more than 100-fold selectivity over the other HR subtypes. The selectivity, high affinity (pK_i of 7.2), and potency superior to histamine make UR KAT471 the favored H_2R agonist for in vitro assays (Kraus et al. 2009).

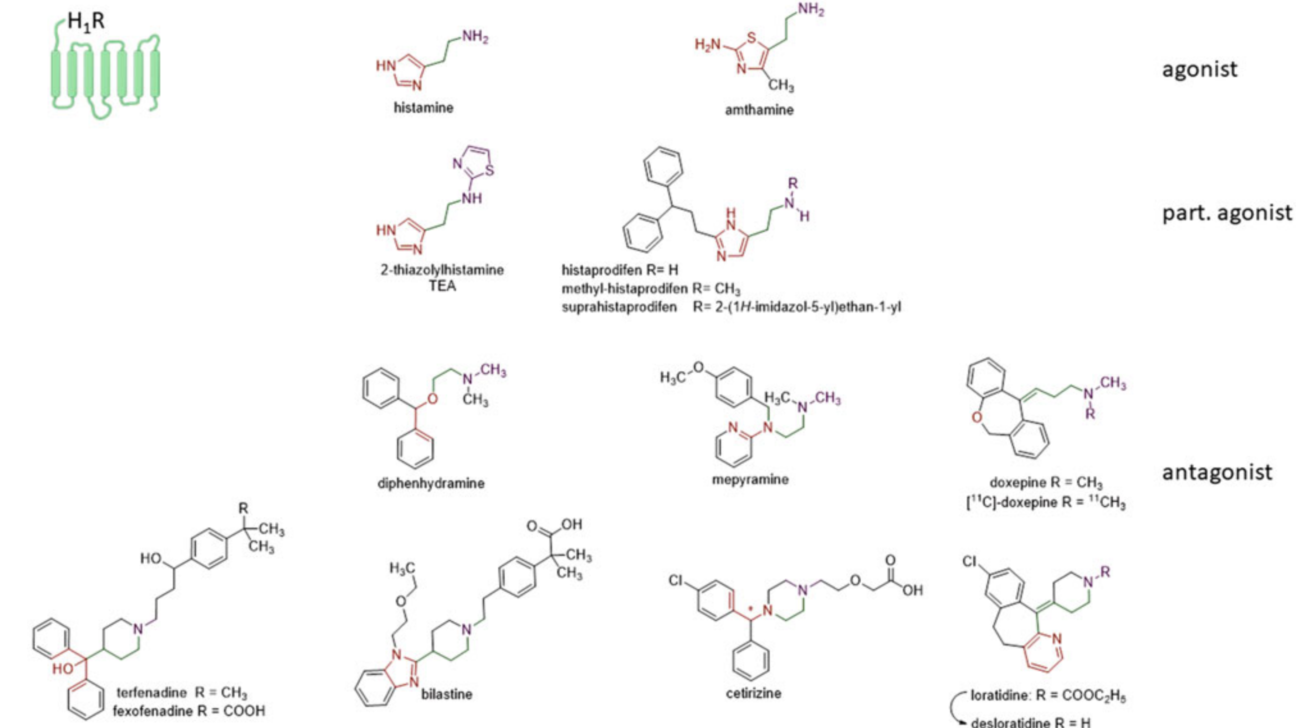

Fig. 2 Selected histamine H_1 receptor agonists, partial antagonists, and antagonists

Table 1 Histamine H_1R ligands and their in vitro data

Compound	H_1R pK_i	H_2R pK_i	H_3R pK_i	H_4R pK_i	Other receptors p$K_i > 6$	Additional information
Histamine (Panula et al. 2015)	4.2	4.3	8.0	7.8		Endogenous ligand
2-Thiazolylhistamine (2-TEA) (Seifert et al. 2003)	5.3			<5.0		Partial agonist (26%)
Methylhistaprodifen (Seifert et al. 2003; Elz et al. 2000)	6.4	4.6[a]	5.8[a]			Partial agonist (77%)
Mepyramine (Wagner et al. 2011)	8.4	4.6	<4	< 4	6.2 (DAT)[b] 6.6 ($5\text{-}HT_{2A}$)[b] 6.2 ($5\text{-}HT_{2c}$)[b] 7.6 (SERT)[b] 6.2 (σ_1)[b]	Antagonist
[^{3}H]Mepyramine (Wagner et al. 2011)	8.4	4.6[c]	<4[c]	<4[c]		PET-ligand
Mepyramin-BODIPY (Rose et al. 2012)	8.9					Fluorescent-labelled
Diphenhydramine (Panula et al. 2015; Mansbach 2008)	7.9	5.8	<5.5	<5.5	6.6 ($5\text{-}HT_{2A}$) 6.2 ($5\text{-}HT_{2B}$)[b] 6.3 ($5\text{-}HT_{2C}$)[b] 7.1 (M_1)[b] 6.4 (M_2)[b] 6.7 (M_3)[b] 7.3 (M_4)[b] 6.9 (M_5)[b]	Antagonist, 1.Gen
Doxepin (Shimamura et al. 2011; Mansbach 2008; Zhou et al. 2018)	9.5		<5.5		7.6 ($5\text{-}HT_{2B}$) 8.0 ($5\text{-}HT_{2A}$)	Antagonist, 1.Gen
Levocetirizine (Panula et al. 2015)	8.15	<6	<6	<4		Antagonist, 2.Gen
Loratadine (Panula et al. 2015; Auerbach 2021)	7.2		< 5	< 5	6.8 ($5\text{-}HT_{2B}$)	Antagonist, 2.Gen
Desloratadine (Hu and Chen 2017; Auerbach 2021)	8.4	6.5	< 5	< 5	7.5 ($5\text{-}HT_2$) 7.7 (M_2) 7.0 (M_3)[b] 7.3 (M_4)[b] 6.7 (M_5)[b] 8.0 ($5\text{-}HT_{2C}$)[b]	Antagonist 2.Gen

(continued)

Table 1 (continued)

Compound	H_1R pK_i	H_2R pK_i	H_3R pK_i	H_4R pK_i	Other receptors p$K_i > 6$	Additional information
					7.6 ($5\text{-}HT_{2B}$)[b] 7.8 ($5\text{-}HT_{2C}$)[b] 6.0 ($5\text{-}HT_6$)[b] 6.9 (SERT)[b] 6.0 (α_{2B})[b] 6.2 (D_3)[b]	
Bilastine (Corcóstegui et al. 2005)	8.2	<6.0	<6.0	<6.0		Antagonist, 2.Gen
[^{11}C]Doxepin	9.5[c]		<5.5[c]			PET-ligand
[^{11}C]Mepyramine	8.4[c]	4.6[c]	<4[c]	<4[c]		PET-ligand

Gen generation
[a]Guinea pig
[b]Data obtained from "DrugMatrix in vitro pharmacology data" database (Auerbach 2021)
[c]Values of unlabelled ligand

Antagonists

Like H_2R agonists, antagonists also show difficulties in terms of selectivity at H_4R. Aminopotentidine is a member of cyano substituted guanidine with a nanomolar affinity (pK_i: 7.4) and shows selectivity over H_1R and H_4R, but not over H_3R. With an iodide substitution at the 3-position of the benzamide group, the affinity to H_2R was significantly improved, resulting in pK_i value of 9.4. In this way, a radiolabelled ligand is designed when using the radioactive isotope ^{125}I (half-live of 59.5 days). Replacement of the substituted guanidino group by square acid resulted in more selective H_2R antagonists. Tritium-labelled UR DE-257 shows high selectivity over the other HRs (>100×) and can be used as a radiolabelled ligand for H_2R. Commercially available H_2R antagonists also contain guanidino group (cimetidine-cyanoguanidine group, ranitidine-nitroethendiamine, and famotidine-sulfamoylamidine). Imidazole in cimetidine was replaced with bioisosteric heterocycles such as furan (ranitidine) and aminothiazole (famotidine) to prevent interaction with CYP450 enzyme complex. These drugs show affinities in a low micromolar to the nanomolar concentration range and are characterized as inverse agonists with an intrinsic activity of −88% (cimetidine and famotidine) and −100% (ranitidine). As in the case of approved H_1R antagonists, the benefit of these drugs is not defined by their high affinity or selectivity but rather on the transferability of in vitro data to clinical outcomes (Fig. 3). Histamine H_2R ligands are summarized in Table 2.

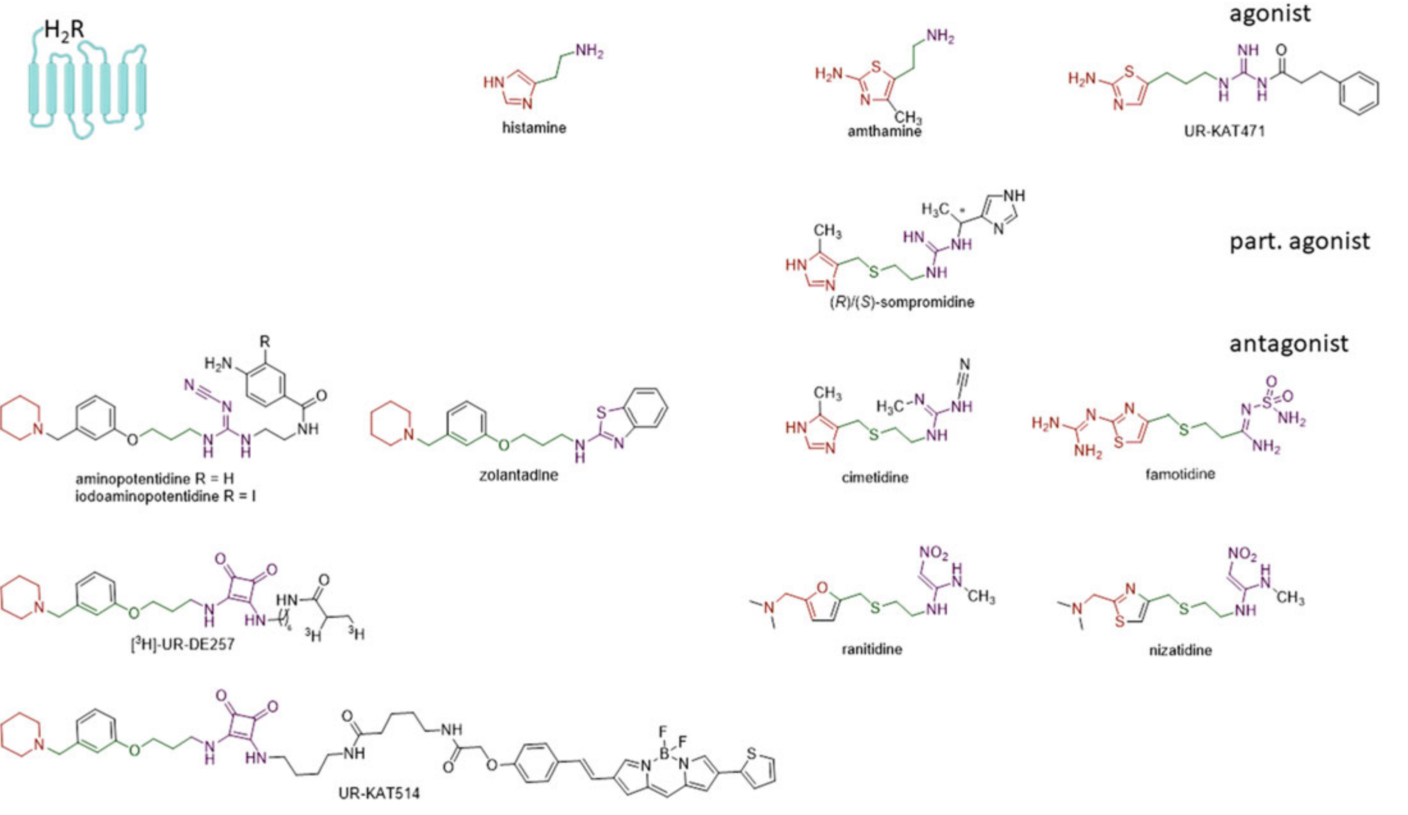

Fig. 3 Selected histamine H_2 receptor agonists, partial agonists and antagonists

Table 2 Histamine H_2R ligands and their in vitro data

Compound	H_1R pK_i	H_2R pK_i	H_3R pK_i	H_4R pK_i	Other receptors p$K_i > 6$	Additional information
Histamine (Panula et al. 2015)	4.2	4.3	8.0	7.8		Endogenous ligand
Amthamine (Igel et al. 2010; Xie et al. 2006)	4.8	5.2		5.3		Agonist (101%)
Impromidine (Igel et al. 2010; Xie et al. 2006; Jablonowski et al. 2003)	5.2	7.2	7.2	7.9		Agonist (79%)
UR KAT471 (Kraus et al. 2009)	<5.0	7.2	<5.0	<5.0		Agonist (82%)
Aminopotentidine (Panula et al. 2015)	<5.5	7.4	7.1	<5.5		Antagonist
[^{125}I]Iodoamino-potentidine (Bosma et al. 2017; Hirschfeld et al. 1992)	5.6	9.4				Antagonist, radioligand
[^{3}H]UR-DE257 (Baumeister et al. 2015)	<5.5	7.6	<5.5	<5.5		Antagonist, radioligand
UR-KAT514 (Grätz et al. 2020) (BODIPY-labelled)		8.4				Antagonist, fluorescent-labelled
Cimetidine (Panula et al. 2015; Alewijnse et al. 1998; Lim et al. 2005)	4.75	5.84	4.69	5.03		Inverse-agonist (−88%)
Famotidine (Panula et al. 2015; Alewijnse et al. 1998; Lim et al. 2005; Angeli et al. 2018)	<5	7.8		<5.0	< 7.0 ($CA_{1,4,9,13,14}$) 7.0 (CA_6) 8.5(CA_7) 7.3(CA_{12})	Inverse-agonist (−88%)
Ranitidine (Panula et al. 2015; Alewijnse et al. 1998; Lim et al. 2005)	4.47	6.67	4.89	<5.0		Inverse-agonist (−100%)

CA carbonic anhydrase

2.1.3 Histamine H_3-Receptor

Agonists

With the discovery of H_3Rs in 1983, numerous H_1R and H_2R ligands were examined due to their affinity to the H_3R. Histamine shows high selectivity for H_3R over H_1R and H_2R, and it was used as a lead structure. Slight variations with methylation of histamine resulted in *R*-α-methylhistamine and N^{α}-methylhistamine (Fig. 4). Both ligands are potent agonists with an intrinsic activity of 100% compared to that of histamine. Like histamine, they show selectivity over H_1R and H_2R of about 100-fold, with a high affinity at H_3R. The following discovery of H_4R disclosed

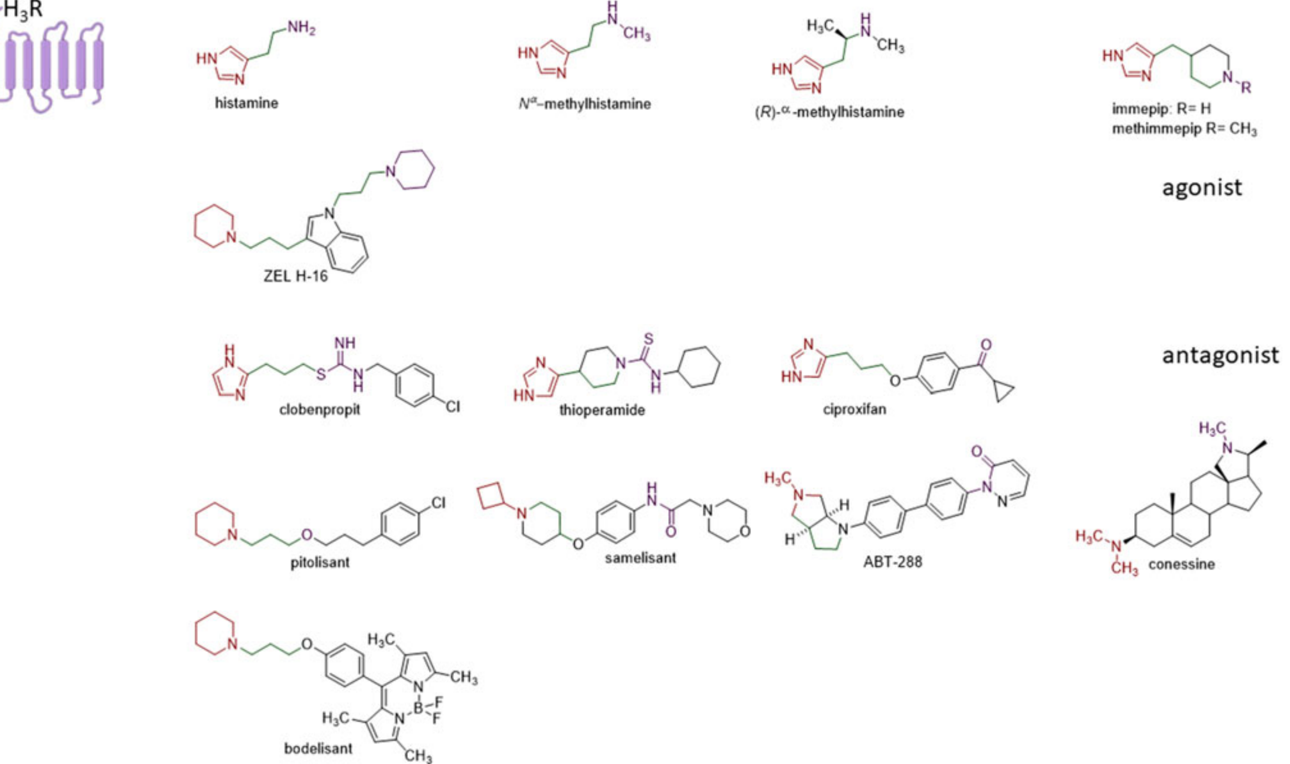

Fig. 4 Selected histamine H_3 receptor agonists and antagonists/inverse agonists

for both ligands full H_4R agonism (100%) with moderate affinities with pK_i values of 6.5 and 6.6, respectively. N^{α}-Methylhistamine is a commercially available [^{3}H] labelled ligand for H_3R binding studies (Panula et al. 2015) leading to good comparability of assay results.

Replacement of the aliphatic alkyl amine by piperidine led to immepip and methylimmepip. Methylimmepip shows high affinity (pK_i value of 9.0) and selectivity to H_3R over H_1R, H_2R, and H_4R (>1,000×) and intrinsic activity of 90%. These features make methylimmepip a valuable chemical probe for in vitro studies. Proxyfan shows an interesting efficacy behavior depending on the assay characteristics; as a selective ligand, it can act as an inverse agonist, antagonist, or (partial) agonist (Sadek and Stark 2016). The only non-imidazole-based agonist described so far, ZEL-H16 (1,3-bis(3-(piperidin-1-yl)propyl)-1*H*-indole), possesses high affinity (pK_i value of 8.6) and selectivity to H_3R. It is a partial agonist with an intrinsic activity of 60% compared with that of histamine (Shi et al. 2012).

Antagonists

The early antagonists of the H_3R, like thioperamide, showed high selectivity over H_1R and H_2R but not over H_4R. (hH_3R pK_i: 7.1, hH_4R pK_i: 7.3). Thioperamide was found to be an inverse agonist at H_3R and an agonist at H_4R. Examining antagonistic properties enabled classifying rat (r), mouse (m), or human (h) H_3R isoforms. Thioperamide shows a slightly reduced affinity to hH_3R compared to rH_3R. Ciproxifan, an H_3R selective inverse agonist, has a 100-fold higher affinity to the rH_3R whereas clobenpropit shows nearly no difference. Clobenpropit shows sub-nanomolar affinity to hH_3R, and even though it has a good selectivity over H_4R, it served as a blueprint for the design and synthesis of H_4R ligands due to its likewise nanomolar affinity to the H_4R (Tiligada and Ennis 2020). Iodoproxyfan also shows a sub-nanomolar affinity and is used as a radiolabelled ([^{125}I]) ligand, with high selectivity over H_1R and H_2R and slight selectivity over H_4R.

Despite the general assumption that the imidazole moiety causes serious interactions due to the CYP450 enzyme class interactions, these compounds have been dosed in low concentration in numerous in vitro and in vivo experiments without any signs of interaction. The receptor selectivity might be a more important aspect concerning off-target affinities (e.g., H_4R). The imidazole replacement by cyclic tertiary amines like *N*-substituted piperidine or pyrrolidine resulted in the next generation of H_3R antagonists. With pitolisant, the affinity to hH_3R as well as the selectivity over H_4R was increased. The FDA and EMA approved the inverse agonist pitolisant for the treatment of narcolepsy with or without cataplexy (Wang et al. 2021). Based on the H_3R pharmacophore of pitolisant, the potent fluorescent-labelled ligand bodilisant was synthesized. As the only H_3R inverse agonist/antagonist on the drug market, pitolisant displays excellent properties as a reference substance. Several other inverse agonists/antagonists were synthesized and investigated in preclinical and clinical assays. ABT-288 showed high affinity and selectivity. In several assays, procognitive effects of ABT-288 were observed. Similar

affinity to human and rat H_3R (pK_i: hH_3R: 8.7, rH3R: 8.1) can simplify the analysis of different assay systems (Esbenshade et al. 2012). The steroidal alkaloid conessine shows structural differences to other H_3R antagonists with comparable receptor affinity (pK_i: 8.5) to pitolisant and ABT-288. The selectivity over other HRs (>1,000×) and other GPCR is high. It is a highly suitable second reference substance to reveal pattern associated unspecific binding in a new assay. An affinity of conessine to adrenergic α_2 receptors should be noted concerning GPCR based assays (Zhao et al. 2008) (Fig. 4). Histamine H_3R ligands are summarized in Table 3.

2.1.4 Histamine H_4 Receptor

Agonists

Several former reported HR ligands showed affinity to H_4R after it was discovered. The high similarity of H_3R and H_4R binding pockets led to some obstacles in finding selective ligands. Histamine and the radiolabelled [^{3}H]histamine show similar high affinities to the receptors. However, it is commonly used as a radiolabelled ligand in H_4R displacement studies. 4-Methylhistamine, synthesized initially as an H_2R ligand, shows a high affinity to H_4R with at least 100-fold selectivity over other HRs (Fig. 5). It is characterized as a full agonist with 100% intrinsic activity compared to histamine. Some other H_2R agonists display H_4R affinities like impromidine (pK_i value of 7.6) and *R*-/*S*-sompromidine (pK_i values of *S*: 5.5, *R*: 6.1). The partial agonist ST-1006 is described as the most potent H_4R agonist (pEC_{50} value of 8.95*)* and shows high affinity and good selectivity over H_1R, H_2R, and H_3R (Sander et al. 2009).

Antagonists

As mentioned, the H_3R inverse agonist iodoproxifan was used as a lead structure for H_4R antagonists. Other H_3R antagonist iodophenpropit showed nearly the same affinity at H_4R (pK_i value of 7.9) and H_3R (pK_i value of 8.1) with agonistic and inverse agonistic activities, respectively, displaying functional selectivity. The ^{125}I-labelled form of iodophenpropit is frequently used as a radiolabelled ligand for H_4R in displacement studies. One of the best-studied and most used reference ligands in the field of H_4R is JNJ-7777120. It possesses a high affinity (pK_i value of 8.4) and selectivity (other HRs > 100×). Although the affinity of humans and rats (pK_i value of 8.6) varies little, the intrinsic activity is different. In humans, JNJ-7777120 acts as an inverse agonist, whereas in rats, it acts as a partial agonist (51% activity compared to that of histamine (100%)).

Moreover, the behavior in humans can change because JNJ-7777120 shows agonist activity in β-arrestin recruitment pathways. It is therefore called a biased agonist (Rosethorne and Charlton 2011). As a chemical probe for in vitro characterizations, this might be acceptable or welcomed to study species differences,

Table 3 Histamine H_3R ligands and their in vitro data

Compound	H_1R pK_i	H_2R pK_i	H_3R pK_i	H_4R pK_i	Other receptors p$K_i > 6$	Additional information
Histamine (Panula et al. 2015)	4.2	4.3	8.0	7.8		Endogenous ligand
Methimepip (Panula et al. 2015; Kitbunnadaj et al. 2005)	<5.5	<5.5	9.0	5.7		Agonist (90%)
[^{3}H]N^α-Methylhistamine (Panula et al. 2015; Igel et al. 2010)	<5.5	<5.5	8.4	6.5		Agonist (100%) H_4R agonist (100%) Radiolabelled
(*R*)-α-Methylhistamine (Panula et al. 2015; Lim et al. 2005)	<5.5	<5.5	8.2	6.6		Agonist (100%) H_4R agonist (100%)
Clobenpropit (Fox et al. 2003) Human	5.6	<5.5	9.4	7.4		Antagonist
Rat			9.7			H_4R antagonist
Thioperamid (Zhao et al. 2008; Fox et al. 2003)					6.9 (α_{2A})	Antagonist
Human	<5.5	<5.5	7.1	7.3	6.5 (α_{2C})	
Rat			8.4			H_4R inverse agonist
Ciproxifan (Zhao et al. 2008; Fox et al. 2003)					7.4 (α_{2A})	Antagonist
Human	<5.5	<5.5	7.2	5.7	7.2 (α_{2C})	
Rat			9.3			Antagonist
Iodoproxyfan (Lim et al. 2005)			9.2	7.9		Antagonist
[^{125}I]Iodoproxyfan (Fox et al. 2003; Istyastono et al. 2011)	5.6	<5.5	8.6	7.8		Antagonist Radiolabelled
Pitolisant (Sadek et al. 2014; Szczepańska et al. 2018) Human (Walter et al. 2010; Riddy et al. 2019)	5.9	<5.5	8.6	<5.5	σ_1: 8.0 (agonist)	Inverse agonist
Rat (Łazewska et al. 2009)			7.8			Inverse agonist
ABT-288 (Esbenshade et al. 2012)						Antagonist
Human	<5.0	<5.0	8.7	<5.0		
Rat			8.1			Antagonist
Conessine (Zhao et al. 2008)	<505	<5.0	8.5	<5.0	α_2C_4: 8.0 α_2C_4: 6.2	Antagonist

(continued)

Table 3 (continued)

Compound	H_1R pK_i	H_2R pK_i	H_3R pK_i	H_4R pK_i	Other receptors p$K_i > 6$	Additional information
Samelisant						Inverse agonist
(SUVN-G3031) (Nirogi et al. 2021)						
Human	< 6.0	< 6.0	8.7	< 6.0		
Rat			9.8			Inverse agonist
Bodilisant (Tomasch et al. 2013)	5.8		8.4	<5.5		Antagonist Fluorescent labelled
S-[^{11}C]Methylthioperamid (Funke et al. 2013)			7.3			PET-ligand
[^{11}C]GSK189254 (Funke et al. 2013)			9.6			PET-ligand

reducing the portability between in vitro and in vivo data. Nevertheless, JNJ-7777120 is a well-characterized tool for understanding the physiology of the H_4R (Thurmond et al. 2004).

One of the well-described H_4R ligands is adriforant (also known as PF-03893787 or ZPL-389), an inverse agonist at hH_4R. Compared to JNJ-777712, adriforant shows species variations in affinity (pK_i values hH_4R: 8.2, hH_4R: 8.2, and dog H_4R: 5.8) and intrinsic activity as it acts as antagonists in dogs and partial agonist in rats. This species-dependent behavior arises from low amino acid sequence identities. The human H_4R only shows around 70% amino acid homology to rats and dogs. Rats again possess only 64% of homology to dogs and even only 84% to mice (Jiang et al. 2008). Also, histamine as an endogenic ligand shows these species differences with pK_i values of 7.8 and 6.9 at human and rat H_4R isoforms, respectively (Fig. 5). Histamine H_4R ligands are summarized in Table 4.

Multi-target Histamine Ligands

The involvement of histamine and its receptors in complex immunological and neurophysiological processes, and the beneficial effects of HR ligands in clinical trials, led to their participation in polyvalent ligands (Łażewska and Kieć-Kononowicz 2018). Such multi-target directed ligands (MTDLs) address more than one target and simultaneously impact pathophysiological conditions (Proschak et al. 2019). The design of such a ligand must differ from "dirty drugs." The latter interacts with several off-targets, while the former has a designed polypharmacological profile. Rationally designed multi-target directed chemicals probes (MTCPs) need to be extremely well described regarding their targets and potential off-targets. MTCPs are necessary tools to study target combinations in vivo and as references in vitro. Compared to single target chemical probes, affinities

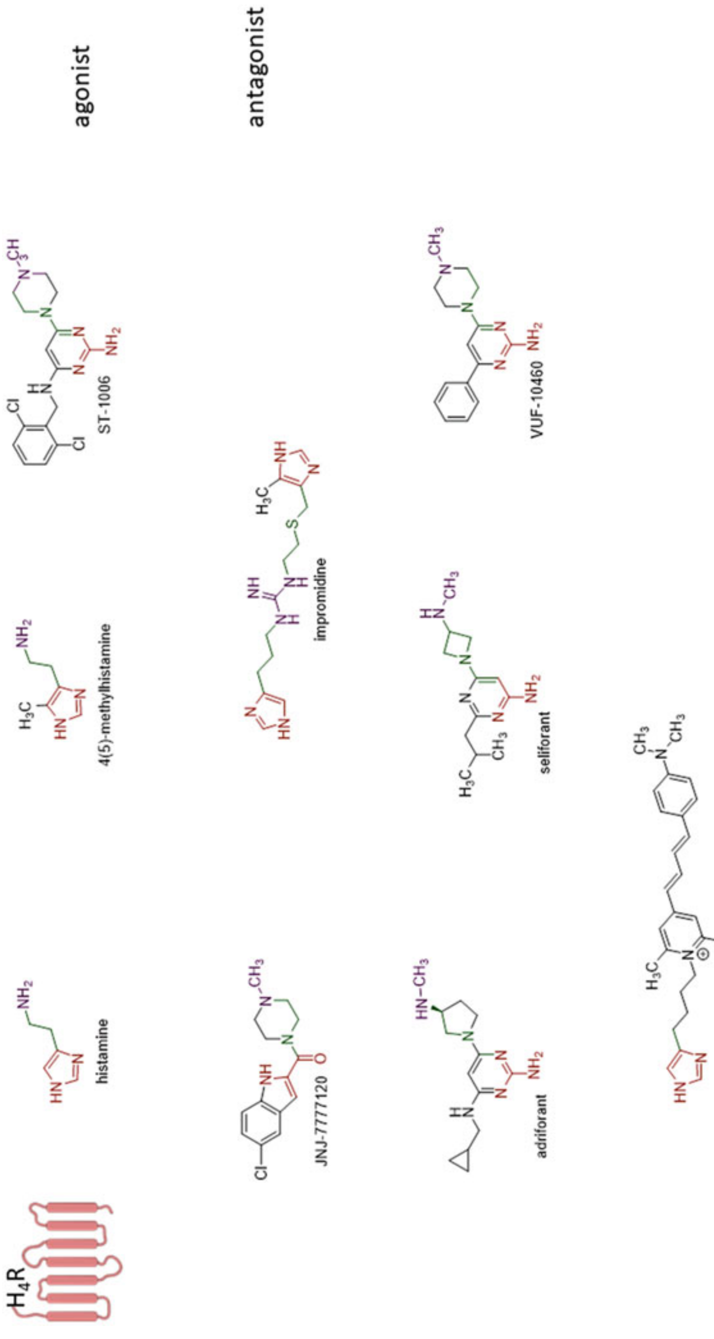

Fig. 5 Selected histamine H_4 receptor agonists and antagonists/inverse agonists

Table 4 Histamine H_4R ligands and their in vitro data

Compound	H_1R pK_i	H_2R pK_i	H_3R pK_i	H_4R pK_i	Other receptors p$K_i > 6$	Additional information
Histamine (Panula et al. 2015)	4.2	4.3	8.0	7.8		Endogenous ligand
4-Methyl-histamine (Lim et al. 2005; Gschwandtner et al. 2013)	<5.5	<5.5	<5.5	7.3		Agonist (100%)
ST-1006 (Sander et al. 2009)	6.0	6.0	6.3	7.9		Agonist (28%)
JNJ-7777120 (Liu et al. 2008) Human (Altenbach et al. 2008; Rosethorne and Charlton 2011)	6.0	<5.5	5.7	8.4	H_4R partial agonist (β-Arrestin)	Inverse agonist (−39%)
Rat (Altenbach et al. 2008; Schnell et al. 2011)				8.6		Agonist (51%)
[^{125}I]Iodophenpropit (Lim et al. 2005)			8.2	7.9		Antagonist Radiolabelled
Adriforant (Andaloussi et al. 2013) Human			6.7	8.2		Inverse agonist
Rat (Tichenor et al. 2015)				7.9		Partial agonist
Dog (Tichenor et al. 2015)				5.8		Antagonist
UR-DEBa242 (Bartole et al. 2020)	<5.5	<5.5	8.6	7.9		Antagonist H_3R antagonist Fluorescent labelled
[^{11}C]JNJN-77771220 (Funke et al. 2013)				8.4		PET-ligand

should be more balanced, e.g., when combining receptor ligands with enzyme inhibitors (Khanfar et al. 2016).

The dual-acting ligand GSK-1004723 possesses a high affinity to its on targets H_1R (pK_i value of 10.2) and H_3R (pK_i value of 10.6) with an excellent selectivity to H_2R and H_4R (>10,000×). Therefore, it is an MTDL prototype because the on-target affinity arises from design and not due to coincidence. As an MTCP it is useful for validating assay systems with more than one HR subtype.

As dopamine plays an important role in neurodegenerative and neurological diseases, tools combining HR and dopamine receptor (DR) affinity are needed. As recently shown, the MTDL ST-2223 combines high H_3R(pK_i value of 8.3), D_2R (pK_i value of 7.7), and D_3R (pK_i value of 8.7) affinities with excellent selectivity to off-targets like H_1R (pK_i value of 7.0), D_1R (pK_i value of 6.3), and D_5R (pK_i value <5.5) (Eissa et al. 2021). ST-2223 and ST-718 showed beneficial effects in autism-like behavior. ST-718 possesses higher selectivity over HRs but lower selectivity and affinity at DRs (Venkatachalam et al. 2021). Contilisant combines H_3R affinity (pK_i value of 8.0) and sigma 1 receptor affinity (pK_i value of 7.2) with

inhibition of enzymes like MAO A (IC_{50} value of 145 nM), MAO B (IC_{50} value of 87 nM), acetylcholine esterase (IC_{50} value of 530 nM), and butyrylcholinesterase (IC_{50} value of 359). It can be used to demonstrate the possibility to combine a different kind of target interactions (enzyme inhibition and receptor binding) (Bautista-Aguilera et al. 2017, 2018). A multi-target ligand recently developed by Cao et al. which has high affinities to dopaminergic, serotoninergic, and histaminergic receptors, showed promising effects and good pharmacokinetics in rats (Cao et al. 2018).

2.2 *Labelled Ligands*

In contrast to reference ligands, labelled ligands are normally not used to compare or transfer data from one to the other experiment. Labelled ligands are necessary for the read-out mechanisms in different assays. As the data obtained is based on the read-out, labelled ligands significantly influence the entire assay. Displacement data can vary between a labelled agonist or antagonist due to their different affinity and binding characteristics. For each histamine receptor subtype, only a few labelled ligands were used in in vitro assays. Radiolabelled ligands contain one or more radioactive atoms, normally beta- or gamma-emitters. PET ligands are labelled with positron emitters. The chemical structure from unlabelled to labelled ligands is only minimally changed, and binding properties are retained. Fluorescent-labelled ligand requires a fluorophore, which is usually not incorporated in the primary ligand. Fluorophores like BODIPY were coupled to an HR pharmacophore. The development of fluorescent chemical probes is a rising research field, as newer techniques like BRET extensively take benefit of these ligands and many laboratories have regulative problems with the use of radioactive materials.

2.2.1 Radiolabelled Ligands

In vitro ligand, characteristics are usually not changed by inserting a radioactive atom in their chemical scaffold. As seen with histamine, binding affinities of radiolabelled ligands at all HR subtypes remain. $[^{3}H]$histamine shows high affinities at H_3R and H_4R and selectivities over H_1R and H_2R. For H_4R, it is a commonly used radiolabelled ligand in displacement studies. As an agonist, the binding mode can differ from the antagonist, and displacement assays can produce different results when a radiolabelled antagonist like $[^{125}I]$iodophenpropit is used.

Also $[^{125}I]$iodophenpropit shows high affinities at H_3R and H_4R and is often used as a radiolabelled ligand. For radioligand displacement assays, both radioligands resulted in similar pK_i values for several H_4R ligands, including, e.g., histamine (pK_i ($[^{125}I]$iodophenpropit) value of 7.6 ± 0.2, pK_i ($[^{3}H]$histamine) value of 7.8 ± 0.1).

For H_1R, histamine's affinity is unfavorable and thus the selective agonist mepyramine was radiolabelled, resulting in $[^{3}H]$mepyramine. Due to its high affinity

and selectivity, it is the mostly used and one of the most suitable radiolabelled ligand for H_1R. It was used for early H_1R visualization studies to determine H_1R distribution in human brains (Martinez-Mir et al. 1990).

Iodination at 3-position of the selective H_2R antagonist (over H_1R and H_4R) aminopotentidine (pK_i value of 7.4) resulted in [^{125}I]iodoaminopotentidine with 100-fold improved the affinity to H_2R (pK_i value of 9.4). The antagonist [^{3}H]UR-DE257 displays the highest selectivity of the other HRs (>100×) and is, therefore, better useable for visualization of receptor expression studies.

In various radiolabelled H_3R ligands, [^{3}H]N^{α}-methylhistamine is the most used one. The affinity and selectivity are comparable, respectively, better than [^{125}I]-iodoproxyfan and [^{125}I]-iodophenpropit (Van Der Goot and Timmerman 2000).

As an H_4R selective ligand, tritium labelled [^{3}H]JNJ-7777120 was synthesized, showing the mentioned advantages and disadvantages of JNJ-777120. In H_4R displacement assays [^{3}H]-histamine is still the most used radiolabelled ligand, despite its low selectivity to H_3R.

2.2.2 Fluorescent-Labelled Receptor Ligands

In the beginning, fluorescent ligands were mainly used as the histological stains for identifying the biogenic amines and their receptors in tissues (McGrath et al. 1996). In 2000 the GPCR was described and visualized using green fluorescent protein-tagged (GFP-tagged) GPCRs taking advantage of molecular biology techniques (Kallal and Benovic 2000). This was a starting point for the drug discovery to study the exact ligand–receptor interaction. For many years, radioligand assays have been conducted to examine receptor–ligand interactions, both in vitro and in vivo (Ma and Zemmel 2002). Fluorescent ligands gain even more attention with the development of new cutting-edge techniques, as Förster resonance energy transfer (FRET), fluorescence correlation spectroscopy (FCS), scanning confocal microscopy (SCM), and bioluminescence resonance energy transfer (BRET). These techniques enabled the development of pharmacological assays on live or fixed tissues, with small amounts of tissue, or on single cells, and the results can be obtained immediately (McGrath et al. 1996; Michalet et al. 2006; Al-Damluji et al. 1997).

Those methods are now widespread in pharmacology. The fluorescent-labelled ligands are used to study subcellular localization, internalization or dimerization, and ligand binding kinetics of receptors. Moreover, using fluorescent ligands enables the measurement of specific and non-specific receptor binding (Mackenzie et al. 2000).

As described in radiolabelled ligands, it is essential to define the fluorescent ligand affinity and selectivity. Other than radiolabelling, fluorescently labelled ligands show some variations of their chemical structure compared to the lead ligand. The fluorophore needs to be attached to the ligand to retain the affinity and selectivity of the starting compound. It is usually obtained by the fluorophore placement far away from the part of the pharmacophore. A variety of fluorophores (e.g., DANSyl, Sanger's reagent, AlexaFluor®, or Bodipy®) could be linked to

ligands with or without a linker, providing possibilities for the design and development of novel, potent, selective, and affine fluorescent ligands (Kuder and Kieć-Kononowicz 2014).

The coupling of BODIPY, boroazaindacene derivative, to mepyramine created a structure called mepyramine-BODIPY 630–650 (short: mepyramine-BY630). The remarkable properties of mepyramine were maintained, whereby the affinity was even slightly increased (Rose et al. 2012).

The beneficial squaric acid moiety of [^{3}H]UR-DE 257 was used to synthesize a fluorescent-labelled ligand and resulted in UR-KAT 51. As mentioned above, also this ligand is coupled to a Bodipy® fluorophore. It is characterized as an antagonist with a pK_i of 8.4 and used in nanoBRET assays, displaying great properties (Grätz et al. 2020).

Bodilisant, a piperidine-based hH3R ligand coupled with the BODIPY pharmacophore, shows ideal chemical probe characteristics as a fluorescent-labelled ligand for H_3R. The high affinity (pK_i value of 8.4) and high selectivity over other HRs was combined with an excellent quantum yield of Φ: 0.92. Bodilisant demonstrated its benefits in H_3R labelling studies and a fluorescence-polarization experiment to determine receptor residence times of different H_3R ligands (Tomasch et al. 2013; Reiner and Stark 2019).

A fluorescent-labelled ligand with high affinity and selectivity for the H_4R has not yet been reported. The fluorescent-labelled ligand UR-DEBa 242 (PY-5 labelled) (Bartole et al. 2020) shows a high affinity to H_4R (pK_i value of 7.9) and selectivity over H_1R and H_2R, but not over H_3R (pK_i value of 8.6).

3 In Vivo Assays

In contrast to the precise criteria defined for the in vitro chemical probes examined (affinity below 100 nM, selectivity over 10-fold against related target), the demands for in vivo chemical probes are far more complex as the processes in living cells and tissues are much more complicated. Therefore, defining general criteria for chemical probes in animal studies is more challenging (Stark 2020) and depends on the experimental design.

It is not simple to set cut-off values in vivo and demonstrate on-target effects in animal models due to enormous differences in species. As chemical probes are not necessarily equal with preclinical candidates, it should be first determined if a chemical probe contains appropriate pharmacodynamic and pharmacokinetic characteristics to be examined in animal models. Moreover, their safety profile and tolerance should be examined in the species of interest. Different chemical probes are chosen based on animal models and targeted disease, and here will be explained which of them reached in vivo preclinical and clinical trials as well as highlight the best chemical probe for each receptor in different behavioral models.

3.1 Histamine H_1 Receptor

Histamine H_1R was the first described receptor subtype and is the most abundant histamine receptor. Hence, it has been cloned over three decades ago, it has been extensively studied, and various in vivo studies that target H_1R have been conducted.

3.1.1 Agonists

H_1R agonists have not raised specific interest in the scientific community, and so far, only a few compounds with agonistic properties have been described. As all histamine receptor ligands, H_1R agonists were first developed with a slight modification of histamine as imidazole derivatives. However, bioisosteric replacement of carbon with sulfur led to H_1R agonist 2-(thiazol-2-yl)ethanamine (2-TEA, 2). Substitution with bulky substituent leads to 2-(3-(trifluoromethyl)phenyl) histamine. These compounds are well tolerated and are used to mimic histamine effects in in vivo studies (Malmberg-Aiello et al. 2000). Further modification leads to histamine-trifluoromethyl-toluidine (HTMT) development, a more potent agonist than histamine, that also shows affinity to H_2R and can be considered as a dual targeting ligand. HTMT is used in vivo studies to examine the role of histamine in immunomodulation, as shown in rabit (Tripathi et al. 2010) and mice (Lapilla et al. 2011). Later developed H_1R agonists were histaprodifen and suprahistaprodifen, which still need to be examined in vivo. Suprahistaprodifen showed partial agonism at H_4R, while histaprodifen derivatives acted as an inverse H_4R agonist (Deml et al. 2009). It is assumed that suprahistaprodifen binds at the H_1R in two different orientations. As the H_1R showed itself a high level of agonist independent constitutive binding (Jongejan et al. 2005), the application of H_1R in vivo models makes it even more complex. Therefore, there is an urge for further development and examination of H_1R agonists.

3.1.2 Antagonists

In contrast to moderately described H_1R agonists, H_1R antagonists are a well-known class that reached blockbuster drugs' status. These ligands are widely used for therapy of allergies, nausea, conjunctivitis, or rhinitis. In general, H_1R antagonists can be divided into two classes.

First-generation includes H_1R antagonists like doxepin, mepyramine, doxepin, and diphenhydramine. They are lipophilic enough to cross the BBB and therefore express sedative effects. Since they show affinity to other receptor subtypes (e.g., cholinergic), they cannot be considered optimal chemical probes. First-generation H_1R antagonists showed reinforcing effects in monkeys as they increased rates of suppressed and non-suppressed behavior (Bergman and Spealman 1986). However,

from a pharmacological point of view, this disadvantage was used in PET tracers' design. As first-generation H_1R antagonist cross the BBB and penetrate CNS, they are often radiolabelled and used to estimate receptor distribution and localization. [^{11}C]mepyramine, and [^{3}H]doxepin are commonly used as a PET tracer for H_1R, both in humans and animals (e.g., guinea pig). However, [^{11}C]doxepin has lower metabolic degradation and provides higher contrast images, and therefore is the most commonly used PET ligand to measure histamine occupancy in the brain in humans (Yanai et al. 1992a, b, 1995; Ishiwata et al. 2007; Zhou et al. 2002; Sato et al. 2013).

The later developed, the second generation of antihistaminic are more polar structures and are in the form of zwitterion at physiological p*H*. Therefore, they cross the BBB only up to a small extent, expressing none to light sedating effects.

Some of these H_1R antagonists represent suitable substrates for P glycoprotein and thus are rapidly effluxed without crossing the BBB to a remarkable extent under physiological conditions. Second-generation antihistaminic includes commercially available drugs: loratadine, desloratadine, cetirizine, levocetirizine terfenadine, fexofenadine, which are well-examined in preclinical studies. Stereoselective separation has led to some enantiomers leading to a higher affinity at H_1R (e.g., levocetirizine). Some of the second-generation antihistamine compounds (e.g., terfenadine) display severe cardiac side effects, prolonging QT interval that can lead to Torsades de Pointes arrhythmias due to hERG channel interaction (human Ether-a-go-go Related Gene for voltage-dependent potassium ion channel). In line with these results, terfenadine has been withdrawn from the market. Structural modifications of terfenadine lead to designing fexofenadine that does not prolong QT interval and has an improved safety profile. Fexofenadine does not cross the BBB and does not occupy histamine H_1R in the central cortex, in contrast to cetirizine (Sato et al. 2013; Tashiro et al. 2002). For review on this therapeutic and safety aspects, see Cataldi et al. Holgate et al. (Cataldi et al. 2019; Holgate et al. 2003).

Bilastine possesses highly suitable characteristics due to a peripheral acting H_1R antagonist for in vivo studies. The high selectivity over several other receptors (including dopamine, serotonin, histamine, adrenaline, acetylcholine, and others) is ideal for studying H_1R antagonism or blocking the peripheral H_1R. Doxepin and mepyramine can be used as brain penetrating H_1R antagonists, although doxepin showed low bioavailability.

Both first- and second-generation antagonists are drugs used daily. However, their use should be controlled in children, as they have seizure-inducing potential (Miyata et al. 2011).

They are used as antiallergic drugs, and both antihistaminic first- and second-generation reduced 48r80-induced scratching behavior in mice (Sugimoto et al. 1998). On the other hand, histamine, H_1R antagonists hydroxyzine and cetirizine, did not prevent the development of acute skin lesions in Maltese-beagle dogs (Bäumer et al. 2011).

To address the problems caused by antihistamines of the first and second generation and improve the treatment of histamine-related diseases, dual ligands have been designed. Dual H_1R/H_4R antagonism presents a promising therapeutic option

Table 5 Pharmacokinetic data of H_1R ligands

Compound	$t_{1/2}$	Bioavailability	BBB penetration	Additional information
Mepyramine (Simons and Simons 2011; Yanai et al. 2011)	8 h		High	
Doxepin (Simons and Simons 2011; Yanai et al. 2011)	17 h	27%	High	High first pass effect (70%) Active metabolite: desmethyldoxepin
Loratadine (Zhang et al. 2003; Jáuregui et al. 2016)	8.4	High	Low	CYP3A4 and CYP2D6 metabolization High first pass effect → desloratadine
Desloratadine (Zhang et al. 2003; Jáuregui et al. 2016)	14	High	Low	Active metabolite of loratadine
Bilastine (Corcóstegui et al. 2005; Jáuregui et al. 2016)	14.5 h	60%	No penetration	No metabolization No CYP interaction PGP substrate

Human data

for allergy treatment due to the involvement of both receptor subtypes in allergy pathology, as shown in the acute murine asthma model in mice. Independent administration of H_4R selective antagonist, JNJ-7777120, and H_1R antagonist, mepyramine resulted in low to moderate eosinophilia effects. However, when they were administered in combination, statistically significant synergic effects were observed, indicating that dual MTDLs can be a new route in developing potent antiallergic reagents (Deml et al. 2009).

Other dual ligands developed are H_1R/H_3R GSK-1004723 and GSK-835726, both currently in clinical trials for allergic rhinitis (Daley-Yates et al. 2012). GSK-1004723 has a high affinity to both receptor subtypes with a long duration of action, potency similar to azelastine. It does not penetrate CNS and therefore does not express sedative effects (Slack et al. 2011). Besides the pharmacodynamic, the pharmacokinetic is important for in vivo measurements (Table 5).

3.2 *Histamine H_2 Receptor*

3.2.1 Agonists

H_2R agonists do not have therapeutic use. However, due to lack of selectivity, they often served as blueprints for the design and synthesis of H_3R and H_4R ligands.

Amthamine and dimaprit were firstly developed by slight modification and bioisosteric replacement in the imidazole ring. Impromidine, developed initially as vasodilators, is used as a chemical probe. It is guanidine derivatives and showed

affinity to H_3R. Stereoselectivity of H_2R ligand plays an important role. It has been demonstrated that the *R*-enantiomer of sopromidine is a potent H_2R agonist, whereas the *S*-enantiomer is the moderate antagonist (Elz et al. 1989). Therefore, sopromidine can be considered a useful chemical probe to gain better insight into functional selectivity and signalling pathways. *N*-acetylation of guanidino group leads to the synthesis of UR-AK381, UR-AK480, UR-BIT82. They are full agonists that showed 4,000 times the potency of histamine at recombinant human and guinea pig H_2R but still display affinity to other receptor subtypes.

3.2.2 Antagonists

As well as in the case of H_1R, H_2R antagonists are far more common and used than H_2R agonists. H_2R antagonists, such as cimetidine, ranitidine, nizatidine, famotidine, and zolantadine, reached the status of blockbuster drugs and were used in the therapy of gastric ulcers, dyspepsia, or GERD (Taha et al. 1996; Lauritsen et al. 1990). Nowadays, they are replaced with more efficient PPI. Burimamide was the first selective H_2R antagonist with moderate efficacy (Wyllie et al. 1972). Cimetidine was the first imidazole-containing H_2R antagonist that reached a blockbuster status, discovered by Sir James Black. It is a potent CYP3A4 inhibitor and can induce drug–drug interaction. To address this problem, new non-imidazole derivatives have been developed. Even though well studied, they are currently subjecting to repurposing. Zolantadine can cross the BBB and has over 30-fold selectivity to H_2R over other receptor subtypes. It is equally potent in rats and guinea pigs. It was examined in rats for possible wake-promoting effects but showed no significant impact (Monti et al. 1990). It has been shown that zolantadine does not alter the in vivo histamine metabolism in the brain of male Sprague-Dawley albino rats (Hough et al. 1988). On the other hand, it has been confirmed that zolantidine reduced in force morphine-induced antinociception in rhesus monkeys, speculating that nociceptive morphine effects are associated with H_2R agonism (Lindsay et al. 1990). The only developed PET H_2R tracer is $[^{11}C]$nizatidine. However, due to its poor BBB permeability, it failed in brain imaging studies. Pharmacokinetic properties of selected H_2R ligands are summarized in Table 6.

3.2.3 COVID Effects

In line with the current COVID-19 situation, histamine receptor antagonists are investigated on repurposing strategies to prevent coronavirus infection (Ishola et al. 2021). Azelastine, an H_1R antagonist, expressed a particular effect on dendritic and T cells interaction in vitro (Schumacher et al. 2014). This antihistaminic agent together with hydroxyzine and diphenhydramine expressed antiviral activity against SARS-CoV-2 in vitro and is currently studied as a potential tool for fighting COVID-19 (Reznikov et al. 2021). Famotidine and cimetidine have higher affinities to H_2R, where famotidine show specificity for HCV (59.5%) and HHV (49.5%)

Table 6 Pharmacokinetic data of H_2R ligands

Compound	$t_{1/2}$ (h)	Bioavailability (%)	BBB penetration	Additional information
Cimetidine (Lin 1991)	2–3	65	Low	IC_{50} in vitro and in vivo are comparable
Ranitidine (Lin 1991)	3–4	50	Low	IC_{50} in vitro and in vivo are comparable
Famotidine (Lin 1991)	2–3	45	Low	IC_{50} in vitro and in vivo are comparable

Human data

(Ishola et al. 2021). Besides, it has been confirmed that patients treated with famotidine had decreased risk of developing severe SARS-CoV-2 symptoms (Freedberg et al. 2020). One plausible explanation is that famotidine binds a papain-like protease encoded by the SARS-CoV-2 genome. This protease is necessary for the entry of SARS-CoV-2 into the cell. Even though reported results were contradictory, reporting both beneficial and no significant effects of histamine and histamine H_2R antagonist are extensively investigated as potential targets for fighting COVID 19 (Ennis and Tiligada 2021). Famotidine is currently in phase III of Multi-site Adaptive Trials for COVID 19, where the effect on the standard of care is being compared with the same therapy with high intravenous doses of famotidine (NCT04370262). These repurposing studies may not lead to a novel therapeutic indication for these compounds but may offer possibilities for the design of new ligands from a different lead structure.

3.3 *Histamine H_3 Receptor*

In contrast to H_1R and H_2R, histamine is nowadays extensively investigated due to novel therapeutic options. The involvement of H_3R in various neurological disorders as a sleep-wake disorder, AD, epilepsy, schizophrenia, and cognitive impairments makes this receptor subtype an interesting target for the design and synthesis of chemical probes and potential drug-like candidates.

3.3.1 Agonists

As with the other two receptor subtypes, slight modifications were made on the histamine core to develop imidazole-based derivatives. Therefore, *R*-α-methylhistamine that expresses high affinity to H_3R was developed. Although it is not selective and shows affinity to other receptor subtypes, it has still been used for labelling in behavioral studies, for examining histamine function in the brain and its connection with other neurotransmitters (Sadek and Stark 2016). For instance, it was confirmed that *R*-α-methylhistamine induces water drinking in rodents

(Clapham and Kilpatrick 1994; Ligneau et al. 1998; Faghih et al. 2002). Alternatively, this ligand provoked dose-dependent inhibition of noradrenaline release in Male albino or the Wistar rats (Di Carlo et al. 2000). The latter effect was abolished when thioperamide, an H_3R antagonist, was administered. [^{3}H]*R*-α-methylhistamine is fast metabolized in humans with a half-life time ($t_{1/2}$) of 1.6 h. Like histamine, it is methylated by the HNMT, and thereby loses agonist properties at the H_3R (Rouleau et al. 2000). To increase the half-life time the prodrug BP2-94 was invented. BP2-94 is non-enzymatically transformed to [^{3}H] *R*-α-methylhistamine. Half-life time of BP2-94 shows a biphasic behavior with $t_{1/2}(1)$: 1 h and $t_{1/2}(2)$: >24 h (Rouleau et al. 1997). Orally administered neither [^{3}H] *R*-α-MeHA nor BP2-94 reached the CNS (Rouleau et al. 2000). Later developed imetit and imepip have higher potency but are not selective, also showing high affinities at H_4R. Imetit inhibited the binding of [^{3}H]*R*-α-MeHA in the rat brain (Garbarg et al. 1992), while imepip decreased histamine release in rats (Jansen et al. 1998).

Methimmepip is a methylated derivative imepip derivative with increased selectivity, over 200-fold selectivity to H_3R over H_4R, and a promising chemical probe for H_3R. Both imepip and methimmepip have gastroprotective effects, as shown in gastric lesions caused by gastric acid in rats (Coruzzi et al. 2011). Even though the reported result about histamine's role in obesity is contradictory, they are very species-dependent (Díaz et al. 2019; Lecklin et al. 1998). H_3R agonists have been extensively researched as potential targets in obesity therapy. Histamine H_3R agonist imetit significantly decreases appetite at fat mass and plasma concentration of leptin and expresses anorexigenic effects in diet-induced obese (DiO) WT mice (Yoshimoto et al. 2006).

3.3.2 Antagonists

Although the role of histamine H_3R is still not fully understood, several H_3R ligands are currently in clinical trials for ADHD, sleep-wake disorder, AD, and cognitive impairments. As well agonists, firstly developed H_3R antagonists were imidazole-based structures. Thioperamide was one of the first synthesized H_3R imidazole-containing antagonists. It is a highly potent H_3R and H_4R agonist. In vivo thioperamide positively impacts cognitive function in male spontaneously hypertensive rat pups (SHR) shown (Komater et al. 2003). Besides, thioperamide did not cause a locomotor sensation as psychostimulants (e.g., amphetamine or methylphenidate) used in ADHD therapy.

Moreover, locomotor hyperactivity induced by amphetamine was inhibited by thioperamide also in male CRH mice (Clapham and Kilpatrick 1994). Therefore, thioperamide represents a possibly safer alternative than currently available therapy, as it also does not express abuse potential. Besides, it has been shown that thioperamide increases appetite and consequently body weight in DiO WT mice when administered twice per day (Yoshimoto et al. 2006). With another imidazole-

based derivative clobenpropit, thioperamide reduced alcohol intake in alcohol-preferring rats and is currently investigated for their abuse potential (Panula 2020).

Besides these two, ciproxifan is another later developed imidazole-based derivative that showed higher affinity at H_3R and is often used as a reference in behavioral studies in rodents, mainly due to its precognitive effects, in combination with good pharmacokinetic properties. For instance, ciproxifan decreased impulsivity and increased attention in adult, male hooded Lister rats (Ligneau et al. 1998; Day et al. 2007), showed precognitive effects in APPTg2576 male mice (Bardgett et al. 2011) and enhanced performance SHR pups (Fox et al. 2002).

To address problems caused by imidazole derivatives, as drug–drug interactions and high affinity to H_4R, non-imidazole derivatives have been developed and extensively studied. These derivatives are not CYP450 substrates and therefore have a safer profile, indicating that they can be better chemical probes, which led to the design and development of preclinical and clinical H_3R candidates.

Pitolisant is the only commercially available H_3R inverse agonist/antagonist (Ligneau et al. 2007), approved by EMA in 2016 and by FDA in 2019 for treatment of narcolepsy with or without cataplexy (Schwartz 2011; Lamb and Pitolisant 2020). Its safe profile and non-abuse potential are confirmed in in vivo animal models and in human studies (Uguen et al. 2013). This led to its non-controlled drug status in the USA (Lamb and Pitolisant 2020).

It is dosed once per day and, due to its safety and low interaction potential, can be considered an ideal chemical probe in behavioral sleep-wake models (Syed 2016). Pitolisant reduced H_3R brain activity in Swiss mice and has been in clinical trials for obstructive sleep apnea, schizophrenia, ADHD, and photosensitive epilepsy (Kuhne et al. 2011). GSK-189254 is a potent H_3R antagonist that reduced narcoleptic episodes in Ox −/− mice (Guo et al. 2009). Another H_3R selective antagonist, JNJ-5207852, can be considered a chemical probe in this model. Ex vivo studies demonstrated that JNJ-5207852 had a high affinity to rat and human receptors and highly occupied H_3R (Kuhne et al. 2011). It expressed wake-promote in male Sprague-Dawley rats and mice in a time-dependent manner (Barbier et al. 2004). Also, it expresses resuscitating effects in Wistar rats suffering from hemorrhagic shock (Jochem et al. 2016), and its mechanism is yet to be explored.

Non-imidazole H_3R antagonist ABT-239 was efficient in multiple behavioral studies to improve social memory and cognitive impairment and is commonly used as a reference. ABT-239 (1.0 mg/kg) attenuated methamphetamine-induced hyperactivity in mice and gating deficits in DBA/2 mice with schizophrenia (Fox et al. 2005). It showed promising effects on cognition deficits induced by prenatal ethanol exposure in male adult rats (Varaschin et al. 2010) and CD1 mice when the histaminergic system had complete integrity (Provensi et al. 2016). Moreover, this H_3R antagonist showed neuroprotective and anticonvulsive effects in male Swiss albino mice (Bhowmik et al. 2014) and expressed attenuation tau hyperphosphorylation (Bitner et al. 2011). In line with these results, ABT-239 can be considered an excellent chemical probe in cognitive-behavioral models. Another chemical probe that can be used in cognitive-behavioral studies is GSK-189254. This selective H_3R antagonist showed 10.000-fold selectivity for human H_3R and

has been used in animal models for attention models as it showed memory improved cognitive performance in rats (Medhurst et al. 2007). It showed antinociceptive potential, as it was confirmed that it modulates neuropathic pain in rats (McGaraughty et al. 2012) and reduced narcoleptic episodes in orexin −/− mice (Guo et al. 2009; Tiligada et al. 2009). DL77 is another new histamine H_3R antagonist that recently gained more interest for its procognitive potential and high in vitro and in vivo potency (EC_{50} 2.1 mg/kg). It showed promising results in ASD-like behaviors in VPA-exposed animals, procognitive effects by significantly ameliorating memory deficits induced by MK-801 in male Wistar rats, and anticonvulsant effects in male Wistar rats (Eissa et al. 2018; Sadek et al. 2016b).

As well as agonist role, antagonist role in obesity therapy has been studied. A-331440 developed by Abbott is a non-imidazole H_3R antagonist that reduced weight in higher doses (5 mg/kg and in 15 mg/kg) in C57BL/6 J mice, previously treated with a high-fat diet (Hancock et al. 2004). However, this compound showed some genotoxic potential in rats, and therefore analogues have been synthesized: A-417022 and A-423579. Both ligands reduced weight in mice in high dosage, and the latter caused statistically significant weight loss in weight-matched Sprague-Dawley female rats (Hancock et al. 2005). Furthermore, H_3R antagonism reduced calorie intake in higher mammalian species of pigs and rhesus monkeys, leading to several ligands that showed promising effects in preclinical studies (Lecklin et al. 1998). SCH- 497079, another H_3R antagonist, reached phase II clinical trial (NCT00642993).

JNJ-39220675 is a novel, potent, and selective H_3R antagonist. PET ligand [^{11}C] JNJ-39220675 showed the excellent BBB permeability and occupied around 90% of H_3R in the female baboon's brain (Logan et al. 2012). It reduced alcohol intake in male adult selectively bred alcohol-preferring rats (Galici et al. 2011) and male JAX®C57BL/6 mice (Nuutinen et al. 2016) and is considered a suitable chemical probe for alcohol-induced behavioral studies. ST1283 is another H_3R antagonist that showed promising effects on reducing alcohol intake in Tuck-Ordinary "TO" mice (Bahi et al. 2013).

Samelisant (SUVN-G3031), an orally available H_3R inverse agonist, shows highly promising results in several preclinical and clinical studies. It is effective for wake-promoting, precognitive, and enhancing cortical arousal in animal models. It possesses high selectivity for the H_3R, with comparable binding affinities to rH_3R and h_3R and no affinities to typical off-targets like 5-HTR or sigma receptors (Nirogi et al. 2021). Furthermore, side effects like CYP interaction, phospholipidosis, QT-time prolongation, and hERG blockade were not observed. Samelisant successfully completed phase I and is under investigation in phase II clinical trail (Nirogi et al. 2019). Thus, it is a promising drug candidate and a useful tool for examining species independent H_3R antagonism/invers agonism.

Different PET tracers have been developed to examine and better understand histamine H_3R role in the brain. [^{3}H]thioperamide, [^{3}H]5-methylthioperamide, and [^{11}C]methylthioperamide were the first PET tracers for H_3R that was used in mice. Several later developed H_3R PET tracers as [^{11}C]-UCL-1829, [^{18}F]-FUB-272, [^{18}F]-VUF-5182, or [^{18}F]-ST-889 failed due to low brain reuptake (Selivanova et al. 2012;

Table 7 Pharmacokinetic data of H_3R ligands

Compound	$t_{1/2}$	Bioavailability	BBB penetration	Additional information
R-α-Methylhistamine (Rouleau et al. 1997, 2000)	1.6 h	Low	Low	Fast metabolization by HNMT
BP 2-94 (Rouleau et al. 1997, 2000)	(1) 1 h (2) > 24 h		Low	Prodrug of *R*-α-methylhistamine
Pitolisant (Kuhne et al. 2011)	11 h	84%	High	CYP2D6 inhibition (IC_{50}: 2.6 μM) QT-time prolongation
Samelisant (Nirogi et al. 2019)	1.5 h[a]	83%[a]	High[a]	

Human data otherwise
[a]Beagle dogs

Funke et al. 2013). [^{18}F]-VUF 5000 has been developed to overcome this obstacle and evaluated in vivo but failed to penetrate the brain (Windhorst et al. 1999).

[^{18}F]Fluoroproxyfan and [^{125}I]iodoproxyfan showed very heterogeneous distribution in the brain, indicating non-specific binding (Funke et al. 2013). On the other hand, [^{125}I]iodophenpropit is commonly used as an iodinated PET tracer in vivo and ex vivo (e.g., in male Swiss mice or Wistar rats) showing over 40-fold preference to H_3R (Ligneau et al. 1994; Stark et al. 1996; Mochizuki et al. 1996; Jansen et al. 1994; Humbert-Claude et al. 2012; Morisset et al. 2000). Later developed [^{11}C]JNJ-10181457 showed sufficient uptake in the rat brain, but the confirmation on the distribution in $H_3R^{-/-}$ mice was failed as a chemical probe. As the most promising candidate for PET studies [^{11}C]GSK189254 stood out. It crosses the BBB, has high uptake, and is metabolically stable. Its binding can be fully blocked with the H_3R selective antagonist JNJ-39220675 or by ciproxifan, indicating a high level of specific binding in the baboon. It is so far the best chemical probe for visualizing these receptor subtypes and estimating receptor occupancy (Ashworth et al. 2010; Plisson et al. 2009; Rusjan et al. 2020). [^{11}C]TASP-0410457 as another promising candidate, showed high brain uptake in rats and monkeys has been developed recently (Koga et al. 2016).

Pharmacokinetic properties of the selected H_3R ligands are summarized in Table 7.

3.4 Histamine H_4 Receptor

Histamine H_4R is the most recently discovered histamine receptor, cloned almost 20 years ago. Despite some discussion on its CNS effects, it is confirmed that this receptor subtype is mainly peripherally distributed and involved in immune processes or chemotaxis. Its association with diseases like asthma, allergic rhinitis,

pruritus, or inflammation processes, in general, has been confirmed. However, the design and synthesis of highly selective histamine H_4R ligand remained to be an up-to-date challenge.

3.4.1 Agonists

Histamine H_4R ligands were developed up to a great extent as modification of other histamine receptor subtypes ligands. One of the first ligands examined on H_4R was H_3R agonist *R*-α-methylhistamine. This enantiomer shows a 17-fold higher H_4R affinity when compared to its *S*-enantiomer (distomer) and is often used in behavioral studies targeting H_4R (Saravanan et al. 2011). 4-Methylhistamine, firstly described as H_2R ligand, showed 100-fold selectivity to H_4R over other receptor subtypes. ST-1006 is an up-to-date one of the most potent H_4R agonist/partial agonist. It was shown to be a partial agonist in hH_4R in $[^{35}S]$-GTP-γS-binding assay, but a full, partial, and inverse agonist for hH_4R, mH_4R, and rH_4R, respectively, in luciferase binding assaies (Adami et al. 2018).

VUF-8430 showed 30-fold selectivity over H_3R rats and expressed lasting dose-dependent antinociceptive and anorexiant effect in male Swiss albino mice in doses 20–40 μg (Galeotti et al. 2013). A higher dose (40 μg) demonstrated an anxiolytic effect. VUF-8430 (10–40 μg) reduced neuropathic pain provoked by oxidative stress in male CD1 mice (Sanna et al. 2017). As for other promising derivatives, VUF-6884 has an over 300-fold affinity to H_4R, and VUF 10460 has a 50-fold selectivity to H_4R. The latter showed an ulcerogenic effect in male Wistar rats and is used in gastric models (Coruzzi et al. 2011).

3.4.2 Antagonists

JNJ-7777120 identified via high throughput screening by Johnson and Johnson represents the most frequently used H_4R ligand in behavioral studies. It showed over a 1,000-fold selectivity for the rat histamine H_4R over the histamine H_3R with comparable affinities to mouse and human isoform and very low affinities to other off target (Thurmond 2015). JNJ-7777120 reduces asthmatic symptoms in female Balb/c mice (Deml et al. 2009), improves lung function in mice, and reduces wheel reaction in dogs in concentration 1.5 μmol (Roßbach et al. 2009). A dose of 100 mg/kg reduces the macroscopic injury, increases the colonic myeloperoxidase as well as TNF-α levels (Varga et al. 2005), and expresses an inhibitory effect on vestibular neuron activity in Male Wistar rats (Desmadryl et al. 2012). It has been confirmed that JNJ-7777120 blocked histamine-induced chemotaxis in mice, expressed anti-inflammatory effects in the peritonitis model of mice, and ameliorated pruritus in mice (Thurmond et al. 2004; Dunford et al. 2007). However, results are very species-dependent, as it has been shown that JNJ-7777120 is a biased ligand. Besides signalling through $G_{\alpha i}$, this ligand activates the β-arrestin 2 signalling cascades (Rosethorne and Charlton 2011). In high concentration, JNJ-7777120 causes ERK

activation and can act as a full agonist (Seifert et al. 2011). Even though the obtained data supported antagonistic profile, the reported IC_{50} differed from another, which is characteristic of a partial agonist rather than an antagonist. Additionally, even if this compound is extensively used as a standard, it has a short half-life in vivo, further interfering with behavioral studies (Neumann et al. 2013). Therefore, special attention should be paid to different JNJ-7777120 effects in different species. JNJ-7777120 is metabolized to the *N*-des-methylpiperazine derivative, which possesses a comparable affinity to the H_4R (pK_i value of 7.6) and higher metabolic stability. The metabolization rate is fast in rodents, but slower in humans (Engelhardt et al. 2009).

JNJ 28307474 was another potent H_4R antagonist developed by Johnson and Johnson that was efficient in the preclinical arthritis model in BALB/c mice in doses of 20–50 mg/kg (Cowden et al. 2014; Buckland 2013). In the same species, it showed an anti-inflammatory effect by inhibiting T_H2-mediated inflammation (Cowden et al. 2010). Auspicious effects were shown in chronic atopic dermatitis model in female wt mice, indicating long-lasting action of this H_4R antagonist (Rossbach et al. 2016).

JNJ-10191584 showed promising profiles: a dose-dependent reduction in macroscopic damage in colitis model male Wistar rats and an inhibitory effect on vestibular neuron activity in Wistar or Long-Evans rats (Desmadryl et al. 2012). VUF-10214 and VUF-10148 also expressed anti-inflammatory properties in the carrageenan-induced paw edema model in male Wistar rats (Smits et al. 2008). Another potential antinociceptive agent is INCB-38579 that expressed at least 80-fold selectivity over other receptor subtypes and antinociceptive effects on female CD-1 mice and Sprague-Dawley rats (Shin et al. 2012). Two other potential PET tracers have been developed: [^{11}C]JNJ-77771220 that can cross the BBB and [^{11}C]VUF-1058 that exerts its action only peripherally (Funke et al. 2013).

H_4R is extensively researched, which resulted in several drug-like candidates reaching clinical trials. Adriforant has been tested in clinical phase for atopic dermatitis second improved inflammatory skin lesions and UR-633225 has been screened for seasonal allergic rhinitis (NCT01260753) (Werfel et al. 2019).

JNJ-39758979 is another selective H_4R antagonist with an over 80-fold selectivity to other receptor subtypes. In ovalbumin-sensitized mice showed a dose-dependent anti-inflammatory effect. Good pharmacokinetic profile and safety in dose range 10–1,200 mg were proved in clinical phase I for asthma (Thurmond et al. 2014). On the other hand, phase II in Japanese patients with atopic dermatitis (100 and 300 mg) was terminated and did not meet the endpoint for safety reasons, as two patients developed neutropenia (Murata et al. 2015). Unfortunately, clinical phase II in asthmatic patients also failed to meet the primary endpoint due to the lack of efficacy (Kollmeier et al. 2018).

Toreforant (JNJ-38518168) was another H_4R antagonist that entered into a clinical trial for rheumatoid arthritis, but failed in clinical phase IIb due to the lack of efficacy (Boyle et al. 2019; Thurmond et al. 2016).

SENS-111 or seliforant has a high affinity to both animal and human isoform H_4R. It was efficient against nystagmus in Long-Evans rats and Wistar rats (10 mg/

Table 8 Pharmacokinetic data of H_4R ligands

Compound	$t_{1/2}$	Bioavailability	BBB penetration	Additional information
JNJ-7777120 (Engelhardt et al. 2009)	2.3 h[a]	22%[a]		High first pass in rodents Low first pass in human Demethylation leads to active metabolite
JNJ-39758979 (Thurmond 2015; Thurmond et al. 2004)	140 h	70%	Crosses the BBB	Side effect: agranulo-cytosis In vivo data correlate with in vitro data Sex dependent accu-mulation (male < female up to 1.6×)
Adriforant (Mowbray et al. 2011)	7 h[a] 24 h[b] 30–34 h[c]	62%[a] 39%[b] 75–95%[c]		High species dependence

Human data otherwise
[a]Rat
[b]Dog
[c]Humans (calculated)

kg), whereby increasing doses (up to 20 mg/kg) resulted in the loss of effectivity. These data are consistent with data from a clinical trial (Petremann et al. 2020). SENS-111 does not have sedative effects and is well tolerated. In phase I clinical studies, it did not significantly impact nystagmus, but improved latency 10–30% and vertigo episodes duration (Venail et al. 2018). The studies are currently halted in phase II where efficacy and safety of two dose-regimens 100 and 200 mg has been examined (NCT03110458) (Dyhrfjeld-Johnsen and Attali 2019).

Pharmacokinetic properties of the selected H_4R ligands are summarized in Table 8.

4 Conclusion

Chemical probes are a potential novel tool that can provide insight into ligands affinity, selectivity, and receptor functional selectivity. Rational design of chemical probes generate ligands which will selectively target the receptor of interest, resolve signalling cascades and reveal the involvement of various proteins and second messengers. Here, selected histamine receptor ligands for all four receptor subtypes have been summarized and reviewed as chemical probes, focusing on in vitro and in vivo studies. The definition of a chemical probe in in vivo studies is more

complex, as in vivo compartments differ enormously from one another. Therefore, a chemical probe needs to be selected explicitly for unique behavioral models. Even though a chemical probe differs from the ligand, already from their design, several highly versatile chemical probes for investigating the effects of histamine receptor subtypes have been developed (Fig. 2). With the description of their advantages and disadvantages as chemical probes, the selection for biochemical and pharmacological studies should be made easier for beginners to experts in this area. Nevertheless, an additional effect of these probes (or their metabolites) on off-targets cannot be ruled out and may be considered to evaluate the experimental results.

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Patho-Pharmacological Research of Anti-allergic Natural Products Targeting Antihistamine-Sensitive and -Insensitive Allergic Mechanisms

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Abstract Histamine H_1 receptor (H1R) has a special up-regulation mechanism by the stimulation of H1R, mediated by protein kinase C-delta (PKCδ) signaling and H1R gene expression, resulting increase in H1R signaling. Increase in H1R mRNA in nasal mucosa was induced after the provocation of nasal hypersensitivity model rats and suppressed by the pre-treatment of antihistamines. Improvement of nasal symptoms and suppression of H1R mRNA expression in nasal mucosa were also observed by the pre-treatment of antihistamines in pollinosis patients. Elucidation of a correlation between symptoms and H1R mRNA level suggests that H1R gene is an allergic disease (AD)-susceptibility gene, targeted by antihistamines. Similar to antihistamines, pre-treatment of *Kujin* extract, an anti-allergic *Kampo* medicine improved nasal symptoms and suppressed H1R mRNA expression in nasal hypersensitivity model rats. (−)-Maackiain targeting heat shock protein 90 (Hsp90) was isolated as an inhibitor of PKCδ signaling-mediated H1R gene expression from *Kujin* extract. In addition to H1R-mediated activation of H1R gene expression as the first mechanism, nuclear factor of activated T-cells (NFAT)-mediated IL-9 gene expression is suggested to participate to allergic symptoms as the second mechanism insensitive to antihistamines. Pyrogallol and proanthocyanidin suppressing IL-9 gene expression were discovered from Awa-tea and lotus root knots, respectively. Combination therapy using medicines suppressing both H1R gene expression and IL-9 gene expression is promising for outstanding alleviation of AD. Multifactorial diseases involving H1R gene expression may be treated by the combination therapy with antihistamine and complementary drugs, and diseases involving PKCδ signaling may be treated by drugs targeting Hsp90.

Keywords Allergic disease · Heat shock protein 90 · Histamine H1 receptor gene · NFAT (nuclear factor of activated T-cells) · Protein kinase C-delta

1 Introduction

Histamine is a principal mediator of type-1 immune hypersensitivity reaction in allergy and causes serious symptoms of allergic diseases. Antihistamines are principal therapeutic drugs for allergic rhinitis, allergic conjunctivitis, and urticaria, because symptoms of these diseases are dominantly mediated through histamine H_1 receptors (H1R). Improved antihistamines have been actively developed. They are now classified into two groups, first and second generations. First generation antihistamines with side effect of strong sedation were replaced by second generation antihistamines by minimizing the side effect. However, insufficiency of alleviation by antihistamine therapy remains to be undissolved, suggesting the existence of antihistamine-sensitive and -insensitive pathological mechanisms in allergic diseases. Demonstration of antihistamine-insensitive pathological mechanisms and development of new therapeutic drugs are highly awaited.

2 Up- and Down-Regulations of Histamine H_1 Receptors as Rate-Limiting Mechanisms of Signal Transduction

The number of H1R molecules is much smaller than that of other signaling molecules, and the receptor signaling is regulated by the expression level (Ohuchi et al. 1998). Then down- and up-regulations of the receptor are the rate-limiting step mechanisms.

Sustained stimulation-evoked H1R desensitization and down-regulation were documented, similar to many other receptors. Involvement of receptor phosphorylation in intracellular loops was demonstrated as a molecular mechanism (Horio et al. 2004a). Phosphorylation of serine and threonine residues, namely Thr^{140}, Thr^{142}, Ser^{396}, Ser^{398} and Thr^{478}, in H1R was suggested to play a crucial role in receptor desensitization and down-regulation (Horio et al. 2004b).

On the other hand, sustained stimulation of H1R induced gene expression-mediated receptor up-regulation (Das et al. 2007). This mechanism is unique to H1R. Stimulation by phorbol 12-myristate 13-acetate (PMA) up-regulated H1R, suggesting the participation of protein kinase C (PKC). Both up- and down-regulation mechanisms of H1R are present in HeLa cells. Actually, H1R were up-regulated by the receptor stimulation, suggesting that up-regulation mechanism is dominant (Fig. 1).

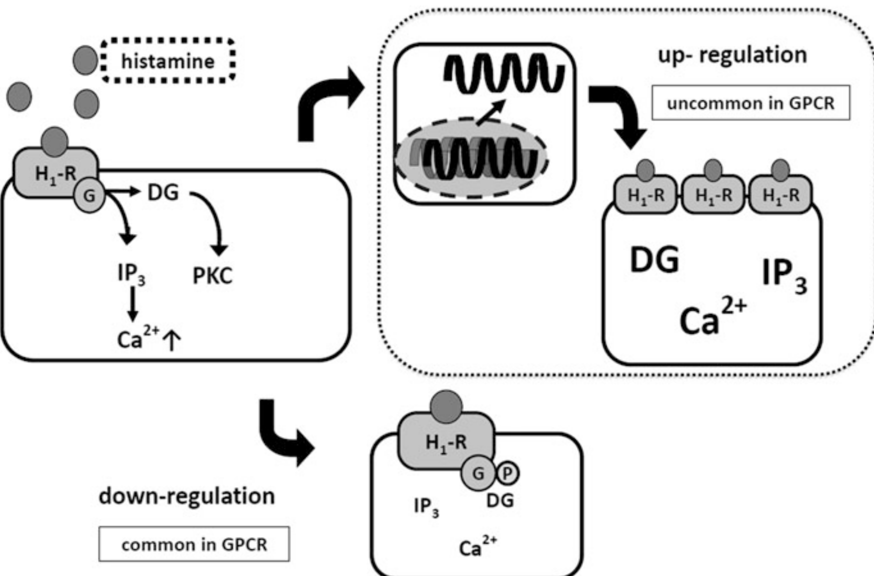

Fig. 1 Schematic representation of up-and down-regulation of histamine H_1 receptor (H1R) protein. Stimulated H1Rs were down-regulated through the common receptor desensitization mechanism. In addition, stimulation of H1R up-regulated the H1R through the H1R gene expression as an atypical mechanism. Adapted from Horio et al. (2004a)

3 H1R Gene as a Susceptibility Gene

Allergic symptoms are dominantly mediated by H1R. However, detailed mechanisms remained to be elucidated. Exacerbation of allergic symptoms was assumed by H1R up-regulation-induced increase in H1R signaling, and function of H1R gene was investigated as a susceptibility gene.

3.1 Activation of H1R Gene Expression in Nasal Mucosa of Allergic Rhinitis Model Rats

Nasal allergic symptoms were investigated in relation to H1R gene expression using allergic rhinitis model rats. Brown-Norway rats were sensitized by toluene 2,4-diisocyanate (TDI), and allergic rhinitis model rats (TDI rats) were created. TDI rats were employed to investigate H1R-mediated mechanism of allergic symptoms. Provocation with TDI successfully induced nasal symptoms and up-regulation of H1R protein and H1R mRNA in nasal mucosa (Mizuguchi et al. 2008). Similar to HeLa cells, target cells in nasal mucosa of Brown-Norway rats may have common H1R up-regulation mechanism. Both symptoms and gene expression were parallelly suppressed by epinastine, an antihistamine. H1R gene was suggested to be an allergic rhinitis-susceptibility gene. The H1R is a GPCR coupled with Gq/11 and PLCβ (Yamashita et al. 1991). PKC activation is a downstream of PLCβ. Among PKC isotypes, PKCδ activation was suggested to participate in H1R gene expression (Mizuguchi et al. 2011, Fig. 2).

Leukotrienes are major allergic mediators next to histamine, and leukotriene antagonists have been developed for the therapy of allergic diseases. When pranlukast, a cysteinyl leukotriene-receptor (LTR) antagonist, was pre-treated to TDI rats, up-regulation of H1R mRNA was suppressed and nasal symptoms were alleviated, suggesting that H1R gene expression mechanism is targeted not only by histamine but also by leukotrienes. However, detailed anti-allergic mechanism of leukotrienes remains to be elucidated. (Kuroda et al. 2013.).

3.2 Correlative Activation of IL-4, IL-5 and Histidine Decarboxylase (HDC) Gene Expression to H1R Gene Expression

Levels of H1R, IL-4, IL-5, and HDC mRNAs were correlatively up-regulated in the nasal mucosa of TDI rats and pollinosis patients, and suppressed by the treatment of antihistamines (Mizuguchi et al. 2008; Kitamura et al. 2012). The results suggest H1R, IL-4, IL-5, and HDC genes form a susceptibility gene group. IL-4 receptors are

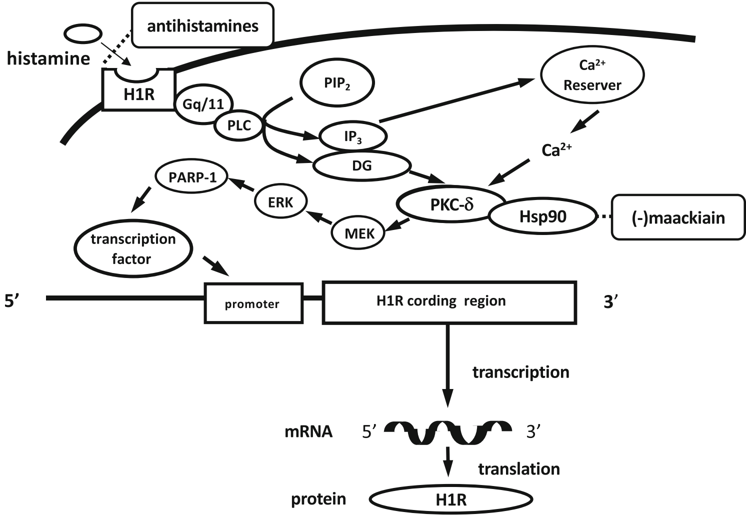

Fig. 2 Mechanism of H1R-mediated H1R gene expression through PKCδ activation. H1R gene is an allergic rhinitis-susceptibility gene whose up-regulation is suppressed not only by antihistamines but also by (−)-maackiain from Sophorae radix (Kujin). Sho-seiryu-to is also a suppressor of H1R gene expression

expressed in peripheral sensory nerves and revealed to participate in chronic itch (Oetjen et al. 2017).

3.3 Alleviation of Symptoms in TDI Rats by Sophorae radix (Kujin)*: An Anti-allergic* Kampo *Medicine*

Kujin, an anti-allergic *Kampo* medicine, is used for the therapy of allergic diseases by *Kampo* formulae such as *Kujin-to*, *Shohu-san,* and *Sanmotsu-ohgon-to*. However, scientific basis of *Kujin* remains to be elucidated. Symptoms of TDI rats after provocation were markedly alleviated by pre-treatment of *Kujin* (Dev et al. 2009). Parallelly, up-regulation of H1R mRNA was declined to the baseline, suggesting that *Kujin* targets H1R-mediated H1R gene expression signaling.

(−)-Maackiain was successfully isolated as an active substance from *Sophorae radix* (*Kujin*, an anti-allergic *Kampo* medicine) (Mizuguchi et al. 2015). Then the target of (−)-maackiain was successfully identified to be heat shock protein-90 (Hsp90) (Nariai et al. 2015, Fig. 2). Hsp90 and PKCδ form a complex. (−)-Maackiain binding to Hsp-90 resulted in the dissociation of complex, and PKCδ signaling was suppressed by the dissociation. Complex of Hsp90 and PKCδ plays an important role in H1R gene expression-mediated symptoms, and Hsp90 is a novel drug discovery target for the therapy of allergic diseases. Antihistamines and

(−)-maackiain target different molecules, H1R and Hsp90, respectively. However, H1R gene expression is the common functional target of both drugs.

Sho-seiryu-to is a popular anti-allergic *Kampo* formula in Japan, compared to *Kujin*. *Sho-seiryu-to* consists of eight medicinal plants, *Hange*; Pinellia ternate, *Kanzo*; *Glycyrrhiza glabra*, *Keihi*; *Cinnamomum cassia*, *Gomishi*; Schisandra chinensis, *Saishin*; Asarum sieboldii, *Shakuyaku*; *Paeonia lactiflora*, Maou; Ephedra, Kankyo; *Zingiber officinale*. Seven plants among eight showed suppressive activities of H1R gene expression. It is hypothesized that anti-allergic activity of seven plants is additively elevated, whereas adverse effects are not additive and remain relatively low. Sho-seiryu-to can be expected for its medicinal effect similar to antihistamines without sedation and sleepiness (Nakano et al. 2021).

When either antihistamine, Kujin or Sho-seiryu-to was administered to TDI rats, H1R mRNA up-regulation in nasal mucosa was completely suppressed, and degree of symptom alleviation was similar in each case. The results suggest that medicinal effect of antihistamines dominantly depends on PKCδ signaling-mediated H1R gene expression.

4 Antihistamine-Insensitive Mechanism of Allergy and Combination Therapy

4.1 Discovery of Antihistamine-Insensitive Mechanism of Allergy Using Suplatast Tosilate

Up-regulation of H1R mRNA in nasal mucosa of TDI rats was completely suppressed to the basal level by the treatment of epinastine, an antihistamine. In spite of complete suppression of up-regulation, alleviation of symptoms was only 60% (Mizuguchi et al. 2008). Remaining symptoms were assumed to be due to antihistamine-insensitive mechanism of allergy.

Suplatast tosilate was developed as a Th2 cytokine suppressor (Furukido et al. 2002). Indication for suplatast is bronchial asthma, atopic dermatitis, and allergic rhinitis. Detailed efficacy mechanism of suplatast remained unknown. Partial alleviation by suplatast of nasal symptoms was observed in TDI rats (Shahriar et al. 2009). Then combination treatment of an antihistamine and suplatast resulted in marked alleviation of nasal symptoms in TDI rats, and up-regulation of IL-9 mRNA was almost completely suppressed by suplatast in the nasal mucosa of TDI rats, but not suppressed by antihistamine (Mizuguchi et al. 2016). In spite of strong suppressive activity of suplatast in TDI rats, no clear medicinal effect is observed in human. The clinical use of the drug is no popular. The reason is speculated that both affinity to the target and drug delivery system of suplatast are poor in human. Then apart from suplatast, suppressive activity of anti-allergic natural sources against IL-9 mRNA up-regulation was examined.

4.2 Discovery and Molecular Pharmacology of Compounds Suppressing IL-9 Gene Expression from Natural Sources

There are two traditions that Awa-tea, a product of tea leaf fermentation in Tokushima, Japan, and extract of lotus in Naruto, Japan, have anti-allergic activities. Combination treatment of an antihistamine and Awa-tea resulted in marked alleviation of nasal symptoms in TDI rats (Nakano et al. 2020). In reality, 90% of alleviation was resulted. Up-regulation of IL-9 mRNA in nasal mucosa was suppressed to the basal level by the treatment of Awa-tea, suggesting that IL-9 gene expression mechanism participates in nasal symptoms insensitive to antihistamines as a new allergic rhinitis-susceptibility gene. Nuclear factor of activated T-cells (NFAT) was revealed upstream of IL-9 gene expression (Mizuguchi et al. 2016). NFAT is downstream of calcium-calmodulin-calcineurin signaling (Wu et al. 2007). Pyrogallol was identified as a suppressor of IL-9 gene expression (Nakano et al. 2020). Poly(U)-binding-splicing factor puf60 (PUF60) was identified as a target of pyrogallol (Mizuguchi et al. 2020). Patho-physiological activity of pyrogallol seems to be the first report. NFAT forms a large cytoplasmic RNA-protein scaffold complex (Sharma et al. 2011). PUF60 has binding activity to the NFAT complex, and NFAT signaling-mediated IL-9 gene expression was suppressed by the knockout of PUF60 (Mizuguchi et al. 2020). The data suggest that PUF60 is a novel drug target for the therapy of antihistamine-insensitive allergic symptoms.

Next to Awa-tea, hot water extract of lotus root knots showed inhibitory activity of IL-9 gene expression (Wakugawa et al. 2020). Nasal symptoms of TDI rats were markedly alleviated by combination treatment of epinastine, an antihistamine, and extract of lotus root knots. Ionomycin Ca^{++} ionophore-induced up-regulation of IL-9 mRNA was completely suppressed by the extract of lotus root knots in RBL 2H3 cells. Proanthocyanidin containing gallocatechin tetramer (PAC) was isolated from lotus root knots as an active compound (Wakugawa et al. 2020). PAC showed dose-dependent suppression of IL-9 mRNA up-regulation in RBL 2H3 cells and marked alleviation of nasal symptoms by the combination treatment with epinastine in TDI rats.

Lotus root powder (LRP) was prepared from lotus root knot extract by spray dry manufacturing method. LRP standardized by determining PAC and total polyphenol levels showed symptom alleviation and suppression of IL-9 mRNA up-regulation by the combination treatment with epinastine in TDI rats. Then randomized, double-blind, parallel-group, placebo-controlled study was performed using LRP and maltodextrin as a control. LRP showed significant improvement in nasal and eye symptomatology scores of Practical Guideline for the management of allergic rhinitis in Japan, color tone of inferior turbinate mucosa, and eye symptomatology score of Japanese Rhinoconjunctivitis Quality of Life Questionnaire without any adverse effect (Nagamine et al. 2020).

IL-9 is an allergic Th2 cytokine. IL-9 is produced mainly in Th9 cells and produced in other T helper cells including Th2 cells, Th9 cells, Th17 cells and regulatory Treg cells, and mast cells (Noelle and Nowak. 2010). In addition to our

present observation that IL-9 participates pathogenesis of nasal hypersensitivity, IL-9 plays roles in other allergic diseases including bronchial asthma and food allergy, immune response to parasite infection, inflammatory bowel diseases, and malignancies including Hodgkin's lymphoma and melanoma (Neurath and Finotto 2016; Zuleta and Sanchez 2017). Pyrogallol and PAC are potential therapeutics not only for allergic rhinitis but also for other IL-9 related diseases.

5 Future Outlook for the Therapy of Allergic Diseases

5.1 Multiple Pathological Mechanisms of Allergic Diseases

Antihistamines gave brilliant contribution to the therapy of type-1 reaction-dominant allergic diseases. However, alleviation of the diseases by antihistamines is insufficient, suggesting the existence of antihistamine-insensitive signaling in allergy. In order to overcome the insufficiency, slow reacting substance of anaphylaxis (SRS-A) as an antihistamine-insensitive allergy signaling was investigated, and chemical mediators such as leukotrienes, prostaglandins, and platelet activation factor and many allergy cytokines have been identified. Newly developed drugs targeting SRS-A and allergic cytokines were expected high level alleviation of allergic symptoms. Unfortunately, these drugs are not effective to pollinosis and other type-1 reaction-dominant allergic diseases. It is thought essential to identify exact factors of type-1 reaction-dominant allergic diseases from multiple factors. However, the problem remains to be solved.

Alternative approach is to elucidate multiple pathological mechanisms of allergy. Although H1R is the target of antihistamines, there is no study how symptoms are alleviated. Our research results demonstrated that histamine-induced H1R gene expression participates in symptoms as an allergic rhinitis-susceptibility gene. On the other hand, as antihistamine-insensitive mechanism, IL-9 gene was identified as the second allergic rhinitis-susceptibility gene (Fig. 3).

Historically, traditional natural medicines have been used for the therapy of various diseases. Then receptors became principal drug targets after developments of antihistamines (histamine H_1 antagonists), histamine H_2 antagonists, and β-adrenaline antagonists for the therapy of allergic diseases, peptic ulcer, and cardiovascular diseases, respectively. Regarding allergic diseases, anti-allergic drugs targeting receptors such as leukotriene-receptor antagonist (LTRA), thromboxane A_2 (TXA_2) receptor antagonists, prostaglandin D_2 (PGD_2) receptor antagonists were newly developed. Alleviation of allergic rhinitis was insufficient by these anti-allergic drugs.

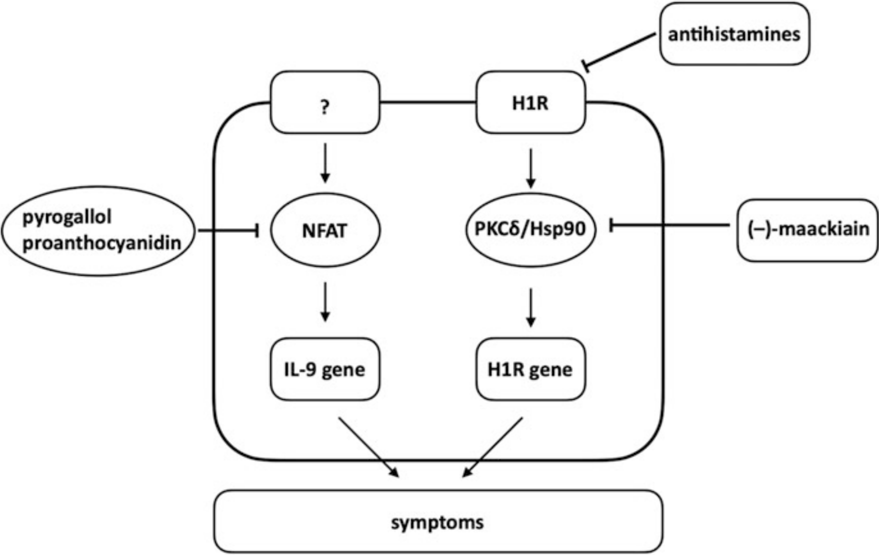

Fig. 3 Two signaling pathways of allergic symptoms. Antihistamine- and (−)-maackiain-sensitive H1R gene expression as the first mechanism and pyrogallol- and proanthocyanidin-sensitive IL-9 gene expression as the second one

5.2 *A New Evaluation System to Develop New Therapeutics*

In order to develop novel therapeutics with new concept, new evaluation system of symptoms is indispensable. Recently, involvement of susceptibility genes was studied in the onset of multifactorial diseases. As antihistamines are principal therapeutics of allergic diseases, their susceptibility genes are to be studied. Good correlation between symptom deterioration and H1R mRNA up-regulation and correlative symptom alleviation and suppression of H1R mRNA up-regulation by the therapy of antihistamines were demonstrated, suggesting that H1R gene is a susceptibility gene for allergic rhinitis (Mizuguchi et al. 2010; Kitamura et al. 2015).

5.3 *Therapeutic Strategy for Multifactorial Allergic Diseases*

Combination therapy is advanced therapeutic intervention for multifactorial diseases and highly expected for allergic diseases. IL-9 gene was identified as a susceptibility gene for antihistamine-insensitive symptoms, and pyrogallol, a suppressive compound of IL-9 gene expression, was successfully identified from Awa-tea. Combination therapy using an antihistamine and pyrogallol showed remarkably advanced alleviation of symptoms in TDI rat, compared to the single treatment of antihistamine (Nakano et al. 2020). The result is promising for the therapy of type-

1 reaction-dominant allergic diseases including allergic rhinitis, allergic conjunctivitis, and urticaria. Clinical trials are awaited.

6 Expanding Histamine Research for the Novel Therapeutic Strategy of H1R-Related Diseases in Future

6.1 H1R and Diabetes Mellitus and Other Diseases

Angiopathy and neuropathy are major pathological changes of diabetes mellitus. Recently, diabetes mellitus has been studying as an inflammatory disease (Donath and Shoelson 2011; Lontchi-Yimagou et al. 2013; Tsalamandris et al. 2019). Histamine is a principal mediator of allergic inflammation. Reports of histamine research related to diabetes mellitus have been accumulating. Increased plasma histamine level and histamine synthesis were reported (Hollis et al. 1985; Gill et al. 1989, 1990). In addition to reports on therapeutic potential of histamine H_3 receptor agonist for diabetes mellitus (Yoshimoto et al. 2006; Henry et al. 2011; Nakamura et al. 2014, 2015), H1R-mediated effects in diabetic condition were also reported. Retinopathy may be deteriorated by H1R-mediated increase in blood-retinal barrier (Enea et al. 1989; Hollis et al. 1992). H1R could contribute to diabetic nephropathy (Anbar et al. 2016). Antihistamines may be indicated to H1R-related diabetic pathologies.

Significance of glucagon in diabetes mellitus was recently reported (Hare et al. 2010). Glucagon secretion was suppressed by PKCδ activation which induces H1R gene expression (Yamamoto et al. 2017). Apart from diabetes mellitus, participation of H1R gene expression to atherosclerosis was suggested (Takagishi et al. 1995). Detailed mechanism of H1R gene expression involved in these pathologies is highly interested.

6.2 H1R Signaling-Related Diseases in the Brain

Histamine is a neurotransmitter in the brain, and H1Rs are responsible for various histaminergic functions. Motion sickness is caused by the disorder of sense of balance. Histaminergic neurons are responsible in sense of balance, and antihistamines are used for the therapy of motion sickness (Takeda et al. 1989). In the motion sickness model rats, H1R mRNA was up-regulated in the hypothalamus and brainstem (Sato et al. 2009). Histaminergic neurons also regulate food intake (Sakata et al. 1988). Scheduled feeding induces c-Fos expression in the caudal part of the arcuate nucleus of hypothalamus (Umehara et al. 2011). The result suggests participation of H1R gene expression in the brain.

U373 cells are astrocyte in cultured cell line and express H1Rs. H1R gene expression was activated by the stimulation by histamine of the cells. However, the mechanism of H1R gene expression in U373 cells is thought different from that in HeLa cells because of different time course and no suppression by PKCδ inhibitors, although detailed mechanism remains to be elucidated (Mizuguchi et al. 2021).

6.3 Strategy of the Therapy for Diseases Susceptible to H1R Gene Expression

The H1R are expressed not only in peripheral tissues but also in the brain, suggesting that H1R gene expression participates various physiological and pathological functions. Involvement of H1R gene expression was extensively studied in allergic rhinitis as a disease susceptibility gene. H1R gene expression was suggested to play roles in diabetes mellitus, atherosclerosis, and motion sickness, and antihistamines may be effective for the therapy. However, most diseases are thought multifactorial. In addition to H1R-related mechanism, elucidation of other pathological mechanisms is indispensable. Then combination therapy using antihistamine and other complementary drugs is thought common in future.

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Molecular Signaling and Transcriptional Regulation of Histamine H_1 Receptor Gene

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Abstract Histamine-activated histamine H_1 receptor (H1R) signaling regulates many gene expressions, mainly through the protein kinase C (PKC)/extracellular signal-regulated kinases (ERK) signaling. Involvement of other signaling, including NF-κB, Wnt, RUNX-2, and Rho A signaling was also demonstrated. In addition, cAMP production through the activation of H1R signaling was reported. H1R gene itself is also up-regulated by the activation of H1R signaling with histamine. Here, we review our recent findings in the molecular signaling and transcriptional

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regulation of the H1R gene. Stimulation with histamine up-regulates H1R gene expression through the activation of H1R in HeLa cells. The PKCδ/ERK/poly (ADP)ribosyl transferase-1 (PARP-1) signaling was involved in this up-regulation. Heat shock protein 90 also plays an important role in regulating PKCδ translocation. Promoter analyses revealed the existence of two promoters in the human H1R gene in HeLa cells. H1R-activated H1R gene up-regulation in response to histamine was also observed in U373 astroglioma cells. However, this up-regulation was mediated not through the PKCδ signaling but possibly through the PKCα signaling. In addition, the promoter region responsible for histamine-induced H1R gene transcription in U373 cells was different from that of HeLa cells. These findings suggest that the molecular signaling and transcriptional regulation of the H1R gene are different between neuronal cells and non-neuronal cells.

Keywords Allergic diseases-sensitive gene · Allergic rhinitis · Histamine H_1 receptor gene · Hsp90 · PKCδ

Abbreviations

17-AAG	17-(Allyl-amino)-17-demethoxygeldanamycin
ERK	Extracellular signal-regulated kinases
GM-CSF	Granulocyte macrophage-colony stimulating factor
GR	Glucocorticoid receptor
GRE	Glucocorticoid-responsive element
H1R	Histamine H_1 receptor
Hsp90	Heat shock protein 90
IL	Interleukin
PARP-1	Poly(ADP)ribosyl transferase-1
PKCδ	Protein kinase Cδ
PMA	Phorbol 12-myristate 13-acetate
RUNX-2	Runt-related transcription factor 2

1 Introduction

Histamine is a biogenic amine, and its actions are mediated by four histamine receptor subtypes, H_1, H_2, H_3, and H_4 receptors (Seifert et al. 2013). Histamine acts as a neurotransmitter in the nervous system (Schwartz et al. 1986; Haas et al. 2008) and as a chemical mediator in the gut, skin, and immune system (Hill 1990, 1992). In the nervous system, H1R is expressed in neuronal and glial cells and involved in the thermal regulation, memory and learning, sleep-wake cycle, food intake, and emotional and aggressive behaviors. In the peripheral, H1R is expressed in airway epithelial and endothelial cells, and involved in the allergy including

allergic rhinitis, atopic dermatitis, anaphylaxis, and asthma (Bousquet et al. 2008). All histamine receptor subtypes are classified as G-protein coupled receptors (GPCRs). Each receptor subtypes is coupled with different G-protein, i.e. H_1 receptors are coupled with Gq, H_2 receptors are coupled with Gs, and H_3 and H_4 receptors are coupled with Gi. Thus, activation of each receptor subtype stimulates different signaling pathways. In some cells, it was reported that the H_2 receptor was coupled with Gq, resulting in IPs formation and an increase in intracellular Ca^{2+} concentration (Kühn et al. 1996; Wang et al. 1996). However, this H_2 receptor-stimulated Ca^{2+} and IPs responses in these cells were both inhibited by cholera toxin treatment, suggesting this is an indirect effect mediated by Gs (Delvalle et al. 1992). It was also reported that in sympathetic and sensory neurons, postsynaptic activation of H_3 receptors stimulates PLC in a subpopulation of striatal neurons, with subsequent activation of the IP_3 pathway followed by increased intracellular concentrations of Ca^{2+} (Rivera-Ramírez et al. 2016). As H1R is coupled with the G_q protein, stimulation of H1R activates inositol phospholipid hydrolysis and intracellular Ca^{2+} mobilization (Daum et al. 1983; Gutowski et al. 1991; Iredale et al. 1993; Leurs et al. 1995; Hill et al. 1997; Leopoldt et al. 1997; Panula et al. 2015). According to the two-state model, H1R is in an equilibrium state between an active form and an inactive form, and a constant level of signal always operates even without histamine stimulation (Bakker et al. 2000; Leurs et al. 2002). Histamine, an agonist, combines and stabilizes the active conformation of the H1R to shift the equilibrium toward the active state. On the other hand, inverse agonists combine with and stabilize the inactive conformation of H1R to shift the equilibrium toward the inactive state, and downregulate the H1R constitutive activity, even in the absence of histamine. Neutral antagonists combine equally with both conformations of H1R, do not affect basal receptor activity but interfere with agonist binding. Antihistamines are a widely employed first-line treatment for the symptoms of allergic diseases because they not only antagonize histamine and prevent histamine from binding to H1R but also work as inverse agonists that suppress constitutive H1R activity (Simons 2004; Mizuguchi et al. 2020).

Pollinosis is seasonal allergic rhinitis caused by hypersensitivity to tree or grass pollens, and it affects about 40% of the Japanese population (Okubo et al. 2017). It was reported that H1R mRNA expression increased in epithelial, endothelial, and neural cells of the nasal mucosa in patients with occupational rhinitis (Hamano et al. 1998; Nakasaki et al. 1999). Up-regulation of H1R gene expression was also observed in patients with allergic rhinitis, and H1R binding in the nasal mucosa was reported to increase during the development of nasal allergies (Shimada 1990; Iriyoshi et al. 1996; Dinh et al. 2005). Thus, it is of interest to understand the H1R signaling and transcriptional regulation of the H1R gene for the development of an effective treatment for allergic diseases.

2 Signaling Pathway of H1R-Activated Gene Expression

The H1R is ubiquitously expressed in many tissues and cells, including nerve cells, respiratory epithelial and endothelial cells, hepatic cells, vascular smooth muscle cells, dendritic cells, and lymphocytes (Akdis and Simons 2006). Activation of H1R by histamine might be involved in the regulation of many gene expressions. Studies using histamine receptor antagonists specific for receptor subtypes and protein kinase C (PKC) isozyme-selective inhibitors revealed that gene expression of granulocyte macrophage-colony stimulating factor (GM-CSF), interleukin (IL)-8, and matrix metalloproteinase-9 was mediated through the PKC/ERK signaling pathway in bronchial epithelial cells and in U373 human astrocytoma cells, respectively (Matsubara et al. 2006; Patel et al. 2016). H1R-activated Egr-1 expression in human aortic endothelial cells was also mediated protein kinase Cδ-dependent ERK activation pathway, in which cAMP response element binding protein that was phosphorylated by ERK is involved in the activation of Egr-1 transcription (Hao et al. 2008). In human keratinocyte, histamine increased nerve growth factor (NGF) mRNA level via H1R stimulation, and it was mediated by the phosphorylation of Ca^{2+}-dependent PKC/ERK signaling pathway, in which histamine induced c-Fos mRNA expression and enhanced transcriptional activity and DNA binding of AP-1 (heterodimer of c-Fos and c-jun) at the PMA-response elements (Kanda and Watanabe 2003; Lipnik-Stangelj 2006). H1R activation with histamine in transfected CHO cells increased forskolin-dependent cAMP production (Leurs et al. 1994) by the activation of adenylyl cyclase through the release of $G_{\beta\gamma}$-subunits from Gq proteins (Maruko et al. 2005). Production of cAMP through the activation of H1R with histamine was also found in rat brain and adrenal gland (Marley et al. 1991). The molecular mechanism of this stimulatory effect of histamine was unknown, but it may be through the activation of Ca^{2+}-stimulated adenylyl cyclase or the release of $G_{\beta\gamma}$-subunits (Halls and Cooper 2011). Activation of H1R caused the activation of Rho and Rac small GTPases through the direct interaction of activated G_{α}-subunit of Gq protein with p63RhoGEF in transfected CHO cells (Notcovich et al. 2010).

Regarding the studies for the H1R signaling not mediated by PKC/ERK signaling, it was reported that H_1-agonist induced NF-κB activation through the H1R activation in H1R-overexpressed COS-7 cells, in which both G_{α}-subunit and $G_{\beta\gamma}$-subunits released from Gq protein suggested to be involved in NF-κB activation (Bakker et al. 2001) and CHO cells (Leurs et al. 1994; Smit et al. 1996). Stimulation of H1R-overexpressed HepG2 cells with histamine also increased NF-κB expression and suppressed apo-A-I gene expression through the enhancement of p65 subunit of NF-κB to the apo-A-I promoter (Haas et al. 2018). Histamine induced up-regulation of Toll-like receptor 3 mRNA expression in HMC-1 via H1R and the PI3K/Akt and MEK/ERK signaling pathways followed by the activation of NF-κB was involved in this up-regulation (Xie et al. 2018). Activation of H1R by histamine also up-regulated gene expressions of alkaline phosphatase (ALP), osteocalcin (OCN), and type I collagen (Col-I) in MC3T3-E1 osteoblastic cells. In these cells, H1R

Table 1 Histamine-induced gene regulation and its signal transduction

Cells	Gene or (protein) regulated	Signal transduction	Reference
Bronchial epithelial cells	GM-CSF IL-8	PKC/ERK	Matsubara et al. (2006)
Cultured astrocytes	NGF	PKC/ERK/AP-1	Lipnik-Stangelj (2006)
H1R-overexpressed CHO	(Adenylyl cyclase)	$G_{\beta\gamma}$-subunits	Leurs et al. (1994)
	Rho and Rac small GTPases	–	Notcovich et al. (2010)
H1R-overexpressed COS-7	–	NF-κB	Bakker et al. (2001)
H1R-overexpressed HepG2	Apo-A-1	NF-κB	Haas et al. (2018)
HeLa	(Glycogen synthase kinase 3-β)	Wnt	Diks et al. (2003)
	H1R	PKCδ/ERK/PARP-1	Das et al. (2007) Mizuguchi et al. (2011) Nariai et al. (2015)
HMC-1	Toll-like receptor 3	PI3K/Akt	Xie et al. (2018)
Human aortic endothelial cells	Egr-1	PKCδ/ERK	Hao et al. (2008)
Human keratinocyte	NGF	PKC/ERK/AP-1	Kanda and Watanabe (2003)
MC3T3-E1	Alkaline phosphatase Osteocalcin	RUNX-2	Sun et al. (2019)
MC3T3-E1	Type I collagen		
	H1R	–	Sun et al. (2019)
Murine macrophage	(Glycogen synthase kinase 3-β)	Wnt	Diks et al. (2003)
Primary cultured astrocytes	H1R	–	Xu et al. (2018)
U373	Matrix metalloproteinase-9	PKC/ERK	Patel et al. (2016)
	H1R	PKC	Miyoshi et al. (2007)

activation caused the phosphorylation of AMP-activated protein kinase, which then activated eNOS and promoted NO generation, leading to the activation of runt-related transcription factor 2 (RUNX-2) (Sun et al. 2019). Activation of H1R-mediated Wnt signaling by histamine caused the inhibition of glycogen synthase kinase 3-β phosphorylation and subsequent degradation of β-catenin, allowing its nuclear transport and transactivation of β-catenin response gene expression in HeLa cells, murine macrophages, and colon cancer cell lines including SW-480 (Diks et al. 2003). H1R-activated gene regulation and its signal transduction are summarized in Table 1.

3 Molecular Signaling of H1R Gene Expression

In addition to the genes described above, up-regulation of the H1R gene itself by histamine stimulation was also reported. H1R gene was up-regulated in the process of differentiation and mineralization of MC3T3-E1 cells induced by osteogenic medium (Sun et al. 2019). Histamine-induced H1R up-regulation was observed in primary cultured astrocytes (Xu et al. 2018). It was also reported that H1R gene up-regulation was mediated by H1R activation with histamine in HeLa cells (Das et al. 2007) and U373 cells (Mizuguchi et al. 2019b). In U373 cells, H1R up-regulation was PKC dependent (Miyoshi et al. 2007).

3.1 Molecular Signaling of H1R Gene Expression in HeLa Cells

3.1.1 HeLa Cells Endogenously Express H1R

In general, repeated stimulation with agonists causes receptor downregulation. However, stimulation of HeLa cells with histamine causes up-regulation of H1R (Das et al. 2007). Therefore, we think that histamine-induced H1R-mediated H1R gene up-regulation found in HeLa cells is a good model to understand the mechanism of the "positive feedback circuit" of an allergic reaction, in which histamine-induced up-regulation of H1R gene expression results in an increase in the H1R protein and makes the cells more sensitive to histamine and exacerbates the allergic response. HeLa cells express H1R endogenously (130 fmol/mg protein) (Mizuguchi et al. 2013). As H1R is coupled with Gq protein, its activation increases intracellular Ca^{2+} concentration followed by IP_3 and diacylglycerol production. Without stimulation with histamine, HeLa cells showed Ca^{2+} oscillation derived from the constitutive activity of H1R (Mizuguchi et al. 2020). Stimulation of HeLa cells with histamine immediately increases the intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) followed by IP_3 formation (Mizuguchi et al. 2013). Pretreatment with antihistamine with inverse agonist activity such as bilastine and fexofenadine decreased constitutive and histamine-stimulated $[Ca^{2+}]_i$ increase and IP_3 formation (Mizuguchi et al. 2020). Stimulation of HeLa cells with histamine also up-regulated H1R gene expression (Das et al. 2007). This elevation of H1R mRNA was suppressed by antihistamines but not ranitidine, an H_2-blocker, indicating that histamine-induced up-regulation of H1R gene expression is mediated by H1R activation.

3.2 *Signaling Pathway of H1R-Mediated H1R Gene Expression Induced by Stimulation with Histamine in HeLa Cells*

As stimulation with phorbol 12-myristate 13-acetate (PMA) up-regulated H1R gene expression in HeLa cells, it is suggested that the signaling pathway of H1R-mediated H1R gene expression is PKC dependent (Das et al. 2007). To date, 11 PKC isoforms have been identified, and the PKC isoforms are divided into three subgroups; that is, conventional PKC (α, β, and γ), novel PKC (δ, ε, η, and θ), and atypical PKC (ξ and ι/λ) based on their structures and cofactor requirements (Dempsey et al. 2000). Among them, HeLa cells express PKC α, β, δ, ε, and ζ isoforms (Kajimoto et al. 2001; Hermoso et al. 2004; Muscella et al. 2004). Ro-31-8220, a non-isoform selective PKC inhibitor, completely inhibited histamine-induced up-regulation of H1R gene expression. Go6976, an inhibitor of the Ca^{2+}-dependent PKC isoforms, did not show any significant inhibitory effects. On the other hand, rottlerin, a selective inhibitor for the PKCδ isoform, suppressed histamine-induced H1R gene expression in HeLa cells. These data indicate that PKCδ is involved in histamine-induced H1R gene expression (Das et al. 2007). Activation of PKCδ with H_2O_2, known as a PKCδ activator (Konishi et al. 1997, 2001) also up-regulated H1R gene expression (Mizuguchi et al. 2011).

Phosphorylation and dephosphorylation of PKCs regulate their activity, stability, and function. Phosphorylation at Tyr^{311} on PKCδ is crucial for enzyme activation (Steinberg 2008). Stimulation with histamine caused phosphorylation of Tyr^{311} on PKCδ. In addition, overexpression of PKCδ protein or knockdown of PKCδ gene increased or decreased, respectively, histamine-induced up-regulation of H1R gene expression, indicating that PKCδ is a key enzyme for H1R-activated H1R gene expression pathway (Mizuguchi et al. 2011).

It is known that PKC activates ERK signaling cascade, in which ERK is activated by MEK. U0126, a MEK inhibitor (Favata et al. 1998), suppressed PMA-induced H1R mRNA elevation (Mizuguchi et al. 2011). Immunoblot analysis showed that histamine- or PMA-stimulation resulted in transient phosphorylation of ERK. Pretreatment with rottlerin inhibited histamine- or PMA-stimulated ERK phosphorylation (Mizuguchi et al. 2011). During the promoter analyses of the H1R gene, PARP-1 has identified as one of the promoter binding proteins (Mizuguchi et al. 2012). PARP-1 is a nuclear chromatin-associated protein that catalyzes the post-translational modification of proteins by poly(ADP-ribosyl)ation (PARylation) and this posttranslational modification of proteins by PARP-1 regulates protein–protein and protein–DNA interactions (D'Amours et al. 1999). PARP-1 also functions as a transcriptional regulator or co-regulator by direct interaction with transcription factors (Rawling and Alvarez-Gonzalez 1997; Hassa and Hottiger 2002; Kraus and Lis 2003). PARP-1 itself is activated by various extracellular signals that activate Raf/MEK/ERK phosphorylation. PARylated PARP-1 amplifies ERK signaling, which targets core histone acetylation and gene transcription. Acetylation or PARylation of histones, then, induces decondensation of the chromatin structure

and activates gene transcription (Willis et al. 2002; Kim et al. 2004; Cohen-Armon et al. 2007). PARP-1 inhibitor DPQ suppressed PMA-induced up-regulation of H1R gene expression (Mizuguchi et al. 2011). Immunoprecipitation assay showed that without stimulation with PMA, PARP-1 interacted with Ku86, another promoter binding protein identified using DNA affinity chromatography. This interaction was disrupted by PARylation of Ku86 by PARP-1 in response to PMA-stimulation and affected H1R gene transcription (Mizuguchi et al. 2012, see Sect. 4). These data indicate that MEK, ERK, and PARP-1 are the signal effectors downstream of PKCδ.

PKCs translocate to various organelles, including the plasma membrane, nucleus, endoplasmic reticulum, mitochondria, and Golgi body in response to various stimuli and phosphorylate isoform-specific substrates, leading to isoform- and/or stimulus-specific cellular responses. Stimulation with histamine promoted PKCδ translocation from the cytosol to the Golgi body (Mizuguchi et al. 2011). Stimulation with PMA also promoted PKCδ translocation to the Golgi body. Pretreatment with rottlerin inhibited the histamine-induced PKCδ translocation to the Golgi body. Stimulation with ceramide also induced PKCδ translocation to the Golgi body in HeLa cells (Kajimoto et al. 2001). As an unphosphorylatable PKCδ mutant (Y311F) could translocate to the Golgi body in response to ceramide, it is suggested that Tyr^{311} was phosphorylated at the Golgi body (Kajimoto et al. 2004).

3.3 Identification of Heat Shock Protein 90 (Hsp90) Involved in the Signaling Pathway of H1R Gene Expression in HeLa Cells

Kujin is the dried root of *S. flavescens AITON* of the Leguminosae family. This Chinese herb has been used extensively in the treatment of allergic diseases and many other pathological conditions for many years in Asian countries. We have isolated (−)-maackiain from Kujin hot water extract and identified as an anti-allergic compound (Mizuguchi et al. 2015). (−)-Maackiain suppressed histamine- or PMA-induced up-regulation of H1R gene expression and inhibited phosphorylation of Tyr^{311} on PKCδ, and its translocation to the Golgi body. However, (−)-maackiain did not inhibit PKCδ kinase activity (Mizuguchi et al. 2015).

Quenching of intrinsic tryptophan fluorescence has been widely used to analyze the interaction of proteins and their ligands (Böhl et al. 2005). Using this technique, we have identified heat shock protein 90 (Hsp90) as a target protein of (−)-maackiain (Nariai et al. 2015). Synthesized (−)-maackiain quenched the intrinsic tryptophan fluorescence of recombinant Hsp90. Fluorescence polarization assay showed that (−)-maackiain bound to the neighborhood of the ATP-binding pocket of Hsp90. In addition, (−)-maackiain did not inhibit Hsp90 ATPase activity. Immunoprecipitation analysis revealed that PKCδ was a client protein of Hsp90, and pretreatment with (−)-maackiain disrupted the interaction of Hsp90 with PKCδ and inhibited translocation of PKCδ to the Golgi body (Nariai et al. 2015). 17-AAG and

celastrol, Hsp90 inhibitors, also suppressed the up-regulation of the H1R gene expression and inhibited phosphorylation of Tyr^{311} on PKCδ, and its translocation to the Golgi body. These data suggest Hsp90 is the additional signal effector in the H1R gene expression pathway to regulate PKCδ translocation and activation (Nariai et al. 2015).

3.4 Signaling Pathway of H1R-Mediated H1R Gene Expression Induced by Stimulation with Histamine in U373 Cells

It was reported that stimulation with PMA up-regulated H1R gene expression in U373 cells, suggesting that the H1R gene expression signaling pathway is PKC-dependent (Miyoshi et al. 2007). Treatment with histamine increased the expression of H1R mRNA in a dose-dependent manner in U373 cells (Mizuguchi et al. 2019b). This H1R gene up-regulation was inhibited by pretreatment with H1R antagonist *d*-chlorpheniramine, but not by ranitidine, ciproxifan, or JNJ77777120, an H2R, H3R, or H4R antagonists, respectively. These data indicate that histamine-induced up-regulation of H1R gene expression in U373 cells is mediated by H1R, which is the same as in the case of HeLa cells. In addition, histamine-induced up-regulation of H1R gene expression was suppressed by pan-PKC inhibitor Ro-31-8220 and by the PKCα/β_1 inhibitor Go6976. However, PKCδ selective inhibitor rottlerin and the PKCβ selective inhibitor Ly333531 did not suppress H1R gene up-regulation, suggesting the involvement of PKCα in the H1R signaling pathway in U373 cells (Mizuguchi et al. 2019b). Time course studies of histamine-induced up-regulation of H1R mRNA in both HeLa and U373 cells revealed altered kinetics for histamine-induced up-regulation of H1R gene, i.e., stimulation with histamine caused a rapid and transient increase in the H1R mRNA level in U373 cells with a maximum at 2–3 h after stimulation, on the other hand, up-regulation of H1R gene expression induced by histamine in HeLa cells was slow and gradual with the maximum H1R gene expression level at 3–9 h after histamine stimulation (Fig. 1; Mizuguchi et al. 2019a). Similar kinetics seen in U373 cells and HeLa cells were also observed in the trigeminal ganglion and nasal mucosa, respectively. These data suggest that the histamine-induced H1R gene expression signaling pathway in U373 cells was different from that in HeLa cells possibly through the use of different promoters in H1R gene expression. In addition, the involvement of PKCα not PKCδ in H1R gene expression in U373 cells suggests that compounds target for PKCδ such as (−)-maackiain could work as peripheral type H1R selective inhibitors without a sedative effect.

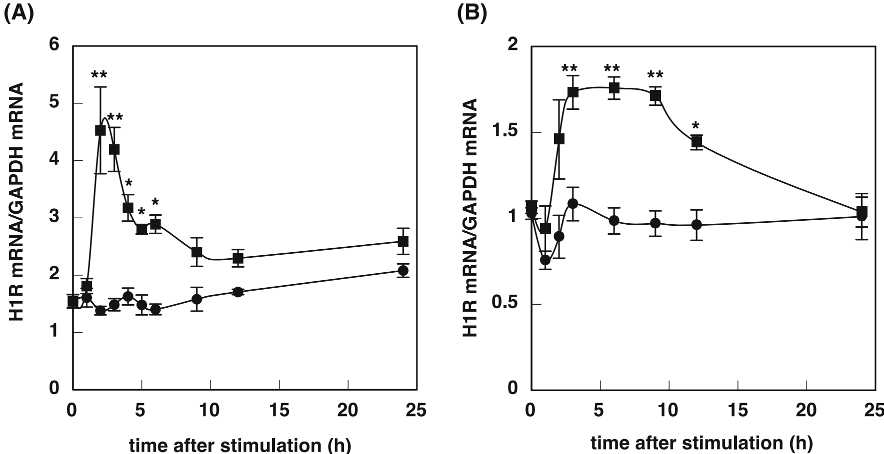

Fig. 1 Time course of histamine-induced up-regulation of H1R mRNA in U373 cells (**a**) and HeLa cells (**b**). At given time intervals after stimulation with histamine, total RNA was isolated and H1R mRNA was determined by real-time quantitative RT-PCR. Closed circles, control; closed squares, histamine stimulation. Data are expressed as means ± S.E.M. (n = 8-12). **$P < 0.01$; *$P < 0.05$ vs. control at the corresponding time

3.5 Up-Regulation of H1R Gene by Signal Molecules Other than Histamine

Hsp90 is a molecular chaperone that mediates the folding and activation of diverse client proteins essential for a variety of signal transduction pathways. It is well known that the glucocorticoid receptor (GR) is a client protein of Hsp90, and it is maintained in its resting state by binding to Hsp90 in the absence of steroids. After the steroid binds to GR, the steroid-GR complex is released from Hsp90 and translocated into the nucleus, where the complex binds to a specific glucocorticoid-responsive element (GRE) and regulates the transcription of steroid-susceptible proteins. In addition, it is also reported that glucocorticoid binds to AP-1 and NF-κB and downregulates transcription of many proinflammatory cytokines and growth factors (Jonat et al. 1990; Konig et al. 1992; Scheinman et al. 1995; Kassel and Herrlich 2007). Activation of H1R enhanced the GR activity through the $G_{\beta\gamma}$-subunits/JNK pathway in HEK293 cells co-transfected with a luciferase reporter plasmid having GRE in combination with plasmids coding for GR and H1R (Zappia et al. 2015). On the other hand, antihistamines with inverse agonist activity potentiated the dexamethasone-induced transcriptional activity of anti-inflammatory GILZ (glucocorticoid-induced leucine zipper) gene but not an inflammation-unrelated SLC19A2 (thiamine transporter 1 or solute carrier family 19 member 2) gene (Zappia et al. 2015). We showed that treatment with (−)-maackiain up-regulated dexamethasone-induced inflammation-related dual specificity phosphatase-1 (DUSP-1) gene expression but not inflammation-unrelated

SLC19A2 gene expression in HeLa cells (Mizuguchi et al. 2019a). It was reported that DUSP-1 specifically dephosphorylated and inactivated members of the MAPK family, such as JNK, p38 MAPK, and ERK, and suppressed the expression of the inflammatory genes (Lang et al. 2006; Owens and Keyse 2007; Shah et al. 2014). As MAPK signaling is involved in the expression of inflammatory genes, stimulation of H1R signaling that activates ERK could increase inflammatory gene expression (Newton and Holden 2007; Clark et al. 2008). Thus, up-regulation of DUSP-1 gene expression by (−)-maackiain could further suppress H1R signaling through the inhibition of ERK phosphorylation. Recently, corticosteroid nasal sprays, in addition to antihistamines, have been frequently used to relieve nasal symptoms. A recent randomized placebo-controlled trial also demonstrated that pre-seasonal prophylactic administration of intranasal corticosteroid (INCS) prevented the worsening of nasal symptoms during peak pollen season in patients with pollinosis (Makihara et al. 2012). INCS also downregulated H1R gene expression in the nasal mucosa of healthy participants with no history of allergic rhinitis (Kitamura et al. 2020). In HeLa cells, dexamethasone inhibited histamine-induced transcriptional activation of H1R through the inhibition of ERK phosphorylation in the signaling pathway involved in H1R gene transcription (Kitamura et al. 2020).

These data suggest the close relation between H1R signaling and GR signaling and pre-seasonal prophylactic administration of INCS could suppress both basal and pollen-induced up-regulation of H1R gene expression in the nasal mucosa of the patients with pollinosis, leading to prevention of the exacerbation of nasal symptoms during the peak pollen season.

Increasing evidence suggests the importance of the histamine-cytokine network in allergic inflammation, in which histamine influences the expression and action of several cytokines and some cytokines modulate the production and release of histamine (Igaz et al. 2001; Marone et al. 2003). Pretreatment with IL-4 primes the release of histamine, in response to FcεRI (Bischoff et al. 1999). Histamine, in turn, modulates the releases of IL-4 from T cells (Lagier et al. 1997) and induces the release of IL-5 (Krouwels et al. 1998). We showed that the level of H1R gene expression was positively correlated with those of Th2 cytokines including IL-4 and IL-5, whose expressions were suppressed by antihistamines (Mizuguchi et al. 2008; Kitamura et al. 2012). Th2 cytokine inhibitor suplatast suppressed H1R gene expression in allergy model rats (Shahriar et al. 2009). Treatment with IL-4 up-regulated H1R gene expression in HeLa cells through the activation of JAK3-STAT6 pathway (Horio et al. 2010). It was also reported that IL-13 caused the increase in H1R mRNA through the activation of STAT6 pathway in human airway smooth muscle cells (Manson et al. 2020).

4 Regulation of H1R Gene Transcription

4.1 Promoter Analysis of Human H1R Gene

Since bovine H1R cDNA has been cloned in 1991 by expression cloning in the classic *Xenopus oocyte* system (Yamashita et al. 1991), many H1R genes were cloned from various species including human, rat, guinea-pig in the 1990s. De Backer reported that 1.8 kb of the region upstream of the transcription start site has promoter activity in the human H1R gene, and several potential general transcription factor-binding sites were identified, including Sp1, AP-1, AP-2, and NF-κB (De Backer et al. 1998). It is known that both AP1 and NF-κB transcription factors are important in the regulation of several inflammatory genes. Swan reported the existence of three 5′-terminal exon splice variants (A/K, B/K, and F/K) in human H1R gene using 5′ rapid amplification of cDNA (RACE) analysis (Swan et al. 2006). Wang identified H1R gene from 14 vertebrates including human, chimpanzee, macaque, orangutan, dog, cow, horse, mouse, rat, opossum, chicken, *Xenopus tropicalis*, zebra fish, and fugu and showed that GR, GCNF, STAT5A, MIF-1, HSF2, and c-Myb regulatory transcription factor-binding sites were found in the promoter region of H1R (Wang et al. 2014). STAT5A is a member of the STAT family of transcription factors. It is activated by a wide variety of cytokines such as IL-2, IL-3, IL-7, GM-CSF, erythropoietin, thrombopoietin, and different growth hormones and is linked to cell specification, proliferation, differentiation, and survival (Hennighausen and Robinson 2008). c-Myb regulates the expression of cell cycle genes and is involved in cell proliferation and carcinogenesis (Haeri et al. 2013).

4.2 Transcriptional Regulation of H1R Gene in HeLa Cells

The 2.1-kb DNA fragment from the upstream regulatory region of the human H1R gene expressed histamine- or PMA-induced promoter activity in HeLa cells (Das et al. 2007). Promoter assay showed that there are two regions, designated region A [from −1,137 to −960; +1 indicates the putative transcription initiation site (De Backer et al. 1998)] and region B (from −65 to −44) are responsible for the promoter activity of H1R gene (Mizuguchi et al. 2012). Bioinformatic analysis of the H1R promoter revealed one putative NF-κB binding site and two putative AP-1 binding sites in region A. The luciferase assay showed that all three sites are necessary for promoter activity. Electrophoretic mobility shift assay (EMSA) and the supershift assay using anti-c-Fos and anti-c-Jun antibodies demonstrated that AP-1 (comprising c-Fos and c-Jun) was bound to two putative AP-1 sites. The promoter assay using a serial deletion mutant between the two AP-1 binding sites revealed that the deletion of 6 or 9 nucleotides enhanced H1R promoter activity, whereas that of 12 nucleotides resulted in complete loss of promoter activity

possibly due to steric hindrance. EMSA and the supershift assay using anti-Ets-1 antibody also showed that Ets-1, not NF-κB, was bound to the putative NF-κB binding site in region A. Bioinformatic analysis also showed two putative NF-κB binding sites and one putative AP-1 binding site in region B. However, none of these sites were found to be responsible for H1R promoter activity. DNA affinity chromatography using the minimum sequence oligonucleotide in region B was conducted and identified Ku86, Ku70, and PARP-1 as DNA binding proteins, in which Ku86 was responsible for DNA binding (Mizuguchi et al. 2012). Ku protein, a heterodimer composed of Ku86 and Ku70 is a regulatory subunit of the DNA-dependent protein kinase and is involved in the phosphorylation of several proteins, including Hsp90, p53, and Sp1, to regulate gene transcription (Lees-Miller et al. 1990; Gottlieb and Jackson 1993; Ludwig et al. 1997; Carter et al. 1998). Ku86 gene knockdown experiments showed that without stimulation with histamine significant H1R mRNA elevation was observed in the Ku86 knockdown cells compared with the control cells, suggesting that the Ku86 expression level affects the H1R mRNA expression level (Mizuguchi et al. 2012). Ku86/Ku70 was also known to be PARylated by PARP-1 and its PARylation reduces DNA binding activity (Li et al. 2004). Immunoprecipitation assay using anti-PARP-1 and anti-Ku86 antibodies showed that without stimulation with histamine, Ku86 was immunoprecipitated by anti-PARP-1 antibody, and PARP-1, in turn, was immunoprecipitated by anti-Ku86 antibody (Mizuguchi et al. 2012). On the other hand, the interaction between Ku86 and PARP-1 was reduced after stimulation with PMA. Immunoprecipitation study using anti-poly(ADP-ribose) antibody also showed that Ku86 but not Ku70 was PARylated after stimulation with PMA. These data suggest that after PARylation in response to stimulation with PMA, Ku86/Ku70 was dissociated from region B and caused the activation of H1R gene transcription (Mizuguchi et al. 2012). The luciferase assay using the reporter plasmid containing the promoter with wild type and/or mutant sequence in region A and region B demonstrated that both region A and region B are downstream regulatory elements of the PKCδ/ ERK/PARP-1 signaling pathway (Mizuguchi et al. 2012). Taken together with the findings described above, the mechanism is proposed for histamine-induced up-regulation of H1R gene expression in HeLa cells. The binding of histamine to H1R PKCδ is translocated to the Golgi body, where PKCδ was activated by phosphorylation at Tyr^{311}, then, PKCδ phosphorylates MEK. MEK, in turn, phosphorylates ERK and phosphorylated ERK, then, activates PARP-1. Activated PARP-1 PARylates core histones, induces relaxation of the chromatin structure, enhances binding of Ets-1 and AP-1 transcription factors to region A, and activates H1R gene transcription. Activated PARP-1 also PARylates and dissociates of Ku86 from region B, causing activating H1R gene transcription (Fig. 2).

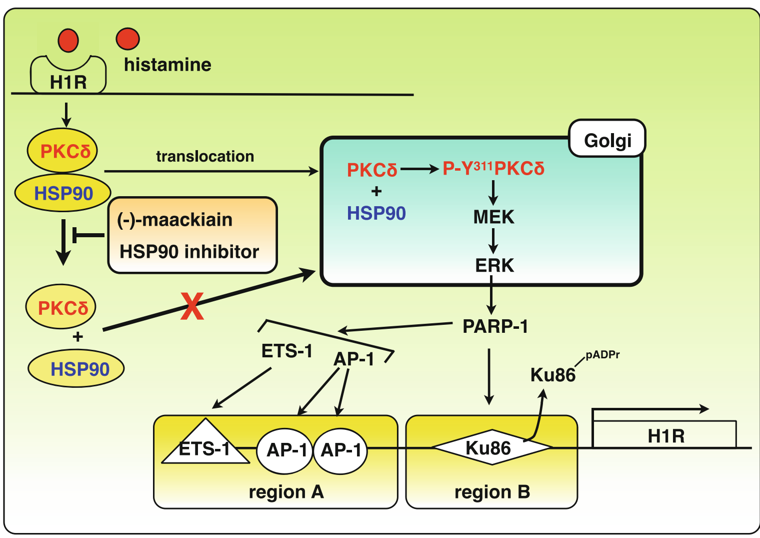

Fig. 2 Schematic presentation of the signaling pathway involved in histamine-induced up-regulation of H1R mRNA expression in HeLa cells. Binding of histamine to H1R translocates PKCδ to the Golgi body, where PKCδ was activated by phosphorylation at Tyr^{311}, then, phosphorylates MEK and ERK. Phosphorylated ERK then activates PARP-1. Activated PARP-1 poly (ADP)rybosilates (PARylates) histone and induces decondensation of the chromatin structure, enhances the binding of Ets-1 and AP-1 transcription factors to region A and activates H1R gene transcription. PARP-1 also PARylates Ku86 and induces dissociation of Ku86 from region B and activates H1R gene transcription. (−)-Maackiain and Hsp90 inhibitors disrupt the interaction of Hsp90 with PKCδ and inhibit translocation of PKCδ to Golgi body

4.3 Transcriptional Regulation of H1R Gene in U373 Cells

Time course studies of histamine-induced up-regulation of H1R mRNA in both HeLa and U373 cells suggest that the transcriptional regulation of the H1R gene expression signaling pathway in neuronal cells is different from that in non-neuronal cells. According to Swan's paper, the B/K splice variant is abundant in brain-derived tissue (Swan et al. 2006). RT-PCR study showed that the B/K splice variant reported by Swan et al. was expressed in U373 cells and the expression of the H/I/K splice variant, corresponding to the transcript in HeLa cells was very faint. Promoter analyses using 2.5-kb 5′-upstream of exon B and exon H showed that promoter region in response to histamine stimulation was found in the 5′-upstream of exon B but not in the 5′-upstream of exon H. These data suggest that the B/K splice variant might be the transcript expressed in U373 cells and responsible for the histamine/PMA-induced rapid and transient increase in H1R mRNA expression in U373 cells.

Human genomic sequencing research revealed that many genes contain multiple first exons including GR, neuronal nitric oxide synthase (NOS1), and UDP glucuronosyltransferase genes (ZhangT and Qiang 2004). Turner et al. also reported

tissue-specific differential usage of the first exons in the human GR gene and suggested that alternative first exons each under the control of specific transcription factors control the tissue-specific GR expression and are involved in the tissue-specific GR transcriptional response to stimulation (Turner et al. 2006). The NOS1 gene was also reported to have two different exons and its transcriptional control via these alternative first exons involved in downregulation of translation (Wang et al. 1999). These studies suggest that a repertoire of distinct usage of exon1 could influence posttranscriptional gene regulation such as processing, export, stability, and translation of mRNA and it also could regulate gene expression in response to a wide variety of signals. Our findings also suggest the complexity of the transcriptional regulation of H1R gene expression and the existence of different regulation between neuronal cells and non-neuronal cells.

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Part II
Clinical Pharmacology

Histamine Neuroimaging in Stress-Related Disorders

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Abstract Although histamine plays a major role in animal models of stress-related disorders, human neuroimaging data are sparse. Histamine H1 receptors in the human brain were first imaged by Professor Kazuhiko Yanai in 1992 by using ^{11}C-doxepin, a potent ligand of H1 receptors, and positron emission tomography (PET). Subsequent work revealed that H1 receptors are reduced in the prefrontal and anterior cingulate cortices in patients with major depressive disorders. A sex difference in H1 receptor binding in the brain has also been found, with women exhibiting more abundant H1 receptor binding than men. Moreover, female patients with anorexia nervosa show higher H1 receptor binding in the amygdala and lentiform nucleus. These studies also found an inverse correlation of depression scores with H1 receptor binding. Histamine is considered to play a major role in the pathophysiology of irritable bowel syndrome (IBS), a representative disorder of brain–gut interactions. Along these lines, hypnotic suggestion dramatically changes the

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waveforms of viscerosensory cerebral evoked potentials in response to electrical rectal stimulation and these changes are modified by the administration of H1 antagonist. The direction of the H1 antagonist-induced changes in the viscerosensory cerebral evoked potentials differs between IBS patients and healthy controls. Thus, histamine likely plays an important role in stress-related disorders. Further histamine brain imaging studies of humans are warranted.

Keywords Anorexia nervosa · Cerebral evoked potential · Depression · Doxepin · H1 receptor · Histamine · Irritable bowel syndrome · Positron emission tomography

Abbreviations

ACC	Anterior cingulate cortex
AN	Anorexia nervosa
BN	Bulimia nervosa
BNST	Bed nucleus of the stria terminalis
H1RA	Histamine H1 receptor antagonist
IBS	Irritable bowel syndrome
INAH	Interstitial nucleus of the anterior hypothalamus
mPFC	Medial prefrontal cortex
OFC	Orbitofrontal cortex
PET	Positron emission tomography
PFC	Prefrontal cortex

1 Introduction

Histamine is one of the best-known mediators released from mast cells (Theoharides et al. 2015). It is intimately involved in inflammation, allergic reactions, and the secretion from the parietal cells in the stomach (Black et al. 1972). Neurons containing abundant histamine are present in both the peripheral organs and central nervous system (Watanabe et al. 1983). The major histamine-containing neurons are localized to the posterior hypothalamic area (Watanabe et al. 1984), which has been identified as the tuberomammillary nucleus (Köhler et al. 1986; Haas and Reiner 1988). Histaminergic neurons project fibers to multiple brain regions, including the cerebral cortex, olfactory nuclei, nucleus tractus diagonalis, amygdala, bed nucleus of the stria terminalis, central gray matter of the midbrain and pons, auditory system, nucleus vestibularis medialis, nucleus originis nervi facialis, parabrachial nucleus, nucleus commissuralis, nucleus tractus solitarii, and dorsal raphe nucleus (Watanabe et al. 1984). Thus, histamine is believed to play important roles in the multifarious functions of the brain.

The brain histaminergic system is involved in various physiological processes, including wakefulness, the sleep–wake cycle, eating behavior, seizures, learning and memory, aggressive behavior, emotion, and locomotor activity (Hill 1990; Itowi et al. 1990; Sakata 1991; Schwartz et al. 1991; Tuomisto 1991; Wada et al. 1991; Yamatodani et al. 1992). However, most data have been derived from animal studies. Human neuroimaging data are thus essential. After a series of basic experiments (Yanai et al. 1988, 1989, 1990, 1991), human neuroimaging of histamine H1 receptors was achieved by Professor Kazuhiko Yanai in the early 1990s (Villemagne et al. 1991; Yanai et al. 1992a, b, c). With use of ^{11}C-doxepin as a potent ligand of H1 receptors, Yanai and colleagues used positron emission tomography (PET) to image H1 receptors in the human brain. The use of ^{11}C-doxepin-PET revealed increased H1 receptor binding in the epileptic focus in pediatric patients (Iinuma et al. 1993). This led researchers to wonder if brain histamine plays a major role in stress-related disorders. In this review, we summarize the present understanding of how histaminergic neurons participate in some representative stress-related disorders.

2 Histaminergic Function in Depression

Major depressive disorder is defined by the coexistence of five or more of the following symptoms during most of the day for more than 2 weeks: depressed mood; anhedonia (loss of interest or pleasure); unintentional weight loss/gain or decrease/increase in appetite; sleep disturbance (insomnia or hypersomnia); psychomotor agitation or retardation; tiredness, fatigue, or low energy; a sense of worthlessness or excessive, inappropriate, or delusional guilt; impaired ability to think, concentrate, or make decisions; and/or recurrent thoughts of death (not just fear of dying), suicidal ideation, or suicide attempts (American Psychiatric Association 2013). Critically, a depressed mood or anhedonia must be present. Some of these symptoms are concordant with behaviors regulated by brain histamine. Indeed, histaminergic neurotransmission is disturbed by acute or chronic stress in animals (Ito et al. 1999; Ito 2000).

In a study by Kano et al. (2004), ^{11}C-doxepin-PET imaging of the brain was performed in ten male patients with major depressive disorder and ten healthy men (Fig. 1). Binding potential values for ^{11}C-doxepin in the frontal and prefrontal cortices and cingulate gyrus were lower in the depressed patients than in the normal controls (Table 1). Conversely, none of the depressed patients showed higher ^{11}C-doxepin binding in the brain than the controls. Region of interest-based analysis also revealed that the binding potential for ^{11}C-doxepin in the frontal cortex and cingulate gyrus decreased in proportion to self-rated depressive scale scores (Kano et al. 2004).

Doxepin is not only a H1 antagonist, but also an antidepressant with sleep-inducing properties, together with mirtazapine (Wichniak et al. 2017). Although reports of dysfunctional histaminergic neurotransmission in depression are sparse,

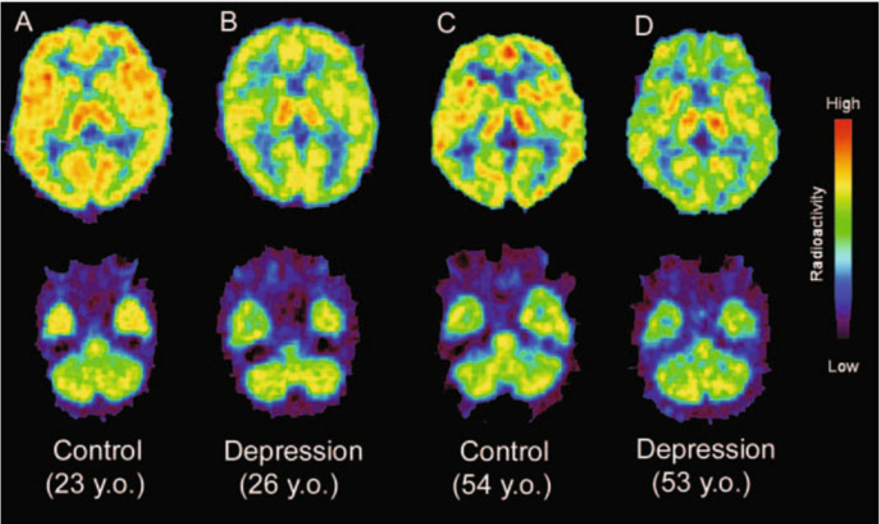

Fig. 1 ^{11}C-doxepin-PET Imaging in Patients with Depression. (**a**) a 23-year-old healthy control; (**b**) a 26-year-old patient with depression; (**c**) a 54-year-old healthy control; and (**d**) a 53-year-old patient with depression. The color bar indicates high vs. low radioactivity. The depressed patients had less H1 receptor binding potential in the brain than the healthy controls. Note that the younger individuals showed higher binding potential of H1 receptors than the older individuals. Reprinted from Kano et al. (2004) with permission

Table 1 Significant differences in binding potential between depressed patients and controls

			Talairach coordinates		
Area (and Brodman area)	Side	*Z*-score	*x*	*y*	*z*
Middle frontal gyrus (10)	L	3.69	−34	50	−6
Inferior frontal gyrus (44)	R	3.64	48	14	16
Inferior frontal gyrus (44)	L	3.45	−44	10	26
Anterior cingulate gyrus (32)	L	3.44	−10	10	40
Precentral gyrus (6)	R	3.40	38	−10	52
Anterior cingulate gyrus (32)	R	3.33	2	38	22
Middle frontal gyrus (10)	R	3.19	38	52	−4

Regional maxima were analyzed by graphical analysis and SPM99 ($p < 0.005$, uncorrected). Reprinted from Kano et al. (2004) with permission

histamine certainly plays an important role in stress-related pathologies, including depression, anxiety, and addiction, via glutamatergic neurons from the prefrontal cortex to the nucleus accumbens through presynaptic H3 receptors (Manz et al. 2021). Function of nucleus accumbens controls positive mood and motivation. There are connections between the prefrontal cortex and D1 receptor expressing neurons in the nucleus accumbens and excitatory postsynaptic current of the D1 receptor expressing neurons is inhibited by histamine via H3 receptors (Manz et al. 2021). Restraint stress attenuates effect of histamine on nucleus accumbens,

suggesting normal mood and motivation are at least in part controlled by endogenous histamine. Clozapine, as a H4 receptor agonist, is often used in augmentation therapy for intractable patients with major depressive disorder (Wright et al. 2013). Further studies of the dynamics of the changes in H1–4 receptors are warranted, along with those of the clinical exacerbation of depression and its improvement.

3 Histaminergic Function in Anorexia Nervosa

Anorexia nervosa is an eating disorder characterized by low weight, fear of gaining weight, and a strong desire to be thin, resulting in food restriction (American Psychiatric Association 2013). It is estimated to occur in 0.9–4.3% of women and 0.2–0.3% of men in Western countries. A greater number of women is liable to anorexia nervosa than men. Concerning to sexual/gender difference in behavioral disorders, sexual dimorphism in the brain is well known in the size of the interstitial nuclei of anterior hypothalamus (INAH). The size of INAH in men is larger than that in women (Garcia-Falgueras and Swaab 2008). INAH in homosexual men is only half size of the nucleus of heterosexual men. Previous animal studies revealed the sexual dimorphism in the histaminergic neurons in the brain (Fig. 2). The density in histamine H1 receptors is higher in female rats than in male rats (Ghi et al. 1999). The hypothalamic histamine release is higher in male rats than that in female rats (Ferretti et al. 1998). Histamine-depleted female mice induced by histidine decarboxylase knockout showed increased anxiety and impaired cognition (Acevedo et al.

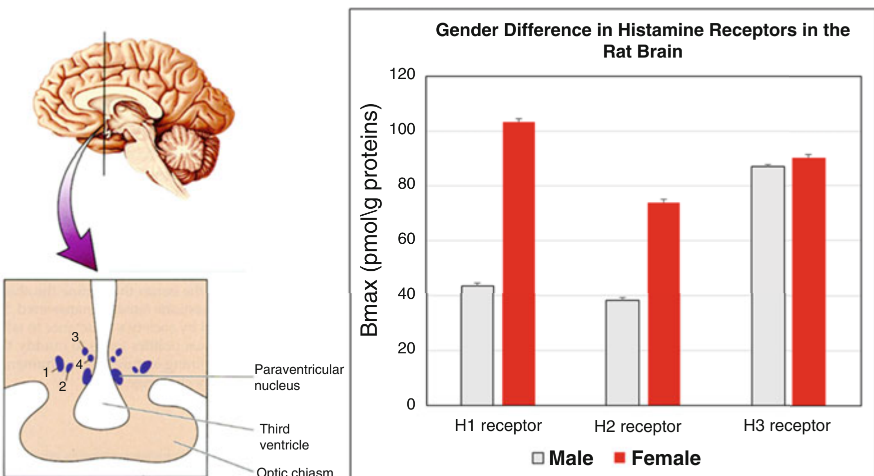

Fig. 2 Sexual Dimorphism in the Brain. Left: interstitial nuclei of anterior hypothalamus (INAH). The numbers 1–4 are names of subnuclei of the INAH. Right: Sexual/gender difference in H1–3 receptors in the rat cortex (Ghi et al. 1999). Data are expressed as the means ± SD of the receptor Bmax (pmol/g proteins)

2006). Therefore, comparison between men and women is indispensable to clarify the role of histaminergic neurons in the brain of anorexia nervosa.

In food-deprived activity stress, rats are forced to run on a wire wheel while food consumption is restricted (Endou et al. 2001). This condition mimics anorexia nervosa. The use of this animal model revealed that the H3 receptor density in the rat brain rapidly declines in the acute phase of stress but gradually returns to the control level in the chronic phase. On the other hand, H1 receptor levels slowly decrease and remain at a low level during the chronic phase. These results show a discrepancy between the levels of H1 and H3 receptors in the acute and chronic phases of stress. Actually, histamine content in the cortex, diencephalon, and hippocampus at 14th day in the rats with food-deprived stress is higher than that in non-stressed rats. Concerning forced swimming stress, histamine content in the cortex at 14th day in the rats with stress is higher than that in non-stressed rats (Endou et al. 2001). Brain histamine content gradually increases during the late phase of both food-deprived activity stress and forced swimming stress.

In the study by Yoshizawa et al. (2009), ^{11}C-doxepin-PET imaging of the brain was performed in 11 healthy men, 12 healthy women, and 12 women with anorexia nervosa (Table 2). The binding potential of ^{11}C-doxepin was higher in the female

Table 2 Characteristics of men, women, and patients with anorexia nervosa

	Control male subjects ($n = 11$)	Control female subjects ($n = 12$)	AN patients ($n = 12$)
Age (years)	21.8 ± 1.3	22.3 ± 2.5	23.4 ± 2.8
BMI	20.4 ± 1.3	20.3 ± 1.1	14.7 ± 1.7[a,b]
Duration of illness (years) (range)	0 ± 0 (0)	0 ± 0 (0)	5.2 ± 2.0 (3–9)
EAT-26 score	3 ± 3.7	1.9 ± 2.7	22.3 ± 13.4[c,d]
SDS score	37 ± 7.2	35 ± 6.2	50 ± 8.1[e,f]
STAI-state score	40 ± 9.5	38.8 ± 9.5	49.6 ± 11.5[g,h]
STAI-trait score	46.5 ± 8.9	41.1 ± 11.2	52.1 ± 11.5[i,j]
Estradiol (pg/mL)		6.7 ± 51.7	13.2 ± 7.3[k]

One-way analysis of variance for three group difference and post hoc analysis using the Tukey's test between two groups were performed. Values are expressed as mean ± SD. *AN* anorexia nervosa, *BMI* body mass index, *EAT-26* Eating Attitudes Test-26, *SDS* Self-Rating Depression Scale, *STAI* State-Trait Anxiety Inventory

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[a] $p < 0.001$ vs. control men
[b] $p < 0.001$ vs. control women
[c] $p < 0.001$ vs. control men
[d] $p < 0.001$ vs. control women
[e] $p < 0.001$ vs. control men
[f] $p < 0.001$ vs. control women
[g] ns vs. control men
[h] $p < 0.05$ vs. control women
[i] ns vs. control men
[j] $p < 0.05$ vs. control women
[k] $p < 0.01$ vs. control women

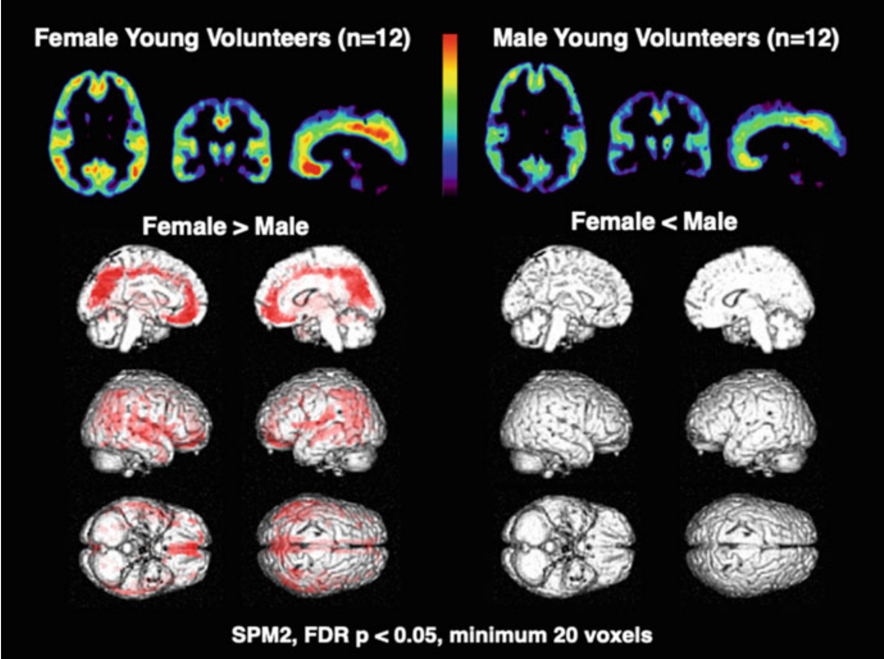


Fig. 3 Sexual/Gender Difference in H1 Receptors in Human Brain. ^{11}C-doxepin-PET imaging of healthy control women (left) and that of healthy control men (right). Women have higher ^{11}C-doxepin binding potential than men. Data were analyzed from the study by Yoshizawa et al. (2009)

participants than in the male participants in the amygdala, hippocampus, medial prefrontal cortex, orbitofrontal cortex, and temporal cortex (Figs. 3, 4, and 5). The women with anorexia nervosa showed higher binding potential of ^{11}C-doxepin in the amygdala and lentiform nucleus than the control female participants (Figs. 4 and 5). Moreover, in the patients with anorexia nervosa, the binding potential of ^{11}C-doxepin in the amygdala and thalamus was negatively correlated with Eating Attitude Test-26 scores. There was also a negative correlation between the binding potential of ^{11}C-doxepin in the amygdala, anterior cingulate cortex, and orbitofrontal cortex and the Self-rating Depression Scale or State-Trait Anxiety Inventory scores of the patients with anorexia nervosa (Yoshizawa et al. 2009). These findings support the hypothesis that women have higher H1 receptor density in the limbic system than men. Moreover, the findings of this ^{11}C-doxepin-PET study suggest that women with anorexia nervosa have higher expression of H1 receptor in the amygdala than healthy control women.

While the 12-month prevalence of anorexia nervosa among young women is about 0.4%, it is far less common among young men, with an estimated 10:1 female: male ratio (American Psychiatric Association 2013). Brain histamine contents

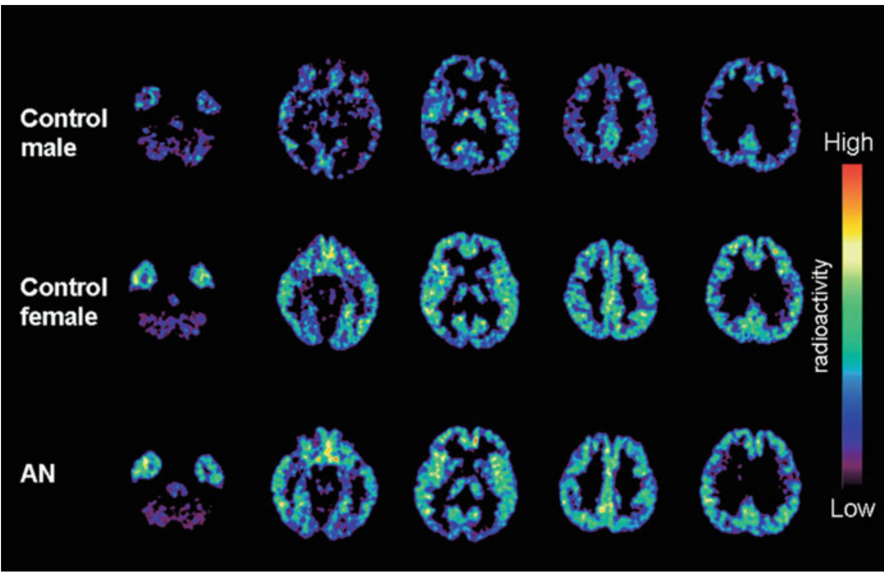
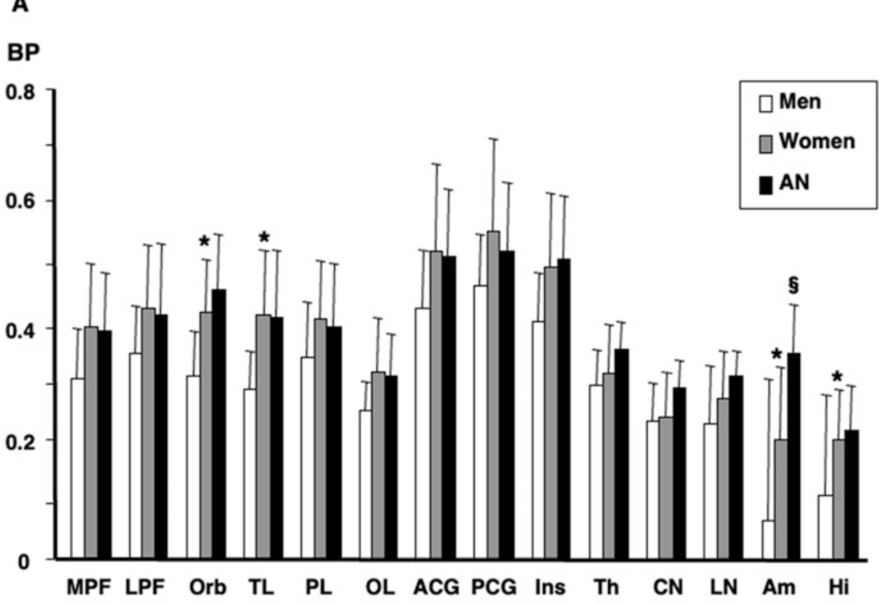


Fig. 4 ^{11}C-doxepin-PET Imaging in Patients with Anorexia Nervosa. Upper panel: a healthy control man; middle panel: a healthy control woman; lower panel: a female patient with anorexia nervosa. The color bar indicates high vs. low radioactivity. Generally, the healthy control women had higher H1 receptor binding potential in the brain than the healthy control men. The female patients with anorexia nervosa showed higher H1 receptor binding potential in the amygdala and lentiform nucleus than the healthy control women. *AN* anorexia nervosa. Reprinted from Yoshizawa et al. (2009) with permission

increase at food-deprived activity stress in rats (Endou et al. 2001). Conversely, clinical use of H1 receptor antagonist often causes obesity (Ratliff et al. 2010). Blockage of hypothalamic H1 receptors by antagonists, including second-generation antipsychotics, activates adenosine monophosphate-activated protein kinase, a well-known feeding regulator (He et al. 2013). Moreover, H1 receptor antagonism in the hypothalamus can reduce thermogenesis by inhibiting sympathetic outflow to the rostral raphe pallidus and rostral ventrolateral medulla in the brainstem, thereby decreasing brown adipose tissue thermogenesis. In addition, antagonism of hypothalamic H1 receptors may contribute to fat accumulation by decreasing lipolysis and increasing lipogenesis in white adipose tissue (He et al. 2013). Findings from the above-mentioned ^{11}C-doxepin-PET study (Yoshizawa et al. 2009) suggest that histaminergic neurotransmission is enhanced in anorexia nervosa. Notably, the negative correlation between H1 receptor binding potential and depressive score was replicated in studies of major depressive disorder (Kano et al. 2004) and anorexia nervosa (Yoshizawa et al. 2009). Pathophysiological changes in H1 receptors may depend on the brain region involved, such as the amygdala or anterior cingulate cortex.



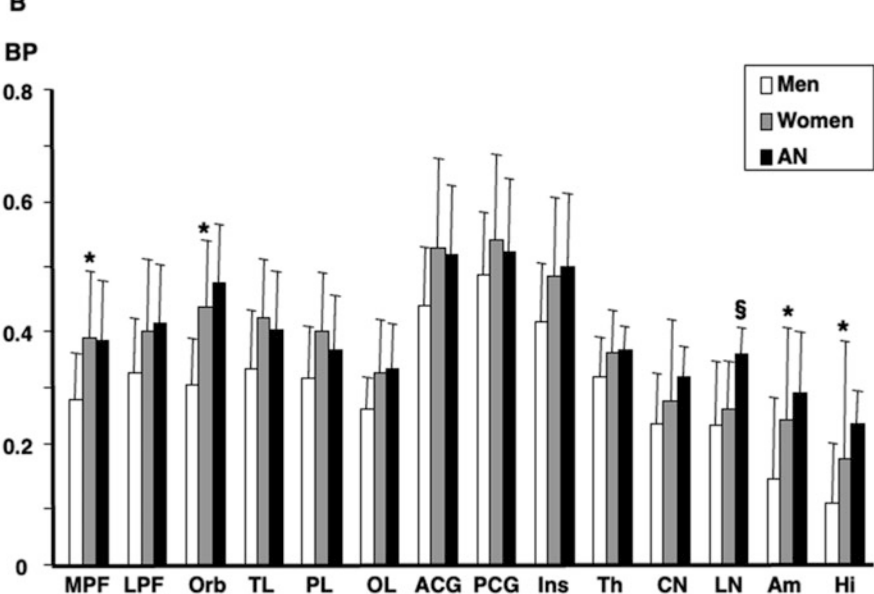


Fig. 5 Comparison of Binding Potential of ^{11}C-doxepin-PET Imaging in Healthy Men, Healthy Women, and Patients with Anorexia Nervosa. Region of interest-based comparisons of binding potential (BP) of ^{11}C-doxepin in the right (**a**) and left (**b**) cerebral hemisphere. One-way analysis of variance and post hoc test using the Tukey's test were performed. *Significantly higher vs. men ($p < 0.05$). §Significantly higher vs. control women ($p < 0.05$). *ACC* anterior cingulate cortex, *Am* amygdala, *AN* anorexia nervosa, *CN* caudate nucleus, *Hi* hippocampus, *Ins* insula, *LN* lentiform nucleus, *LPC* lateral prefrontal cortex, *MPC* medial prefrontal cortex, *OC* occipital cortex, *Orb*

4 Histaminergic Function in Brain–Gut Interactions and Irritable Bowel Syndrome

Irritable bowel syndrome (IBS) is a representative disorder of brain–gut interactions (Fukudo 2013). In Rome IV criteria, IBS is defined as chronic or recurrent abdominal pain at least once per week for more than 3 months with an onset at least 6 months before the diagnosis (Lacy et al. 2016). The abdominal pain must be characterized by at least two of the following: (1) related to defecation, (2) associated with a change in stool frequency, and (3) associated with a change in stool form (appearance). A role for histamine in the pathophysiology of IBS has long been proposed, with emphasis on mast cells in the mucosa of the lower gastrointestinal tract (Fukudo 2007). The proposed model involves a stress-induced or corticotropin-releasing hormone-induced abnormality in macrophages and degranulation of mast cells (Fig. 6). This concept was revised some years later but the essential concept remains the same (Fig. 7). Psychosocial stress with the involvement of altered gut microbiota increases mucosal permeability, which is usually aggravated by

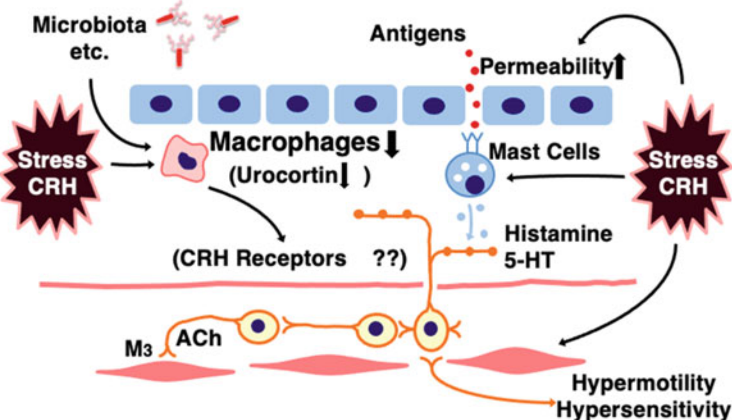


Fig. 6 Proposed Pathophysiology of Irritable Bowel Syndrome in Relation to Histamine. The horizontal cells are the gut epithelium. The pink horizontal line indicates the muscularis mucosa. Psychosocial stress and the release of corticotropin-releasing hormone (CRH) together with a certain composition of the gut microbiota increase gut mucosal permeability via degranulation of mast cells in IBS patients. Subepithelial scavenger macrophages, which contain urocortin, are malpositioned. Thus, low-grade inflammation occurs in the mucosal layer of the lower gastrointestinal tract. Histamine and protease released from mast cells stimulate and sensitize neurons in the enteric nervous system. Described as text in Fukudo (2007) and converted into a schema in this article

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Fig. 5 (continued) orbitofrontal cortex, *PC* parietal cortex, *PCC* posterior cingulate cortex, *ROI* region of interest, *TC* temporal cortex, *Th* thalamus. Reprinted from Yoshizawa et al. (2009) with permission

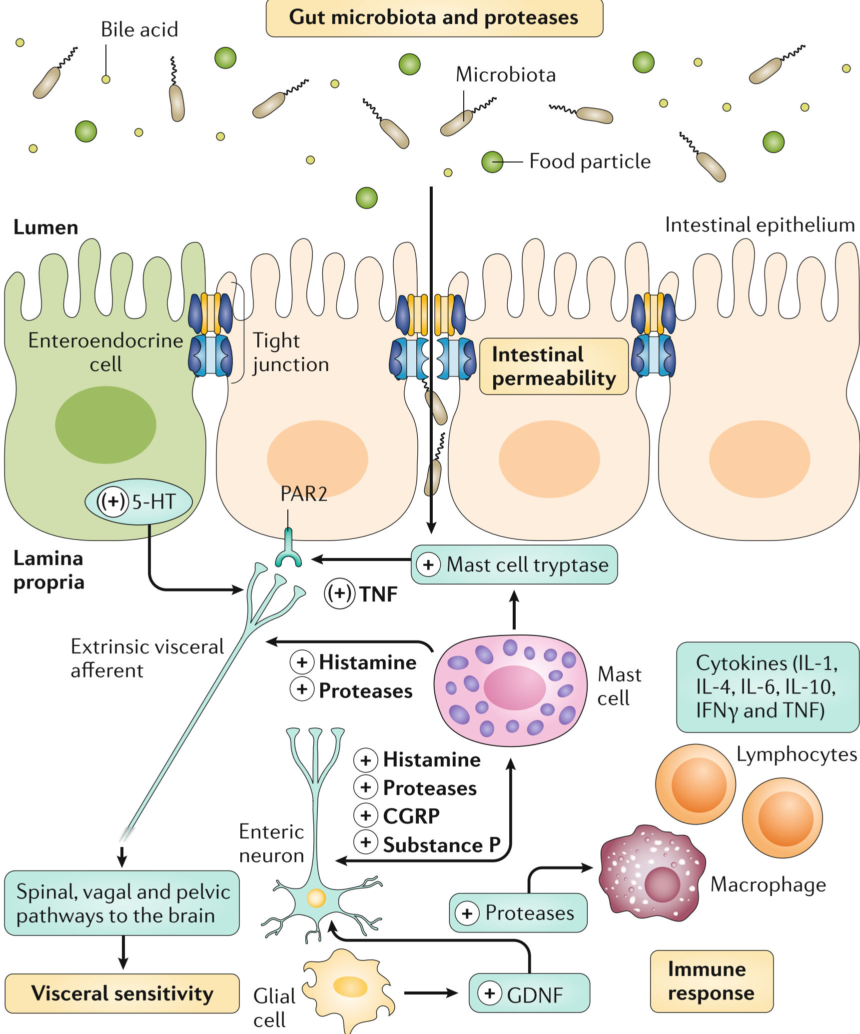

Fig. 7 Current Understanding of Irritable Bowel Syndrome. More detailed substances/mediators have been identified in IBS. Reprinted from Enck et al. (2016) with permission

degranulation of mast cells (Enck et al. 2016). Thus, low-grade inflammation is evoked and results in the sensitization of visceral afferent neurons, which influence brain function via gut-to-brain pathways. Studies of rectal biopsy specimens from patients indicated the involvement of H1 receptor-mediated sensitization of the transient reporter potential channel V1 in IBS (Wouters et al. 2016). Therefore, a pathophysiological mechanism involving histaminergic signaling in the periphery is certainly present in IBS.

Hypnotic suggestion has also been used to examine central histaminergic function in the brain–gut interaction in humans. Hypnosis is a verbal and behavioral procedure to alter the conscious state of the subject with deep relaxation. Suggestion is sequential words to change the direction of subject's mind. In a study by Watanabe et al. (2007), 12 healthy male individuals were studied on two separate days in a randomized order: one day involving intravenous administration of the histamine H1 receptor antagonist d-chlorpheniramine 100 μg/kg, and another day involving administration of the same volume of placebo saline. Using electroencephalography, cerebral evoked potentials to 100 rectal electrical stimuli were measured after the use of neutral, hyperalgesic, or analgesic hypnotic suggestion to modulate the visceral perception. The instructions for hypnotic induction were taken from the Harvard Group Scale of Hypnotic Susceptibility, Form A (HGSHS-A, Shor and Orne 1962). The analgesic suggestion reduced the amplitude of the deepest positive peak of the viscerosensory evoked potentials. In contrast, administration of histamine H1 antagonist diminished the analgesic suggestion-induced attenuation of the viscerosensory evoked potentials (Fig. 8). In another study (Watanabe et al. 2005), IBS patients showed abolished hypnotic suggestion-mediated modulation of evoked potentials in response to rectal electrical stimulation. In the IBS patients, the amplitude of the P1/N2 component was increased, and the latency of the P1 component was shorter during analgesic than neutral suggestions. During analgesic suggestion, the amplitude of the P1/N2 component was greater in the IBS group than in the healthy participants. Our own unpublished data indicate that the amplitude of the waveforms of the evoked potentials is reduced after the administration of H1 receptor antagonist. These data imply that IBS patients struggle to modulate visceral sensation in response to external verbal suggestion that triggers body changes and that the pain modulatory direction is the opposite of that of healthy individuals. Recently, we successfully imaged brain H1 receptors using ^{11}C-doxepin-PET in patients with IBS (Morishita et al. 2019, and unpublished data). The mechanism underlying the regulation of abnormal visceral pain by histaminergic neurons in IBS patients will undoubtedly be determined soon.

The above-mentioned phenomena suggest that the central pain modulatory system in the brain is activated by hypnotic suggestion and that brain histamine is a mediator of the hypnotic modulation of the visceral sensory pathway as well as of the control of the consciousness level. These findings indicate possible new treatments for controlling visceral perception. Indeed, ebastine, a second-generation antagonist of H1 receptors, reduces visceral hypersensitivity, symptoms, and abdominal pain in patients with IBS (Wouters et al. 2016). Along these lines, the clinical practice guidelines of the Japanese Society of Gastroenterology recommend antiallergics for treating IBS patients with a strong recommendation and level of evidence A (Fukudo et al. 2021).

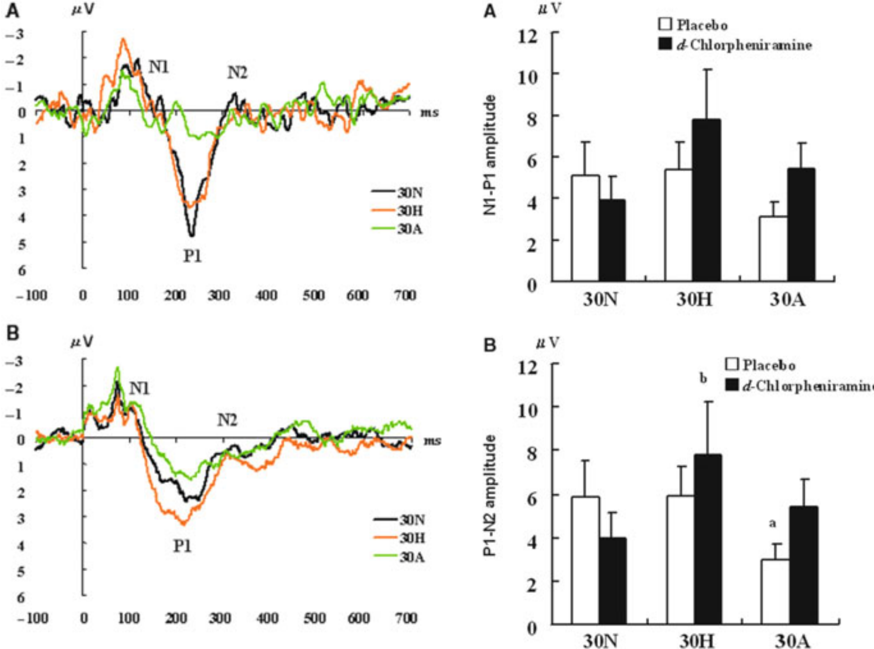

Fig. 8 Role of Histamine in the Modulation of Visceral Nociception. Left panel: viscerosensory evoked potentials at 1 day with (**a**) placebo or (**b**) d-chlorpheniramine as histamine H1 receptor antagonist. The rectal mucosa was electrically stimulated 100 times with 30 mA to evoke abdominal pain. A hypnotic state was induced with the Harvard Group Scale of Hypnotic Susceptibility, Form A. Black line (30N): 30-mA stimulation with neutral suggestion; orange line (30H): 30-mA stimulation with hyperalgesic suggestion; and green line (30A): 30-mA stimulation with analgesic suggestion. Note that distinct triphasic (N1-P1-N2) waves were seen with neutral and hyperalgesic suggestion but that the P1 wave was very shallow with analgesic suggestion on the placebo day. On the day with the H1 receptor antagonist, the waveform of the viscerosensory evoked potential was modified. Right panel: changes in the amplitude (μV) of the N1-P1 (A) and P1-N2 (B) waves. [a]Denotes a significant decrease in amplitude compared with neutral suggestion ($p = 0.043$). [b]Denotes a significant increase in amplitude compared with neutral suggestion ($p = 0.007$). Values are expressed as mean ± SE

5 Summary of the Data and Future Direction

The most noteworthy findings of the literature are summarized in Table 3. Future directions of histamine neuroimaging research would comprise clarification of H1–4 receptor dynamics in the corticostriatal pathway in major depressive disorder and of the sexual dimorphism of histaminergic neurons, including the interstitial nucleus of the anterior hypothalamus and the bed nucleus of the stria terminalis, neuroimaging of recovered anorexia nervosa and bulimia nervosa patients, and H1–4 receptor imaging in terms of brain–gut interactions in healthy controls and IBS patients. Further determinants of histaminergic neurotransmission should be explored, including genes and the environment, the gut microbiota, and, in particular, severe adverse

Table 3 Role of brain histamine in representative stress-related disorders

	Parameter	Findings	Future direction
Depression	^{11}C-doxepin-PET[a]	Depr. < Cont. ACC PFC	H1–4 receptor dynamics in the corticostriatal pathway
Sexual dimorphism	^{11}C-doxepin-PET[b]	Women > men mPFC OFC Temporal cortex Hippocampus Amygdala	Sexual dimorphism, including the INAH and BNST
Anorexia nervosa	^{11}C-doxepin-PET[b]	AN > Cont. Lentiform Amygdala	Recovered AN and BN
Brain–gut interaction	Evoked potentials[c]	H1RA diminishes attenuation of waveforms	H1–4 receptor imaging
IBS	Evoked potentials[d]	H1RA attenuates hypnosis-resistant deep waveforms	H1–4 receptor imaging[e]

ACC anterior cingulate cortex, *AN* anorexia nervosa, *BN* bulimia nervosa, *BNST* bed nucleus of the stria terminalis, *H1RA* histamine H1 receptor antagonist, *INAH* interstitial nucleus of the anterior hypothalamus, *mPFC* medial prefrontal cortex, *OFC* orbitofrontal cortex, *PET* positron emission tomography, *PFC* prefrontal cortex
[a]Kano et al. (2004) Eur J Neurosci
[b]Yoshizawa et al. (2009) Biol Psychiatry
[c]Watanabe et al. (2007) Neurogastroenterol Motil
[d]Watanabe et al. (2005) J Psychosom Res
[e]Morishita et al. (2019) Gastroenterology. See the references in detail

events such as abuse, life-threatening experience, and/or neglect in the early life (Rudzki et al. 2021).

6 Conclusion

Histamine likely plays an important role in stress-related disorders. Further studies of human histamine brain imaging are warranted.

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Histamine-4 Receptor: Emerging Target for the Treatment of Neurological Diseases

Ling Shan, Gerard J.M. Martens, and Dick F. Swaab

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Abstract A major challenge in the field of the biogenic amine histamine is the search for new-generation histamine receptor specific drugs. Daniel Bovet and Sir James Black received their Nobel Prizes for Medicine for their work on histamine-1 receptor (H_1R) and H_2R antagonists to treat allergies and gastrointestinal disorders. The first H_3R-targeting drug to reach the market was approved for the treatment of the neurological disorder narcolepsy in 2018. The antagonists for the most recently identified histamine receptor, H_4R, are currently under clinical evaluation for their potential therapeutic effects on inflammatory diseases such as atopic dermatitis and pruritus. In this chapter, we propose that H_4R antagonists are endowed with prominent anti-inflammatory and immune effects, including in the brain. To substantiate this proposition, we combine data from transcriptional analyses of postmortem human neurodegenerative disease brain samples, human genome-wide association studies (GWAS), and translational animal model studies. The results prompt us to suggest the potential involvement of the H_4R in various neurodegenerative diseases

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and how manipulating the H_4R may create new therapeutic opportunities in central nervous system diseases.

Keywords Histamine 4 receptor · Microglia · Parkinson's disease and amyotrophic lateral sclerosis

1 Introduction

Histamine and histamine receptors are known for their involvement in allergic and inflammatory reactions in the periphery (Dale and Laidlaw 1910). Dr. Daniel Bovet won the 1957 Nobel Prize for Physiology or Medicine for his discovery of a histamine 1 receptor (H1R) antagonist which has been widely used in allergy medication (Leurs et al. 2011; Tiligada and Ennis 2020). Sir James Black was awarded the Nobel Prize for Medicine in 1988 for the development of a histamine 2 receptor (H_2R) antagonist that has been used for the treatment of stomach ulcers (Leurs et al. 2011; Tiligada and Ennis 2020).

A neurotransmitter function for histamine became apparent from the pharmacological identification of the H_3R (Arrang et al. 1983) and the localization of the exclusive site of neuronal histamine production in the tuberomammillary nucleus (Watanabe et al. 1983; Panula et al. 1984). H_3R is an auto- and heteroreceptor that regulates multiple physiological functions including release of neurotransmission, not only the release of histamine but also of other biogenic amines (acetylcholine, dopamine, 5-hydroxytryptamine, and noradrenaline) (Passani and Blandina 2011; Panula et al. 2015). Its functions/features highlighted the therapeutic potential of H_3R ligands for the treatment of neurodegenerative disease and sleep disorders. The successful development of the H_3R antagonist/inverse agonist pitolisant for the treatment of excessive sleepiness in narcolepsy encouraged a search for clinical targets of the most recently discovered histamine receptor H_4R.

Different from the other histamine receptors, the H_4R has been discovered by a genomic approach and was described almost simultaneously by six laboratories (Nakamura et al. 2000; Oda et al. 2000; Liu et al. 2001; Zhu et al. 2001; Morse et al. 2001; Nguyen et al. 2001). H_4R antagonists show positive effects in several preclinical models of human diseases including asthma, dermatitis, collagen-induced arthritis, colitis, and histamine-induced pruritus (Thurmond et al. 2008; Mehta et al. 2020). Applications of these antagonists are, therefore, currently advancing into clinical trials such as for atopic dermatitis and pruritus (Thurmond et al. 2008, 2017; Leurs et al. 2011). However, there are also potential applications of H_4R for the treatment of central nervous system diseases. This review intends to give an overview of the emerging role for the H_4R in the brain and suggests therapeutic potentials of H_4R ligands for the treatment of neurodegenerative diseases.

1.1 Neurobiology of Histamine

Histaminergic neurons are located solely in the posterior hypothalamic tuberomammillary nucleus and innervate a large number of brain areas, such as the cerebral cortex, hippocampus, amygdala, thalamus, hypothalamus, and spinal cord (Panula and Nuutinen 2013; Shan et al. 2013). In the tuberomammillary nucleus, neuronal histamine is synthesized from histidine through the key enzyme histidine decarboxylase (HDC) (Haas et al. 2008). Brain histamine is mainly reduced to its inactive form tele-methylhistamine (t-MeHA) by histamine N-methyltransferase (HMT). The alternative inactivation, oxidation, also takes place in the brain by diamino-oxidase (DAO). Histamine exerts its functions via the four types of G protein-coupled histamine receptors ($H_{1\text{-}4}R$) (Panula et al. 2015). In general, these receptors are involved in basic physiological functions including sleep–wake cycle modulations, energy metabolism, endocrine homeostasis, sensory and motor functions, cognition, addiction, pain, learning, and memory (Haas et al. 2008). As several authoritative reviews have discussed the pharmacology, signal pathways, and physiological functions of histamine receptors ($H_{1\text{-}4}R$) (Passani and Blandina 2011; Panula et al. 2015; Yoshikawa et al. 2020), we here focus on the therapeutic potentials of H_3R and H_4R.

H_3R was first characterized as an auto-receptor regulating histamine synthesis in the tuberomammillary nucleus and histamine release from the cerebral cortex, striatum, and hippocampus in the rat (Arrang et al. 1985a, b, 1988b). In the human cerebral cortex, H_3R inhibits histamine release (Arrang et al. 1988a). Deficiency of the histamine-stimulated presynaptic auto-receptor in H_3R knockout mice demonstrated increased concentrations of histamine and tele-methylhistamine (t-MeHA) in the hypothalamus and thalamus (Takahashi et al. 2002). H_3R knockout mice showed increased anxiety and improvements in spatial learning and memory in the Barnes maze (Rizk et al. 2004) and pronounced sleep fragmentation (Takahashi et al. 2002; Gondard et al. 2013). It should be noted that H_3R knockout animals lack both auto and heteroreceptors; therefore, the phenotypical changes may also be related to other neurotransmitter systems. Several clinical trials have been conducted or are ongoing to explore the positive therapeutic effects of H_3R antagonists, including the treatment of Alzheimer's disease, schizophrenia, and narcolepsy. Unfortunately not much positive cognitive effects have been reported in humans. To date, one H_3R antagonist/inverse agonist, pitolisant, successfully reached both the US and the European markets for the treatment of narcolepsy type 1.

Postmortem human brain findings are an invaluable starting point for the development and validation of animal models for psychiatric disorders and neurological diseases. Pitolisant is a good example of how postmortem findings increase our insight and direct the search for validated translational animal models for preclinical tests. Narcolepsy type 1 is a rare and often disabling disorder that is characterized by excessive daytime sleepiness, short-onset rapid eye movement sleep, and cataplexy (sudden loss of muscle tone), accompanied by hypnagogic hallucinations, sleep paralysis, and disturbed nocturnal sleep (Bassetti et al. 2019). Although narcolepsy

has been recognized by clinicians nearly 150 years ago, a breakthrough was the finding in postmortem studies on narcoleptic patients with cataplexy that the number of hypocretin (orexin)-producing neurons has decreased by 90% (Peyron et al. 2000; Thannickal et al. 2000). Earlier, a dog model, later linked to a mutation in the hypocretin receptor 2 gene, was generally accepted as narcoleptic animal model, because it exhibited strong cataplexy and sleep impairment similar to the symptoms of patients with narcolepsy (Nishino et al. 1991). Based on the postmortem findings, a number of rodent narcolepsy models have been developed, including the hypocretin knockout mouse (reviewed in (Shan et al. 2015a)). Hypocretin peptides are produced exclusively by a cluster of neurons in the medial and lateral hypothalamus, which are adjacent to and functionally interact with histaminergic neurons (Shan et al. 2015b). Histaminergic neurons promote cortical activation and wakefulness (Anaclet et al. 2009; Yu et al. 2015). Increased histamine signaling might counteract a tendency toward hypersomnia and help to maintain consciousness during cataplexy by preventing full transitions into rapid eye movement sleep. In line with this hypothesis, H_3R antagonists elevate the cortical level of t-MeHA in hypocretin knockout mice and significantly improve the main symptoms of narcolepsy, including excessive daytime sleepiness and short rapid eye movement sleep latency at sleep onset (Lin et al. 2008; Guo et al. 2009). Two follow-up randomized, double-blind placebo-controlled trials confirmed the efficacy and safety of pitolisant in narcolepsy types 1 and 2 (Dauvilliers et al. 2013; Szakacs et al. 2017). In contrast with other treatments such as amphetamines and sodium oxybate (Bassetti et al. 2019), the use of pitolisant is not associated with addictive features in preclinical rodent and primate models (Uguen et al. 2013; Brabant et al. 2016; Huyts et al. 2019). Based on these experimental data, both the European Medicines Agency and the United States Food and Drug Administration approved pitolisant for the treatment of excessive sleepiness in narcolepsy (Kollb-Sielecka et al. 2017). We will therefore follow the same approach, from postmortem human brain findings to validated animal models, to search for potential therapeutic targets of H_4R manipulation.

1.2 Neurobiology of the H_4R

Based on the phenotypes of its knockout mice, H_4R modulates a series of distinct functions, including locomotor activity, anxiety, nociception, and feeding behavior, without an influence on working and recognition memory (Sanna et al. 2017). However, the phenotype of a genetically modified animal is not sufficient to determine the role of the receptor in different conditions. Compensatory mechanisms can be always present and contribute to the phenotype observed. Pharmacological modulation is therefore an important addition to understand the functional aspects of the receptor. Because of the controversy around the specificity of H_4R receptor antibodies (Beermann et al. 2012; Schneider and Seifert 2016), we here selectively focus on mRNA expression data and data from using specific H_4R ligands. Reverse

transcription polymerase chain reaction (RT-PCR) revealed H_4R mRNA expression in many human and rat brain regions, including the amygdala, cerebellum, corpus callosum, frontal cortex, and thalamus (Strakhova et al. 2009). In addition, H_4R-mRNA is expressed in a range of sensory signaling pathways, such as in the vestibular nucleus neurons in rats (Desmadryl et al. 2012), and in the thalamus and in the spinal cord of both rat and human (Strakhova et al. 2009). Of note, H_4R antagonists have a pronounced inhibitory effect on vestibular neuronal activity (Desmadryl et al. 2012; Petremann et al. 2020). The involvement of H_4R in both acute (Galeotti et al. 2013) and persistent inflammatory pain (Hsieh et al. 2010) made this receptor a promising target for neuropathic pain treatment (Sanna et al. 2015, 2020). However, the exact role of the H_4R in neuropathic pain is thus far unclear (reviewed in (Obara et al. 2020)).

H_4R mRNA is selectively expressed in the periphery in cells of hematopoietic origin including dendritic cells, mast cells, eosinophils, monocytes, basophils, and T cells known to be involved in inflammatory and immune responses (Nakamura et al. 2000; Oda et al. 2000; Liu et al. 2001; Zhu et al. 2001; Morse et al. 2001; Nguyen et al. 2001). Moreover, H_4R-mRNA is expressed in rat brain endothelial cells where this receptor is important for the regulation of blood-brain barrier (BBB) permeability (Karlstedt et al. 2013). A number of neurological diseases show an impairment of BBB integrity, causing the interaction of different neural and immune cells (Profaci et al. 2020). Systemic and chronic administration of the specific H_4R antagonist JNJ7777120 reduced ischemic neuronal damage and improved sensorimotor deficits in an ischemia model where the BBB was severely damaged. These changes were accompanied by a reduction in the number of ionized calcium-binding adaptor molecule-1 (Iba-1)-positive microglial cells in the rat brain (Dettori et al. 2018). Interestingly, microglia largely originate from the hematopoietic system (Eglitis and Mezey 1997; Bian et al. 2020). H_4R-mRNA has been identified in immortalized microglia N9 cells, in cortical slice cultures and explants (Ferreira et al. 2012), and rodent primary microglial cultures (Dong et al. 2014). Single-cell RNA-sequencing of human surgical-derived cortical microglia showed that H_1R-, H_2R-, and H_4R-mRNAs are present at comparable levels (Masuda et al. 2019). It should be noted that the H_4R has an nM affinity for histamine that is similar to that of H_3R and higher than of the H_1R and H_2R which are in the μM range (Panula et al. 2015). H_4R plays a key role in microglial activation in vivo (Ferreira et al. 2012; Dong et al. 2014; Zhang et al. 2020). The results regarding the effects of H_4R on microglia in in vitro and in vivo studies have been contradictory. Lipopolysaccharide (LPS)-induced pro-inflammatory cytokine interleukin-1β (IL-1β) release from both the N9 microglia cell line and hippocampal organotypic slice cultures were inhibited by the H_4R agonist 4-methylhistamine (Ferreira et al. 2012). In contrast, other reports have shown that H_4R activation has a pro-inflammatory effect. Activation of microglia was mediated by both the H_1R and the H_4R and led to the augmentation of the inflammatory cytokines interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) (Dong et al. 2014; Zhang et al. 2020). This observation is in agreement with in vivo data showing that *intracerebroventricular (ICV)* infusion of an H_4R agonist increased the total microglia cell number and the density of ramifications as

indicated by the marker ionized calcium-binding adaptor moleculei1 (Iba-1) in wild-type mouse brains (Frick et al. 2016). The same study also showed that an H_4R antagonist blocked the effects of histamine on microglial cells (Frick et al. 2016).

2 Neurological Diseases and H_4R

2.1 Parkinson's Disease (PD)

The second-most prevalent neurodegenerative disease is PD. The motor symptoms of PD are mainly caused by the loss of dopaminergic neurons in the substantia nigra (Hirsch et al. 1988; Damier et al. 1999). PD is characterized by the tremor in rest, bradykinesia, rigidity, flexed posture loss of postural reflexes, and freezing of gait (Sulzer 2007). A neuropathological hallmark of the disease is the presence of α-synuclein accumulation, Lewy bodies and Lewy neurites in multiple brain areas (Braak et al. 2003; Shan et al. 2012b). We found that in an unbiased RNA-sequencing of the postmortem human basal ganglia, H_4R was strongly upregulated in the substantia nigra of PD patients (Fang et al. 2020), which is in line with the results of our previous independent qPCR analyses which showed a 4.3–6.5-fold upregulation of H_4R-mRNA in the basal ganglia of PD patients (Shan et al. 2012a). Not only our previous postmortem observations, but also others found increased density of histaminergic fibers in the substantia nigra (Anichtchik et al. 2000) and enhanced histamine levels in both the substantia nigra and the putamen of PD patients (Rinne et al. 2002) and were confirmed by a targeted gene-set enrichment analysis using the ROAST test, a hypothesis-driven analysis (Fang et al. 2020). In addition, gene-set enrichment and pathway analyses of transcriptome-wide RNA-sequencing results showed that H_4R was in the top-four functional categories of "neuroactive ligand–receptor interaction" for PD treatment targets (Fig. 1) (Fang et al. 2020). Little information is available on the associations between H_4R and PD, except that the top three from the list, gastric inhibitory polypeptide receptor, adrenoceptor alpha 2B, and purinergic receptor P2X7, have been recognized as potential treatments of PD (Savola et al. 2003; Mittal et al. 2017; Athauda et al. 2017; Searles Nielsen et al. 2018) (ClinicalTrails.gov Id: NCT03918616).

The postmortem study does not allow us to conclude whether the H_4R is a potential target for treatment of the disease. A translational PD model, the rotenone-lesioned rat model, exhibited a strong degeneration of dopaminergic neurons in the substantia nigra, PD neuropathology and α-synuclein accumulation (Betarbet et al. 2000; Cicchetti et al. 2009), as well as strongly increased H_4R-mRNA levels in the substantia nigra (Zhou et al. 2019). Intracerebroventricular administration of the H_4R antagonist JNJ7777120 ameliorated the degeneration of dopaminergic neurons in the substantia nigra of this PD rat model. The protective effects were also supported by the reduction of α-synuclein accumulation in both substantia nigra and striatum (Zhou et al. 2019; Fang et al. 2020). Thus, blocking the H_4R plays a protective role in rotenone-lesioned PD rats. JNJ7777120 acts through the inhibition of the pro-inflammatory phenotype of microglia (Zhou et al. 2019).

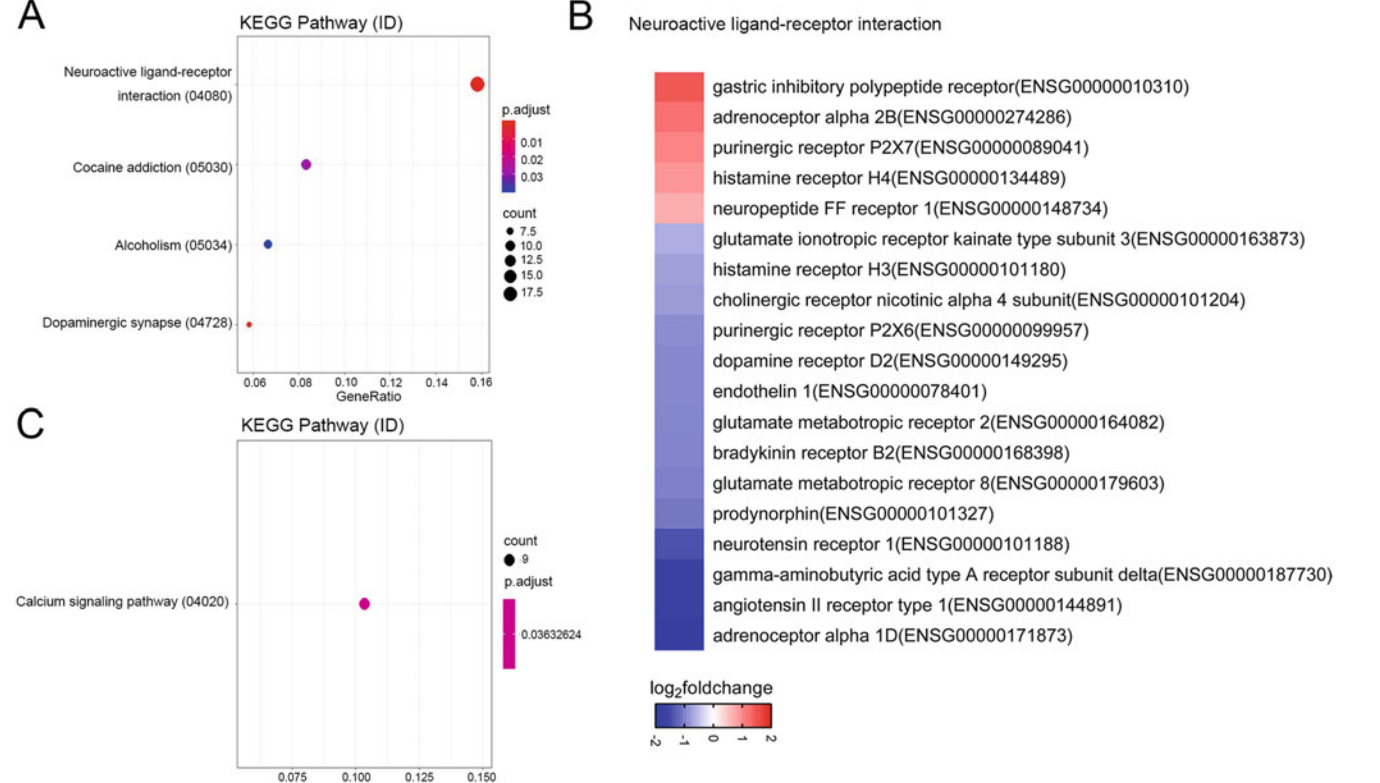

Fig. 1 Biological pathways enriched in both substantia nigra and putamen from PD patients relative to controls. Enriched Kyoto Encyclopedia of Genes and Genomes (KEGG) biological pathways mapped from 39 top upregulated and 41 top downregulated transcripts in the substantia nigra (**a**) and in the putamen (**c**) of PD patients relative to controls. (**b**) Heatmap showing the $\log_2$ fold expression changes of the genes differentially expressed in PD substantia nigra and being in the top-enriched KEGG pathway "Neuroactive ligand–receptor interaction" (Fig. 1 (Fang et al. 2020) with permission)

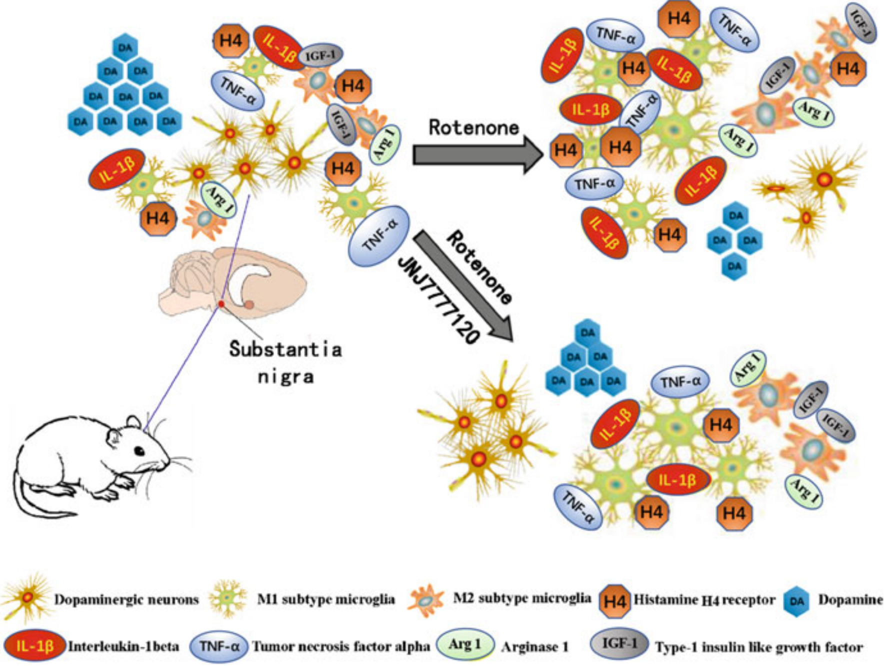

Fig. 2 Schematic of the effects of H_4R antagonist JNJ7777120 on the rotenone-lesioned PD rat model. JNJ prevents dopaminergic neuron degeneration and dopamine level diminishment in the rotenone-lesioned PD rat model by reducing the pro-inflammatory phenotype of microglia (marked by IL-1β and TNF-α) but not the neuroprotective phenotype of microglia (marked by Arg1 and IGF-1) (Fig. 9 (Zhou et al. 2019) with modifications and permission)

Reductions in the number of Iba-1-positive microglia in the substantia nigra, as well as the size of microglia in the striatum, were observed in the JNJ7777120-treated rotenone-induced PD rat model (Zhou et al. 2019; Fang et al. 2020). In addition, the H_4R antagonist inhibited the pro-inflammation phenotype of microglia (marked by reduced expression of IL-1β and TNF-α at both mRNA and protein levels), while not affecting the neuroprotective phenotype of microglia (marked by arginase-1 (Arg1) and insulin-like growth factor-1 (IGF-1)) (Zhou et al. 2019) (Fig. 2).

On the other hand, not only the dopamine level, but also alterations of γ-aminobutyric acid (GABA)ergic and cholinergic tones, and a reduced serotonin level have been associated with motor symptoms of PD (Qamhawi et al. 2015; Lozovaya et al. 2018). There was no information regarding the effect of blocking the histamine receptor H_4R on the levels of neurotransmitters in the basal ganglia. We showed for the first time that the H_4R antagonist rescued dopamine levels and recovered levels of serotonin and its main metabolite 5-hydroxyindoleactic acid in

basal ganglia of the PD rat model without influencing glutamine and acetylcholine levels (Fang et al. 2020).

Therefore, the results of both the postmortem human brain (Shan et al. 2012a) and the preclinical animal model studies (Zhou et al. 2019; Fang et al. 2020) indicated that blocking the H_4R might provide a promising therapeutic target for PD treatment.

2.2 Amyotrophic Lateral Sclerosis (ALS)

ALS is a neurodegenerative disease with fast disease progression and characterized by motor neuron loss, leading to respiratory insufficiency and death after 3–5 years (Hardiman et al. 2017). Multi-omics-based data have indicated that the histaminergic system is dysregulated in sporadic ALS. In particular, genome-wide analysis has shown multiple genomic variations in H_4R single nucleotide polymorphisms in non-familial ALS patients (Apolloni et al. 2019). H_4R-mRNA is dysregulated together with other histaminergic gene transcripts in the two subgroups of sporadic ALS patients (sALS1 and sALS2) (Apolloni et al. 2017, 2019) that were based on transcriptome analysis and separated by unsupervised hierarchical clustering (Aronica et al. 2015). The cortical mRNA expression studies showed that H_4R was downregulated in sALS1 and was upregulated in sALS2 compared to healthy individuals (Apolloni et al. 2017). This sALS2 finding is in line with the observed approximately 1.5-fold increase of H_4R protein level in the cortex of an ALS mouse model, the pre-symptomatic phase of the copper-zinc superoxide dismutase 1 SOD1-G93A mutant (Volonté et al. 2019).

Increased activation and an increase in the number of microglia are a hallmark of ALS pathology and may contribute to motor neuron degeneration (Boillée et al. 2006; Chiot et al. 2020; Spencer et al. 2020). In line with this pathology, inhibiting the inflammatory response of microglia in ALS animal models robustly slowed the course of the disease (Boillée et al. 2006; Chiot et al. 2020). Histamine induced a reduction of the microglial inflammatory markers nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) and nicotinamide adenine dinucleotide phosphate oxidase 2 (NOX2) and an increase in Arg1 and P2Y12 receptor in primary cultures of microglia from SOD1-G93A mice. The H_4R antagonist JNJ7777120 brought the microglial NF-kB levels back to control levels (Apolloni et al. 2017). Furthermore, this anti-inflammatory effect was mainly elicited by the H_4R, and not the H_3R, because the H_4R antagonist JNJ7777120, but not the H_3R antagonist thioperamide, significantly blocked the NOX2 and Arg1 effects in the microglia of the ALS mouse model (Apolloni et al. 2017). Together, these results indicate that blocking the H_4R might be a promising approach to reduce the ALS-specific activation of microglia, a conclusion that warrants future tests in the preclinical animal models.

3 Concluding Remarks and Future Perspectives

H_4R is involved in the regulation of BBB permeability and microglial activity, which are both dysfunctioning in neurodegenerative diseases. Data from transcriptional analyses and human GWAS indicate that H_4R is linked to neurodegenerative diseases. Specifically, H_4R-mRNA is highly upregulated in the basal ganglia of PD patients (Shan et al. 2012a; Fang et al. 2020) and H_4R single nucleotide polymorphisms are strongly associated with sporadic ALS patients (Apolloni et al. 2019). Transcriptomic analysis of subgroups of sporadic ALS patients (sALS1 and sALS2) showed that H_4R-mRNA is downregulated in sALS1 and upregulated in sALS2 (Volonté et al. 2019).

Translational animal models have been used to study H_4R function and preclinical efficacy in the treatment of PD and ALS. An H_4R antagonist alleviated dopaminergic neuron degeneration and α-synuclein neuropathology in both substantia nigra and striatum of a PD animal model. These protective effects were largely elicited by inhibiting the pro-inflammatory phenotype of microglia and did not affect the neuroprotective phenotype of microglia. Furthermore, the same H_4R antagonist significantly blocked inflammatory markers in microglia of an ALS mouse model. Current knowledge of the potential therapeutic effects of H_4R ligands in brain is still in an early explorative phase. Nevertheless, analysis of the current literature and our own experimental data as well as the emergence of disease-associated microglia showing unique transcriptional and functional signatures in PD and ALS (Deczkowska et al. 2018) all point out that the H_4R may represent a promising target for the treatment of central nervous system diseases.

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Imaging Histamine H3 Receptors with Positron Emission Tomography

Pablo Martín Rusjan and Bernard Le Foll

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Abstract Positron emission tomography (PET) provides a unique tool to study the biochemistry of the human brain in vivo. By using PET probes that are binding

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selectively to certain receptor subtypes, b*rain* PET allows the quantification of receptor levels in various brain areas of human subjects. This approach has the potential to reveal abnormal receptor expressions that may contribute to the physiopathology of some psychiatric and neurological disorders. This approach also has the potential to assist in the drug development process by determining receptor occupancy in vivo allowing selection of proper drug dosage to produce therapeutic effects. Several PET tracers have been developed for histamine H3 receptors (H3R). However, despite the potential of PET to elucidate the role of H3R in vivo, only limited work has been conducted so far. This article reviews the work that has been done in this area. Notably, we will cover the limitations of the first-generation PET radioligand for H3R and present the advantages of novel radioligands that promise an explosion of clinical PET research on the role of H3R in vivo.

Keywords [11C]GSK189254 · [11C]MK8278 · [11C]TASP457 · [18F]FMH3 · Histamine H3 receptors · Human brain · Pitolisant · Positron emission tomography · Receptor occupancy study

1 H3 Receptor Quantification Using PET

1.1 Positron Emission Tomography

Positron emission tomography (PET) has contributed significantly to our ability to study neurotransmission in vivo in humans. PET uses a radiotracer (i.e., a molecule that has been labeled with a radioactive isotope) to produce a high-resolution image of the concentration of some protein in the body, or specifically for the interest of this review, in the brain. PET requires significant research infrastructure (e.g., cyclotron to generate the radioactive tracers, state-of-the-art chemistry laboratory, PET camera, expertise on PET signal quantification, expertise on PET methodology, pharmacology, etc.). Therefore, there are limited centers that have been able to implement PET approaches successfully. By applying some principles that are adapted from in vitro receptor binding pharmacology to an in vivo situation, PET provides a unique way to study the biochemistry of the human brain. Simply put, the underlying assumption is that a drug that has high affinity for a receptor of interest will bind to this receptor. In order to be used, each target protein to be studied requires the development of a specific radioligand that has high affinity/selectivity for the target protein. There are radiotracers available for various targets including neurotransmitter precursors, receptors, transporters, and metabolizing enzymes, allowing the study of various aspects of a given neurotransmitter system. After administration of the radiotracer to a human subject, it is then possible (with the use of the PET camera) to measure the evolution over time of the radioactive signal originating from the radiotracer in various brain areas and at various time points. Interpretation of the PET outcome measures is complex and depends on the context of the study and the radiotracer used. Various methods of quantifications have been

developed that are beyond the scope of the present review (see Ref. (Carson 2005) for an introduction). Commonly used outcome measures in PET studies are "distribution volume" and "binding potential," which are used in various ways as indicators of receptor density, or receptor occupancy (notably for studies evaluating the occupancy of a target receptor by an unlabeled drug).

1.2 Radioligand Properties for PET Imaging

The pharmacokinetic properties of the radioligand will affect the ability to quantify the levels of the protein of interest using PET approach. Typically, the best PET radiotracers for brain imaging quantification are reversible (able to get off the receptors), present a high affinity and selectivity for the target protein versus off-target sites, have the ability to penetrate the blood–brain barrier following intravenous injection, have low non-specific binding and lack of brain-penetrant radiometabolites (Pike 2016). Typically, PET experiments should be performed at tracer dose so the system to be studied is not perturbed. In practice, tracer dose means that around 5% or less of the receptor is occupied by the radiotracer. Going above 5–10% of receptor occupancy by the radiotracer could lead to a significant bias in the measurement of the protein (Innis et al. 2007). It should be noted that only a small proportion of ligand injected in the subjects is radioactive. The proportion of radioactive ligand to total ligand injected is referred to as the "molar activity" (the ratio between activity and mass of compound) at the time of injection. The process of synthesis and radiolabeling of the ligand imposes a constraint to the maximum molar activity achievable. Therefore, at a given activity injected, the molar activity of the radioligand at the time of injection determines the mass of ligand injected. The choice of radionuclides is sometimes dictated by pharmacology requirements (i.e., due to the structure of the molecule, only certain radionuclides can be used to generate radiotracers) or sometimes for practical reason due to the radioactive half-life. Most of the studies are using ^{11}C or ^{18}F as radionuclides. The intensity of the PET signal decays when the radioactivity decays and the maximum radioactive injected is limited, among other reasons (e.g., toxicological effects), by the maximum radiation dose recommended and the maximum mass to stay at tracer dose (i.e., do not occupy a significant amount of target receptors). So typically, between 10 and 20 mCi of ^{11}C ($T_{1/2} = 20.4$ min) and between 5 and 10 mCi of ^{18}F ($T_{1/2} = 109.8$ min) are used and required for human PET scans to have a useful signal for quantification.

1.3 Principles of PET Signal Quantification

In the typical PET experiment, the radioligand is injected as a quick bolus. The kinetic modeling of PET radioligands requires monitoring the temporal evolution of radioactivity (time-activity curve (TAC)) in a target region in the brain and in the arterial

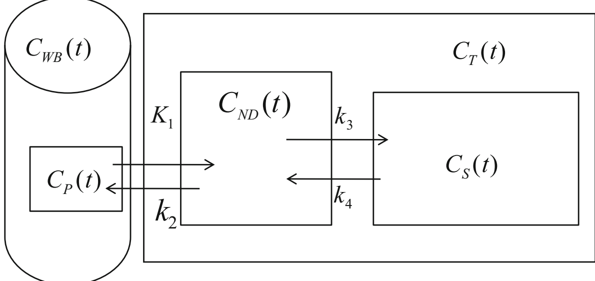

Fig. 1 The two tissue-compartment model (2TCM). The concentration of radioligand free in plasma [C_P(t)] specifically bound in tissue [C_S(t)] or free or non-specifically bound in tissue [C_{ND}(t)] can be characterized by a compartment. The regional time-activity curves [$C_T(t)$] of reversible radioligands acquired with PET usually are described approximately well with the differential equation of this simple model assuming first-order kinetic with rate constant [K_1,k_2,k_3 and k_4] for the exchange of radioligand between compartments. The model also can account for the radioligand in blood [C_{WB}(t)] in the capillaries, cerebral arterioles, and venules

blood. The concentration of radioactivity due to unmetabolized ligand (parent compound) in arterial plasma must also be determined to generate an "input function." The methodological challenges determining the input function are often an important source of variability of the outcome measurement (Collste et al. 2016). In brief, arterial blood samples are extracted along the scan automatically and/or manually. Some of the samples are centrifuged to separate platelet-poor plasma (PPP). The radioactivity in aliquots of PPP is studied with an HPLC (or similar) to determine the fraction arising from the unmetabolized radioligand. The processing of the samples is a race against time as the radioactivity of the samples decays along the measurement. After 1 h due to both drug clearance from plasma and radioactive decay, the activity in the samples is not very different to the background radiation and the measurements are susceptible to large errors. Some radioligands present stickiness to the syringes and other materials for the processing. Automatic blood sample systems are prone to clog and suffer from dispersion. The post processing for the creation of the input function involves interpolation but also sometimes dangerous extrapolations of the samples. Arterial samples are also used to determine protein binding (or free fraction in plasma). Usually, the free fraction measurement presents a high error and, the inclusion in the analysis, increases the between-subject variability rather than decreases it.

The binding of the radiotracers to various elements of the body can be represented as compartmental models and can be quantified by kinetic modeling. In those models, the various compartments represent various entities with certain specificity for binding (e.g., specific binding, non-specific binding, unbound radioligand, etc.). Kinetic modeling can generate some quantification parameters from the signal obtained at different time points (TACs). The noise in the data rarely allows for models with more than four variables ("rate constants"). The two tissue-compartment model (2TCM, Fig. 1) has one compartment that represents the specific binding and one compartment that represents non-displaceable radiotracer

concentration (free or non-specifically bound radioligand). The radiotracer is transferred between compartments and plasma following first-order kinetics characterized by rate constants: the rate constants K_1 and k_2 describe the influx and efflux rates, respectively, for radioligand diffusion through the blood–brain barrier (Ginovart et al. 2001), and the rate constants k_3 and k_4 describe the transfer from the first to second compartment and vice versa. The contribution of vascular fraction in brain tissue (V_B) to the regional brain TAC (i.e., radioactivity in the capillaries, cerebral arterioles and venules) is estimated with an average value (ca. 5%). Usually off-target binding (displaceable binding to other protein than that for which the radioligand was developed to bind) and brain-penetrant metabolites are assumed negligible. On some occasions, the equilibrium between free, non-specifically, and specifically bound radiotracer is reached so quickly that the TAC does not distinguish these compartments independently, and the radioligand is then modeled with a single compartment (1TCM). While one of the rate constants is proportional to the concentration of the protein of interest, the values of the rate constants are correlated and present low identifiability. The typical outcome of the compartment models is the total distribution volume (V_T) which combines the rate constants in such a way that the correlations are cancelled out. The V_T for the 1TCM can be expressed as function of the rate constants as $V_T = \frac{K_1}{k_2}$, and for the 2TCM $V_T = V_{ND}\left(1 + \frac{k_3}{k_4}\right)$with $V_{ND} = \frac{K_1}{k_2}$. The V_T is indeed an index of the concentration of target protein, but it also contains a contribution of the free and non-specifically bound radiotracer in tissue (non-displaceable distribution volume (V_{ND})), and it is affected by changes in the protein binding.

For some radioligand, there are areas in the brain devoid of the target protein. When V_{ND} of those regions is similar to the region of interest, those areas can be used as reference tissue for the quantification. A reference tissue overcomes the need for an input function, simplifies the PET experiment considerably, and improves reproducibility. When a reference region is available, the binding potential with respect to the non-displaceable compartment (BP_{ND}) – an outcome parameter independent of V_{ND} – can be defined as $BP_{ND} = \frac{V_T - V_{ND}}{V_{ND}}$. While it is rare to find a region without a particular protein in the brain for practical purposes, for some neuroreceptors, the cerebellar and/or the occipital cortex provide an acceptable reference region. The radioligands need to have moderate lipophilicity to cross the brain-blood barrier and the white matter is richer in lipophilic molecules as sources of non-specific binding components than the gray matter. Despite potentially having a different V_{ND}, the white matter has shown to be an acceptable reference region for some radioligands (e.g., SV2A radioligands (Rossano et al. 2020)). Similarly, other normalizations that remove variability arising from the input function (and/or free fraction) and are expected (or can be shown) to be unaltered in a particular experimental design have been useful in some situations (e.g., (Bloomfield et al. 2016)) but often leaving some degree of uncertainty in the interpretation of the results (e.g., (Narendran and Frankle 2016)).

1.4 Use of PET to Study Occupancy of Receptors by Drugs in Humans

PET is a valuable tool for drug development. PET can help study tissue exposure, target engagement (or occupancy), and pharmacologic activity of the drug (Gunn and Rabiner 2017). Using a radioligand that binds to the same target of the drug of interest, a PET study can be performed at baseline (or after placebo administration) and can be performed at a given time after the drug dose. The comparison of the radioligand specific binding under those two conditions will allow the receptor occupancy by the drug to be calculated (at that specific dose and time). In addition, if a drug can be radiolabeled, it is possible to use PET to provide in vivo brain concentration of a drug at different time points (and in relation to the plasma pharmacokinetics of the drug).

When there is no brain reference region available (as is the case for H3R PET radiotracers), the brain occupancy of the target (*Occ*) can be calculated as the slope of the linear regression given by the Lassen plot (Lassen et al. 1995; Cunningham et al. 2010):

$$V_{\mathrm{T}}^{\mathrm{placebo}} - V_{\mathrm{T}}^{\mathrm{blocked}} = \mathrm{Occ}\left(V_{\mathrm{T}}^{\mathrm{placebo}} - V_{\mathrm{ND}}\right) \tag{1}$$

where $V_{\mathrm{T}}^{\mathrm{placebo}}$ and V_{T}^{blocked} are vectors with the V_{T} values of several brain regions sharing the same Occ and V_{ND}. This linear regression will work better when the spread of V_{T} values (i.e., concentration of protein of interest) across brain regions is broader, which is the case for H3R.

The occupancies provided by PET and the plasma concentration of the drug (pConc) are related by a Hill-type function (Gunn and Rabiner 2017):

$$\mathrm{Occ} = \frac{p\mathrm{Conc}^{h}\mathrm{Occ}_{\max}}{\mathrm{EC}_{50}{}^{h} + p\mathrm{Conc}^{h}} \tag{2}$$

where $\mathrm{Occ}_{\max}$ is the maximum occupancy achievable, EC_{50} is the concentration of drug in plasma that produces the half of the $\mathrm{Occ}_{\max}$, and h is a coefficient (usually $h = 1$ for classical antagonist drug binding (Andree et al. 2000)).

2 Presentation of H3 PET Studies According to Radioligands Used

Histamine has four main receptor subtypes, H1, H2, H3, and H4 (Arrang et al. 1983). The H3 receptor (H3R) was first characterized in 1983 as an autoreceptor that regulates extracellular histamine levels (Arrang et al. 1983), but is also a heteroreceptor regulating the function/release of other neurotransmitters. The brain

areas that have the highest H3R expression are the basal ganglia, hippocampus, and neocortex (Martinez-Mir et al. 1990). The concentration of H3R is highly variable across brain areas and there seems to be no brain area that does not express H3, preventing the use of a reference region for PET quantification of the radiotracer kinetics in the brain. Histamine antagonist/inverse agonists, such as pitolisant, have been shown effective to treat excessive daytime sleepiness and cataplexy in adults with narcolepsy and have been approved for this indication by several countries in the world.

In 2009, the radiolabeling of the H3R antagonist 6-[(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-N-methyl-3-pyridine carboxamide hydrochloride (GSK189254) with ^{11}C was published (Plisson et al. 2009). Previously, several radiotracer candidates did not show promising properties in preclinical (or in vitro) studies (Plisson et al. 2009). [^{11}C]GSK189254 was the first H3R PET radioligand used for human subjects (Ashworth et al. 2010) followed by [^{18}F]FMH3 (Tamagnan et al. 2011), [^{11}C]MK-8278 (Van Laere et al. 2014), and [^{11}C]TASP457 (Kimura et al. 2016). Despite the availability of PET radioligands for more than a decade, the number of studies published in human H3R PET is very scarce: only one study focusing on its role in the brain (Ito et al. 2018) and seven occupancy studies evaluating H3R antagonist drugs. All the studies so far were performed on healthy subjects. Perhaps the technical weakness of the two first radioligands ([^{11}C]GSK189254 and [^{11}C]MK-8278) was partially the reason for the lack of attraction to study H3R with PET. While the information of [^{11}C]TASP457 is limited, this ligand may have overcome some problems of the first-generation PET tracers, and newer promising radioligands are becoming available (e.g., [Carbonyl-^{11}C]AZ13198083 (Dahl et al. 2018)).

2.1 [^{11}C]GSK189254

GSK189254 and its radiolabeled version [^{11}C]GSK189254 are high affinity, selective, and brain-penetrant H3R antagonist/inverse agonist. In vivo PET experiments determined its K_D as 10 pM (Ashworth et al. 2010; Gallezot et al. 2017). It is difficult to synthesize this radioligand at a high enough molar activity such that the mass required for an injection of 10 mCi would be considered *tracer* dose. Thus, the mass injected for a PET scan (which includes both [^{11}C]GSK189254 and GSK189254) produces an appreciable occupancy of the H3R (non-tracer dose effect). Consequently, V_T depends on H3R concentration but also on the mass injected. Moreover, when two scans are performed on the same day, the second scan will show a reduced V_T reflecting H3R occupancy by the remaining cold ligand from the first scan ("carryover" effect).

The metabolization and clearance from plasma of GSK189254 is very slow. Unmetabolized [^{11}C]GSK189254 accounts for more than 90% of activity in plasma 90 min after injection. In addition, the human brain concentration of H3R at baseline conditions is too high compared to the ligand affinity producing undesirable

properties for PET quantification: The TACs of a healthy subject at baseline H3R level do not reach a peak within 90 min after injections. For some brain regions, the TACs do not reach a peak even when H3R are highly blocked by a ligand. At first glance, the TACs within the length of the scan would correspond to an irreversible radioligand (Slifstein 2010), however, it is known to be reversible binding. Usually, 2TCM fits slightly better the TACs than 1TCM and this difference is more marked in the TACs of the partially blocked condition than the TACs of the baseline condition. However, when fitting the TACs using the 2TCM, quite often the rate constants are not identifiable, which sometimes results in very small values of the rate constant k_4 and as a result, values of V_T that are artificially too high. Different approaches have been taken to deal with this situation. Ashworth et al. (2010) used a modified version of the 2TCM, including a variable to account for the dispersion in the arterial line of the automatic blood sample system (k_{disp}), and fitting simultaneously across all the regions of interest (ROIs) the variables V_{ND}, k_4, and k_{disp}. Gallezot et al. (2017) and us (Rusjan et al. 2020) found it sufficient to fit only V_{ND} simultaneously across ROIs (it is sometimes referred to as "coupled fit of V_{ND}"). In contrast, Jucaite et al. used 1TCM (Jucaite et al. 2013). Some linearized models are independent of the number of compartments, Gallezot et al. (2017) wrote that Ichise multilinear analysis (MA1) (Ichise et al. 2002) could also be used to quantify V_T. However, we found that while the Logan's graphical plot based on a linear model (Logan et al. 1990) works well for [^{11}C]GSK189254 in the estimation of V_T, the data points corresponding to the striatal regions sometimes aligned worse in subsequent Lassen plot than those estimated with the 2TCM with coupled fit of V_{ND}. [^{11}C]GSK189254 was used for human occupancy studies of H3R antagonist including GSK189254 (Ashworth et al. 2010), GSK239512 (Ashworth et al. 2014), AZD5213 (Jucaite et al. 2013), BF2.649 (Rusjan et al. 2020), and PF-03654746 (Gallezot et al. 2017).

2.1.1 Studies with [^{11}C]GSK189254 and GSK189254

Early studies with GSK189254 suggested it might have therapeutic potential for diseases where cognitive deficits occur such as Alzheimer's disease, other dementias, and schizophrenia (Medhurst et al. 2007). The clinical trial NCT00366080 (clinicaltrials.gov 2017) to assess the effectiveness and safety of the drug GSK189254 in treating patients with narcolepsy was terminated based on the interim results of a futility test (clinicaltrials.gov 2017) and there have not been new publications about GSK189254 in recent times. However, the PET occupancy studies of GSK189254 were vital for the kinetic characterization and strategies of quantification of [^{11}C]GSK189254.

Adult healthy volunteers were scanned at baseline and 4 and/or 24 h after an oral dose of GSK189254 between 10 and 100 μg. All scans were performed during normal waking hours when the levels of histamine in the brain are known to be stable. Four hours after GSK189254 administration ($n = 9$), the authors observed high occupancy (80–94%) for oral dosage >25 μg and slightly lower (56–74%) for a

10 μg oral dosage. The occupancies were still high ($\bar{x} \pm sd$, 68 ± 12%, $n = 5$) 24 h after an oral dose of 25 μg, which the authors found consistent with the persistence of the drug in the systemic circulation. Using the occupancies at 4 h and the oral dosage normalized by the weight of the subject, they demonstrated that the oral dose of GSK189254 required for 50% occupancy of the available receptor sites (ED_{50}) was 0.055 ± 0.014 μg/kg of body weight. With previous data of plasma concentration to that oral dose and a free fraction $fp = 0.36$, they found an $EC_{50} = 0.011$ nM. This value was remarkably close to $K_D = 0.0095$ nM deduced from the "carryover" effect in a test-retest study with 2 h of difference between initiations of the scans ($n = 6$). This affinity ($1/K_D$) in vivo was one order of magnitude higher than the value previously determined in vitro (pK = 9.59–9.90), which highlights the use of PET in drug development. The authors also estimated the in vivo density of H3R for the cerebellum (0.59 ± 0.18 nM), occipital cortex (0.7 ± 0.17 nM), and putamen (3.8 ± 0.9 nM).

2.1.2 Studies with [^{11}C]GSK189254 and PF-03654746

PF-03654746 is a potent, selective antagonist of the human H3R, developed by Pfizer. It was in the clinical trial phase II for the treatment of excessive daytime sleepiness associated with narcolepsy, Tourette syndrome, anti-allergy applications (Stokes et al. 2012), and in phase I of a clinical trial for the treatment of schizophrenia and Alzheimer's disease, but these investigations were discontinued (NCATS 2019) (https://drugs.ncats.io/substance/G3QE979K1X).

A target engagement PET study for this drug also proposed a method to correct for the effect of self-occupancy of [^{11}C]GSK189254 due to non-tracer dose and consequent carryover on a posterior scan. Six male subjects were scanned three times with [^{11}C]GSK189254, first at baseline and 3 and 24 h after an oral dosage of PF-03654746 at different doses: 0.1, 0.25, 0.5, 0.5, 1.5, and 4 mg (Gallezot et al. 2017). Two venous blood samples were drawn at the beginning and end of each scan to measure PF-03654746 in plasma concentration using an HPLC tandem mass spectrometric method (HPLC-MS/MS).

The dose-dependent occupancy fell from 71–97% 3 h after the dose to 4–41% to 24 h after the dose. The occupancies at 3 and 24 h fell on a single pattern when plotted against plasma concentration of PF-03654746. It means that the level of drug in tissue is in quick equilibrium with the level of drug in plasma. Using the Eq. 2, the estimation obtained indicated $Occ_{max} = 100\%$ and $EC_{50} = 0.144 \pm 0.010$ ng/mL (Gallezot et al. 2017) which correspond to unbound plasma EC_{50} of 0.313 nM (Sawant-Basak et al. 2017). This value again showed a higher-than-expected in vivo potency of PF-03654746 in humans (Sawant-Basak et al. 2017) than in vitro potency (K_i was 2.3 nM (Wager et al. 2011)).

2.1.3 Studies with [^{11}C]GSK189254 and GSK239512

When the PET study described below was published in 2013, GSK239512 was presented as "under development" for the symptomatic treatment of cognitive impairments in mild-to-moderate Alzheimer's disease (Ashworth et al. 2014). In a subsequent clinical trial with doses up to 80 μg/day, an improved Episodic Memory was found in patients with mild to moderate Alzheimer's disease but no improvements in executive function/working memory or other domains of cognition (Grove et al. 2014). More recently, GSK239512 shows a small but positive effect on remyelination in patients with relapsing-remitting multiple sclerosis compared with placebo (Schwartzbach et al. 2017).

A [^{11}C]GSK189254 PET study investigated the H3R brain occupancy as a function of the plasma concentration of GSK239512 (Ashworth et al. 2014). The level of drug in plasma was measured based on protein precipitation, followed by HPLC-MS/MS analysis. PET scans were acquired at baseline, at the time of maximum plasma concentration ($T_{max} = 4$ h), and 24 h after an oral dose of 6, 14, or 120 μg of GSK239512. The results of PET scans obtained on seven healthy male volunteers at the age between 37 and 45 years were reported.

Radioligand self-occupancy was corrected with the method proposed in the study on PF-03654746 (Gallezot et al. 2017). The brain occupancies 4 h after 6 μg ($n = 3$) or 14 μg ($n = 3$) oral dosage ranged from 50 to 75% and were higher (98%) 4 h after a 120 μg oral dosage ($n = 1$). The occupancies were still high ranging from 24 to 64% 24 h after dosage of 6 μg ($n = 3$) or 14 μg ($n = 2$) and stayed at 85% 24 h after dosage of 120 μg ($n = 1$). A single Hill's function shown in Eq. 2 (with $Occ_{max} \equiv 100$) could describe occupancy curves both 4 and 24 h after the dosage, indicating a prompt equilibrium between the brain and plasma drug levels without hysteresis. This enabled estimation of EC_{50} as 0.0068 ng mL^{-1}. Using a previously determined *fp* value (0.25), the in vivo affinity p*K* was determined as 11.3 and was again higher than the in vitro p*K* (9.9–9.7) (Wilson et al. 2013).

2.1.4 Studies with [^{11}C]GSK189254 and AZD5213

AZD5213 is a highly selective H3R antagonist/inverse agonist which is rapidly reversible ($T_{max} = 0.7$–2.0 h after oral administration and half-life between 5 and 7 h (AstraZeneca 2021)). It was developed to achieve a pharmacokinetic profile permitting circadian fluctuations of H3R occupancy, such that it would show the pro-cognitive, wake-promoting effects during the day but it would not produce the adverse effects such as detrimental changes in sleep regulation during the nighttime (Jucaite et al. 2013).

This [^{11}C]GSK189254 PET study, based on seven young male healthy volunteers, was different regarding the following aspects: (a) [^{11}C]GSK189254 was administered at masses lower than 1.92 μg to minimize the self-occupancy by the radioligand; (b) V_T was calculated with 1TCM; (c) striatal areas were excluded from

the Lassen plot analysis. Subjects were scanned first in the baseline condition and up to twice either 2–4 h ($n = 7$) or 24–26 h ($n = 5$) after a single oral dosage. The oral solution was administered in the morning with a dose ranging from 0.05 to 2.5 mg for the studies 2–4 h after the dosage and from 2 to 30 mg for the studies at 24–28 h after the dosage (Jucaite et al. 2013). It is not clear whether the baseline and post-drug scans were conducted on the same day or different days. Plasma concentrations of AZD5213 were measured in venous blood samples for 48 h following the oral dose.

The occupancy of H3R in the brain by the drug was dose dependent. The relationship between the brain occupancy of H3R by AZD5213 and its plasma concentration was independent of the time of acquisition of the scan indicating quick equilibrium between brain and plasma levels of this drug without notably hysteresis. All the points were pooled together and fitted with Eq. 2 with $Occ_{max} \equiv 100\%$ resulting in $EC_{50} = 1.14$ nM. Having the time course of the plasma concentration of the AZD5213 for 48 h and different oral doses, Eq. 2 predicted the occupancy along the time for each oral dose. The authors observed in this small sample size that the occupancy was higher than 80% during the first 12 h after the drug dosage of 1–10 mg but was lower during the next 12 h. For the 30 mg dose, the occupancy was continuously high. They speculate that daily low doses of 1 mg will not accumulate in plasma; therefore, it will keep a periodical occupancy pattern (Jucaite et al. 2013).

2.1.5 Studies with [^{11}C]GSK189254 and Pitolisant

BF2.649 (pitolisant; Wakix®), an H3R inverse agonist/antagonist, was approved in the European Union (EU) on March 31, 2016, for the treatment of narcolepsy with or without cataplexy in adults and by the Food and Drug Administration (FDA) for the treatment of cataplexy in adults with narcolepsy.

Prior to the PET occupancy study, it was determined that the therapeutic efficacy was demonstrated by daily doses between 20 and 40 mg (Dauvilliers et al. 2019). Pitolisant plasma concentration peaked approximately 3 h after administration, and it had a plasma half-life of 10–12 h. Five or six days after repeated administrations, a steady state was achieved and the serum level was twofold of the level after a single dosage (EuropeanCommission 2018).

Six healthy adult participants were scanned twice with [^{11}C]GSK189254. The first time 3 h after oral administration of placebo and the second 3 h after oral administration of 40 mg pitolisant hydrochloride (Fig. 2). [^{11}C]GSK189254 regional V_T's were estimated in nine brain ROIs with the 2TCM with arterial input function using a common V_{ND} across the regions. V_T's decreased strongly in the second scans for all the ROIs (Fig. 3) and the brain H3R occupancies calculated with the Lassen plot were 84 ± 7% (Rusjan et al. 2020).

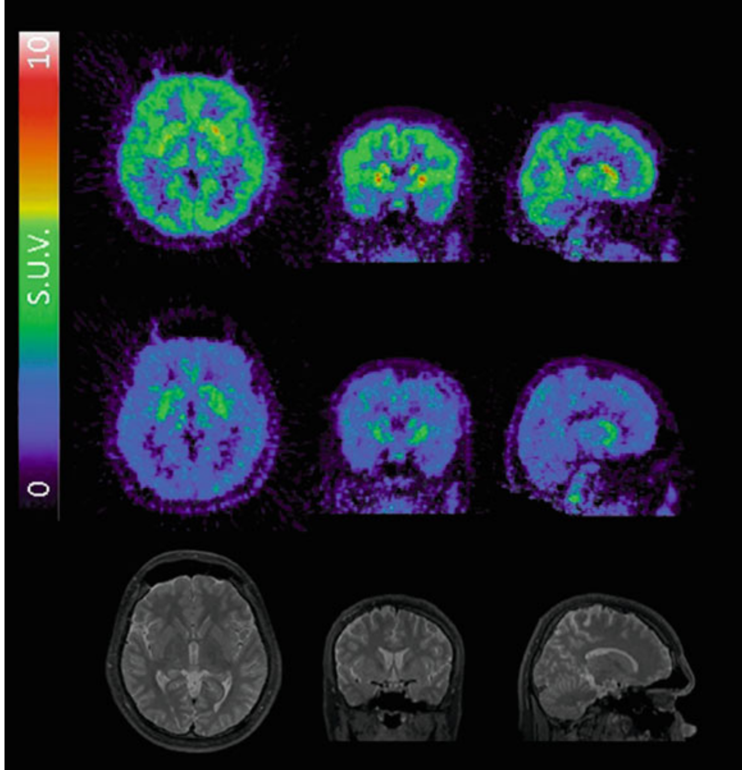

Fig. 2 H3 receptor quantification with PET and ^{11}C-GSK189254. Representative PET images after [^{11}C]GSK189254 administration to a healthy human subject 3 h after oral administration of placebo (top) and 3 h after oral administration of 40 mg of pitolisant hydrochloride (middle). Mean SUV images over 0–90 min after the ligand injection are shown with structural MR image for same subject (bottom)

2.2 Studies with [^{11}C]MK-8278

[^{11}C]MK-8278 has a lower affinity (0.54 nM) for H3R than [^{11}C]GSK189254. It has relative low lipophilicity (log *P* (pH 7.4) = 2.2) and good selectivity. MK-8278 is a poor substrate for human P-glycoprotein and shows low plasma protein binding. The kinetic modeling study for this radioligand included six healthy male volunteers. The TACs showed good uptake with gray matter regions peaking between three and four SUV. TACs of the extra-striatal regions showed excellent reversibility within 90 min of the tracer administration. The TAC of the striatum showed a broad and delocalized peak and slower washout of activity. 1TCM fitted the TACs at baseline well for the control subjects and 80 min was the optimal scan length to get V_T (Van Laere et al. 2014).

The metabolization of the radioligand is slow, and at 60 min, 50% of the radioactivity in plasma is still the parent compound. Each of the subjects underwent

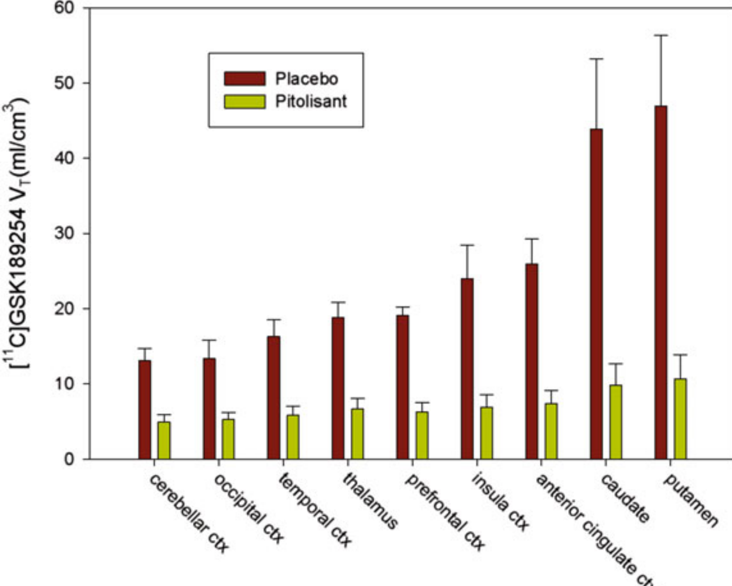

Fig. 3 Occupancy of H3 receptor by pitolisant. Six healthy adult participants were scanned with [^{11}C]GSK189254. Participants underwent a total of two PET scans on separate days, 3 h after oral administration of placebo or after pitolisant hydrochloride (40 mg). [11C]GSK189254 regional V_T were estimated in nine brain ROIs with the 2TCM with arterial input function using a common V_{ND} across the regions. (Reproduced from online abstract of Rusjan et al. (2020))

two PET scans on the same day with an interval of 3–4 h. The reproducibility of V_T was good for extra-striatal regions but poor for the caudate and putamen. Usually, the input function is a higher source of variability than the image data, and the authors claim that the reproducibility was poor because of the difficulties in the blood radioactivity measurement at later time points (Van Laere et al. 2014). However, it is inconsistent with the fact that the extra-striatal regions were very reproducible. It is expected that V_T's in regions with the slowly reversible radioligand kinetics are more difficult to quantify. The reproducibility depends on all the steps in the acquisition and analysis. It represents the stability of the target, and the hardware of acquisition, skills of the technicians, and software, algorithms and protocol applied. The statements on the hardware for blood sampling and processing are unclear in this report and there is no information whether motion correction, which is the most common cause affecting reproducibility (Norgaard et al. 2020), was performed. While a small region with slow reversibility like the head of the caudate will be the weakest point of the radioligand, the reproducibility can eventually be improved with a different protocol of acquisition and processing.

It is claimed that the pons can be used as a reference region and the simplified reference tissue model can be applied. The simplified reference region model requires that V_{ND} in the reference region and target regions be the same and that

the reference region does not have specific binding components. While it is possible, it is not shown with an occupancy experiment that this is true for [^{11}C]MK-8278. The chemical composition of the white matter abundant in fat is different from the gray matter, therefore there could be a considerable difference in V_{ND} between the cortex and myelin-rich pons. Moreover, there is H3R in the pons: the [^{11}C] GSK189254 V_{T} in the pons decreases by 25–50% after an oral administration of 40 mg of pitolisant, according to our unpublished data. With the low lipophilicity and low affinity of [^{11}C]MK-8278, it cannot be ruled out that the pons can work as a reference region. However, it should be proved with an occupancy experiment analyzing the data with a full kinetic model. When the reference region contains a specific binding, it is anticipated that the measured occupancy (Occ′) underestimates the true occupancy (Occ) as a function of the BP_{ND} of the reference region in the blocked experiment ($\mathrm{BP}_{\mathrm{ND}}^{\mathrm{reference,blocked}}$) (Christian et al. 2004) with the following relation: $\mathrm{Occ}' = \mathrm{Occ}/\left(1 + \mathrm{BP}_{\mathrm{ND}}^{\mathrm{reference,blocked}}\right)$ (Asselin et al. 2007).

2.2.1 Studies with [^{11}C]MK-8278 and MK-0249

This PET tracer has been used to study H3R brain occupancies by the drug MK-0249. MK-0249 is an H3R inverse agonist which showed promising results in preclinical models of cognitive disorders. However, posterior clinical trials failed to replicate the efficacy in the treatment of adult attention-deficit/hyperactivity disorder (Herring et al. 2012), the cognitive impairment in patients with schizophrenia (Zhao et al. 2013) and with mild to moderate Alzheimer's disease (Egan et al. 2012). The time of the plasma maximal concentration (T_{max}) of MK-0249 and MK-3134 (see below) was determined as 6 h. Subjects were scanned at baseline and 6 h after a single oral dose between 2.5 and 50 mg of MK-0249. Subjects with 10 mg were scanned also at 27 h after the oral dose. The TACs of the striatum showed a remarkable change following the administration of the inverse agonists. Occupancies were determined using the BP_{ND} of the striatum with the pons as a reference region. They were dose-dependent and ranging from 60% to 94%. Occupancies by 10 mg of MK-0249 at 27 h stayed higher than 68% and were only 17% lower than occupancies at 6 h. The plot brain occupancy vs plasma level suggests that the data points at 6 and 27 h can be fitted all together by a single Hill's function without hysteresis, which would mean that the drug specifically bound in the brain is in quick equilibrium with the available drug in plasma (Van Laere et al. 2014).

2.2.2 Studies with [^{11}C]MK-8278 and MK-3134

This PET tracer has been used to study H3R brain occupancies by the inverse agonist of the H3R MK-3134. In a clinical study MK-3134 (25 mg) ameliorated the scopolamine-induced decline in cognitive impairment in healthy subjects (Cho et al. 2011).The occupancy PET study showed that MK-3134 with doses of 0.1,

0.5, 5, and 25 mg ($n = 3$ for each) produced a dose-dependent occupancy ranging from 43 to 96% (Van Laere et al. 2014).

2.3 *Studies with [^{11}C]TASP457*

2.3.1 PET Evaluation of [^{11}C]TASP457

The evaluation of the [^{11}C]TASP457 quantification was based on 90 min PET and arterial plasma measures in five subjects whose parent fractions in plasma were obtained successfully. The TACs show excellent uptake peaking at three to six SUV. The pallidum was the region with the slowest washout of activity but still, the peak was reasonably localized. 2TCM fitted the TACs better than 1TCM. It was found that 80 min scan data were optimal for robustly estimating V_T in the ROIs. In mice, there was a penetrating radiometabolite responsible for 50% of the brain radioactivity at 30 min after injection. The metabolization in humans was slow and after 90 min, 70% of the activity in plasma was coming from the unmetabolized parent compound (Kimura et al. 2016). A slight increase in V_T with the length of the scan led the authors to suggest reducing the length of the scan to 60 min, which decreases the identifiability but would protect from the effects of an eventual penetrating radiometabolite, and the uncertainties in determining the fraction of the parent compound at a later time point (Kimura et al. 2016). The study included neither reproducibility results nor blocking experiment. A blocking experiment will give more information about whether a radioactive radiometabolite could affect the quantification.

2.3.2 Evaluation of In Vivo Role of H3R with [^{11}C]TASP457

The only work published about the in vivo role of H3R in a human PET study was performed with [^{11}C]TASP457. Of note, a clinical trial including Alzheimer's disease patients with [^{18}F]FMH3 (NCT01268020 (Ashworth et al. 2010)) has never been published.

The study relates working memory with the [^{11}C]TASP457 V_T in 10 healthy subjects (Ito et al. 2018). An fMRI study was used to identify three clusters in the dorsolateral prefrontal cortex activated by an increased working memory load. ROIs in these locations with a radius of 4 mm were delineated in the PET space and the V_T was calculated for those regions. For the smallest cluster (21 voxels) in the fMRI study, the contrast coefficients of the activated cluster inversely correlated with the [^{11}C]TASP457 V_T. The authors recognized that further studies with a larger sample size are required and they suggest using H3R agonists/antagonists to explore whether they can modify the working memory performance.

2.4 Studies with [^{18}F]FMH3

This is the only ^{18}F radioligand tested in humans. However, the public information about its use in humans is limited to a conference abstract (Tamagnan et al. 2011). The uptake of this radioligand (2–2.5 SUV) was lower than the ^{11}C radioligands presented above and peaked in all regions examined within 15 min after injection. Using the pons as a reference region, the BP_{ND}'s are similar to those of [^{11}C]MK-8278 with the advantage of being ^{18}F and the disadvantage of lower brain uptake.

3 Discussion

All PET radioligands present challenges in their quantification and H3R radioligands are no exceptions. It is not uncommon to use different approaches, including scan protocols, kinetic models, blood samples acquisition and process to analyze data in the PET field. For example, it has been studied systematically for [^{11}C]DASB. In 105 original research articles published by 21 different PET centers, multiples ways to acquire and quantify images have been shown (Norgaard et al. 2019), which could sometimes lead to different conclusions (Norgaard et al. 2020). Imperfect radioligands can be used successfully provided the results are interpreted with caution by taking into consideration the limitations of its quantification. The studies with H3R radioligands clearly illustrate how various quantification strategies have been used by PET kinetic modelers to deal with challenges in quantification.

[^{11}C]GSK189254 was analyzed with 1TCM, 2TCM coupling V_{ND} across ROIs, 2TCM coupling k_4, and V_{ND} across ROIs. Striatal regions sometimes have been included but sometimes have been excluded in the Lassen plot. The impact of the non-tracer dose of the ligand was evaluated and/or managed. [^{11}C]GSK189254 has been a successful tool for target engagement studies and it was able to highlight the importance of PET in the development of new drugs. It is also clear from those occupancy studies that the therapeutic dosage of pitolisant (the first H3R drug put on the market) is associated with very high H3R occupancy (Rusjan et al. 2020). However, it is possible that [^{11}C]GSK189254 may not have the ideal sensitivity required to explore differences in the target expression and function among diverse clinical populations. It is possible that the newer radioligands tested in humans have a better profile for signal quantification but further evaluation is necessary. For example, the reproducibility of V_T of the striatal areas [^{11}C]MK-8278 eventually could improve with a different protocol of acquisition or image processing. The use of the pons as a reference region should be further studied with occupancy studies and simulations. [^{11}C]TASP457 appears to have the optimal affinity to quantify all the brain regions with very different concentrations of H3R simultaneously. Occupancy studies will elucidate whether the penetrating radiometabolite that was observed in mice could affect the quantification in humans. The results of [^{18}F]

FMH3 will likely be published in the future. ^{18}F radioligands present some advantages over ^{11}C radioligands as follows: a) they allow longer scans and b) they may not need on-site production if deliveries of the radiopharmaceuticals are available. Studies conducted in baboons with [^{18}F]FMH3 showed good reversibility and high specificity but low uptake and quick metabolization (Sandiego et al. 2019). If those properties persist in humans, it could result in low reproducibility of the quantification. Finally, [Carbonyl-^{11}C]AZ13198083 has shown high brain uptake, slow metabolization, adequate affinity, and low non-specific binding in non-human primates (cynomolgus monkeys), and it is a good candidate to try in humans (Dahl et al. 2018).

4 Conclusion

The limited PET studies conducted so far indicate that it is possible to develop H3R PET radiotracers that are suitable for receptor quantification. To date, those PET tracers have been primarily used to study receptor occupancy following drug administration. The recent PET study with pitolisant indicates that the therapeutic effect of this drug for narcolepsy is obtained with high degree of H3R occupancy (Rusjan et al. 2020). Further studies are required to explore possible abnormal regulation of H3R in various psychiatric and neurological disorders and to explore in vivo the functional role of H3R in humans with PET.

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Therapeutic Potential of Histamine H3 Receptors in Substance Use Disorders

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Abstract Substance use disorders are a leading cause of morbidity and mortality, and available pharmacological treatments are of modest efficacy. Histamine is a biogenic amine with four types of receptors. The histamine H_3 receptor (H_3R) is an autoreceptor and also an heteroreceptor. H_3Rs are highly expressed in the basal ganglia, hippocampus and cortex, and regulate a number of neurotransmitters including acetylcholine, norepinephrine, GABA and dopamine. Its function and localization suggest that the H_3R may be relevant to a number of psychiatric disorders and could represent a potential therapeutic target for substance use disorders. The purpose of the present review is to summarize preclinical studies investigating the effects of H_3R agonists and antagonists on animal models of alcohol, nicotine and psychostimulant use. At present, the effects of H_3R antagonists such as thioperamide, pitolisant or ciproxifan have been investigated in drug-induced locomotion, conditioned place preference, drug self-administration, reinstatement, sensitization and drug discrimination. For alcohol and nicotine, the effects of H_3R ligands on two-bottle choice and memory tasks, respectively, have also been investigated. The results of these studies are inconsistent. For alcohol, H_3R antagonists generally decreased the reward-related properties of ethanol, which suggests that H_3R antagonists may be effective as a treatment option for alcohol use disorder. However, the effects of H_3R antagonists on nicotine and psychostimulant motivation and reward are less clear. H_3R antagonists potentiated the abuse-related properties of nicotine, but only a handful of studies have been conducted. For psychostimulants, evidence is mixed and suggests that more research is needed to establish whether H_3R antagonists are a viable therapeutic option. The fact that different drugs of abuse have different brain targets may explain the differential effects of H_3R ligands.

Keywords Alcohol · Amphetamine · Cocaine · Histamine · Nicotine

1 Introduction

Histamine is a biogenic amine involved in many physiological processes and has been studied as a treatment for various psychiatric disorders. (Alleva et al. 2013; Harwell and Fasinu 2020; Hu and Chen 2017; Schwartz 2011). Histamine has four receptor subtypes, H_1, H_2, H_3 and H_4 (Arrang et al. 1983). Of note, the H_3R was characterized in 1983 as an autoreceptor that regulates histamine levels (Arrang et al. 1983). The H_3R is also an heteroreceptor highly expressed in the basal ganglia, globus pallidus, hippocampus and cortex (Martinez-Mir et al. 1990). It regulates the release of a number of neurotransmitters, including acetylcholine (Ach) (Blandina

et al. 1996), norepinephrine (NE) and GABA, as well as dopamine (DA) (Schlicker et al. 1994). Antagonism of H_3R increases Ach, NE and DA levels (Medhurst et al. 2007). Thus, the pharmacology and localization of the H_3R suggest it may be a potential therapeutic target for psychiatric disorders.

Early studies of the function of the H_3R identified it as important in vigilance and wakefulness (Bonaventure et al. 2007).In fact, time spent awake was increased after administration of a number of different H_3R antagonists (Barbier et al. 2004; Griebel et al. 2012; Lin et al. 1990). An early H_3R antagonist, BF2.649, or pitolisant (Wakix™), received a great deal of attention and has been approved in some countries for the treatment of narcolepsy with or without cataplexy. The effect of pitolisant in narcolepsy treatment has been demonstrated in a number of clinical trials that have been reviewed a number of times (Calik 2017; de Biase et al. 2021; Harwell and Fasinu 2020; Lamb 2020; Wang et al. 2021). In a PET study in humans, pitolisant has been shown to bind effectively to H_3R (80–90% occupancy) at therapeutic doses (Rusjan et al. 2020).

H_3Rs have also been shown to be important in cognitive function (Brabant et al. 2013; Komater et al. 2003; Pascoli et al. 2009; Passani et al. 2017). Thus, H_3R antagonists were proposed as a viable treatment approach for various disorders characterized by cognitive dysfunction (Hu and Chen 2017; Sadek et al. 2016) including Alzheimer's disease (Harwell and Fasinu 2020) and the cognitive impairment in schizophrenia (Ligneau et al. 2007a), with variable results (Jarskog et al. 2015; Kubo et al. 2015). The success of pitolisant in treating narcolepsy, coupled with its relative lack of abuse potential (Setnik et al. 2020; Uguen et al. 2013), suggests that further investigation of H_3R antagonists as therapeutic agents is warranted.

Early studies that found a relationship between drug reward and histaminergic mechanisms suggested that H_3R ligands may be useful in the treatment of substance use disorders (Lintunen et al. 2001). Further, dopamine (DA) has a well-established role in substance use disorders (Wise 1978; Di Chiara et al. 1991) and H_3R regulate DA levels (Medhurst et al. 2007). Of relevance for addiction, the H_3R is located post-synaptically on striatal neurons (Arias-Montano et al. 2001; Ferrada et al. 2008; Garcia-Ramirez et al. 2004). The purpose of the present review is to synthesize studies conducted to date that have investigated H_3R ligands in preclinical models of drug motivation and reinforcement. This narrative review of preclinical studies will focus on the drugs of abuse with the most investigations in relation to H_3R agents (alcohol, nicotine and psychostimulant). Over the years, there has been interest in studying H_3R agents for psychiatric disorders and a number of agonists and antagonists have been developed (Hu and Chen 2017), which have been summarized in previous papers (Bonaventure et al. 2007; Harwell and Fasinu 2020; Hu and Chen 2017; Lazewska and Kiec-Kononowicz 2010). An overview of the agonists and antagonists reviewed in the present review are provided in Table 1.

Table 1 H_3R ligands cited in the present review

Antagonist/inverse agonist	Reference	Agonist	Reference
ABT-239	(Cowart et al. 2007)	R-(alpha)-methyl-histamine (RAMH)	(Kilpatrick and Michel 1991)
A-331440	(Hancock et al. 2004)	Immepip	(Panula et al. 2015)
BF2.649 (pitolisant; Wakix)	(Ligneau et al. 2007b)	Imetit	(Panula et al. 2015)
JNJ-39220675	(Letavic et al. 2010)		
ST1283	(Bahi et al. 2013)		
DL77	(Bahi et al. 2015)		
Ciproxifan	(Panula et al. 2015)		
Thioperamide	(Panula et al. 2015)		
JNJ-10181457	(Galici et al. 2009)		
Conessine	(Zhao et al. 2008)		
Clobenpropit	(Campbell et al. 2005)		

1.1 Alcohol

Some early evidence for a role of histamine in alcohol motivation and intake came from a study by Lintunen et al. (2001). In this study, they investigated brain histamine content in alcohol-preferring rats selectively bred to prefer ethanol to water, in comparison to alcohol-avoiding rats (Eriksson 1968); and they have neurochemical differences from non-preferring rats (Nuutinen et al. 2012). In one study, it was found that alcohol-preferring rats had more than a two-fold higher histamine concentration in tissue in various brain areas (Lintunen et al. 2001). The binding to H_3R was lower in alcohol-preferring rats in many brain areas, particularly the primary motor and insular cortex, accumbal region and hippocampus (Table 2).

Alcohol-preferring rats are also tested in other measures of alcohol preference/ consumption, including the two-bottle choice paradigm. In this test, the relative preference for water or ethanol is assessed daily and the percentage of ethanol solution consumed is calculated. Total ethanol intake over days can also be calculated. In general, mice and rats prefer ethanol solutions to water after training to drink ethanol. In alcohol-preferring rats, the H_3R antagonist JNJ-39220675 (0.3, 4 and 10 mg/kg) reduced alcohol intake (Galici et al. 2011). In addition, preference for alcohol was reduced after the medium and high doses. This effect was also observed after a three-day deprivation from alcohol when the motivation for alcohol

Table 2 Summary of studies of the effects of H_3R ligands on animal models of substance use. All effects presented were reported as significant by the authors. *WT* wild type, *KO* knock out, *CPP* condition place preference

Animal model	Drug	Finding	Reference
Alcohol			
Two-bottle choice	JNJ-39220675	↓ Ethanol consumption ↓ Preference for ethanol	(Galici et al. 2011)
	ST1283	↓ Ethanol consumption ↓ Preference for ethanol	(Bahi et al. 2013)
	DL77	↓ Ethanol consumption ↓ Preference for ethanol	(Bahi et al. 2015)
	WT vs KO	↓ Ethanol consumption in KO ↓ Preference for ethanol in KO	(Nuutinen et al. 2011a)
Binge drinking	WT vs KO	↓ Ethanol consumption in KO	(Nuutinen et al. 2011a)
Self-administration	JNJ-39220675	↓ Self-administration of ethanol	(Galici et al. 2011)
	Thioperamide Clobenpropit r-α-methylhistamine	↓ Self-administration of ethanol (thioperamide, clobenpropit) ↑ Self-administration of ethanol (r-α-methylhistamine)	(Lintunen et al. 2001)
Cue-induced reinstatement	Ciproxifan JNJ-39220675	↓ Cue-induced reinstatement	(Nuutinen et al. 2016)
CPP	ST1283	↓ Acquisition of ethanol-induced CPP	(Bahi et al. 2013)
	DL77	↓ Acquisition of ethanol-induced CPP	(Bahi et al. 2015)
	Ciproxifan JNJ-10181457	↓ Acquisition of ethanol-induced CPP	(Nuutinen et al. 2011b)
	WT vs KO	KO failed to acquire ethanol-induced CPP	(Nuutinen et al. 2011a)
	Ciproxifan	↑ Acquisition of ethanol-induced CPP	(Nuutinen et al. 2010)
	Conessine	No effect on acquisition of ethanol-induced CPP	(Morais-Silva et al. 2016)
Ethanol-induced activity	ST1283	↓ Ethanol-induced locomotion	(Bahi et al. 2013)
	Ciproxifan	↓ Ethanol-induced locomotion	(Nuutinen et al. 2010)
	Ciproxifan	Ciproxifan extended the locomotor response of low dose ethanol Immepip inhibited ethanol stimulation of locomotor response	(Nuutinen et al. 2011b)
	Conessine	↑ The locomotor stimulation of ethanol	(Morais-Silva et al. 2016)
	WT vs KO	No increase in locomotion after ethanol in the KO	(Nuutinen et al. 2011a)

(continued)

Table 2 (continued)

Animal model	Drug	Finding	Reference
Motor coordination	Ciproxifan Immepip	Ciproxifan: no effect on alcohol-induced impairment Immepip: enhanced impaired balance beam performance	(Nuutinen et al. 2011b)
	JNJ-39220675	NO effect on alcohol-induced ataxia	(Galici et al. 2011)
	WT vs KO	KO less impaired on balance beam but similar to WT on rotarod	(Nuutinen et al. 2011a)
Nicotine			
Radial arm maze	Thioperamide	Increase in choice accuracy impairment	(Kholdebarin et al. 2007)
Elevated plus-maze	ABT-239	ABT-239 potentiated the effects of nicotine to improve memory acquisition and consolidation	(Kruk et al. 2012)
Sensitization	ABT-239	Potentiated the acquisition of nicotine-induced sensitization with no effect on the expression of nicotine-induced sensitization	(Miszkiel et al. 2011)
Withdrawal	Intracerebroventricular Thioperamide	Increased nicotine withdrawal-induced anxiety	(Patel et al. 2021)
Psychostimulants			
Amphetamine-induced activity	Thioperamide	↓ Amphetamine-induced locomotion	(Clapham and Kilpatrick 1994)
	ABT-239	↓ Methamphetamine-induced hyperactivity	(Fox et al. 2005)
	JNJ-10181457, pitolisant, ABT-239	↓ Methamphetamine-induced hyperlocomotion	(Kitanaka et al. 2020)
	Imetit	↓ Methamphetamine-induced locomotion	(Banks et al. 2009)
Cocaine-induced activity	Imetit	No effect on cocaine-induced locomotion	(Banks et al. 2009)
	Thioperamide	↑ Cocaine-induced hyperlocomotion	(Brabant et al. 2009)
	Thioperamide	↑ Cocaine-induced activity	(Brabant et al. 2005)
	Thioperamide	↑ Cocaine-induced activity	(Brabant et al. 2006)
	A-331440, immepip	No effect on cocaine-induced locomotion	(Brabant et al. 2009)
	Pitolisant	No effect on cocaine-induced locomotion	(Brabant et al. 2016)
CPP	Pitolisant	No effect on acquisition of cocaine-induced CPP	(Brabant et al. 2016)

(continued)

Table 2 (continued)

Animal model	Drug	Finding	Reference
	Thioperamide	No effect on acquisition of cocaine-induced CPP, but induced a CPP when paired with a subthreshold dose of cocaine	(Brabant et al. 2005)
Drug discrimination	Thioperamide, clobenpropit A-methylhistamine	Thioperamide and clobenpropit did not substitute fully for cocaine. All produced a leftward shift in the dose-response function	(Campbell et al. 2005)
	Thioperamide A-methylhistamine	Neither substituted for methamphetamine. Thioperamide produced a leftward shift in dose-response curve, but α-methylhistamine had no effect	(Munzar et al. 1998)
	Thioperamide Clobenpropit	↑ In methamphetamine-appropriate responding when given with a sub-threshold dose of methamphetamine	(Munzar et al. 2004)
Self-administration	Thioperamide Clobenpropit	↑ Responding for low dose of methamphetamine and ↓ responding for higher doses of methamphetamine	(Munzar et al. 2004)
	Pitolisant	No effect on responding for cocaine when given 5 min before the session, but when given 60 min prior, a high dose decreased responding for cocaine. When injected 5 min before the session, the highest dose decreased responding under a PR schedule. Authors conclude there is no effect of pitolisant because the effective doses were very high and non-selective	(Huyts et al. 2019)
Sensitization	Thioperamide	No effect on acquisition of cocaine-induced sensitization	(Brabant et al. 2006)
	Ciproxifan	↓ Methamphetamine-induced sensitization	(Motawaj and Arrang 2011)
Avoidance paradigm	Imetit	No effect on methamphetamine- or cocaine-induced increases in avoidance responding	(Banks et al. 2009)

is enhanced. It should be mentioned that total fluid intake was reduced, suggesting that the effects of JNJ-39220675 must be interpreted with caution in view of the reduced general fluid intake. These findings were also observed in rats that are not selectively bred to prefer alcohol solutions.

In another study (Bahi et al. 2013) it was found that the histamine H_3 antagonist ST1283 (5 and 10 mg/kg) reduced the choice of a 10% ethanol solution in a two-bottle choice paradigm. In this study, the decrease in ethanol preference was not due to a general decrease in fluid consumption, because ST1283 did not affect

the intake of fluids flavoured with either saccharin or quinine, suggesting that H_3 antagonists do not simply influence the preference for a flavour of the liquid. A histamine H_3 agonist R-(alpha)-methyl-histamine (RAMH) reversed this attenuation of ethanol intake, suggesting the effect was mediated by histamine H_3 receptors. In a follow-up study by the same group, they found that the histamine H_3 antagonist DL77 also suppressed voluntary ethanol intake at higher doses (10 and 30 mg/kg) but not at the lower doses (3 mg/kg) (Bahi et al. 2015). DL77 also decreased preference for an ethanol solution, without any effects on fluid intake, consumption or preference patterns for saccharin or quinine. Changes in ethanol consumption were reversed by the histamine H_3 agonists RAMH. By comparison to the effects of agonists and antagonists on alcohol consumption and preference, one published study looked at differences between H_3 knockout (KO) and wild-type (WT) mice (Nuutinen et al. 2011a). Compared to the WT mice, KO mice drank less ethanol and had a reduced preference for alcohol than compared to water, in a two-bottle choice task. Preferences for saccharin or quinine were not different in the KO and WT, suggesting that differences in alcohol drinking were not due to taste neophobia. In summary, despite a lack of consistency in some findings, it appears that H3 antagonists decrease the choice of ethanol in two-bottle tests. This change, which can be reversed by H3 agonists, suggests a histamine H3 receptor mediated mechanism of action.

The role of histamine H_3 receptors has also been tested in a binge drinking paradigm (Drinking in the Dark). When permitted free access to alcohol for 2 and 4 h in a limited access binge drinking paradigm, H_3R knock out mice drank significantly less alcohol over both intervals as compared to WT mice (Nuutinen et al. 2011a). However, it should be noted that sucrose consumption and total daily fluid consumption were also lower for the KO mice, suggesting that the effects may have been confounded somewhat by a change in general drinking patterns, appetitive behaviours or activity. To further investigate this, WT mice were injected with the H3 antagonist ciproxifan before the alcohol drinking sessions. Ciproxifan reduced the volume of alcohol consumed but had no effect on sucrose intake. Similarly, the H_3 agonist immepip also had no effect on sucrose intake but increased alcohol intake. These results extended findings from the two-bottle choice experiments by suggesting that H3R agents may selectively alter alcohol consumption.

A more direct measure of the reinforcing and rewarding properties of substances of abuse is to measure the propensity with which animals will self-administer them (Weeks and Collins 1964). In the self-administration paradigm, animals are placed in operant chambers that contain one or two levers, and responses on one of the levers (the 'active' lever) produce delivery of the drug through an automated delivery system such as an infusion pump. Responses on the other lever, the 'inactive' lever, are recorded but have no programmed consequences; they serve as a control for changes in general motor output. Natural rewards are often used as controls to test whether changes in operant responding reflect a general change in motivation or motor ability. In one study, the H_3 antagonist, JNJ-39220675, reduced operant self-administration of alcohol intake with no effects on intake of saccharin (Galici et al. 2011). In this study, a lack of effect of the H3 antagonist on responding for saccharin

suggests that the effect was specific to the reinforcing effects of ethanol. Notably, JNJ-39220675 also had no effect on alcohol-induced ataxia, suggesting that the effects were not due to non-selective sedative effects (Galici et al. 2011). In another study, the histamine H_3 antagonists thioperamide and clobenpropit dose-dependently reduced alcohol intake, while an histamine H_3 agonist increased alcohol intake (Lintunen et al. 2001), suggesting that alcohol motivation is partly regulated by histamine H_3 receptors.

Alcohol use disorder, like other substance use disorders, can be characterized as a chronic relapsing disorder (Leshner 1997). In addition to the reinforcing effects of drugs, it is of interest to determine whether potential drugs can influence relapse to drug use. In animals, relapse to drug use is studied with the reinstatement model (de Wit and Stewart 1981; Epstein and Preston 2003). In this model, animals are trained to self-administer the drug of interest, after which the drug is removed. During the period when animals do not have access to the drug, the response for the drug decreases, or extinguishes. Responding is then reinstated (an analogue of relapse), by introducing one of three events that are known to induce relapse in humans: stress, exposure to the drug itself or cues associated with use of the drug. In one recent study (Nuutinen et al. 2016), it was found that cue-induced reinstatement of alcohol seeking was reduced by the histamine H_3 antagonists, ciproxifan and JNJ-39220675. Effects specific to the active lever suggest that histamine H_3 antagonists block the reinstating properties of the cue and do not affect general motor or motivational properties of the drugs.

Another means of assessing the rewarding properties of drugs of abuse is through the conditioned place preference (CPP) paradigm (Tzschentke 1998). Rats are trained to associate two distinct sides of a chamber with either saline or the drug. The two sides of the chamber are distinguished by their visual and sensory properties. Animals are placed in one side of the box and given ethanol for a number of days, and then they are given saline in the other side of the box for a number of days. On the test day, the animal is placed in the middle of the two chambers and the time spent on the two sides is recorded. When pre-treated with ST1283, a H_3R antagonist, prior to conditioning with ethanol, it was found that ST1283 treatment reduced the acquisition of a conditioned place preference for an alcohol-associated chamber (Bahi et al. 2013). In a follow-up study by the same authors, DL77, another H_3R antagonist, also blocked the acquisition of a conditioned place preference (Bahi et al. 2015). These results are consistent with other findings that the H_3R antagonists ciproxifan (3 mg/kg) or JNJ-10181457 (5 mg/kg) also inhibited the acquisition of a conditioned place preference (Nuutinen et al. 2011b), confirming the results obtained in other studies (Vanhanen et al. 2013). Finally, when compared to the WT, KO mice lacking the H_3R failed to acquire a conditioned place preference for alcohol (Nuutinen et al. 2011a). The H_3R agonist immepip (30 mg/kg) had no effect on conditioned place preference, suggesting that the effects of agonists and antagonists are not necessarily reciprocal (Nuutinen et al. 2011b). It should be noted that in a previous study (Nuutinen et al. 2010), ciproxifan enhanced the acquisition of a conditioned place preference; the authors concluded that differences in the results of these studies could be due to strain differences in the mice. In the study in which

ciproxifan enhanced the acquisition of the conditioned place preference, the 129/Sv strain may not have been optimal. These results should be interpreted in the context of another study that found no effects of conessine, a steroid alkaloid found in a number of plant species, which acts as H_3R antagonist, on acquisition of an ethanol-induced conditioned place preference in mice (Morais-Silva et al. 2016). In summary, there is some evidence for a role of H_3R in the rewarding properties of alcohol, as measured with CPP. However, there are some inconsistencies in the literature.

One early and well-established means of testing the rewarding properties of substances of abuse is through tests of locomotor activation (Wise and Bozarth 1987). Rodents are naturally active and inquisitive and substances of abuse that increase locomotor activity are believed to activate a natural reward-seeking response in animals. In one study, the H_3R antagonist ST1283 attenuated alcohol-induced locomotion (Bahi et al. 2013), as did ciproxifan (Nuutinen et al. 2010). By comparison, in another study, ciproxifan extended the locomotor response of low dose ethanol (1.0 g/kg), but had no effect on higher dose of ethanol (1.5 g/kg) (Nuutinen et al. 2011b). The authors proposed that the discrepancy in the findings of their two studies may be related to mouse strain differences in sensitivity to the locomotor-stimulating effects of ethanol. Indeed, in another study, it was found that conessine, an H_3R antagonist, potentiated the locomotor stimulation effects of ethanol in mice (Morais-Silva et al. 2016). In a study with KO mice lacking the H_3R, KO mice did not display increases in locomotion after treatment with ethanol (Nuutinen et al. 2011a). Most studies seem to suggest that H_3R antagonists attenuate ethanol-induced locomotion, but there are some inconsistencies.

H_3R antagonists have also been tested in measures of motor coordination such as the rotarod test and balance beam test. In the rotarod test, the latency for the mice to fall off a 3 cm diameter rotarod that is accelerating (5–30 rpm) is measured. In the balance beam, mice are trained to walk along a 100 cm long, 1.5 cm diameter beam placed in their home cage. Measures are time to cross the beam and number of foot slips. In the rotarod test, the H_3R antagonist ciproxifan and H_3R agonist had no effect on their own. The antagonist also had no effect on ethanol-induced impairment while the agonist potentiated it, but not significantly. In the balance beam, the agonist enhanced the number of ethanol-induced foot slips. Ciproxifan had no effect and neither affected the time to cross the beam (Nuutinen et al. 2011b). Similarly, JNJ-39220675 had no effect on alcohol-induced ataxia (Galici et al. 2011). In KO mice lacking the H_3R, performance on the balance beam after ethanol was less impaired, but performance on the rotarod was not different from that of the WT (Nuutinen et al. 2011a). Together, this suggests a subtle role of H_3R in changes in motor coordination after alcohol administration.

Attempts have been made to delineate the site of effect of H_3R antagonists and whether changes in alcohol pharmacokinetics could be related to the observed effects. It has been found that the H_3R antagonists, ST1283 (Bahi et al. 2013), ciproxifan (Nuutinen et al. 2011b) or DL77 (Bahi et al. 2015) had no effect on alcohol levels in the blood after administration of ethanol, while in other studies JNJ-39220675 also did not affect alcohol elimination rates (Galici et al. 2011; Vanhanen et al. 2013). Similarly, the H_3R agonist immepip had no effects on

changes in blood alcohol levels (Nuutinen et al. 2011b), and blood alcohol levels in H_3R KO mice were similar to those in the WT after a challenge with ethanol (Nuutinen et al. 2011a). Together, these findings suggest that the effects of H_3R antagonists on alcohol reward are not related to alcohol pharmacokinetics. Instead, H_3R antagonists may act centrally in the brain. In this regard, the H_3R antagonist in one study was without effect on alcohol-induced DA levels (Galici et al. 2011; Nuutinen et al. 2016) or turnover in the nucleus accumbens as measured by microdialysis (Morais-Silva et al. 2016). There were also no effects of the H_3R antagonist conessine on alcohol-induced changes in DA or metabolites in the ventral tegmental area or caudate putamen (Morais-Silva et al. 2016). However, a H_3R antagonist increased histamine release in the nucleus accumbens (Nuutinen et al. 2016); and conessine blocked ethanol's effects on DA and NE concentrations in the prefrontal cortex of mice and decreased dopaminergic metabolites in the substantia nigra (Morais-Silva et al. 2016). In H_3R KO mice, few significant differences in DA or serotonin were found, but metabolites of DA were lower in the H_3R KO mice in the prefrontal cortex, when compared to the WT mice (Nuutinen et al. 2011a).

In summary, it appears that H_3R antagonists generally decrease ethanol consumption and reward. In addition, H_3R antagonists decrease the self-administration and cue-induced reinstatement of ethanol seeking. Studies of the effects of H_3R antagonists on CPP and locomotor activity are somewhat discrepant, but it appears that H_3R antagonists may generally decrease ethanol-potentiated locomotor activity and CPP. The mechanism of action seems to be centrally-mediated and cannot be explained by a change in the pharmacokinetic properties of ethanol after administration of H_3R antagonists.

1.2 Nicotine

In one study, the effects of a H_3R antagonist, thioperamide, alone or in combination with nicotine, was tested on a radial arm maze (Kholdebarin et al. 2007). The radial arm maze is a test of memory in which bait is placed at the end of certain arms of a maze that has eight arms. The rat is trained to approach the end of the arms that have the bait. At the start of every trial, the rat is placed in the centre of the maze and entries to the various arms are scored. In one study, entries into any arm other than first time entry to the baited arm was counted as an error. When administered various doses of thioperamide (0, 2.5, 5, and 10 mg/kg) prior to performance on the radial arm maze, it was found that the highest dose produced an increase in choice accuracy impairment over the course of the session. Nicotine co-treatment reversed this impairment. Given on its own, the 0.4 mg/kg dose of nicotine prevented significant learning over sessions, suggesting that nicotine causes a deficit in memory in this task. The 5 mg/kg dose but not the 2.5 or 10 mg/kg doses of thioperamide reversed this deficit in learning produced by nicotine. Thus, at high doses, H3 antagonists can block learning, but at moderate doses a reversal in nicotine-induced memory deficit can be seen.

In another test of memory, nicotine and/or the H_3R antagonist, ABT-239, were administered prior to testing on an elevated plus-maze (Kruk et al. 2012). When administered on their own prior to the acquisition trial, acute nicotine (0.0175–0.35 mg/kg) but not acute ABT-239 (0.1–3 mg/kg) reduced the latency to enter the enclosed arm in the test trial, consistent with an improvement in memory. When administered together, ABT-239 potentiated the effects of nicotine, suggesting an improvement in memory. When subthreshold doses of ABT-239 (0.1 mg/kg) and nicotine (0.0175) were given, latencies were decreased. The same results were found when the mice were tested for consolidation of memory. That is, nicotine and/ABT-239 were administered after the acquisition trial and tested subsequently in the test trial. By injecting the mice after the acquisition, the consolidation, or 'stamping in' of the memory after training is evaluated. Neither ABT-239 nor nicotine had any effects on locomotor responses, suggesting that changes in performance were not due to any motor deficits. Thus, it appears that H_3R antagonists can improve nicotine-enhanced memory.

In another study, the effects of ABT-239 on nicotine-evoked acquisition and expression of locomotor sensitization were tested (Miszkiel et al. 2011). Locomotor sensitization was induced by injecting rats with nicotine for 5 days and then resting undisturbed for days 6–9. On day 10, rats were tested for nicotine-induced sensitization. When given ABT-239 together with the nicotine during the acquisition phase, nicotine-induced sensitization was potentiated as compared to co-administration of a vehicle with nicotine during the acquisition phase. When given during the expression phase on day 10, ABT-239 did not affect the expression of locomotor sensitization. This suggests that histamine H_3 antagonists may potentiate the acquisition, but not expression, of locomotor sensitization induced by nicotine. Given on its own, ABT-239 (0.3, 1, and 3 mg/kg) had no effects on locomotor activity in rats and it did not affect nicotine-induced hyperactivation, suggesting that changes in sensitization were not due to effects on motor output.

The effects of H_3R antagonists have also been tested on the somatic signs of nicotine withdrawal (Patel et al. 2021). To induce withdrawal, mice were injected three times daily for 12 days with nicotine. At 24 h post nicotine withdrawal time, mice were tested in a number of situations. First, the mice were subjected to a light and dark model to assess the amount of time spent in light or dark areas (mice preferring the dark). Abstinence scores were also evaluated in 30 min sessions. Somatic measures were grooming, rearing, jumping, body shakes, forelimb tremors, head shakes, abdominal constrictions, scratching, empty mouth chewing or teeth chattering, genital licking, tail licking. When given intracerebroventricularly, thioperamide-pretreated mice exhibited increased anxiety scores as evidenced by a reduction in the percentage of time spent in the light compartment. In addition, thioperamide pre-treated mice also exhibited more somatic signs of withdrawal.

In summary, it appears that H_3R antagonists may accentuate the effects of nicotine on memory and may increase some symptoms and signs associated with nicotine withdrawal. H_3R antagonists may also increase the addictive properties of nicotine, given that H_3R antagonists potentiated the locomotor sensitization measured after repeated doses of nicotine. It should be noted that those models are not

the most relevant to study addictive properties of nicotine in animals and further studies testing the impact of H_3R ligands on more relevant models are required (e.g., conditioned place preference, nicotine intravenous self-administration and reinstatement of nicotine-seeking behaviours).

1.3 Psychostimulant

Studies of the effects of H_3R agents on methamphetamine and cocaine-induced locomotion have yielded conflicting results with some important implications. In an early study it was found that the H3 antagonist thioperamide inhibited amphetamine-induced activity (Clapham and Kilpatrick 1994), consistent with studies that investigated the effects of ABT-239, pitolisant, JNJ-10181457 and conessine on methamphetamine-induced activity (Fox et al. 2005; Kitanaka et al. 2020). H3 antagonists had no effects on their own, suggesting that the effects were on amphetamine-stimulated locomotion. The agonist, α-methylhistamine had no effect on amphetamine-induced activity but reversed the thioperamide-induced suppression of locomotor activity (Clapham and Kilpatrick 1994). In contrast to the Clapham and Kilpatrick (1994) study, the H_3R agonist, imetit, suppressed locomotion induced by methamphetamine but not cocaine (Banks et al. 2009), but had no effects on basal locomotor activity in mice when administered alone. The authors propose that these results are likely different from the Clapham and Kilpatrick (1994) study due to differences in the potencies of the H_3R agonists used. Further, the authors propose that it is not clear if the lack of effect on cocaine-induced locomotion was due to a lack of power or real lack of effect ($n = 5/6$ per group). Further, differences between the effects of H_3R agonists on methamphetamine or cocaine could be due to differential actions on a dopamine releaser (methamphetamine) as opposed to reuptake inhibitor (cocaine). The story is further complicated by findings that mice treated with combinations of thioperamide and cocaine were more active than mice treated with cocaine alone (Brabant et al. 2005, 2006, 2009). Thioperamide had no effect on locomotion on its own. Interestingly, the H_3R agonist immepip only partially attenuated the effects of thioperamide on cocaine-induced hyperactivity (Brabant et al. 2009). The authors explain the discrepancy between this result and the Clapham and Kilpatrick (1994) study by stating that thioperamide increases cocaine-induced activity through a mechanism that is partly independent of H_3R. This is supported by their findings that A-331440 (a non-imidazole inverse agonist) had no effect on spontaneous locomotion or cocaine-induced locomotion. Thus, thioperamide may have its effects because it is an imidazole antagonist and may have a mechanism independent of H_3R. Thioperamide increased plasma cocaine concentrations, suggesting that this drug may have its effects through peripheral mechanisms of the elimination of cocaine and not through a central mechanism at the H_3R (Brabant et al. 2016). Indeed, high doses, but not low doses, of the non-imidazole H_3R antagonist pitolisant depressed spontaneous locomotor activity. Pitolisant had no effects on the locomotor activity induced by cocaine

(Brabant et al. 2016). Together, these studies support a role of H_3R antagonists in the locomotor response induced by methamphetamine. However, there are a number of answered questions regarding the role of H_3R antagonists in hyperactivity induced by cocaine.

Studies have revealed a role for H_3R antagonists in the rewarding properties of cocaine, as measured with CPP. When tested on its own, the non-imidazole H3 antagonist pitolisant did not induce a CPP. When given prior to pairing cocaine with a side of the chamber, pitolisant did not block the acquisition of a CPP. Pitolisant also had no effects on locomotor activity at low doses (Brabant et al. 2016). The imidazole H_3R inverse agonist, thioperamide, also did not attenuate the acquisition of a cocaine-induced CPP. Further, when paired with a subthreshold dose of cocaine, thioperamide given with cocaine induced a CPP. Importantly, thioperamide did not induce a CPP on its own, indicating no rewarding or addictive properties (Brabant et al. 2005). The authors conclude that thioperamide produces a leftward shift in the dose-response function of cocaine; that is, it lowers the effective dose of cocaine. Although compelling, this interpretation should be viewed with some caution given the findings that imidazole H_3R inverse agonists such as thioperamide may have their locus of action independent of H_3R (Brabant et al. 2016):

Some evidence that H3 antagonists produce a leftward shift in the dose-response function for psychostimulants comes from studies of drug discrimination. In this paradigm, the animal demonstrates the ability to differentiate between a rewarding drug and a control substance, such as saline. The test drug is then given and responses to the lever previously associated with the reward suggest that the test substance has interoceptive properties that are similar to the rewarding drug. In one study (Campbell et al. 2005), the H_3R antagonists thioperamide and clobenpropit produced some cocaine-appropriate responding but did not substitute fully for cocaine. This suggests that H_3R antagonists can potentially have effects that are similar to cocaine. In this same study, the antagonists and the agonist α-methylhistamine produced a leftward shift in the dose-response function for cocaine (0.01, 0.1, 1, and 10 mg/kg) when administered prior to responding for cocaine. In another study, thioperamide and the agonist α-methylhistamine also did not substitute for methamphetamine in a test of drug discrimination (Munzar et al. 1998). Thioperamide decreased the response rate, but the agonist had no effect. Consistent with the results of Campbell et al. (2005), thioperamide shifted the dose-response curve to the left, but the agonist had no effect. This is also consistent with other findings that H_3R antagonists increased methamphetamine-appropriate responding (Munzar et al. 2004). When given with thioperamide, the shift to the left was blocked by the agonist, suggesting an H_3R mediated effect. Thioperamide, but not the agonist, also extended the time course of the effects of methamphetamine, providing further evidence for a potentiation in the effects of methamphetamine. Together with some of the results of tests of CPP, it seems that H_3R antagonists may potentiate the effects of psychostimulants.

Consistent with this notion, one study found that thioperamide and clobenpropit potentiated responding for a low dose of methamphetamine (Munzar et al. 2004). However, in this same study, these antagonists also decreased responding for a high

dose of methamphetamine-, suggesting a dose-response function. On their own, the antagonists failed to maintain self-administration, suggesting that their effects were on the reinforcing properties of methamphetamine. In contrast, when injected 5 min prior to the session, pitolisant had no effect on nose pokes for cocaine, but when given 60 min prior, a high dose of pitolisant decreased nose pokes for cocaine (Huyts et al. 2019). When injected 5 min but not 60 min before the test session, there was a slight decrease in responding at the highest dose under a progressive ratio (PR) schedule. PR schedules of reinforcement provide a sensitive measure of the reinforcing properties of drugs (Richardson and Roberts 1996). Under a PR schedule, the number of responses required for each subsequent reinforcement is gradually incremented. Eventually the animal reaches a 'break point' where they no longer make increasing numbers of responses for the drug. In this same study, when pitolisant was substituted for cocaine, nose pokes decreased over days, suggesting no reinforcing effects of pitolisant (Huyts et al. 2019). As well, animals did not acquire self-administration of pitolisant further suggesting no reinforcing effects of pitolisant. The authors offer the conclusion that pitolisant does not affect the reinforcing properties of cocaine because the effective dose in this study also decreased locomotor activity in other studies (Brabant et al. 2016); thus the effects may be due to non-specific effects of pitolisant on motor output. In sum, there are some conflicting results on the effects of H_3R antagonists on the reinforcing properties of psychostimulants, which may be related to differences in the drugs (methamphetamine or cocaine) or perhaps to differences in study methodology.

A number of studies have investigated the effects of H_3R antagonists on the acquisition of drug sensitization. In one study, it was found that thioperamide did not induce locomotor sensitization when animals were injected for 5 days straight then again on days 10, 15, 22, or 30 (Komater et al. 2003). By comparison, cocaine induced a robust sensitization, as expected. In another study, thioperamide had no effect on the acquisition of cocaine-induced sensitization when animals were pre-treated with thioperamide when receiving cocaine injections (Brabant et al. 2006). By contrast, ciproxifan attenuated methamphetamine-induced sensitization (Motawaj and Arrang 2011). Discrepancies in these findings could be due to the fact that H_3R antagonists may differentially impact methamphetamine or cocaine reward-related processes. As suggested by Brabant et al. (2016), this may be due in part to actions of thioperamide on hepatic enzymes, and not due to any actions on H_3R (Brabant et al. 2016).

One final study looked at the effects of a H_3R agonist, imetit, on an avoidance paradigm (Banks et al. 2009). In this study, a red light was illuminated and the animal had 3 s to press the lever to terminate an electrical stimulus to the tail. Responding on the lever was under a fixed interval 300-s schedule, meaning that the shock was terminated after pressing the lever for 300 s. Both methamphetamine and cocaine increased responding under this schedule in squirrel monkeys, as expected for psychostimulants. Imetit had no effect on basal levels of lever pressing or on stimulant-induced increases in lever pressing. This suggests that H_3R are not involved in avoidance learning, but it should be noted that H_3R antagonists were not tested.

1.4 Clinical Translation of H_3R Ligands for Substance Use Disorders

The aggregate findings from preclinical studies of H_3R ligands and drug-related phenotypes appear to support efforts to translate these findings to early human studies of alcohol-related outcomes. In contrast, preclinical findings concerning nicotine and psychostimulants do not yet appear to offer a particularly convincing basis for translation; further studies are needed, notably with more relevant preclinical models. Translational studies of H_3R drugs as candidate therapies for alcohol use disorder (AUD) should take into account several considerations, including regulatory status of the compounds reviewed above, their potential side effect profiles and human data regarding medication effects on in vivo measures of H_3R occupancy. The approval of pitolisant for the treatment of daytime sleepiness in narcolepsy, coupled with a favourable side effect profile and the availability of post-marketing surveillance data, make pitolisant particularly well positioned for near-term clinical research in human samples. As noted, initial work with pitolisant indicates high occupancy for H_3R in vivo following oral administration of the drug (40 mg). A review of registered trials indicates that pitolisant is currently being studied in populations of heavy drinkers and stimulant users. Additionally, other recent studies are underway to study other H_3R antagonists in Phase II studies of heavy drinkers. Results of these studies will provide initial indication of whether H_3 antagonists can produce changes in clinically relevant outcomes (e.g., alcohol craving and consumption) in heavy drinkers.

Other considerations for clinical translation include drug tolerability and side effect profiles in clinical populations. For the indication of excessive daytime sleepiness in patients with narcolepsy, pitolisant is administered once daily (typically in the morning), with a gradual upward titration from 8.9 mg to 35.6 mg over 3 weeks. Notably, in patients with moderate hepatic or renal impairment, a lower recommended dose (17.8 mg) is recommended. Pitolisant is also contraindicated in those with severe hepatic impairment. These profiles raise considerations for clinical use of H3 receptor antagonists for patients with AUD, and suggest the importance of screening for hepatic impairment prior to treatment initiation. Pitolisant is also contraindicated in patients with known QT prolongation, as the medication prolongs the QT interval. Based on clinical trials of patients with narcolepsy, the most common side effects of pitolisant are insomnia (6% of patients), nausea (6%) and anxiety (5%), with these rates occurring at 2–3 times those observed in the placebo group. This profile suggests that clinical monitoring is warranted when using H_3R ligands in AUD populations. In particular, some of these side effects are commonly observed during alcohol withdrawal (e.g. insomnia, anxiety), and H_3 antagonists could augment these symptoms under conditions of withdrawal. Further Phase II research is necessary to characterize the tolerability and side effect profiles of pitolisant in AUD populations. Additionally, the cognitive enhancement profile of pitolisant suggests that studies examining cognitive enhancement or recovery in

patients with substance use populations may serve as another future direction for Phase II studies.

1.5 Conclusions

The effects of H_3 agonists and antagonists have been studied in a number of animal models, including CPP, drug self-administration, drug discrimination, sensitization and locomotor responding. In addition, for nicotine, the involvement of H_3R was also studied in tasks designed to assess memory. In summary, the results of these studies seem to suggest that there are inconsistent effects of histamine H_3 agonists and antagonists on these various tasks. However, The fact that different drugs of abuse have different brain targets may explain the differential effects of H_3R ligands.

By comparison, the ability of H_3R antagonists to serve as viable treatment options for nicotine dependence is less convincing. At this point, more studies with more relevant preclinical models are required to determine the potential of H_3R ligands for nicotine use disorder. By far the most inconclusive effects of H_3R antagonists are on the reward-related properties of psychostimulants. The availability of ligands such as pitolisant which allow direct testing in human subjects would allow to clarify the potential of H_3R ligands for psychostimulant use disorder.

To date, the most compelling evidence for a therapeutic potential of H_3R antagonists in substance use comes from studies of alcohol use. In general, H_3R antagonists decreased preference for ethanol and reduced binge drinking, ethanol self-administration and cue-induced reinstatement of alcohol seeking. The results of studies of CPP and locomotion are less consistent but in general suggest that H_3R antagonists decrease CPP and ethanol-induced locomotion. Converging evidence suggests that the effects of H_3R antagonists are not non-selective but rather reflect an action on the abuse properties of alcohol. It is likely that the effects of H_3R antagonists are due to actions on the H_3R and not mediated through a change in the elimination of alcohol. Together, these studies suggest that H_3R antagonists may be viable treatment strategies for alcohol use disorder, as has been previously suggested (Panula 2020; Panula and Nuutinen 2011).

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Efficacy and Safety of Non-brain Penetrating H_1-Antihistamines for the Treatment of Allergic Diseases

Kazuhiko Yanai, Takeo Yoshikawa, and Martin K. Church

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Abstract H_1 receptor antagonists, known as H_1-antihistamines (AHs), inactivate the histamine H_1-receptor thereby preventing histamine causing the primary symptoms of allergic diseases, such as atopic dermatitis, pollinosis, food allergies, and urticaria. AHs, which are classified into first-generation (fgAHs) and second-generation (sgAHs) antihistamines, are the first line of treatment for allergic diseases. Although fgAHs are effective, they cause adverse reactions such as potent sedating effects, including drowsiness, lassitude, and cognitive impairment; anticholinergic effects, including thirst and tachycardia. Consequently, the use of fgAHs is

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not recommended for allergic diseases. Today, sgAHs, which are minimally sedating and, therefore, may be used at more effective doses, are the first-line treatment for alleviating the symptoms of allergic diseases. Pharmacologically, the use of sedating fgAHs is limited to antiemetics, anti-motion sickness drugs, and antivertigo drugs. The use of histamine H_1-receptor occupancy (H_1RO) based on positron emission tomography (PET) has been developed for the evaluation of brain penetrability. Based on the results of the H_1RO-PET studies, non-brain-penetrating AHs (nbpAHs) have recently been reclassified among sgAHs. The nbpAHs are rapidly acting and exhibit minimal adverse reactions and, thus, are considered first-line drugs for allergic diseases. In this review, we will introduce recent topics on the pharmacodynamics and pharmacokinetics of AHs and make recommendations for the use of nbpAHs as first-line treatment options for allergic diseases.

Keywords Allergic disease · Antihistamines · Efficacy · Histamine H_1-receptor occupancy · Non-brain-penetrating · Pharmacokinetics · Potency

Abbreviations

AHs	Antihistamines
BBB	Blood-brain barrier
Cmax	Maximum plasma concentration
CNS	Central nervous system
EMA	European Medicines Agency
Emax	Maximal response
FDA	Food and Drug Administration
fgAHs	First-generation antihistamines
H_1RO	Histamine H_1-receptor occupancy
hERG	Human ether-a-go-go-related gene
nbpAHs	Non-brain-penetrating antihistamines
OTC	Over-the-counter
PAF	Platelet-activating factor
PET	Positron emission tomography
P-gp	P-glycoprotein
REM	Rapid eye movement
RT	Receptor residence time
sgAHs	Second-generation antihistamines
T½	Half-life
Tmax	Maximum plasma concentration

1 Classification of Antihistamines

H_1 receptor antagonists, known as H_1-antihistamines (AHs), have been used as anti-allergic drugs since their first introduction for clinical use in 1942 (Church and Rihoux 1992; Simons and Simons 2011; Church 2017). In the early stages of development, many first-generation antihistamines (fgAHs), such as promethazine, also served as prototypes of central nervous system drugs such as antipsychotics and antidepressants. In fact, some antidepressants and antipsychotic drugs are the most potent H_1 antagonists (Sato et al. 2013; Sato et al. 2015). Although fgAHs were efficacious against allergic diseases, they caused strong sedating effects owing to blood-brain barrier (BBB) penetration. In addition, their selectivity for H_1-receptors was low, and the frequency of adverse reactions, such as thirst, urinary retention, and tachycardia, was high. To overcome these significant drawbacks, second-generation antihistamines (sgAHs) with high H_1-receptor selectivity, low brain penetrability, and long plasma half-life have been developed (Simons and Simons 1994; Timmerman 2000; Casale et al. 2003). It is reasonable to classify AHs into sedating and non-sedating drugs according to the presence or absence of sedating properties (Yanai et al. 2017; Kawauchi et al. 2019).

In sgAHs, hydrophilic functional groups (-COOH, $-NH_2$) were introduced to decrease the BBB penetrability, thereby lowering the sedating effects. Global guidelines for allergic diseases, including Japanese, American, and European, recommend sgAHs with low central nervous system penetrability as first-line drugs (Holgate et al. 2003; Zuberbier et al. 2009; Church et al. 2010; Bousquet et al. 2020). Carboxyl group-type AHs have high specificity for H_1-receptors (Fig. 1).

(Z)Olopatadine

(R)(S)Cetirizine
(R)Levocetirizine

(S)Bepotastine

Bilastine

(R)(S)Fexofenadine

Fig. 1 Carboxyl group-type non-sedating antihistamines (AHs). Carboxyl group-type AHs have high specificity for H_1 receptors and are recommended as first-line drugs for allergic diseases (Yanai et al. 2017; Kawauchi et al. 2019). Asymmetric carbons involved in optical isomerism are marked with an asterisk (*). Although unrelated to optical isomers, double bonds involved in geometric isomers (cis-trans isomers) of different stereo-structures are marked with a hash symbol (#)

Fig. 2 Non-carboxyl group-type non-sedating antihistamines (AHs). The characteristic feature of non-carboxylgroup-type AHs is that they block not only H_1 receptors but also other receptors (Yanai et al. 2017; Kawauchi et al. 2019). Rupatadine, anti-H_1 + anti-platelet-activating factor (PAF) + anticholinergic effects; desloratadine, anti-H_1 + anticholinergic effects; loratadine, anti-H_1 + anticholinergic effects; epinastine, anti-H_1 + anti-PAF + anti-leukotriene effects, and mequitazine, anti-H_1 + anticholinergic effects. * Asymmetric carbon is involved in the optical isomerism. Peripheral anticholinergic effects may be related to anti-allergic, anti-common cold, anti-gastric acid secretion, anti-gastrointestinal motility, and anti-chronic obstructive pulmonary disease effects, as well as amelioration of overactive bladder, and thus may be clinically useful

Non-carboxyl group-type drugs which have protonated amines at physiological pH, such as mequitazine and desloratadine, have low specificity and block other receptors such as muscarinic receptors (Fig. 2). Drugs such as rupatadine and loratadine are converted to the active metabolite desloratadine in the body. Because loratadine is metabolized by CYP3A4 and CYP2D6, enzymes that are susceptible to drug–drug interactions, the active metabolite desloratadine is often used as an sgAH.

Several studies have suggested hydrophilicity alone is not sufficient to keep drugs from entering the brain but that an active efflux transporter in the BBB may be involved. The most extensively studied of the active efflux proteins is P-glycoprotein (P-gp), which is known to efflux a wide variety of structurally dissimilar drugs (Seelig and Landwojtowicz 2000; Chen et al. 2003). In vitro, studies of P-gp-mediated efflux from caco-2 cells have shown cetirizine, desloratadine, and hydroxyzine to have weak but significant efflux ratios while that of fexofenadine was much greater (Crowe and Wright 2012). Similar studies have shown that bilastine also has a high efflux ratio (Burton et al. 2007; Church 2011). The failure of bilastine and fexofenadine to enter the brain and occupy histamine H_1-receptors has been confirmed using positron emission tomography (PET) (Farre et al. 2014). Thus, these two drugs appear to be truly “non-sedating” H_1-antihistamines, and the most likely reason for their lack of brain penetration is that they are actively pumped

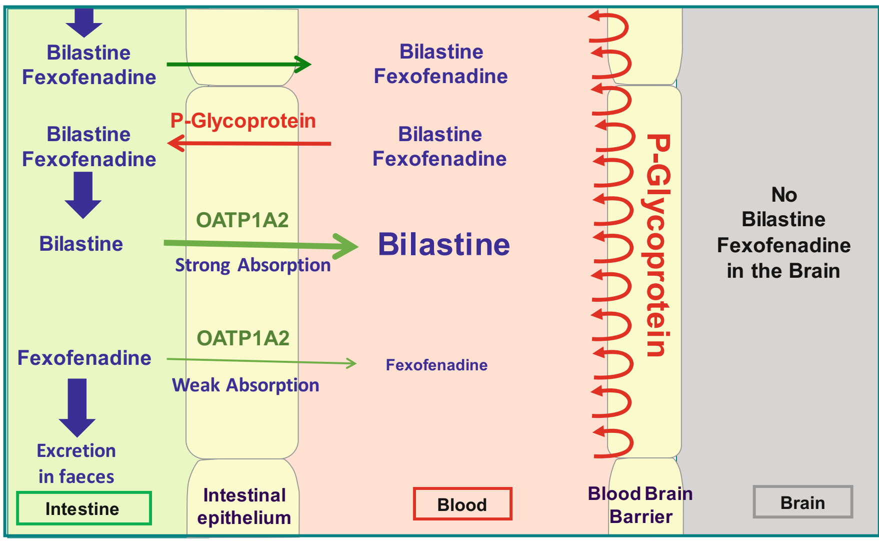

Fig. 3 Absorption, excretion, and prevention of brain penetration of bilastine and fexofenadine. The top left-hand corner shows the passive absorption of both from the intestine into the blood. Both drugs are then partially excreted by the membrane pump p-glycoprotein. Both drugs are then actively absorbed by the transporter OATP1A2, bilastine more effectively than fexofenadine. Both drugs are prevented from entering into the blood and brain by p-glycoprotein

out of the BBB by P-gp as shown in Fig. 3 (Schinkel 1999; Chen et al. 2003; Church 2011; Maurer et al. 2011; Montoro et al. 2011).

2 Constitutive Activity of Histamine H_1 Receptors

In cultured cells, the levels of the H_1 receptor increase in the presence of histamine (Mizuguchi, et al. 2020). In contrast, some AHs decreased the expression levels of the H_1 receptor. In fact, H_1 receptor levels in the nasal mucosa of patients with allergic rhinoconjunctivitis are increased and then decreased with the use of AHs. Signal transduction is considered to begin only when the agonists are bound to receptors. However, with increased receptor expression, signal transduction occurs in the absence of agonists, and this type of receptor activation is known as constitutive activation. When receptors are constitutively activated, AHs act as inverse agonists to inhibit the activated receptors and return to a non-activated state (Bakker et al. 2001; Leurs et al. 2002). Early treatment for allergic rhinoconjunctivitis, in which AHs are administered before the pollinosis season, is provided to directly block histamine and inhibit constitutive activity.

3 Efficacy and Potency of AHs

The binding affinity (potency) of non-sedating AHs toward the H_1 receptor varies widely, and the difference in potency can be $\geq$100 times (Yanai et al. 2011). Although the potency of AHs varies widely, clinical efficacy, which is expressed by the maximal response (Emax), is almost the same when the drug is used at sufficient doses. Therefore, when efficacy is insufficient, non-sedating AHs are to be used at higher doses up to four-fold the standard dose in Europe (Makris et al. 2013). For the clinical use of non-sedating AHs, a better understanding of the pharmacodynamic concepts related to potency and efficacy is necessary. The clinical effectiveness of steroids, AHs, and anti-allergic drugs for the treatment of allergic diseases are different, in the order of steroids > AHs > anti-allergic drugs. A recent randomized controlled study has reported that there are no additive effects with the combined use of AHs and leukotriene antagonists and that monotherapy with AHs will suffice for seasonal allergic rhinoconjunctivitis (Lavorini et al. 2020).

The potency of a drug is generally expressed as binding affinity, which is measured in vitro at equilibrium between receptors and drugs. It is usually measured using radioactive ligands, and the binding of the ligands to the receptors under equilibrium conditions is expressed as the inhibitory binding concentration, K_i (Yanai et al. 2011). As shown in Fig. 4a, the lower the K_i value, the more potent is the binding affinity. The binding affinity of the H_1 receptor to histamine per se is far lower than that of the H_1 receptor to AHs; thus, any AH can sufficiently block the binding of histamine to the H_1 receptor at a clinically useful level. Shimamura et al. (2011) reported the crystal structure of human histamine H_1 receptor complex with doxepin and binding models of AHs. The recently -reported cryo-electron microscopy structure of the human H_1 receptor also improved understanding of the competition of histamine binding sites by AHs (Xia et al. 2021).

Binding affinity can also be measured under kinetic conditions between a receptor and radioactive ligand (Bosma et al. 2017; Bosma et al. 2018). The kinetic method measures the receptor residence time (RT), which is the reciprocal of the rate of dissociation from the receptor at a non-equilibrium state k_{off}. The larger the RT, the higher is the potency. Different AHs have different K_i and RT values, as shown in Fig. 4b. Notably, the in vitro RTs of classical AHs, such as diphenhydramine, are considerably shorter than those of non-sedating sgAHs, indicating that the length of time for which classical AHs act on H_1 receptors is very short. However, as RT was determined in vitro, it might not be applicable to true in vivo conditions. Once they penetrate the brain, the AHs remain for a considerable period (see Fig. 7). It has been reported that the in vivo association and dissociation of [^{3}H]pyrilamine in the brain were much slower than those of in vitro binding at 37°C (Yanai et al. 1990).

Although determination of K_i and RT, indicators of the in vitro potency of an AH, may help in the best selection of candidate AHs, the large differences in the volume of distribution and tissue accumulation in humans may preclude K_i and RT from being a good predictor of clinical efficacy (Church and Maurer 2012).

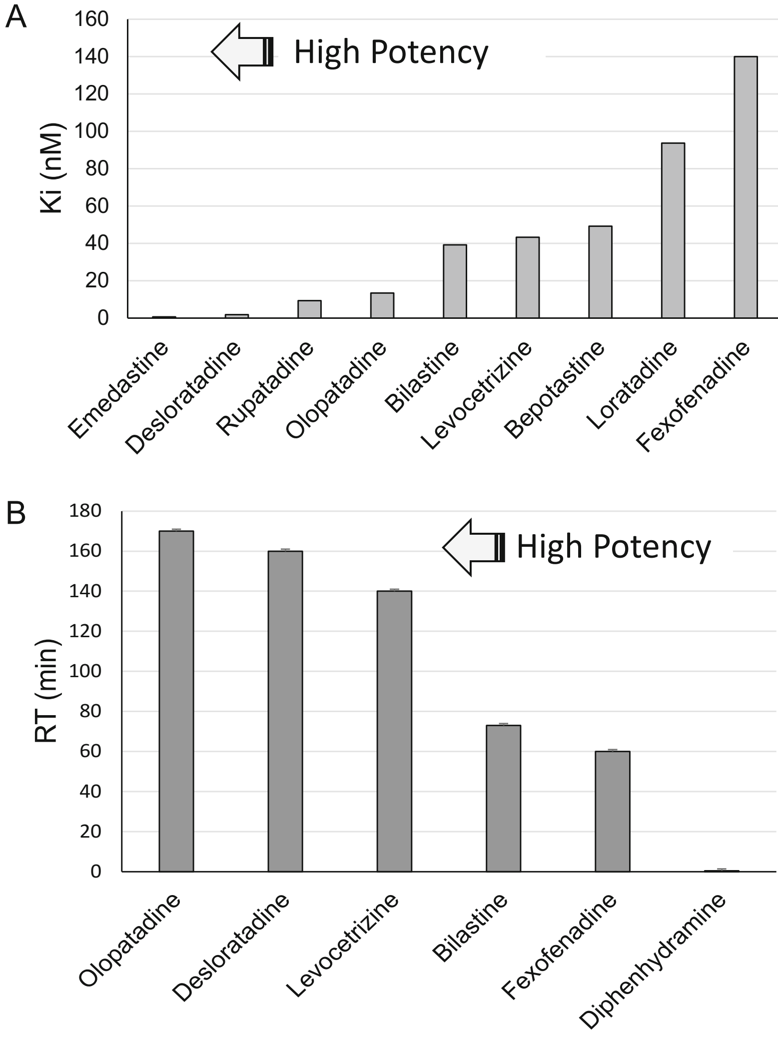

Fig. 4 Potency of antihistamines: Measurement at the equilibrium (**a**) and dynamic states (**b**). (**a**) Binding affinity (Ki value) measured at equilibrium in vitro; (**b**) Receptor residence time (RT) measured by in vitro kinetics. The RT can also be measured based on changes in intracellular Ca^{2+} concentration without the use of radioactive ligands. Note that clinical efficacy does not necessarily depend on the potency of receptor binding. Modified from Yanai et al. (2011) and Bosma et al. (2017, 2018)

4 Functions of the Histaminergic Nervous System in the Brain

There are approximately 64 000 histamine-producing neurons, located in the tuberomammillary nucleus of the human brain. When activated, these neurons stimulate histamine receptors in all the major parts of the cerebrum, cerebellum, posterior pituitary, and spinal cord (Haas and Panula 2003).

The actions of histamine on H_1-receptors in the brain have been implicated in arousal in the circadian sleep/wake cycle, reinforcement of learning and memory, fluid balance, suppression of feeding, control of body temperature, control of cardiovascular system, and mediation of stress-triggered release of ACTH and β-endorphin from the pituitary gland (Brown et al. 2001).

Studies in genetically modified mice have confirmed the stimulatory effects of histamine in the central nervous system (CNS) (Yoshikawa et al. 2021). H_1-receptor knockout mice are less active during the active period, sleep insufficiently during the resting period, and are likely to gain weight (Inoue et al. 1996; Schneider et al. 2014). Obesity owing to atypical antipsychotics and antidepressants with potent H_1-antagonistic activity is caused by the blocking of H_1 receptors (Kim et al. 2007; He et al. 2013; Singh et al. 2019). When the histaminergic nervous system actively acts on H_1-receptors in animals, their eating behavior is suppressed. Interestingly, the sleep-wake cycle and obesity were considered to be completely different phenomena. But they are not. They were found to be closely linked. An article entitled "Sleep it off" which means that increasing sleep is a possible way to control obesity was published in Nature in 2006 (Pearson 2006). Maintaining a normal sleep-wake cycle can prevent obesity.

In addition, H_3 receptor antagonists, which activate the histaminergic nervous system, increase spontaneous motility by raising alertness levels and decrease the amount of food intake (Provensi et al. 2016). Recently, an H_3 receptor antagonist, pitolisant was approved for the treatment of narcolepsy in Europe and the USA (Guevarra et al. 2020).

5 Central Effects of Sedating AHs

The central effects of fgAHs are caused by blocking the functions of the histaminergic and cholinergic nervous systems in the brain. Blockade of the histaminergic pathways leads to the sedating effects of AHs which include sleepiness and impaired performance (Church et al. 2010). However, sleepiness and impaired performance are often confused. Emotion comprises emotional experience and emotional expression (Darwin 1872): sleepiness is an emotional experience, and impaired performance is an emotional expression. Blockade of cholinergic pathways, particularly with long-term use by elderly people increases the risk of developing Alzheimer's disease due to cognitive function decline (Gray et al. 2015).

While prescription of fgAHs by the medical profession is minimal today, their availability as over-the-counter (OTC) drugs for the common cold has become a social problem. Some people become addicted to the foggy feeling resulting from the ingestion of sedating AH-containing OTC drugs and buy a large amount of these drugs. When the histaminergic nervous system is inhibited, the brain reward system, such as the dopamine system, can be activated, resulting in drug dependence similar to that of commonly abused drugs.

The use of sedating AHs in children also requires caution, especially when the drugs are used for a long time. The use of sedating AHs in children with convulsion predisposition induces seizures (Takano et al. 2010; Kim et al. 2021), and their long-term use may lead to obesity (Saad et al. 2020). The frequency of occurrence of sedating effects in children is also high, which decreases learning ability. In fact, an observational study on 7-year-old children revealed that use of sedating AHs may reduce the intelligence quotient by approximately 10 points (Jedrychowski et al. 2013). The US Food and Drug Administration (FDA) states that "sedating AHs must not be used in children for sedating purposes" and has recommended pharmaceutical companies to withdraw sedating AH-containing OTC drugs for common cold for children younger than two years, thus prompting pharmaceutical companies to voluntarily withdraw such products from the market (Hampton et al. 2013). The efficacy of sedating AHs in children has not been verified, and there is a high possibility that these drugs may only cause adverse effects. Therefore, they should not be used in children (Church et al. 2020). The sgAHs, such as levocetirizine and fexofenadine, which can be used in infants aged six months or older, are available.

6 Evaluation of the Sedating Effects via H_1RO

We have been objectively evaluating the sedating effect of AHs by measuring H_1RO using PET (Yanai et al. 1995). The brain H_1ROs for medical drugs with H_1 antagonistic activity are shown in Fig. 5. Cetirizine, for example, penetrates the brain in a dose-dependent manner and binds to a considerably large number of H_1 receptors at a dose of 20 mg, causing mild cognitive impairment (Tashiro et al. 2009). While the sedating fgAHs block 50% or more of the brain H_1 receptors, the sgAHs block 30% or less. Note that even sgAHs penetrate the BBB, but to a lesser extent than fgAHs. We propose to classify AHs according to H_1RO into three categories: sedating, H_1RO $\geq$ 50%; less-sedating, H_1RO 20–50%; and non-sedating, H_1RO $\leq$ 20%. However, there are large differences in H_1RO among non-sedating AHs (Yanai et al. 2017).

The Consensus Group on New Generation Antihistamines (CONGA) conference stated that true "non-sedating antihistamines" do not exhibit a sedating effect even when they are administered in excess of usual doses (Holgate et al. 2003). In view of the relationship between plasma drug concentration and H_1RO, they also added that

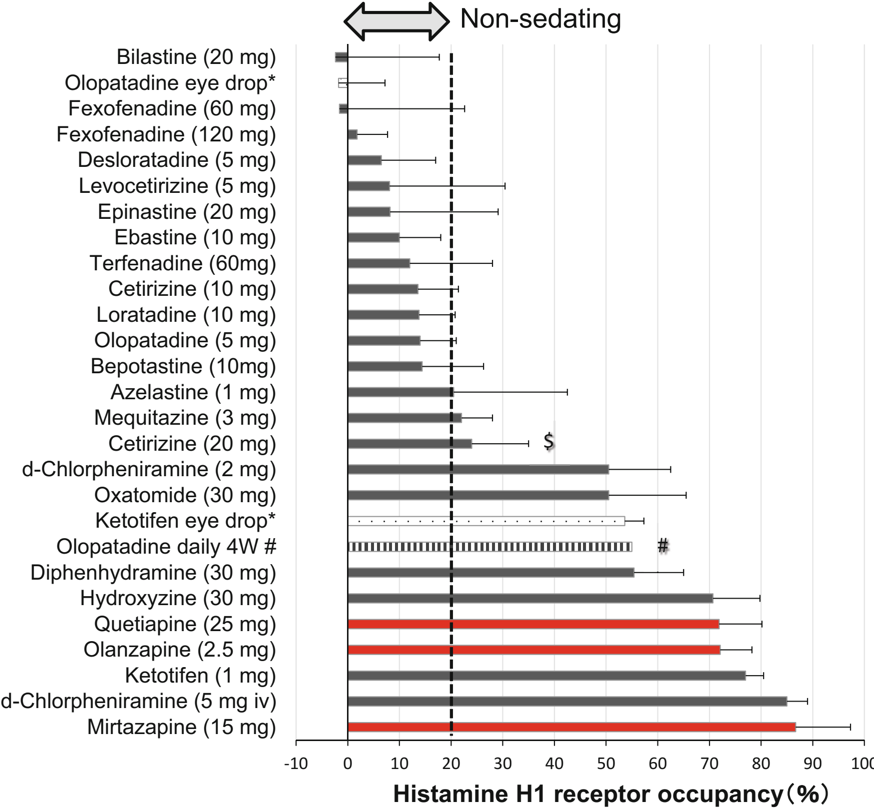

Fig. 5 Histamine H_1 receptor occupancy (H_1RO) in the human brain. Evaluation of the sedating effects of H_1 antagonists based on H_1RO. Antihistamines (AHs) were administered to healthy subjects, and H_1 receptor levels were measured at the maximum plasma concentration (Tmax) using positron emission tomography. The H_1RO data are shown as mean ± SD. As shown in red bars, an antidepressant (mirtazapine) and antipsychotics (olanzapine and quetiapine) showed potent sedating effects and occupied most of the brain H_1 receptors at the minimum doses. Olanzapine 5 mg is also effective against chemotherapy-induced nausea and vomiting. *: eye drop; iv: intravenous injection. # When olopatadine 5 mg was repeatedly administered twice daily (morning and evening) for 4 weeks, the H_1RO increased from 15 to 55%. For the other drugs, a single oral dose was administered. $ Cetirizine has a sedative effect when its dose is increased from 10 mg to 20 mg. Modified from Yanai et al. (2016, 2017) and Nakamura et al. (2019)

"to be truly non-sedating, the drugs should not decrease H_1 receptor binding even when their plasma levels are high." From this viewpoint, non-sedating AHs can be further subclassified into "non-brain-penetrating antihistamines" (nbpAHs) as shown in Fig. 6 (Kawauchi et al. 2019).

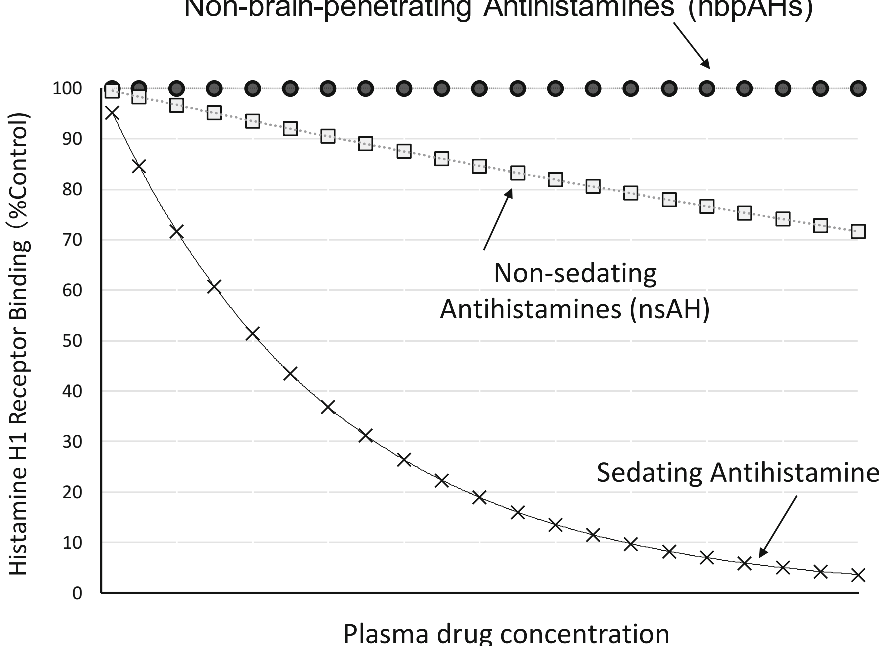

Fig. 6 Conceptual model of “non-brain-penetrating antihistamines (nbpAHs).” The relationship between plasma concentration and H_1 receptor binding after administration of H_1 receptor antagonists is shown. To ensure that sedating effects never occur, it is essential that H_1 receptor binding does not decrease even with an increase in the plasma drug concentration. Some non-sedating AHs can penetrate the brain in a dose-dependent manner after repeated administration, causing sensitive patients to feel drowsy. Sedating AHs rapidly occupied H_1 receptors in a dose-dependent manner, exhibiting a potent sedating effect

7 Recent Topics in the Clinical Pharmacokinetics of AHs

Most H_1-antihistamines are absorbed passively into the blood from the intestine. Peak plasma levels of passively absorbed drugs occur at around 1–4 h (Geha and Meltzer 2001; Simons 2004; Kawauchi et al. 2019). The pharmacokinetics of sgAHs are better than those of fgAHs. The shorter the time to maximum plasma concentration (Tmax), the faster is the treatment effect, and the frequency of administration is determined based on the plasma half-life (T½) as shown in Fig. 7. A remarkable characteristic of sgAHs is that they are affected by several transporters in intestinal absorption and brain penetration through BBB (see Fig. 3). For example, bilastine and to a lesser extent fexofenadine have a more rapid uptake as they are substrates for an organic anion transporting polypeptide, OATP1A2 (Russell et al. 1998; Cvetkovic et al. 1999; Tannergren et al. 2003; Shimizu et al. 2005; Lucero et al. 2012; Church and Labeaga 2017). The role of this transporter is supported by its inhibition by grapefruit juice (Dresser et al. 2005; Crean et al. 2007; Akamine et al.

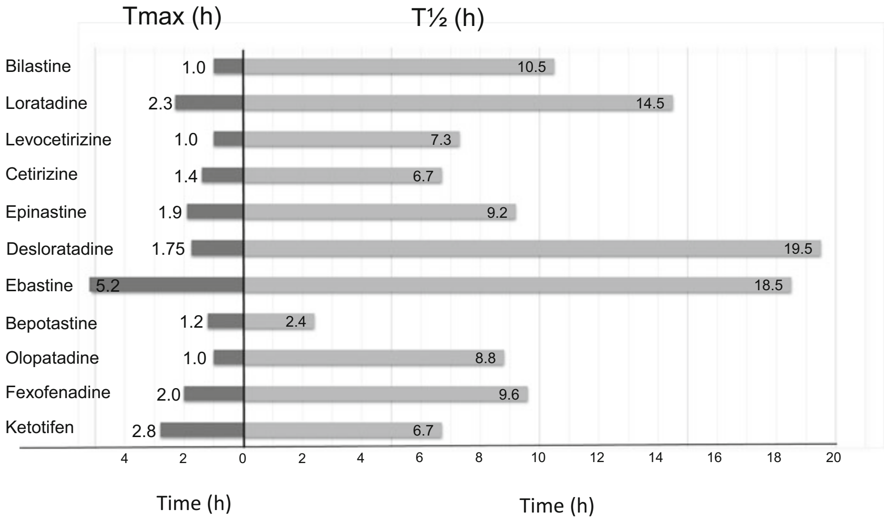

Fig. 7 Plasma pharmacokinetics of antihistamines. The numbers of columns are the respective Tmax and T½ of sgAHs as expressed as hours (h). Equilibrium of plasma concentration is reached at approximately 3–4 half-lives (T½) after continuous administration. The tissue half-life is different from the plasma half-life. The brain half-life is much longer than that of the plasma as shown in Fig. 8

2015). The mean oral bioavailability of bilastine has been estimated to be around 61% in healthy human volunteers (Lucero et al. 2012), while that of fexofenadine is 30% (Lappin et al. 2010), showing that the affinity for anion pump is stronger with bilastine. Here, we introduce three recent topics regarding the pharmacokinetics of AHs.

7.1 *In Vivo Brain RT of AHs in the Human Brain*

The next-day residual sedative effect after nighttime administration of the OTC sleep aid diphenhydramine was previously verified by direct PET measurement of H_1RO (Zhang et al. 2010). Figure 8 illustrates how long the sedating AH, diphenhydramine, remains in the brain as determined by PET. The in vivo half-life in the brain can be estimated by examining the changes in H_1RO by measuring the histamine H_1 receptor by PET three times, before, at 3 h, and 23 h after the administration of sedating AHs, in the same subjects. The half-lives of diphenhydramine 50 mg and ketotifen 1 mg in the brain were approximately 30 and 45 h, respectively (Yanai et al. 2016). Because the plasma half-lives of the two drugs were in the range of 6–8 h, their brain RT in vivo was found to be substantially longer. The H_1ROs of AHs in the skin and nasal mucosa are also considered to last long (Gillman et al. 2009).

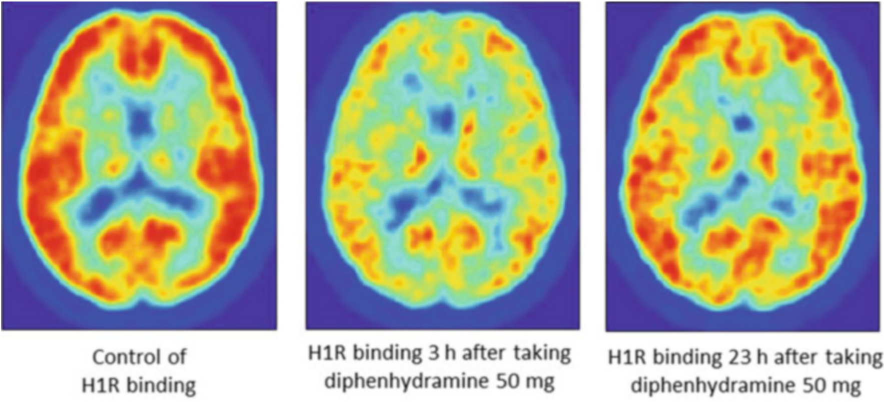

Fig. 8 [^{11}C]doxepin binding to histamine H_1 receptor (H_1R) at baseline (left), 3 h (middle), 23 h (right) after taking diphenhydramine 50 mg in humans. Once the antihistamines (AHs) penetrate the brain, they remain there for a long time. Therefore, a withdrawal period of at least 72 h is necessary after the half-life in the brain has elapsed. The use of sedating AHs at night deteriorates the quality of sleep because they occupy the brain receptors for a long time. Therefore, it is preferable to use non-sedating AHs for allergic diseases at night. Considering the possible hangover effect of over-the-counter AH sleep aids, care needs to be taken during their administration. Modified from Yanai et al. (2016)

7.2 Brain Penetrability of AH in Eye Drops

Eye drops containing AHs are often used to alleviate the eye-related symptoms of pollinosis. The OTC eye drops often contain sedating AHs. However, the risk is not sufficiently communicated to general users. To measure the brain penetrability and obtain H_1RO data for eye drops, histamine H_1receptors in the brain were measured by PET before and after the application of ketotifen eye drops and olopatadine eye drops as a 1-day dose each (Yanai et al. 2016). The H_1ROs after the application of olopatadine and ketotifen eye drops were $-1.\ 8\% \pm 9.0\%$ and $53.6\% \pm 3.7\%$ ($n = 7$), respectively. Thus, although olopatadine eye drops did not affect the brain H_1 receptors, ketotifen eye drops accounted for approximately 50% of the H_1 receptors. With local mucosal administration, drugs are absorbed rapidly. In addition, because there is no first-pass effect, they are likely to rapidly penetrate the brain. The plasma level of ketotifen is nearly zero because of its rapid penetration into the brain. Because eye drops can be absorbed from the nasal mucosa through the nasolacrimal duct, as well as from the cornea and conjunctiva, to measure the H_1 receptor binding by PET, the subjects were instructed to press the upper part of the nose when applying the eye drops. The sgAH-containing eye drops olopatadine, epinastine, and bepotastine, are marketed as medicine. These sgAH-containing eye drops are recommended as first-line treatment for allergic conjunctivitis as they have low brain penetration.

7.3 Transdermal Patch AH Preparation

A transdermal patch containing emedastine difumarate was developed for the treatment of allergic rhinitis in Japan (Okubo et al. 2018; Tanida et al. 2018). Percutaneous absorbable preparations showing systemic effects similar to those of oral drugs have been developed for use as drugs for angina pectoris, asthma, and neurological and psychological diseases; hormone preparations; smoking cessation aids; and narcotic analgesics. Percutaneous absorbable preparations are absorbed more slowly and can maintain constant plasma levels for a longer duration than orally administered drugs. Although emedastine is a potent sedating AH, its percutaneously absorbable preparation might be considered to exhibit less frequent subjective feelings of drowsiness than its oral preparation because the former preparation is absorbed more slowly (Fig. 9). However, because sedating effects appear in a dose-dependent manner, the risky operation of machinery, such as car driving, must be avoided.

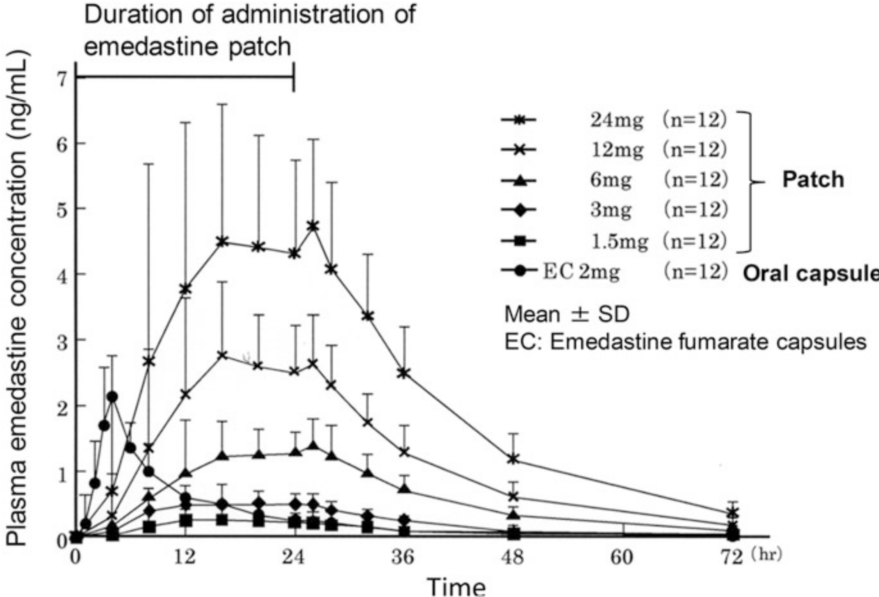

Fig. 9 Changes in plasma concentrations of emedastine administered as percutaneously absorbable and oral preparations. The Tmax of the emedastine patch was 16–20 h, which was approximately 4–5 times longer than that of the oral capsule. In addition, the T½ of the former is approximately twice that of the latter. The maximum plasma concentration (Cmax) of the oral preparations for repeated administration and that of the percutaneously absorbable preparations were adjusted to be the same. Pharmacokinetic data of oral preparations were obtained after a single oral dose of 2 mg. EC: emedastine fumarate capsules. Modified from Tanida et al. (2018)

8 AHs Present in OTC Rhinitis Drugs and OTC Common Cold Drugs

In Japan, epinastine was launched in 2011 as the first OTC allergic rhinitis drug that was less likely to cause drowsiness. Thereafter, OTC allergic rhinitis drugs containing fexofenadine, cetirizine, loratadine, ebastine, and bepotastine were marketed, and the share of non-sedating AHs, which are "less likely to cause drowsiness," has risen to nearly 70% in the market. Impaired performance owing to sedating AHs has become common. In Japan, the only sedating AHs are present in OTC common cold drugs. Several cases of traffic accidents due to the ingestion of OTC common cold drugs have been reported.

Nasal symptoms due to both allergic rhinitis and the common cold involve histamine and acetylcholine as the main chemical mediators. Therefore, antihistamines and anticholinergic drugs that exhibit antagonistic effects on the receptors of these mediators are effective for treating nasal symptoms (De Sutter, et al. 2015). In Japan, non-sedating sgAHs have been used to treat acute upper respiratory inflammation and acute bronchitis in the clinical setting of off-label use. In many countries, sgAH-containing OTC drugs have been approved and marketed for rhinitis and common cold. For example, in the USA and China, as well as in European countries, loratadine is present in rhinitis drugs and common cold drugs.

9 Cardiotoxicity of Sedating AHs

Adverse reactions caused by sedating AHs include cardiotoxicity, lowering of seizure threshold, and obesity, in addition to sedating effects. Several reports appeared in the literature indicating the rare occurrence of a form of polymorphic ventricular dysrhythmia, the "torsade de pointes," after the administration of astemizole or terfenadine. The mechanism most frequently involved in cardiotoxicity induced by several AHs is the blockade of hERG (human Ether-a-go-go-Related Gene, Kv11.1) voltage-gated K^+ channels (Taglialatela et al. 1999; Hazell et al. 2017). It has been pharmacologically verified that non-sedating sgAHs are less likely to cause cardiotoxicity than fgAHs. In particular, the guideline-recommended dose escalation up to four times the usual dose in treatment-resistant patients is considered safe in healthy individuals (Cataldi et al. 2019). The first-generation AH, hydroxyzine, is pro-arrhythmogenic, and the European Medicines Agency (EMA) called attention to this adverse effect in 2015 (Morales et al. 2021). Particular caution should be exercised when hydroxyzine is used in patients with chronic kidney disease because it may cause QT prolongation (Poluzzi et al. 2015; Snitker et al. 2017).

10 Conclusion and Perspectives

In this review, we have looked as fgAHs which penetrate the brain to cause sedation, sgAHs which penetrate the brain poorly and a minimally sedating, and nbpAHs which do not penetrate the brain at all and avoid sedative effects. While the sedative action of fgAHS indicates they are useful as sleep aids, this should be strongly discouraged for two reasons. First is that they have very long half-lives in the brain, some up to 24 h, resulting in hangover in the morning when wakefulness is required. Second is fgAHs increase the latency to the onset of rapid eye movement (REM) sleep and reduce the duration of REM sleep (Boyle et al. 2006; Rojas-Zamorano et al. 2009). This leads to a poor-quality sleep.

Sedating AHs that penetrate the central nervous system have other clinical uses. They are useful as antiemetics, anti-motion sickness drugs, and antivertigo drugs. This is because H_1-receptors and muscarinic receptors are associated with the vomiting center of the brain. Histamine is also involved in nociception, and transmission of noxious stimuli in the ascending pain pathway, such as in the spinal cord (Yanai et al. 2003; Obara et al. 2020). The inhibition of pain associated with migraine, visceral pain, postoperative pain, and cancer pain by sedating AHs has been reported (Worm et al. 2019). However, pain inhibition by non-sedating AHs has not been fully investigated except for irritable bowel syndrome (Wouters et al. 2016). Further studies regarding the utility of AHs for pain control are warranted.

Some basic and epidemiological studies have reported that patients using AHs are less likely to contract COVID-19 than non-users. The University of California examined 219,000 people who were tested for the SARS-CoV-2 infection using PCR and reported that those who were on AHs were significantly less likely to contract the virus (Reznikov et al. 2021). A Spanish study also reported that AH users were more likely to test negative for COVID-19 infection (Vila-Córcoles et al. 2020). Proposed mechanisms for the antiviral effects of AHs include their interactions with the SARS-CoV-2 spike glycoprotein receptor binding domain, sigma-1 receptor, and heparan sulfate (Ennis and Tiligada 2021; Hou et al. 2021). Further research on AHs developed by the Nobel laureate Daniel Bovet should be conducted.

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Part III
The Immune and Inflammatory Response in the Brain

The Histamine and Multiple Sclerosis Alliance: Pleiotropic Actions and Functional Validation

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Abstract Multiple sclerosis (MS) is a disease with a resilient inflammatory component caused by accumulation into the CNS of inflammatory infiltrates and macrophage/microglia contributing to severe demyelination and neurodegeneration. While the causes are still in part unclear, key pathogenic mechanisms are the direct loss of myelin-producing cells and/or their impairment caused by the immune system. Proposed etiology includes genetic and environmental factors triggered by viral infections. Although several diagnostic methods and new treatments are under development, there is no curative but only palliative care against the relapsing-remitting or progressive forms of MS. In recent times, there has been a boost of

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awareness on the role of histamine signaling in physiological and pathological functions of the nervous system. Particularly in MS, evidence is raising that histamine might be directly implicated in the disease by acting at different cellular and molecular levels. For instance, constitutively active histamine regulates the differentiation of oligodendrocyte precursors, thus playing a central role in the remyelination process; histamine reduces the ability of myelin-autoreactive T cells to adhere to inflamed brain vessels, a crucial step in the development of MS; histamine levels are found increased in the cerebrospinal fluid of MS patients. The aim of the present work is to present further proofs about the alliance of histamine with MS and to introduce the most recent and innovative histamine paradigms for therapy. We will report on how a long-standing molecule with previously recognized immunomodulatory and neuroprotective functions, histamine, might still provide a renewed and far-reaching role in MS.

Keywords Clinical trials · Demyelination · Drug therapy · Experimental autoimmune encephalomyelitis · Histamine · Multiple sclerosis

Abbreviations

BBB	Blood brain barrier
CNS	Central nervous system
CSF	Cerebrospinal fluid
DAO	Diamine oxidase
EAE	Experimental autoimmune encephalomyelitis
HDC	l-Histidine decarboxylase
HNMT	Histamine-*N*-methyltransferase
MS	Multiple sclerosis
OPC	Oligodendrocyte precursor cells

1 The Histamine System

Heterogeneous genetic and molecular mechanisms contribute to multiple sclerosis (MS), a disabling central nervous system (CNS) disease causing permanent deterioration of axons. These gradually lose their myelin ensheathment because of an autoimmune reaction to myelin, caused by T lymphocytes entering the brain after blood-brain-barrier (BBB) injury. Signs and symptoms of MS are very variable and depend on the extent and exact location of axonal damage. While there is no cure for MS, pharmacological treatments can modulate disease progression, manage the symptoms, and accelerate recovery (Derdelinckx et al. 2021; McGinley et al. 2021).

The potent physiological actions of the hydrophilic vasoactive histamine have been identified a while ago by Sir Henry Dale and Patrick Laidlaw (Dale and

Laidlaw 1910). Over the years, histamine has proven to be a master molecule in pharmacology and immunology, with two Nobel Prizes awarded for the identification of anti-H1R and anti-H2R antagonists. In addition to their use for allergic, gastric, and immune disorders, histamine drugs have entered clinical testing for obesity, neurological disorders, and memory [for reviews (Hu and Chen 2017; Ghamari et al. 2019; Volonté et al. 2019; Provensi et al. 2020a, b)].

Histamine is obtained exclusively from decarboxylation of the amino acid histidine, a reaction catalyzed by l-histidine decarboxylase (HDC, encoded in humans by *HDC* gene, generating an active homodimer of 54 kDa per unit), which is localized in the intracellular compartment of specific cell phenotypes. Major histamine producing cells are: (1) mast cells (resident cells of connective tissue that contain many histamine and heparin granules, a sort of granulocytes derived from myeloid stem cells and part of the immune and neuroimmune systems); (2) basophil (the least common type of granulocyte, representing about 0.5% to 1% of circulating white blood cells); (3) enterochromaffin-like cells (a type of neuroendocrine cell found beneath the epithelium of gastric mucosa gland cells and contributing to the production of gastric acid via the release of histamine); (4) and histaminergic neurons (histamine releasing neurons present exclusively in the tuberomammillary nucleus of the posterior hypothalamus, and involved in the control of arousal, learning, memory, sleep, and energy balance). Minor histamine producing cells are also dendritic, T cells, macrophages/microglia, neutrophils, monocytes, platelets, and epithelial cells (Huang et al. 2018; Thangam et al. 2018).

Once synthetized intracellularly, histamine can be stored in intracellular granules/vesicles, released extracellularly, and/or rapidly metabolized by its primary degradative enzymes. The vesicular monoamine transporter-2 is responsible for loading monoamines, among them also histamine, into secretory vesicles (Schafer et al. 2013). Histamine degrading enzymes are histamine-N-methyltransferase (HNMT, encoded by *HNMT* gene in humans, generating a 33 kDa protein) catalyzing the methylation of histamine, and diamine oxidase (DAO, encoded in humans by *AOC1* gene, generating a homodimer of theoretical 73 kDa per unit) catalyzing oxidative deamination, an enzyme whose shortage in the human body causes allergy or histamine intolerance (Comas-Basté et al. 2020). The HNMT enzyme resides in the cytosol, whereas DAO metabolizes extracellular free histamine. Synthesis, storage in granules/vesicles, degradation, and release of histamine are highly regulated mechanisms, under the control of a plethora of different extracellular and intracellular signals among them trophic factors, hormones, transmitters, and various stressors, thus rendering the histaminergic system a complex sensor and effector of cellular and environmental modifications (Haas et al. 2008).

Active extracellular release of histamine from granules/vesicles occurs mainly by wide diffusion through a concentration gradient and slow transmission mechanisms, being mediated: (1) by IgE/antigen crosslinking, complement activation, or the presence of allergens in mast cells and basophils (Borriello et al. 2017); (2) by somatostatin- or gastrin-dependent activation in enterochromaffin-like cells (Barocelli and Ballabeni 2003); (3) by activation of N-methyl-D-aspartate, U opioid, D2 dopamine, or serotonin receptors in histaminergic neurons (Haas et al. 2008).

The actions of released histamine are terminated not only by DAO (see above), but also by the cellular reuptake system through specific monoamine transporters such as serotonin, dopamine, and norepinephrine transporters, i.e. Na^+- and Cl^--dependent high affinity transporters, defined as uptake-1 system, and through Na^+- and Cl^--independent low affinity, high-capacity uptake-2 system transporters (Slamet Soetanto et al. 2019).

In the extracellular space, histamine exerts its effects by primarily binding to the 7-transmembrane rhodopsin-like family of G protein-coupled receptors classified as H1R, H2R, H3R, and H4R, respectively, encoded in humans by *HRH1*, *HRH2*, *HRH3*, and *HRH4* genes (Haas et al. 2008). Recently, histamine was also shown to activate ligand-gated chloride channels in the brain and intestinal epithelium (Panula et al. 2015).

In eukaryotic cells, H1R is found in smooth and cardiac muscles, vascular endothelial cells, and in the CNS. The downstream pathways activated after binding of histamine to H1R are Gq protein, phospholipase C leading to inositol triphosphate-dependent release of calcium from intracellular stores, and diacylglycerol formation with modulation of voltage-dependent calcium channels (Leurs et al. 2002). As a key regulator of inflammatory processes, NF-κB expression and downstream pathways are tightly controlled by activation or constitutive activity of H1R in target cells, to the point that H1R antagonists were shown to mitigate inflammation through NF-κB modulation (Apolloni et al. 2016). The class of molecules commonly known as H1R antihistamines and generally used to treat allergies can function as either receptor antagonists or inverse agonists at H1R, although only limited H1 antihistamines act as inverse agonists (H1 receptor. IUPHAR/BPS Guide to Pharmacology, http://www.guidetopharmacology.org). In the CNS, H1R activation induces excitatory stimulation, moreover controls nutritional state and wake–sleep cycles, and also regulates neuroinflammatory processes (Fukui et al. 2017).

H2R is present in vascular smooth muscles, where it controls muscle relaxation and vasodilation; in neutrophils, it prevents activation and chemotaxis; in T and B cells, it modulates proliferation and antigen-specific responses as antibody synthesis and cytokine production; in gastric gland cells, it stimulates gastric acid secretion (Thangam et al. 2018); not last, in mast cells enriched in histamine granules. In the CNS, the receptor is found in cerebral cortex, caudate-putamen, hippocampus, and dentate nucleus of cerebellum, playing a role in neuronal plasticity, synaptic transmission, and cognitive performance (Haas et al. 2008). H2R is positively coupled to adenylate cyclase through activation of Gs protein that induces cyclic adenosine monophosphate production, protein kinase A activation, and phosphorylation of target proteins.

H3R is mainly expressed in cortical and subcortical areas of the CNS (being involved in cognitive processes, wakefulness, and eating behaviors) and, to a lesser extent, in the peripheral nervous system (Nieto-Alamilla et al. 2016), other than in the heart, lung, and gastrointestinal tract and endothelial cells. H3R shows very little sequence homology with H1R and H2R. Differently from the other histamine receptors, H3R has the peculiarity to act as autoreceptor in presynaptic histaminergic

neurons and to feedback regulate the turnover of histamine by inhibiting its synthesis and release. This inhibitory activity is exerted also on presynaptic dopamine, gamma-aminobutyric acid, glutamate, noradrenaline, serotonin, and acetylcholine receptors, thus H3R also behaves as inhibitory heteroreceptor (Panula et al. 2015). Consequent to histamine binding to H3R, the first downstream effector to become activated is Gi protein, causing inhibition of cyclic AMP production. Through inhibition of N-type voltage-gated Ca^{2+} channels mediated by β and γ subunits of G proteins, H3R also inhibits Ca^{2+} uptake mediated by action potentials, thus further reducing neurotransmitter release.

In humans, H4R is a receptor subtype mainly present peripherally in oral epithelium, bone marrow, and leukocytes, where it regulates neutrophils release from bone marrow, eosinophil shape change, and mast cells chemotaxis, through modulation of actin polymerization and cytoskeleton stability. It operates through Gαi-dependent inhibition of adenylate cyclase and Gβγ-dependent stimulation of phospholipase C, leading to inositol triphosphate and diacylglycerol formation, Ca^{2+} mobilization from intracellular stores, and activation of protein kinase C (Thurmond 2015).

Histamine is an important pleiotropic factor actively participating in multiple physiological functions such as neurotransmission, circadian rhythms, sleep–wake cycle, mood, learning, appetite, and eating behavior. Moreover, histamine levels are modulated in the CNS as a function of age, sex, and disease insurgence and progression. Histamine deficiency is related to narcolepsy, food intake and sleep disorders, and to neuropsychiatric conditions comprising schizophrenia and several different neurodegenerative/neuroinflammatory diseases (Cacabelos et al. 2016a, b). Several studies have described the histaminergic system as directly involved in various pathological conditions of the CNS, among them ischemia, traumatic brain and spinal cord injury, Alzheimer's, Huntington's, Parkinson's diseases, Wernicke's encephalopathy, Tourette syndrome and, of course, MS. The pathophysiological relevance of central histamine signaling has thus accelerated several attempts to pharmacologically manipulate brain histamine concentrations for the treatment of various neurological disorders (Naganuma et al. 2017). We believe that further research will certainly stimulate a deeper comprehension of disease-related histaminergic mechanisms, with potential identification of histamine-dependent therapeutic opportunities.

2 From Central and Peripheral Inflammation to Myelination Defects in MS

MS is a chronic autoimmune, inflammatory, and neurodegenerative disease that affects both white and gray matter of the CNS, although historically identified as a predominantly affecting white matter disease. MS occurs within various stages and evolves as a continuum from a clinically isolated acute syndrome to a secondary-progressive disease through relapsing-remitting phases. MS is very heterogeneous

indeed: in approximately 85% of patients the disease exhibits a relapsing-remitting course characterized by acute attacks followed by partial or complete recovery. Over time, many relapsing-remitting patients switch to the secondary-progressive phase, where neurological lesions and disabilities gradually accumulate even without further relapses. On the other hand, about 10–15% of patients have a progressive primary course, characterized by a continuous accumulation of neurological lesions and disabilities that already start at the insurgence of the disease (Milo and Kahana 2010).

Pathological studies described the presence of cerebral and cerebellar cortical demyelination in MS patients and led to the identification of three types of lesions: subpial, intracortical, and leukocortical (Bö et al. 2006). Cortical demyelination also present in early MS phases is topographically associated with conspicuous meningeal inflammation and may precede white matter plaques formation in MS patients, and be associated with irreversible disability and cognitive impairment (Popescu and Lucchinetti 2012). The pathogenic events that characterize MS are various and include lymphocytes infiltration through the BBB, inflammation, microglia activation, and astrocyte proliferation with consequent nerve conduction impairment, demyelination, axonal transection, and neuronal injury. These causally related events lead to plaques formation (Ciccarelli et al. 2014).

Although MS can be considered as a primary autoimmune disease [“outside-in” hypothesis (Lucchinetti et al. 2011; Malpass 2012; Baecher-Allan et al. 2018)], many scientists now doubt that inflammation and/or autoimmunity are really the unique promoters of the disease and have proposed that MS originates as a neurodegenerative disease [the “inside-out” hypothesis (Stys et al. 2012; Duffy et al. 2014)]. Although the exact etiology remains unknown, the debate on whether the immune or the nervous system initiates the disease is certainly open, and now scientists tend to consider MS a neuroimmune system disease, initiated when multiple biochemical signals triggered by neurotransmitters, neurohormones, cytokines, chemokines, and growth factors in neurons, glia and immune cells lose their homeostasis. With no doubt, MS is a disease with critically altered communication between the nervous and immune systems.

Clear evidence now suggests that the contribution of the immune system is less in the progressive than in the initial acute forms of the disease. In the progressive form, CNS resident cells as microglia and astrocytes indeed sustain a low-grade inflammation that leads to oligodendrocyte damage and neurodegeneration (Correale and Farez 2015; das Neves et al. 2020; Prinz et al. 2021).

In particular, the astrocytes highly contribute to inflammation and play a dual role in MS, characterized by both pathogenic alterations and beneficial repair, depending on the stage of the disease, the type and microenvironment of the lesion, the interaction with other cell phenotypes and several exogenous factors (Williams et al. 2007; Nair et al. 2008; Correale and Farez 2015; Amadio et al. 2017; Rao et al. 2019; das Neves et al. 2020). This dual function is documented by means of RNA sequencing, electron microscopy, immunohistochemistry, and imaging techniques that have recognized also high degrees of astrocyte heterogeneity. Indeed, astrocytes are a diversified population of cells possessing specific properties and

functions according to their localization and pathophysiological state (Khakh and Deneen 2019; Linnerbauer et al. 2020; Escartin et al. 2021; Schirmer et al. 2021; Werkman et al. 2021).

In addition, the brain-resident immune cells, microglia, exhibit high heterogeneity in MS, contributing to both damage and repair events (Tsouki and Williams 2021). Not surprisingly, one of the pathological hallmarks of MS is the infiltration of microglia into CNS lesions, where they become the first responders and remain within the lesions until they heal the damaged tissue, or until the damage becomes irreversible and the lesion inactive. As for astrocytes, microglia are conditioned by the microenvironment, the anatomical location of the lesion, and the presence or absence of remyelination during the different stages of MS (Guerrero and Sicotte 2020; Pons and Rivest 2020; Zia et al. 2020).

Also mast cells generally associated with allergic reactions are crucial players of the innate immune system and involved in autoimmune diseases and particularly MS. First of all, brain mast cells are located in the perivascular space where they can secrete various pro-inflammatory and vasoactive molecules able to further weaken an already damaged BBB during MS. Second, several neural factors including substance P, myelin basic protein, and corticotropin-releasing hormone can induce mast cells to release inflammatory mediators during MS. Finally, mast cells can directly participate to inflammation and demyelination in MS by presenting myelin antigens to T cells and permitting inflammatory cells and cytokines to enter through the BBB. Not surprisingly, compounds blocking mast cells can reduce T cell stimulation and EAE (Theoharides et al. 2008; Conti and Kempuraj 2016; Elieh-Ali-Komi and Cao 2017).

3 An Overview of Histamine Preclinical Studies

Different features of MS among them inflammation, demyelination, remyelination, and neurodegeneration have been studied using different animal models, none of which, however, covers the full spectrum of clinical, pathological, or immunological characteristics of the disease. So, the right model for MS research needs to be selected at each time, depending on the specific aspects to be addressed (Lassmann and Bradl 2017). The experimental autoimmune encephalomyelitis (EAE) mouse model and the cuprizone/rapamycin toxic demyelination (useful to investigate only mechanisms of protection and repair, but not inflammation) are among the most frequently used models to study MS. However, EAE can be induced in all vertebrates with different degrees of efficacy, frequently using mice, rats, and primates. Because the EAE models share several histopathological and immunological features with MS, their use has allowed to dissect the pathogenic mechanisms of relapsing-remitting and progressive forms of the disease, proving to be excellent systems for preclinical experimentation as well (Schreiner et al. 2009).

As described above, histamine is a ubiquitous inflammatory mediator involved in the pathogenesis of various allergic, autoimmune, inflammatory, and

neurodegenerative diseases (Hu and Chen 2017; Branco et al. 2018). For this reason, numerous studies were conducted also on the involvement of histamine in EAE, overall demonstrating that the histaminergic system indeed plays a significant role in MS pathogenesis (Panula and Nuutinen 2013). However, the interaction of histamine with its cell surface receptors can induce either detrimental or beneficial actions in the context of EAE, often with multiple and contrasting effects depending on the specifically activated receptors and target tissues (Passani and Ballerini 2012). For instance, histamine can modify the BBB permeability and increase the number of infiltrated cells in the CNS, therefore inducing a process of deleterious neuroinflammation. On the other hand, histamine can sustain a protective role in MS and EAE by reducing demyelination and improving remyelination (Jadidi-Niaragh and Mirshafiey 2010). Through the years, thanks to the use of genetically modified mice deprived of histaminergic enzymes or receptors, and the availability of relatively selective agonists and antagonists, scientists have identified and characterized the direct involvement of histamine and its receptors in EAE/MS (Fig. 1).

3.1 Targeting H1 Receptor

A key mechanism in the development of EAE and MS is the breakdown of the BBB. Sensitization of the endothelium by environmental factors such as *Bordetella pertussis* or biogenic amines such as histamine is believed to lead to increased permeability of the BBB. Pertussis-induced histamine sensitization is an intermediate phenotype of EAE controlled by the histamine receptor H1R. Ma and collaborators have shown that susceptibility to pertussis-induced histamine sensitization and EAE needs expression of *Hrh1*, the gene encoding H1R. Indeed, the authors observed a decreased EAE susceptibility in H1R-KO mice (Ma et al. 2002), while the expression of H1R in T cells is instead disease promoting (Noubade et al. 2007).

To highlight the cell-specific effects of the *Hrh1* in the pathogenesis of EAE and to optimize any cell phenotype-specific therapeutic intervention, Saligrama and collaborators re-expressed H1R in CD11b+ cells of H1R-KO mice, in order to test the hypothesis that H1R signaling in CD11b+ monocytes, macrophages/microglia, and natural killer cells might contribute to EAE susceptibility. Unpredictably, the re-expression of H1R exclusively in CD11b+ cells did not restore EAE severity and affect T cell responses in H1R-KO mice (Saligrama et al. 2012b). The propathogenic role of H1R was also confirmed in additional work in which drug treatment with the H1R antagonist hydroxyzine (known to block mast cells) or pyrilamine reduced clinical severity and pathology in EAE rats and mice, respectively (Dimitriadou et al. 2000; Pedotti et al. 2003).

In contrast, the selective transgenic overexpression of H1R in endothelial cells of *Hrh1*-KO mice demonstrated that these mice were resistant to *Bordetella pertussis*-induced histamine sensitization, also having reduced permeability of the BBB and greater protection from EAE than H1R-KO mice. This suggested that endothelial H1R may be important for sustaining cerebrovascular integrity (Lu et al. 2010).

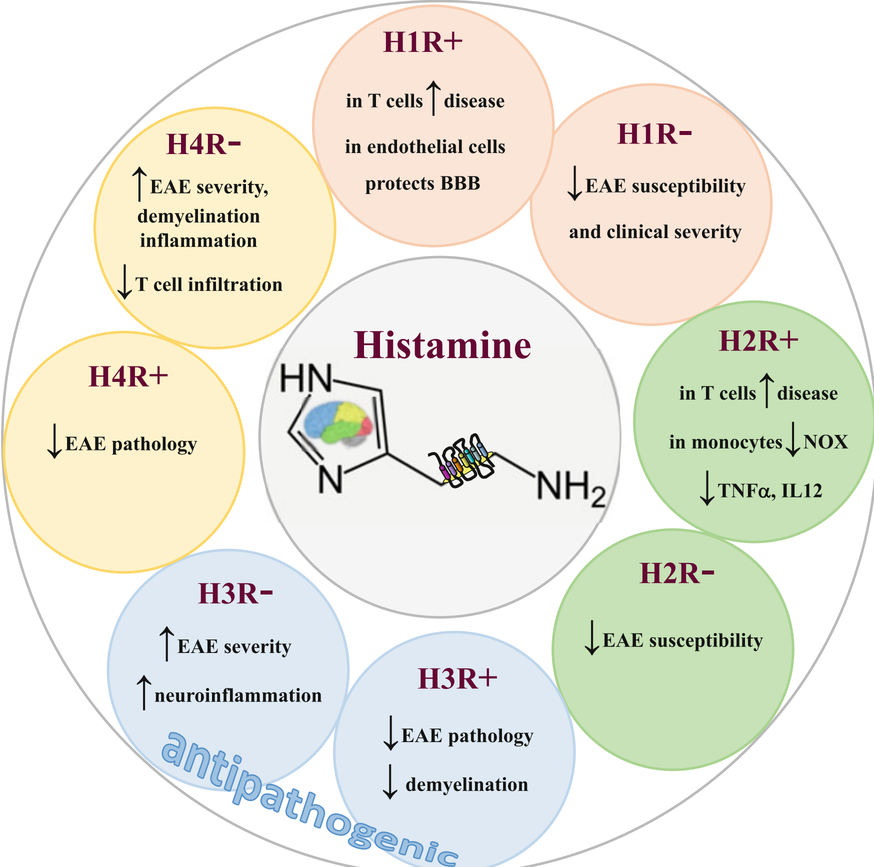

Fig. 1 The dual effect of histamine in improving or worsening EAE pathological features is due to several properties of four histamine receptors. Genetic or pharmacological inhibition (HR-), as well as presence or activation (HR+) of H1-4R receptors can induce different courses of the disease. H3R is the only receptor playing an overall antipathogenic role

3.2 Targeting H2 Receptor

Gene targeting studies established that also H2R plays significant roles in EAE/MS pathogenesis and vulnerability. Similarly to H1R, H2R appears to have a propathogenic role, but in addition H2R induces a beneficial restraint of the autoimmune response, thus assuming a concomitant antipathogenic action. In particular, in H2R-KO mice the attenuation of Th1 effector cells with decreased susceptibility to acute early-phase EAE compared to wild-type mice is due to dysregulation of cytokine production by antigen presenting cells (Teuscher et al. 2004). By breeding transgenic mice expressing H2R exclusively in T cells, Saligrama and collaborators (Saligrama et al. 2014) have extended the previous study determining that T-cell

intrinsic H2R signaling is necessary and sufficient to re-establish EAE susceptibility as in wild-type control mice, as previously observed also with H1R (Noubade et al. 2007). Furthermore, the results demonstrated that EAE severity and neuropathology in H2R-KO mice expressing H2R exclusively in T cells become the same as in wild-type mice, only when adjuvant pertussis toxin modeling environmental factors and susceptibility to disease is used to induce EAE (Saligrama et al. 2014). This proves that unlike H1R, the H2R is also linked to inhibition of inflammatory states, thus possessing also an antipathogenic role. H2R was previously found on monocytes and associated with the suppression of superoxide formation via inhibition of NADPH oxidase (Burde et al. 1990), an enzyme highly involved in the development of EAE (van der Veen et al. 2000). A second possible mechanism for the antipathogenic role of H2R is the inhibition of the production of pro-inflammatory cytokines involved in EAE insurgence. Activation of H2R decreases TNF-α production by inflammatory cells and suppresses IL-12 expression (Vannier et al. 1991; Azuma et al. 2001). For these reasons, treatment with the H2R agonist dimaprit reduces clinical severity and pathology associated with EAE in both C57BL/6 and iNOS deficient EAE mice (Emerson et al. 2002).

3.3 Targeting H3 Receptor

The H3R, unlike the other histaminergic receptors, is not present on hematopoietic cells, but mainly in the CNS (Passani et al. 2011). In 1983, Arrang and collaborators identified the H3R as an autoreceptor that controls the activities of histaminergic neurons such as histamine production, release and electrophysiological response (Arrang et al. 1983). In addition, behaving as a presynaptic heteroreceptor, H3R regulates the release of a variety of other neurotransmitters (Passani and Blandina 2011), thus rendering this receptor a fundamental player at the crossover of central neurotransmission.

Teuscher and co-workers established the antipathogenic role of H3R in EAE pathology (Teuscher et al. 2007). H3R-KO mice develop more severe EAE and neuroinflammation. This result is associated with dysregulation of BBB permeability and increased expression of chemokines/chemokine receptors on peripheral T cells facilitating their entrance into the CNS. H3R effects on EAE seemed to be related both to neurogenic control of cerebrovascular tone and to alterations of immune cells that however do not express H3R. The authors suggested that the lack of presynaptic inhibition in H3R-KO mice leads to increased release of neurotransmitters and augmented postsynaptic activity that performs a neurogenic control of BBB permeability and T cell chemokine profile (Teuscher et al. 2007). Consequently, activation of H3R may be a potential strategy to treat MS/EAE. Indeed, further studies proved that a strong and highly selective histamine H3R agonist, immethridine, could alleviate the severity of EAE when used in EAE mouse model (Shi et al. 2017). EAE mice treated with immethridine showed lower clinical scores and reduced pathology with respect to control EAE mice. Fewer inflammatory infiltrates and

decreased demyelination in spinal cord were also reported. In addition, reduced levels of inflammatory cytokines such as TNFα, IFN-γ, and IL-17A were observed in splenocytes isolated from EAE mice treated with immethridine, thus suggesting a widespread action of this agonist in improving the severity of EAE. Later studies reported that in immethridine-treated EAE mice compared to control EAE the percentage of Th1 and Th17 cells were decreased, and surface molecules such as CD40, CD86, and MHCII were downregulated on dendritic cells thus inhibiting their function (Shi et al. 2017).

Furthermore, an antipathogenic role of H3R has been confirmed in a very recent work in which two new soluble piperidine derivatives acting as histamine H3R antagonists/inverse agonists reduce the lymphocyte numbers and diminish disease symptoms in EAE (Imeri et al. 2021).

3.4 Targeting H4 Receptor

Expression of H4R is mostly restricted to T and B cells, monocytes, eosinophils, dendritic and natural killer cells, therefore playing an important role in the modulation of the immune system. Not surprisingly, this selective localization suggested therapeutic use in inflammatory disorders and autoimmune diseases (Zampeli and Tiligada 2009). However, evidence also demonstrated the topological and functional localization of H4R in human and rodent CNS (Strakhova et al. 2009).

In light of these findings, del Rio and collaborators investigated the potential role of H4R in MS, by inducing EAE in H4R-KO mice and demonstrating that the presence of H4R elicits an antipathogenic role and modulates EAE severity. In addition, H4R signaling exerts control over the abundance of regulatory T cells in secondary lymphoid tissues, regulates their chemotaxis and suppressive ability. H4R-KO mice exhibit augmented neuroinflammation, increased BBB permeability, and more severe EAE compared with wild-type mice. Consistent with this, H4R deficiency leads to lower infiltration of regulatory T cells into the CNS during the acute phase of the disease, causing impairment of anti-inflammatory responses in association with increased encephalitogenic Th17 cells (del Rio et al. 2012).

These data were corroborated by Ballerini and co-authors, which demonstrated that the H4R antagonist JNJ7777120 administrated to EAE mice caused increased inflammation and demyelination in spinal cord, augmented expression of IFN-γ and suppression of IL-4 and IL-10 in lymph nodes, with a general worsening of disease symptoms, thus suggesting a protective role of this receptor in the context of EAE (Ballerini et al. 2013). Despite this antipathogenic action, conflicting results were reported on its propatogenic/antipathogenic role during immune and allergic responses, with a growing interest in the therapeutic anti-inflammatory potential of H4R antagonists in the immune system, where the H4R is ubiquitous. In light of these results, there is urgent need to further investigate this receptor to anticipate potential clinical benefits and/or predict possible deleterious effects (Passani and Ballerini 2012).

3.5 Targeting HDC

Due to the overlapping but often opposite functions played by the different histamine receptors in the presence of endogenous histamine, single receptor-blocking strategies cannot always attain complete elimination of histamine signaling in vitro; similarly, it is difficult to achieve complete and long-lasting inhibition of histamine receptors using pharmacological or genetic approaches in vivo (Ohtsu et al. 2001). Therefore, HDC-deficient mice were generated to provide a more exhaustive model in which to ablate endogenous histamine synthesis and study biological responses in the CNS.

In particular, Musio and co-workers using HDC-KO mice investigated the effect of endogenous histamine removal in the insurgence and progression of EAE. They established that EAE pathology is significantly more severe in histamine-deficient mice, showing diffuse inflammatory infiltrates with a prevalent granulocytic component in the brain and cerebellum. In particular, splenocytes from HDC-KO mice do not produce histamine in response to myelin antigen immunization, but secrete increased amounts of pro-inflammatory cytokines, such as IFN-γ, TNF, and leptin. Therefore, endogenous histamine notably restrains the harmful autoimmune response against myelin and immune impairment in the CNS (Musio et al. 2006).

These results were confirmed by Saligrama and collaborators, who studied the function of endogenous histamine on EAE susceptibility in H1-4R-KO and HDC-KO mice, both deficient in histamine signaling. Surprisingly, H1-4R-KO mice were found to be significantly resistant to EAE, whereas HDC-KO mice were highly susceptible. H1-4R-KO mice develop less severe neuropathological conditions and EAE symptoms than wild-type and HDC-KO mice. Furthermore, splenocytes from immunized H1-4R-KO mice produce lower amounts of Th1/Th17 effector cytokines. Overall, these findings suggest that histamine can mediate increased resistance to EAE also acting through mechanisms independent from its known receptors (Saligrama et al. 2013).

3.6 Combinatorial Histamine Receptor Actions

The previous results, in addition to the pleiotropism of histamine, created some difficulties in the comprehension of the exact pathophysiological roles of histamine in EAE, further complicated by the simultaneous recruitment on the same cell of different histamine receptors that sometimes play different, or even opposite, functions. While the selective combinatorial expression of different receptors subtypes on a given cell can contribute to explain diverse pathological conditions (Volonté et al. 2006, 2008), a similar mechanism can also apply to EAE/MS. In trying to explain the accurate and peculiar alliance between histamine and MS, a study indeed suggested that combinatorial targeting of histamine receptors may be an effective disease-modifying therapy in MS. H3H4R-KO EAE mice developed a significantly

more severe clinical disease course than control or H1H2R-KO EAE mice. Furthermore, histopathological analysis demonstrated increased inflammation and pathology in the brain, but not spinal cord, of H3H4R-KO mice that moreover exhibited augmented BBB permeability during the acute early phase of the disease, compared to H1H2R-KO mice. These data indicate that the joined effect of deleting H1R and H2R signaling becomes antipathogenic in EAE, whereas the combined H3R and H4R ablation is propathogenic. It's important to notice that EAE severity and pathology in H1H2R-KO and H3H4R-KO mirrors that of the single HR-KO mice, where EAE is less severe in H1R-KO and H2R-KO mice, but more pronounced in H3R-KO and H4R-KO mice. This might occur because of a compensatory upregulation of residual HRs in single HR-KO, H1H2R-KO, and H3H4R-KO mice. As a consequence, simultaneous treatment with H1R and H2R antagonists may be protective in the CNS, perhaps due to the upregulation of the antipathogenic H3R and H4R. On the other hand, the absence of H3R or H4R signaling has a negative effect on EAE susceptibility and encephalitogenic T-cell activity, suggesting that H3R and H4R agonists might have a beneficial impact in the treatment of CNS diseases by intervening on histamine signaling through the propathogenic H1R and H2R subtypes (Saligrama et al. 2012a).

So far, we have reported that genetically modified mice lacking single or different combinations of histaminergic enzymes or receptors, together with fairly selective histamine receptor agonists and antagonists, have greatly contributed to identify and in part characterize the involvement of histaminergic signaling in EAE/MS. To allow more successful preclinical development of therapeutic strategies against MS, it is mandatory to have access to more extensive data on the disease progression in animal models, to broader understanding of disease pathology, and to more robust outcome measures that can be used to assess treatment efficacy. We are confident that renewed experimental interest and research on histaminergic axis and mechanisms in EAE/MS will contribute to fill this gap.

4 Histamine Markers in Biological Fluids and CNS Tissues from MS Patients

Discovering reliable and early biomarkers is of fundamental importance in neurological disorders where the diagnosis often occurs after the onset of symptoms, mainly due to lack of specific markers that allow discriminative diagnosis for different pathologies. Significant variations in the peripheral and central levels of histamine have been detected in patients with neurological diseases (Cacabelos et al. 2016a) and histamine levels have been extensively investigated in biological fluids of MS patients as well.

The first study aimed to evaluate histamine-related changes in MS reported that in the cerebrospinal fluid (CSF) of a small cohort of patients with remitting and progressive forms of the disease, histamine levels were about 60% higher than in

controls, and the patients showed a concomitant decrease in histamine-degrading enzyme HNMT, indicating an altered histamine metabolism in the CNS during MS (Tuomisto et al. 1983). Furthermore, a significant increase of the mast cell-specific proteolytic enzyme tryptase (an enzyme released with histamine when mast cells are activated as part of immune responses or allergic hypersensitivity) was found in the CSF of MS patients with respect to control subjects or patients affected by other neurological diseases, suggesting that the activation of mast cell was a pathological feature of MS (Rozniecki et al. 1995). In accordance with these observations, in a recent trial enrolling 36 MS patients and 19 age- and gender-matched healthy volunteers, histamine content was found significantly higher in the CSF of MS patients. Remarkably, the authors demonstrated that histamine levels further increased with age in the CSF of patients (Kallweit et al. 2013). Finally, gene-microarray analysis has shown that H1R expression is upregulated in acute MS lesions (Lock et al. 2002). Independently from the relative up or down values of expression, the overall modulated levels of central histamine found in MS patients could be correlated with enhanced inflammatory response known to contribute to the onset and progression of the disease.

Interestingly, in the serum of MS patients histamine shows an opposite trend with respect to the CNS (Cacabelos et al. 2016b). In particular, the levels of both histamine and the enzyme responsible for its degradation, DAO, have been found decreased in the serum of relapsing-remitting MS patients compared to healthy individuals (Rafiee Zadeh et al. 2018). Moreover, a recent study has shown that the levels of histamine precursor histidine are lower in the serum of MS women with disabling and persistently perceived fatigue, suggesting a strong involvement of histamine also in MS-associated symptoms (Loy et al. 2019).

Finally, by analyzing the expression of *HRH1*, *HRH2*, and *HRH4* genes in peripheral blood mononuclear cells derived from patients with different forms of MS, i.e. relapsing-remitting, primary-progressive, and secondary-progressive, Costanza and co-authors demonstrated that H1R transcript was significantly decreased in secondary-progressive-MS patients compared to healthy individuals and, conversely, H4R was increased in secondary-progressive-MS compared to controls and relapsing-remitting-MS, indicating a distinct involvement of histamine receptors in the different forms of the disease (Costanza et al. 2014). A synoptic view on the modulation of histamine-related markers in biospecimen from MS patients is reported in Table 1.

5 Toward a Histamine-Based Pharmacology in MS Patients

As discussed above, MS is a complex disease requiring different approaches for investigation such as prevention strategies, disease-modifying drugs, and symptomatic treatments. Recently, histamine-based pharmacology has been confirmed as a new avenue in the field of neurodegenerative diseases, especially those associated with a strong neuroinflammatory component. Particularly in MS, histamine-related

Table 1 Modulation of histamine-related markers in MS patients

Marker	CSF		Serum		Brain	
Histamine	↑	(Tuomisto et al. 1983; Kallweit et al. 2013)	↓	(Cacabelos et al. 2016a, b; Rafiee Zadeh et al. 2018)		ND
Histidine		ND	↓	(Loy et al. 2019)		ND
HNMT	↓	(Tuomisto et al. 1983)		ND		ND
DAO		ND	↓	(Rafiee Zadeh et al. 2018)		ND
H1R		ND	↓	(Costanza et al. 2014)	↑	(Lock et al. 2002)
H3R		ND		ND	↑	(Chen et al. 2017)
H4R		ND		ND	↑	(Costanza et al. 2014)
Tryptase	↑	(Rozniecki et al. 1995)		ND		ND

CSF cerebrospinal fluid, *HNMT* histamine N-methyltransferase, *DAO* diamine oxidase, *H1R* histamine H1 receptor, *H3R* histamine H3 receptor, *H4R* histamine H4 receptor, *ND* not detected

molecules are getting to the root causes of the disease and are emerging as potential therapeutic strategies.

Actually, transdermal application of histamine was adopted more than 20 years ago to treat the symptoms of both relapsing-remitting and progressive MS, demonstrating efficacy in improving extremity strength, balance, fatigue in daily activities and cognitive abilities. The authors linked these effects to a rise of histamine in the CNS, leading to improved cerebral blood flow, decreased autoimmune responses, and augmented remyelination of demyelinating fibers (Gillson et al. 1999, 2000). Accordingly, as measured by the Modified Fatigue Impact Scale, the feeling of fatigue was moreover reduced in a small cohort of MS patients compared to placebo group in a 12-week trial with the therapeutic mixture Prokarin, a blend of histamine and caffeine (Gillson et al. 2002).

Regarding H1R, the antagonist hydroxyzine has shown efficacy in reducing mood symptoms in a pilot open-label clinical trial with relapsing-remitting or relapsing-progressive MS patients (Logothetis et al. 2005). Moreover, the compound AVN-101, a BBB-permeable 5-HT7 receptor antagonist with anxiolytic and anti-depressive efficacy in animal models of CNS diseases, also exhibiting high affinity for H1R, demonstrated good tolerability in a phase I MS study, thus suggesting its potential use in alleviating mood symptoms in MS (Ivachtchenko et al. 2016).

Finally, an epidemiological study aimed to associate the risk of developing MS to environmental, lifestyle factors and former pharmacological treatments demonstrated a reduced incidence of MS in patients exposed to sedating H1R antagonists, thus confirming the involvement of H1R in MS and suggesting the use of these drugs as potential targets to prevent MS (Yong et al. 2018).

H2R as well was investigated for its potential involvement in MS. In particular, H2R drugs used to treat gastric disorders were suggested to affect the activation state of the immune system (Atabati et al. 2021). In particular, activation of H2R could serve as anti-inflammatory strategy and, conversely, inhibition of H2R by

antagonists commonly adopted as standard therapy for gastritis could become pro-inflammatory by over-stimulating the immune system. In line with this hypothesis, studies on MS animal models demonstrated that H2R blockers often used as antacids for treating corticosteroid-dependent dyspeptic pain in MS patients have damaging effects in accelerating the disease (Biswas et al. 2012). In addition, H2R antagonists and additional antacid drugs as proton pump inhibitors could also modify the intestinal microbiota, which may in turn activate immune responses. Confirming this hypothesis, an interesting issue concerns the activation of intestinal H2R as one of the mechanisms proposed for the beneficial effects of probiotics on the immune system during several multisystemic inflammatory diseases among them MS (Liu et al. 2018).

The finding that an exonic single nucleotide polymorphism in the *HRH3* gene was linked to higher susceptibility to develop MS (Chen et al. 2017) demonstrated the strategy of directly targeting H3R as promising for improving remyelination. In particular, high expression of H3R was detected in oligodendrocytes present in demyelinated lesions of MS patients, and H3R antagonists/inverse agonists were soon identified by high-content screening assays as compounds able to stimulate the differentiation of oligodendrocyte precursor cells (OPC). Interestingly, the authors demonstrated that the expression of H3R was first upregulated and then downregulated during OPC differentiation. Remarkably, while the knockdown of *HRH3* gene in OPC augmented the expression of differentiation markers and the number of mature oligodendrocytes, its overexpression exerted opposite effects, by decreasing both differentiation markers and the number of mature oligodendrocytes (Chen et al. 2017).

Furthermore, the BBB-permeable H3R inverse agonist GSK247246 reduced intracellular cyclic AMP and cAMP response element-binding protein phosphorylation in vitro, leading to improved remyelination and axonal integrity in a mouse model of demyelination induced by cuprizone/rapamycin. This result strengthens the role of H3R in promoting remyelination during MS (Chen et al. 2017). Finally, the high H3R expression in oligodendroglial cells from patients with MS presenting demyelinating lesions has validated a genetic association between an exonic single nucleotide polymorphism in *HRH3* and the susceptibility to MS (Chen et al. 2017). Following this evidence, the efficacy, safety, and pharmacokinetics of another potent and brain penetrant H3R inverse agonist, GSK239512, were evaluated in patients with relapsing-remitting MS in a phase II, randomized, parallel-group, placebo-controlled, double-blind, multicenter study (NCT01772199). As measured by the magnetization transfer ratio, i.e. by magnetic resonance imaging for myelination markers, the once-daily oral dose of GSK239512, along with interferon-β1a or glatiramer acetate, demonstrated a small but positive effect on lesion remyelinating activity, with an incidence of adverse events in patients very similar to that found in the placebo group (Schwartzbach et al. 2017).

6 Concluding Remarks

Ever since the achievement of the human genome sequence, clinicians and scientists through molecular and phenotypic analysis characterizing genetic keystones of many common and rare diseases and introducing transformative-targeted therapies have obtained more refined diagnoses, rational treatments, and prevention of diseases. We are just beginning to see the fruits of these efforts also in MS. Thanks to the use of genetically modified mouse models deprived of histaminergic enzymes or receptors, and the availability of relatively selective agonists and antagonists, scientists have now recognized and started to dissect the role of histamine and its receptors in EAE/MS, as we have described in this work. However, successful clinical translation depends on the quality of preclinical findings and on the predictive value of the experimental models used in the initial drug development. Further research on the pleiotropic actions and functional validation of histaminergic signaling in the various EAE models of MS will certainly help to shed further light on the disease. Ultimately, we have also presented a bulk of information that highlights the use of histamine biomarkers to trace MS pathology and the pitfalls of successfully moving a histaminergic therapeutic strategy to the clinic.

In our quest in understanding MS, providing essential evidence for innovative treatments, and designing successful clinical trials, we trust that the data we described about the histamine alliance in MS will become an invaluable source for inspiring further research and approaches to modify the disease course.

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Histamine and Microglia

Tomomitsu Iida, Kazuhiko Yanai, and Takeo Yoshikawa

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Abstract Microglia, a category of glial cells in the central nervous system (CNS), have attracted much attention because of their important role in neuroinflammation. Many translational studies are currently ongoing to discover novel drugs targeting microglia for the treatment of various CNS disorders, such as Alzheimer's disease, Parkinson's disease (PD), and depression. Recent studies have shown that brain histamine, a neurotransmitter essential for the regulation of diverse brain functions, controls glial cells and neurons. In vitro studies using primary microglia and

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microglial cell lines have reported that histamine receptors are expressed in microglia and control microglial functions, including chemotaxis, migration, cytokine secretion, and autophagy. In vivo studies have demonstrated that histamine-related reagents could ameliorate abnormal symptoms in animal models of human diseases, such as amyotrophic lateral sclerosis (ALS), PD, and brain ischemia. Several human studies have revealed alterations in histamine receptor levels in ALS and PD, emphasizing the importance of the CNS histamine system, including histamine-dependent microglial modulation, as a therapeutic target for these disorders. In this review article, we summarize histamine-related research focusing on microglial functions.

Keywords Amyotrophic lateral sclerosis · Histamine · Microglia · Parkinson's disease

1 Microglia

In 1919, Rio-Hortega discovered microglia as phagocytic cells in the brain and reported their mesodermal origin (Sierra et al. 2016), although microglial research did not progress rapidly after this discovery. However, several outstanding breakthroughs such as microglial synaptic pruning (Blinzinger and Kreutzberg 1968), establishment of primary microglial culture (Giulian and Baker 1986), and microglial imaging (Ito et al. 1998) have accelerated microglial research. In the last 20 years, the microglial research field has expanded explosively and has become one of the most popular fields of neuroscience.

Microglia account for 5–12% of the total cellular population of the mouse brain (Lawson et al. 1990). Ginhoux et al. revealed that microglia of the yolk sac origin appear in mouse E8.5 (Ginhoux et al. 2010) and proliferate in the central nervous system (CNS). Although microglia are observed throughout the CNS, their distribution in the CNS is not homogeneous; the dentate gyrus, ventral pallidum, and substantia nigra have a higher number of microglia, while the cerebellum and brain stem have a relatively lower number of microglia (Lawson et al. 1990). Microglia persistently survey the microenvironment of their surroundings to identify pathological events and alter their characteristics in response to pathogens, including bacteria, fungi, and viruses, as well as immunogens, including lipopolysaccharides (LPS), extracellular nucleotides, and neurotransmitters. Their characteristics are also determined by the brain region and developmental stage (Masuda et al. 2019). Once microglia detect abnormal changes around their surroundings, they change their morphology from ramified to amoeboid form and secrete various bioactive molecules to maintain brain homeostasis.

It is well known that microglia are categorized into two different subtypes: neurotoxic M1 and neuroprotective M2 (Tang and Le 2016). M1 microglia secrete proinflammatory cytokines such as tumor necrosis factor (TNF)-α and interleukin

(IL)-1β and M2 microglia produce anti-inflammatory cytokines such as IL-4, IL-10, and arginase to attenuate inflammation and promote tissue repair, indicating that microglia exert cytotoxic or neuroprotective effects according to the phenotype activated. Recent studies using innovative techniques such as single-cell RNA sequencing have shown that microglia have unique molecular patterns in brain regions in an age-dependent manner. Cultured microglia from different brain regions and ages exhibit distinct outcomes (Lai et al. 2011; Stratoulias et al. 2019). Additionally, several reports described that disease-associated microglia, a novel subset of microglia associated with neurodegenerative diseases, play a protective role by removing neuronal damage (Keren-Shaul et al. 2017; Krasemann et al. 2017; Mrdjen et al. 2018). Functional differences between male and female microglia have been examined using a variety of rodent species (Han et al. 2021) and the relevance of mouse microglial activation in neuropathic pain was dependent on gender (Chen et al. 2018). Therefore, microglial heterogeneity and its role in brain disorders are now extensively investigated (Masuda et al. 2020).

The contribution of microglia to brain homeostasis is so prominent throughout the lifetime that abnormal microglial activity results in dysregulated brain homeostasis and is associated with a wide range of CNS diseases such as Alzheimer's disease, Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), chronic pain, and depression (Askew and Gomez-Nicola 2018). Therefore, microglial cells are one of the most important targets for drug development against various CNS disorders such as neuropathic pain, tauopathy, and PD (Fatoba et al. 2020) and several candidate compounds modulating microglial activity are currently under clinical trials.

Understanding the regulatory mechanism of microglial activity is a prerequisite for further translational research. Indeed, extensive investigations of purinergic signaling in chronic pain have led to drug development targeting P2X4 receptors (Tozaki-Saitoh and Tsuda 2019; Tsuda et al. 2003). Several neurotransmitters such as glutamate, GABA, norepinephrine, and acetylcholine control microglia in health and disease and have attracted attention as potential candidates for treatment (Liu et al. 2016). Recent studies have also reported the involvement of brain histamine, a monoamine neurotransmitter, in microglial activity. In this review article, we summarize the effects of histamine and histamine receptor reagents on microglia in vitro and in vivo.

2 Histamine

The physiological functions of histamine (2-(1*H*-imidazol-4-yl)ethanamine) were first reported by Nobel laureate Sir Henry Dale in 1910 (Dale and Laidlaw 1910). Histamine is involved in allergic reactions and gastric acid secretion at the periphery. Histamine also induces chemotaxis and phagocytosis of macrophages (Czerner et al. 2014). The possible involvement of histamine in the differentiation of monocytes into macrophages has also been reported (Triggiani et al. 2007). In the CNS, this bioactive monoamine plays an important role as a neurotransmitter (Haas and Panula

2003). Brain histamine is mainly produced by histaminergic neurons that express histidine decarboxylase (HDC), an essential enzyme for histamine synthesis from L-histidine (Watanabe et al. 1983). Histamine neurons are exclusively located at the tuberomammillary nucleus of the posterior hypothalamus and project their axons throughout the entire brain. Histamine interacts with four histamine receptors, namely histamine H1 to H4 receptors, to control various brain functions, such as the sleep-wake cycle, aggression, and appetite regulation (Yoshikawa et al. 2021). Brain histamine concentration is regulated by histamine *N*-methyltransferase, a histamine-metabolizing enzyme (Yoshikawa et al. 2019). Various clinical studies have shown that lower activity of the histaminergic nervous system is associated with brain disorders such as narcolepsy and Alzheimer's disease, leading to drug development targeting the brain histamine system. Indeed, pitolisant, which increases histamine release as an inverse agonist of the histamine H3 receptor (H3R), was approved as a drug for narcolepsy in the USA and Europe (Szakacs et al. 2017). A case report showed the therapeutic potential of pitolisant in adolescents with Prader-Willi syndrome (Pennington et al. 2021) and the development of novel H3R inverse agonists is ongoing (Hino et al. 2020), emphasizing the therapeutic potential of the brain histamine system for various disorders.

Recent studies have also revealed the substantial impact of histamine on glial cells. Astrocytes express histamine H1 receptor (H1R), histamine H2 receptor (H2R), and H3R and control their neuroprotective effects (Xu et al. 2018). Karpati et al. showed that astrocytic histamine receptors contributed to glutamate release and mouse behaviors (Karpati et al. 2018, 2019). Chen et al. investigated the involvement of histamine in oligodendrocyte functions and revealed that the differentiation and remyelination of oligodendrocytes are negatively controlled by H3R (Chen et al. 2017). Additionally, a pharmacological assay using the H3R inverse agonist GSK247246 indicated that this reagent induced myelination in a mouse model of multiple sclerosis (Rangon et al. 2018). These results emphasize that histamine plays an important role in the regulation of glial cells and neurons. Although Bader et al. reported that histamine could induce intracellular Ca^{2+} increase in microglia in the early 1990s (Bader et al. 1994), investigations into the interaction of histamine and microglia were extensively carried out after 2010. Recent in vitro studies on microglia have shown the expression of histamine receptors, the impact of histamine on intracellular signaling, and histamine-induced alteration of microglial properties, including chemotaxis, phagocytosis, and cytokine secretion. In vivo studies using pharmacological reagents such as H3R inverse agonists have indicated the important role of histamine-dependent microglial regulation on brain functions and the therapeutic potential of histamine-related compounds in neuropsychiatric disorders through the modulation of microglial activity (Apolloni et al. 2016b; Zhou et al. 2019). The interaction between microglia and other cell types such as neurons, astrocytes, and mast cells has also been reported (Dettori et al. 2018; Dong et al. 2017).

3 Histamine and In Vitro Microglial Functions

As G-protein coupled receptors (GPCRs), histamine receptors are known to regulate a wide range of cellular mechanisms, including second messengers and various kinases in gastric parietal cells, smooth muscle cells, and neurons (Panula et al. 2015). Naturally, activation of histamine receptors on microglia results in the modulation of second messengers such as cAMP and intracellular Ca^{2+} and in the regulation of protein phosphorylation, leading to the alteration of microglial functions, including migration, chemotaxis, phagocytosis, and inflammatory/anti-inflammatory cytokine production (Chen et al. 2020; Dong et al. 2014a; Iida et al. 2015). In this section, we review the role of each histamine receptor in the intracellular signaling and functions of primary microglial cells and microglial cell lines. The intracellular signaling induced by histamine receptors is shown in Fig. 1.

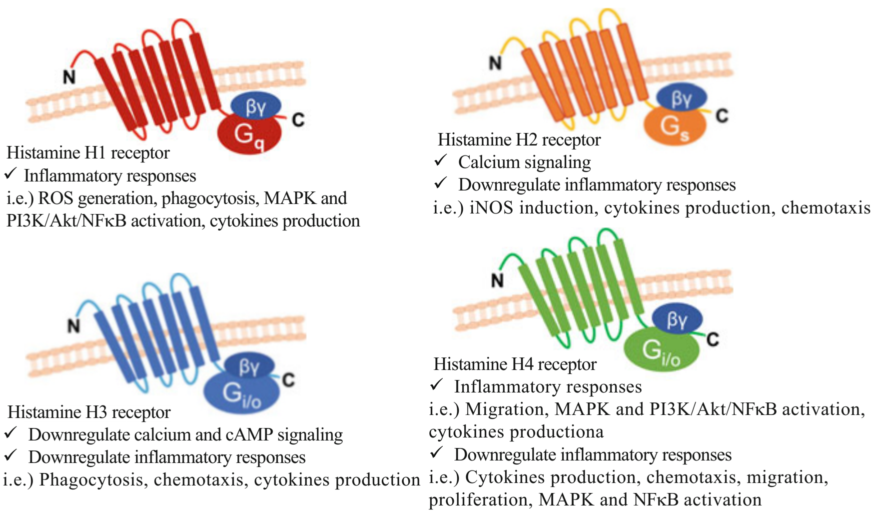

Fig. 1 Histamine receptor activation modulates microglial signaling pathways and functions. Microglia express G protein-coupled histamine receptors (H1R, G_q, H2R, G_s, H3R, $G_{i/o}$, H4R, and $G_{i/o}$). H1R activation induces inflammatory responses, including nuclear factor (NF)-κB activation, ROS generation, pro-inflammatory cytokine production, and phagocytosis (Dong et al. 2014a; Rocha et al. 2016; Zhu et al. 2014). H2R activation induces Ca^{2+} signaling and reduces microglial NFκB activation and pro-inflammatory cytokine production (Chen et al. 2020; Xia et al. 2021). H3R activation downregulates second messenger signaling, chemotaxis, phagocytosis, and cytokine production (Chen et al. 2020; Iida et al. 2015). Although H4R activation promotes NFκB activation, migration, and pro-inflammatory cytokine secretion (Dong et al. 2014a; Ferreira et al. 2012; Zhu et al. 2014), LPS-induced inflammatory responses are suppressed by its activation (Shan et al. 2019)

3.1 Histamine H1 Receptor

H1R, coupled to $G_{q/11}$ protein, typically promotes phospholipase C activity that cleaves phosphatidylinositol bisphosphate into inositol trisphosphate and diacylglycerol (DG), resulting in the elevation of intracellular Ca^{2+} concentration and the activation of protein kinase C. As G_q-coupled receptors such as P2Y6 receptor regulate microglial functions including phagocytosis and cytokine secretion (Anwar et al. 2020), H1R activation in the microglial cell line N9 enhances phagocytosis of IgG-coated beads and generates reactive oxygen species through Rac1-NOX dependent pathways (Rocha et al. 2016). In addition, H1R activation in primary microglia induces TNF-α and IL-6 secretion through the p38, JNK, and Akt pathways (Dong et al. 2014a; Zhu et al. 2014). However, a recent study using the H1R agonist 2-pyridylethylamine did not confirm the involvement of H1R activation in phagocytosis as well as Ca^{2+} transient (Xia et al. 2021), indicating that the association between H1R and microglial phagocytosis is still controversial. Several reports have shown the involvement of the H1R antagonist, clemastine, in microglial autophagy. Clemastine reduced NLRP3 inflammasome activation by oxygen-glucose deprivation (Xie et al. 2020) and increased the autophagic marker LC3-II (Apolloni et al. 2016a), indicating that clemastine promotes microglial autophagy. Recent studies have shown that autophagy induction suppresses microgliosis, promotes the removal of amyloid-β and α-synuclein, and reduces the production of inflammatory cytokines, leading to the improvement of neuroinflammation (Berglund et al. 2020; Choi et al. 2020; Heckmann et al. 2019), and H1R antagonization might be useful for neurological disorders via autophagy activation. However, the H1R-independent effects of antihistamines such as anticholinergic effects and proton current inhibition (Kim and Song 2017) should be considered. In addition to pharmacological assays, alteration of H1R expression in microglia by genetic engineering will elucidate the detailed role of H1R in microglia.

3.2 Histamine H2 Receptor

H2R, a Gs protein-coupled receptor, interacts with adenylate cyclase to increase cAMP concentration, which in turn results in protein kinase A activation. Several single-cell RNAseq analyses of isolated mouse microglia revealed robust expression of H2R, while other histamine receptors were poorly detected (Matcovitch-Natan et al. 2016). Age- and region-dependent alterations in H2R expression were also observed by RNAseq analysis (Grabert et al. 2016). Additionally, several in vitro studies have confirmed the expression of H2R in microglia. Although the H2R agonist amthamine fails to increase forskolin-induced cAMP levels in primary mouse microglia (Iida et al. 2015), amthamine induces Ca^{2+} transients in a small population of freshly isolated microglia from the cortex and in situ cortical microglia

(Xia et al. 2021). Chen et al. showed that amthamine treatment of microglia activated PI3K/Akt signaling and suppressed the expression levels of TNF-α, IL-1β, and inducible NO synthase and LPS-induced migration (Chen et al. 2020). Although these studies demonstrated the importance of H2R in in vitro microglial functions, the involvement of H2R in in vivo microglial functions is not well documented. Further studies using microglia-specific H2R knockout models or pharmacological reagents will strongly accelerate the understanding of H2R effects on microglia and brain function.

3.3 Histamine H3 Receptor

H3R, an inhibitory GPCR, is the most abundant histamine receptor in the CNS and is mainly localized at the nerve end terminal to regulate histamine release (Haas et al. 2008). Activation of H3R inhibits adenylate cyclase and voltage-dependent Ca^{2+} signals (Schlicker et al. 1994; Silver et al. 2002). Microglia also express H3R (Apolloni et al. 2017; Dong et al. 2014a; Ferreira et al. 2012), and its activation inhibits forskolin-induced cAMP accumulation and ATP-induced Ca^{2+} transients (Iida et al. 2015). ATP-dependent Ca^{2+} signals mediate microglial process extension, chemotaxis toward damaged regions, and cytokine release, resulting in the promotion of neuroinflammation (Madry et al. 2018). Therefore, suppression of ATP-induced Ca^{2+} transients by H3R could inhibit microglial inflammatory tone. H3R activation negatively regulates major microglial functions, such as phagocytosis, chemotaxis, and proinflammatory cytokine production (Iida et al. 2015). Intriguingly, Chen et al. showed the association of PI3K/Akt/FOXO pathways mediated through H3R to reduce LPS-induced microglial activation (Chen et al. 2020). Taken together, microglial H3R might negatively mediate microglial function by regulating intracellular Ca^{2+} concentration and PI3K/Akt pathways.

3.4 Histamine H4 Receptor

H4R, a G_i-GPCR, is mainly expressed in bone marrow-derived immune cells and regulates a variety of immune functions (Zampeli and Tiligada 2009). Studies using microglial cell lines have shown that H4R activation promotes migration and pro-inflammatory cytokine production (Dong et al. 2014a, 2014b; Ferreira et al. 2012; Zhu et al. 2014). These H4R-dependent histamine actions are mediated through p38 MAPK and Akt pathways. A recent study using a microglial cell line by Shan et al. showed another intracellular signaling pathway induced by H4R activation (Shan et al. 2019). They revealed that H4R could interact with TNF receptor-associated factor 6, which is a downstream target of toll-like receptor signaling, leading to the inhibition of inflammatory cytokine release.

3.5 Histidine Decarboxylase

A previous report by Katoh et al. showed that a microglial cell line expressed HDC, an enzyme essential for histamine synthesis (Katoh et al. 2001). A later study using primary mouse microglia and RNAseq analysis confirmed HDC expression in microglia (Grabert et al. 2016; Iida et al. 2015), indicating that microglia could supply histamine in the CNS, such as histaminergic neurons and brain-resident mast cells. Similar to mast cells, LPS stimulation dramatically increases Hdc expression and promotes histamine secretion, although basal histamine production in microglia is undetectable. Hence, microglia might secrete histamine during the activation states, which in turn regulate their own functions via histamine receptors or recruit various immune cells in an autocrine/paracrine manner. Since cell-type specific HDC conditional knockout mice had been generated (Yamada et al. 2020), studies using microglial HDC conditional knockout mice will help to understand the role of microglial HDC in the brain.

4 Histamine and In Vivo Microglial Functions

4.1 Amyotrophic Lateral Sclerosis

ALS is a common neurodegenerative disease. ALS is a motor neuron disorder characterized by motor neuron loss in the spinal cord and brain, resulting in muscle weakness and respiratory failure. Astrocytes and microglia play crucial roles in the pathophysiology of ALS (Vahsen et al. 2021). Human positron emission tomography (PET) studies have revealed microglial activation in patients with ALS, and post-mortem examinations have shown an association between microglial alteration and motor neuron loss. Experiments using several ALS mouse models, such as SOD1^{G93A} and TDP43 transgenic mice, have shown the involvement of microglia in these models. Apolloni et al. examined the effect of clemastine, a histamine H1 receptor antagonist, on SOD1^{G93A} mouse models. Immunohistochemical analysis showed that clemastine decreased the expression level of CD68, a marker of microglial activation, in the spinal cord of SOD^{G93A} mice. They also reported that 10 mg/kg clemastine slightly improved motor activity but not the survival probability of SOD^{G93A} mice (Apolloni et al. 2016b). Additionally, this research group revealed that a short treatment with 50 mg/kg clemastine ameliorated disease progression in SOD^{G93A} mice (Apolloni et al. 2016a). They also investigated the impact of daily histidine treatment on ALS model mice. Intraperitoneal injection of histidine, which is a precursor of histamine essential for the brain histaminergic system (Yoshikawa et al. 2014), modified the expression levels of inflammatory/anti-inflammatory markers in microglia and ameliorated ALS symptoms, including lifespan and motor functions (Apolloni et al. 2019). In this study, altered expression of histamine-related genes such as *HRH1*, *HRH3*, and *HNMT* in the post-mortem

spinal cord of ALS patients and in SOD^{G93A} mice supports the potential of the histamine system in ALS treatment. However, these results seem to be controversial because both antihistaminic and histamine precursor supplementation have therapeutic effects on ALS behaviors. The authors indicated that histaminergic compounds should be prescribed for a limited duration to alleviate ALS symptoms (Volonte et al. 2019). Clemastine antagonizes muscarinic receptors as well as histamine H1 receptor (Kubo et al. 1987) and potentiates purinergic P2X7 receptors (Norenberg et al. 2011), indicating that cholinergic and/or purinergic involvement should be considered for clemastine-dependent therapeutic actions in microglia and ALS mouse models. Histidine is also important as an essential amino acid for protein synthesis and plays a role as an antioxidant in the prevention of oxidative stress (Wade and Tucker 1998). Further studies using specific H1R antagonists or microglia-specific H1R deficient mice will be required to elucidate the importance of H1R in ALS. It is of interest to use other ALS model mice to confirm the importance of microglial histamine receptors in ALS pathophysiology.

4.2 Parkinson's Disease

PD is a progressive neurodegenerative disorder characterized by a deficit of dopaminergic neurons in the substantia nigra. The dominant contribution of microglia to the neuroinflammatory response in PD has been extensively reported (Perry 2012). Indeed, treatment with minocycline, an inhibitor of microglia, in PD model mice resulted in a lower inflammatory reaction and protection of dopaminergic neurons (Tomas-Camardiel et al. 2004). Therefore, suppression of microglial activation is a therapeutic target for PD treatment (Vedam-Mai 2021). Rocha et al. first reported the involvement of histamine in dopaminergic neurons in the substantia nigra. H1R activation by histamine injection produces reactive oxygen species and induces toxicity in dopaminergic cells. Thus, the authors indicated the therapeutic potential of H1R antagonists for PD treatment (Rocha et al. 2016). Zhou et al. examined the impact of the H4R antagonist JNJ7777120 on rotenone-induced PD model rats and evaluated its effect on microglia. In this PD model, an increase in H4R expression and microglial activation was confirmed. JNJ7777120 suppressed the expression of inflammatory cytokines such as IL-1β and TNF-α, prevented dopaminergic neuronal loss coupled with the reduced dopamine level, and attenuated apomorphine-induced rotational behavior (Zhou et al. 2019). Recently, Fang et al. compared the expression levels of histamine-related genes in the substantia nigra and putamen of control and PD patients and revealed reduced expression of *HRH3* and increased expression of *HRH4* in the substantia nigra of PD patients. They again confirmed that JNJ7777120 ameliorated PD pathology with altered microglial properties in rotenone-induced rats (Fang et al. 2021). Although they also confirmed the little impact of JNJ7777120 on undifferentiated SH-SY5Y cells, a cell line of dopaminergic neurons, pharmacological assays could not rule out the possibility that JNJ7777120 affected other cell types to alleviate PD pathology and symptoms in model animals.

4.3 Brain Ischemia

Stroke is one of the leading threats to human health due to its high morbidity, disability, and mortality (Benjamin et al. 2019). Abnormal glutamate release induced by brain ischemia exerts excitotoxicity and exacerbates neuronal cell death, accelerating the development of drugs which inhibit glutamate release or antagonize NMDA receptor in stroke patients (Lai et al. 2014). Previous reports have shown that brain ischemia also increases histamine release and alters histamine receptor expression (Lozada et al. 2005; Subramanian et al. 1981), suggesting a possible contribution of brain histamine to the pathophysiology of ischemia. Adachi et al. revealed that intracerebroventricular injection of histamine exerted beneficial effects on ischemic damage through H2R activation (Adachi 2005). Additionally, an H3R antagonist, which induces histamine release, improves cognitive impairment caused by chronic hypoperfusion (Wang et al. 2019). Although microglia have been recognized to exacerbate brain injury in ischemic stroke, recent studies have demonstrated that microglia are also required to regenerate brain tissue (Zhang 2019). Dettori et al. investigated the impact of JNJ7777120 on the detrimental effects of transient occlusion of the middle cerebral artery in rats. Chronic administration of JNJ7777120 decreased infarction size in the cortex and striatum, with a reduction in activated microglia and astrocytes (Dettori et al. 2018). Another group reported the therapeutic potential of the H1R antagonist clemastine in a rat model of bilateral common carotid artery occlusion (Xie et al. 2020). Clemastine inhibited IL-1β and nod-like receptor protein 3 expression in microglia. They suggested that suppression of microglial activity by clemastine improved axonal myelination, encouraging the restoration of brain function after ischemic conditions. These reports showed that antagonization of the histamine system has therapeutic potential in ischemic brain injury. However, previous reports have suggested a protective role of histamine in ischemic brain injury (Adachi 2005). Further studies are required to elucidate the importance of histamine-induced microglial modifications in the pathophysiology of brain ischemia.

4.4 Depression-Like Behaviors

Major depressive disorder (MDD) is the most common mood disorder, with over 300 million people suffering. Although activation of serotonergic neurons by serotonin selective reuptake inhibitors is a central player in the treatment of MDD, recent studies have emphasized the involvement of abnormal microglial activity in MDD pathophysiology. A human PET study reported that microglial activation in the anterior cingulate cortex is correlated with major depressive episodes (Setiawan et al. 2015). In contrast, a post-mortem study showed a lower glial density in the amygdala (Bowley et al. 2002) and several case studies have reported the association of anti-inflammatory drugs with depression and suicide attempts (Deng et al. 2020).

Unbalanced microglial activity may underlie the onset and progression of depression. Iida et al. investigated the impact of JNJ10181457, an H3R inverse agonist, on depression-like behaviors in a mouse model of depression (Iida et al. 2017). JNJ10181457 reduced the expression of inflammatory cytokines such as IL-1β, IL-6, and TNF-α in purified microglia and restored depressive-like behaviors in the tail suspension test. Su et al. reported the therapeutic potential of clemastine in chronic unpredictable mild stress-induced depression model mice (Su et al. 2018). Clemastine decreased pro-inflammatory cytokine expression in the hippocampus and reversed depression-like behaviors. However, a previous study reported that clemastine regulated macrophage activity independently of histamine H1 receptors, indicating that the importance of microglial control by histamine in depression should be further investigated.

4.5 Interaction with Brain-Resident Mast Cells

Mast cells release various chemical mediators, such as histamine and cytokines, and play a central role in acute allergic reactions in peripheral organs. Although previous reports indicated the existence of mast cells in the CNS, the presence of brain-resident mast cells had been controversial for many years (Silver et al. 1996). Nautiyal et al. reported that the number of mouse brain-resident mast cells but not mast cells from the periphery increased from 150 to 500 during development and mast cells contributed to hippocampal functions in the absence of inflammation (Nautiyal et al. 2012). Recent studies have shown that brain-resident mast cells act as single-cell glands delivering active biomolecules such as histamine and serotonin and contribute to neuroinflammation (Hendriksen et al. 2017). An interaction between mast cells and microglia in the CNS was also indicated (Sandhu and Kulka 2021). Dong et al. reported that degranulation of brain mast cells altered the expression levels of microglial histamine receptors in the hypothalamus (Dong et al. 2017). Lenz et al. investigated the importance of mast cell–microglia interactions in the developing brain for adult sexual behavior (Lenz et al. 2018). They reported that histamine from brain-resident mast cells activates microglial H1R and H4R, resulting in microglial prostaglandin E2 (PGE2) secretion from microglia. PGE2 induces sexual differentiation of dendritic spines in early life that enable male copulatory behavior in adulthood (Lenz et al. 2018). Recent studies have demonstrated the involvement of histamine release from brain mast cells in glucose homeostasis and the sleep–wake cycle (Chikahisa et al. 2013, 2017). It is of interest to examine the importance of histamine released from mast cells for microglial functions in various neurological disorders.

5 Future Perspectives

Although extensive investigations have been performed to show the expression of histamine receptors in microglia in vitro and in vivo, the results are still inconclusive. Indeed, several reports indicated that histamine increased M1 marker proteins such as TNF-α and IL-6 (Dong et al. 2014a; Zhu et al. 2014), although Chen et al. reported that H2R/H3R agonists inhibited the secretion of TNF-α and IL-1β and increased the production of IL-10 (Chen et al. 2020). To further understand the involvement of the histamine system in microglial function, microglial heterogeneity in homeostatic and disease conditions should be carefully considered (Masuda et al. 2019). Most experiments using microglial primary cultures do not separate male and female microglia and sex differences in histamine receptor actions have been revealed (Easton et al. 2004; Ghi et al. 1999; Li et al. 2015), suggesting that male and female microglia might have distinct responses to histamine. Rat microglia respond differently to various stimuli compared to mouse microglia (Geirsdottir et al. 2019; Lam et al. 2017). Indeed, histamine induces Ca^{2+} transients in a population of rat microglia three times larger than that of mouse microglia (Bader et al. 1994; Pannell et al. 2014). It is well known that microglial cell lines have different molecular profiles and activation responses (Butovsky et al. 2014; Das et al. 2016). Additionally, Ca^{2+} imaging studies have shown that 0–10% of the total population of microglia respond to histamine treatment (Pannell et al. 2014), strongly emphasizing the heterogeneous microglial response to histamine. Thus, further studies are essential to reveal the involvement of histamine on these different aspects of microglia.

Since microglia colonize the developing brain from E9, several reports demonstrate the importance of microglia for neural development (Thion and Garel 2020). Indeed, microglial pruning of immature synaptic connection during development is essential for functional connectivity and microglial dysfunction is implicated in neurodevelopmental disorders such as autism spectrum disorders and schizophrenia. Several reports have indicated that histamine regulates the proliferation and differentiation of neural stem cells and facilitates synaptic plasticity during embryonic and postnatal development (Carthy and Ellender 2021). Although histamine-dependent microglial regulation might underlie the impact of histamine on the neurodevelopment, further studies are essential to reveal the importance of histamine for microglial function in the developmental stages.

Previous pharmacological experiments have reported the involvement of histamine in microglial function in animal models. Unfortunately, histamine receptors are expressed in neurons and astrocytes (Juric et al. 2016), and it is quite difficult to rule out the possibility that neuronal and/or astrocytic alterations by pharmacological reagents affected the results. Microglia-specific deletion of histamine-related genes using CX3CR1-Cre mice (Zhao et al. 2019) or TMEM119-Cre (Kaiser and Feng 2019) will be required to understand the microglial histamine system. Chemogenetic microglial activation and/or inhibition (Saika et al. 2020) of histamine receptors are also intriguing.

In conclusion, extensive investigations have revealed histamine receptor expression in microglia and histamine-dependent regulation of microglial functions, including chemotaxis, phagocytosis, and cytokine secretion. In vivo studies have indicated the involvement of the microglial histamine system in the pathophysiology of various CNS disorders. Although further studies using gene engineering are essential to accelerate this field, the microglial histamine system could be an important target for the treatment of neuropsychiatric disorders.

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Histamine in the Crosstalk Between Innate Immune Cells and Neurons: Relevance for Brain Homeostasis and Disease

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Abstract Histamine is a biogenic amine playing a central role in allergy and peripheral inflammatory reactions and acts as a neurotransmitter and neuromodulator in the brain. In the adult, histamine is produced mainly by mast cells and hypothalamic neurons, which project their axons throughout the brain. Thus, histamine exerts a range of functions, including wakefulness control, learning and memory, neurogenesis, and regulation of glial activity. Histamine is also known to modulate innate immune responses induced by brain-resident microglia cells and peripheral circulating monocytes, and monocyte-derived cells (macrophages and dendritic cells). In physiological conditions, histamine per se causes mainly a pro-inflammatory phenotype while counteracting lipopolysaccharide-induced inflammation both in microglia, monocytes, and monocyte-derived cells. In turn, the activation of the innate immune system can profoundly affect neuronal survival and function, which plays a critical role in the onset and development of brain disorders. Therefore, the dual role of histamine/antihistamines in microglia and monocytes/macrophages is relevant for identifying novel putative therapeutic strategies for brain diseases. This review focuses on the effects of histamine in innate immune responses and the impact on neuronal survival, function, and

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differentiation/maturation, both in physiological and acute (ischemic stroke) and chronic neurodegenerative conditions (Parkinson's disease).

Keywords Histamine · Innate immunity · Microglia · Monocytes · Neurodegenerative diseases · Parkinson's disease · Stroke

1 Overview of the Functions of Histamine in the Brain

Histamine is an endogenous biogenic amine commonly known as an inflammatory mediator of allergic reactions. Studies suggest that these conditions may affect brain function and contribute to neurodegenerative processes (Klein et al. 2016; Sarlus et al. 2012). Histamine is formed by decarboxylation of the essential amino acid L-histidine in a reaction catalyzed by L-histidine decarboxylase (HDC). Several stimuli such as injury, day/night cycle, inflammation, among others, regulate histamine production. Besides the endogenous production, diet (e.g., fermented food, chocolate, wine) provides an exogenous histamine (or L-histidine) source. Histamine degradation occurs by methylation, catalyzed by histamine N-methyltransferase (HNMT), or oxidation, catalyzed by diamine oxidase (DAO), which depends on the species and tissues. In the brain, most histamine is *N*-methylated by HNMT, and the product *N*-methylhistamine is further oxidized by monoamine oxidase-B (MAO-B), which is expressed in histaminergic neurons and astrocytes (Brown et al. 2001). This metabolic pathway is particularly relevant in the context of brain diseases where MAO-B inhibitors are used for therapy, such as Parkinson's disease (PD; discussed in Sect. 3.1). Histamine mediates its actions by G protein-coupled receptors, the histamine receptors H1-4 (H1-4R) (Brown et al. 2001). H1R and H2R are low-affinity receptors expressed in the central nervous system and periphery and mediate excitatory actions. H1R recruits $G_{q/11,}$ which leads to the activation of phospholipase C, the formation of inositol triphosphate (IP3), and diacylglycerol (DAG), which induces calcium release from internal stores and activation of protein kinase C (PKC); while H2R recruits G_s proteins that activate the adenylyl cyclase and protein kinase A (PKA) (Brown et al. 2001). The activation of H1R is mainly associated with allergic reactions. The most well-described physiological function of H2R is in controlling the release of gastric acid, but recent data showed that it is also involved in cell differentiation and immune reactions. H3R and H4R are high-affinity receptors with predominant inhibitory effects. H3R are abundant in the central and peripheral nervous systems and recruit $G\alpha_{i/o}$ proteins inhibiting adenylyl cyclase and PKA activation. H3R acts as a presynaptic receptor, inhibiting the release of histamine or other neurotransmitters (e.g., glutamate, noradrenaline, serotonin, dopamine, GABA, acetylcholine). Recently it was shown that H3R also forms heterodimers with dopamine receptors D1 and D2 and adenosine A2A receptors, therefore modulating dopaminergic and purinergic neurotransmission, respectively (Márquez-Gómez et al. 2018; Moreno

et al. 2011; Moreno-Delgado et al. 2020). The best-known physiological actions modulated by H3R include food intake, nociception, cognition, and sleep-wake control (Brown et al. 2001; Nieto-Alamilla et al. 2016; Ito et al. 2018). H4R is mainly expressed by peripheral immune cells and recruits $G\alpha_{i/o}$ proteins that inhibit cAMP production via adenylyl cyclase inhibition and activate the mitogen-activated protein kinase (MAPK) signaling. H4R can also activate the $G\beta\gamma$ subunits that activate phospholipase C and increase intracellular calcium concentration. H4R is mainly involved in inflammatory reactions. Several inflammatory and injury stimuli regulate the expression of histaminergic receptors in a temporal and spatial (cells, tissues)-specific manner, which impacts the functional effects induced by histamine.

In the brain, histamine is produced mainly by mast cells and hypothalamic neurons in the tuberomammillary nucleus (TMN). Mast cells are mainly located in the area postrema, the choroid plexus, hypothalamus, hippocampus, the parenchymal border of the blood–brain barrier, thalamus, and in the meninges (Silverman et al. 2000; Mattila et al. 2011). These immune cells react quickly to several stimuli, releasing histamine and other inflammatory and vasoactive mediators from intracellular secretory granules (Chikahisa et al. 2013). On the other side, histaminergic neurons project ramifications and release histamine throughout the entire brain, allowing histamine to be involved in a broad range of physiological functions, such as sleep-wake control, emotions, learning and memory, neuronal survival, and neurogenesis (Panula and Nuutinen 2013; Bernardino et al. 2012; Saraiva et al. 2019; Rocha et al. 2016; Ferreira et al. 2012). In the healthy brain, histamine is found at nanomolar levels (Soya et al. 2008; Croyal et al. 2011; Bourgogne et al. 2012). However, several brain pathological conditions may be associated with changes in circulating histamine levels (blood and cerebrospinal fluid) and histaminergic neuronal innervations, suggesting that histamine plays a role in regulating neuronal survival, function, and behavior. Alterations in histamine levels and metabolism depend on the specific injury/pathology. For example, an increase of histaminergic innervations was found in substantia nigra of PD patients (see Sect. 3.1), and elevated cerebrospinal fluid histamine levels were found in multiple sclerosis patients (Vizuete et al. 2000; Kallweit et al. 2013; Anichtchik et al. 2000). In contrast, no or residual changes of histamine or histamine metabolite levels were found in Alzheimer's disease patients (Gabelle et al. 2017; Motawaj et al. 2010).

The histaminergic system is involved in the proliferation and commitment of neuronal precursor cells in the embryonic and adult brain. Embryonic and adult neural stem and progenitor cells express histamine receptors (H1R, H2R, H3R) (Agasse et al. 2008; Escobedo-Avila et al. 2014), being H1R responsible for the increase of intracellular calcium levels in immature cells (Escobedo-Avila et al. 2014; Molina-Hernández et al. 2013; Grade et al. 2010) and neuronal differentiation (Bernardino et al. 2012; Molina-Hernández et al. 2013; Molina-Hernández and Velasco 2008; Rodríguez-Martínez et al. 2012). Histamine is one of the first molecules to appear in the rodent embryonic brain, reaching its maximal value at embryonic day 14, when neurogenesis of deep layers occurs in the cerebral cortex. Indeed, histamine increased proliferation and differentiation of FOXP2 deep layer

cortical neuronal cells via H1R activation in cerebrocortical neural precursor cultures and infused in the cerebral ventricles through intrauterine injection (Molina-Hernández et al. 2013; Rodríguez-Martínez et al. 2012). Histamine also affected dopaminergic lineage during development by reducing the proliferation and survival of embryonic ventral mesencephalon dopaminergic precursors via H1R activation in vitro and in vivo. Neural progenitors (E10 and E12) were exceptionally responsive to histamine actions, while differentiated dopaminergic neurons (E14 and E16) were mainly spared (Escobedo-Avila et al. 2014). The same research group showed that the systemic administration of the H1R antagonist/inverse agonist chlorphenir-amine increased dopaminergic differentiation in embryos (E16) while in 21-day-old pups reduced the number of dopaminergic neurons in the substantia nigra *pars compacta* and dorsal striatum, reduced dopamine levels in the striatum, and induced motor impairments. This suggests that histamine inhibited embryonic dopaminergic differentiation at E14-E16, while having the opposite actions in the post-natal period, with H1R being responsible for these effects (Márquez-Valadez et al. 2019). We showed that histamine induces neuronal commitment and axonogenesis of neonatal subventricular zone (SVZ) neural stem cells through upregulation of the expression of the proneurogenic genes *Mash1*, *Dlx2,* and *Ngn1* and activation of JNK MAPKinase, respectively, in vitro (Bernardino et al. 2012). Moreover, the intracerebroventricular (i.c.v.) administration of adult mice with histamine increased the number of SVZ-derived neuroblasts capable of migrating towards the olfactory bulb which differentiate into mature neurons (Eiriz et al. 2014). We have also developed histamine-releasing microparticles, which were highly efficient in inducing neuronal differentiation. SVZ cells pretreated with histamine-loaded microparticles and then grafted into the dentate gyrus of hippocampal organotypic slice cultures or the dentate gyrus and striatum in vivo showed increased neuronal differentiation compared with non-treated ones (Bernardino et al. 2012). Recent studies suggest that histamine also modulates hippocampal neurogenesis via H1R or H3R activation (Ambrée et al. 2014; Guilloux et al. 2017). H1R knockout (KO) mice showed a reduced number of proliferative cells in the hippocampal dentate gyrus (DG) together with pronounced deficits in spatial learning and memory (Ambrée et al. 2014). Additionally, the chronic treatment for 28 days with S 38093, a brain-penetrant antagonist/inverse agonist of H3R, increased hippocampal neurogenesis in young (3-month-old) and aged (16-month-old) mice. In aged mice, S 38093 increased the expression of brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF) and improved the cognitive performance in a context discrimination task (Guilloux et al. 2017). These studies indicate that histamine potentiates hippocampal neurogenesis, which correlates with hippocampus-related behaviors. We found that the intrahippocampal administration of histamine induces a slight increase of neuronal differentiation while decreasing the volume and complexity of DG immature neurons. Notably, histamine counteracted the negative impact induced by lipopolysaccharide (LPS) on DG neurogenesis (Saraiva et al. 2019). Altogether, these results emphasize the multidimensional effects of histamine in the modulation of SVZ and SGZ

neurogenic niches, which may be differentially responsive due to particular characteristics of each niche and/or differential expression of histamine receptors.

One of the most well-known functions induced by histamine is its involvement in wakefulness regulation. The neuronal production of histamine shows diurnal fluctuations in healthy individuals, with increased levels of histamine found during the day. Recently, it was demonstrated that mice displaying chronic histamine depletion, induced by adeno-associated virus expressing Cre recombinase microinjected into the TMN of HDC flox adult mice, exhibited a decrease in wakefulness and increased in non-rapid eye movement sleep throughout the day. Moreover, these mice showed induced depression-like behavior, decreased locomotor activity, and impaired aversive memory (Yamada et al. 2020). Neuronal histamine fluctuations are also altered in patients with neurodegenerative diseases, which in turn impact circadian rhythms. Healthy adult subjects showed high HDC mRNA levels during the daytime, suggesting a role for neuronal histamine in regulating day-night rhythms. In contrast, the HDC mRNA day-night fluctuation was markedly distinct in the TMN of patients with neurodegenerative diseases such as PD, Alzheimer's disease, and Huntington's disease (Shan et al. 2012a).

Aging, the leading risk factor for most neurodegenerative diseases, is also accompanied by alterations in histamine levels, signaling, and metabolism. Aged mice (24-month-old) showed lower expression of H1R mRNA in the cortex, hypothalamus, hippocampus, and medulla relative to adult (3-month-old) animals. Age-related changes in H2R mRNA levels were restricted to the pons and cerebellum, and decreased H3R mRNA was found only in the medulla. Histamine levels were increased while HNMT activity significantly decreased in the hypothalamus, midbrain, and cortex of 12 versus 3-month-old rats (Terao et al. 2004; Mazurkiewicz-Kwilecki and Prell 1984). Further studies should address whether these changes of the histaminergic system during aging contribute to the etiology and/or progression of neurodegenerative diseases.

The histaminergic system is also gender-dependent (Acevedo et al. 2006). Histamine levels and the cortical levels of H1R and H2R are higher in female animals than in males (Lebel et al. 1980; Ghi 1999). In particular, higher levels of H1R were found in the median eminence and neurohypophysis of aged rodent females (Cacabelos et al. 2016). The mast cells' degranulation and histamine release are also gender-dependent, with mast cells from rat females being more susceptible than males to the effects of sex steroids (Muñoz-Cruz et al. 2015). In humans, the levels of the metabolites of histamine, tele-methylhistamine (t-MH), and tele-methylimidazoleacetic acid (t-MIAA) were higher in cerebrospinal fluid from older subjects, being higher in females than in males (Prell et al. 1990). A general experimental procedure to investigate the impact of gender in function and behavior is by removing the reproductive organs. It was found that ovariectomized female mice were more sensitive to the arousal-reducing effects of the histamine H1R antagonist pyrilamine than castrated males (Easton et al. 2004). Moreover, HDC KO female mice did not show impairment in object recognition as reported in HDC KO males while showed impairments in spatial learning and memory compared with the males that showed increased water-maze acquisition and memory retention

(Acevedo et al. 2006; Dere 2003). Moreover, female rats are more sensitive than males to histidine-induced anorexia (Kasaoka et al. 2005). These reports raise the importance of considering age and gender aspects in studying the impact of the histaminergic system on brain function and behavior.

2 The Functions of Histamine in Innate Immune Cells

Histamine plays a crucial role in the modulation of the activity of innate immune cells. The innate immune system is the first line of defense against pathogens. Contrary to the adaptive immune system, this response is non-specific and immediately prevents the spread of pathogens. The following sections focus on the effects of histamine on brain-resident microglia and circulating peripheral monocytes and macrophages, the most well-described innate immune cells.

2.1 Microglia

Microglial cells, the resident innate immune cells in the brain, can patrol and protect brain parenchyma against injuries or infections. Lesion or degeneration activates microglial cells becoming amoeboid, phagocytic, capable of migrating to the injury site and releasing inflammatory factors (Prinz et al. 2019). In vitro, microglia express HDC, HNMT and can release histamine (Iida et al. 2015; Katoh et al. 2001). Moreover, microglial cells express all four types of histamine receptors (H1-4R) in vitro and in vivo (Zhang et al. 2020), whose expression is regulated by several inflammatory conditions (Shan et al. 2019). At the functional level, histamine increases microglia mobility through signaling pathways involving α5β1 integrin, p-38, and Akt (Ferreira et al. 2012) and promotes phagocytosis by the activation of H1R (Rocha et al. 2016). Moreover, it promotes the release of pro-inflammatory mediators, namely tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), IL-1β, and IL-10, and the production of reactive oxygen species (ROS) (Zhang et al. 2020; Dong et al. 2014). These pro-inflammatory actions are mediated mainly by H1R or H4R activation (Rocha et al. 2016; Ferreira et al. 2012; Zhou et al. 2019). Other evidence supported the role of microglial H3R for brain homeostasis by showing that JNJ10181457, an H3R inverse agonist, suppressed ATP-induced microglial migration in hippocampal slices, inhibited microglial engulfment of dead neurons induced by N-methyl-d-aspartate in hippocampal slices and prefrontal cortex, and reduced the LPS-induced upregulation of microglial pro-inflammatory cytokines and improved depression-like behavior in vivo (Iida et al. 2017). In contrast, under an inflammatory context mimicked by LPS, histamine acts as an anti-inflammatory and neuroprotective agent (Saraiva et al. 2019; Barata-Antunes et al. 2017). Some evidence suggest that this effect may be due to the interaction of H4R with tumor necrosis factor receptor-associated factor 6 (TRAF6), which decreased

TRAF6-mediated ubiquitination of K63, inhibited NF-kB activation ultimately resulting in an inhibition of the release of inflammatory cytokines in LPS-induced microglial cells (Shan et al. 2019). Other evidence suggests that histamine and imetit (H3R agonist) inhibited microglial chemotaxis, phagocytosis, and LPS-induced cytokine production, probably reducing forskolin-induced cAMP accumulation and ATP-induced intracellular calcium transients in vitro (Iida et al. 2015). Recently, a study showed that histamine 2/3 receptor agonists inhibited exploratory laparotomy-induced and LPS-induced cognitive decline, microglia activation, and the release of inflammatory factors (TNF-α, IL-1β, IL-10) and signaling (NF-κB) by activating the PI3K/AKT/FoxO1 pathway (Chen et al. 2020). We also demonstrated that histamine could revert LPS-induced hippocampal neuroinflammation by decreasing the expression of markers for activated glial cells (Iba-1, HMGB1), and markers correlated with neuronal functionality and synaptic strength (CREB, PSD-95), indicating a reversion of LPS-induced cognitive decline in the adult hippocampus (Saraiva et al. 2019). Thus, histamine seems to have a dual role in microglial functions depending on the microenvironment, the activation state of cells, and which histamine receptor is activated. Table 1 summarizes the studies mentioned above supporting the role of histamine in microglial cells.

2.2 Monocytes/Macrophages

In contrast to microglia, monocytes are short-lived cells generated throughout life from bone marrow resident hematopoietic stem cells. Circulating monocytes patrol the bloodstream and, upon recruitment to tissues, give rise to tissue-resident macrophages or dendritic cells. Human monocytes and monocyte-derived macrophages express H1R and H2R at the mRNA and protein levels, while the protein expression of H4R is controversial due to limitations in the specificity of available antibodies (Werner et al. 2014a; Werner et al. 2014b; Triggiani et al. 2007). The expression of histamine receptors may depend on the inflammatory milieu (Capelo et al. 2016). Moreover, differentiation of monocytes into macrophages or dendritic cells is associated with changes in histamine receptor expression, specifically an increase of H1R and downregulation of H2R (Mommert et al. 2018; Triggiani et al. 2007; Wang et al. 2000). This change in histamine receptors' expression through differentiation may explain the differential effects of histamine in these immune cell populations.

Histamine induces monocytic expression of monocyte chemoattractant protein-1 (MCP-1/CCL2) and its receptor CCR2 and the endothelial expression of adhesion molecules (Kimura et al. 2004), which facilitate transmigration. Histamine is involved in the reactions of human monocytes to allergens. Monocytes from allergic rhinitis patients stimulated with allergen extracts of house dust mite release IFN-γ via H4R activation and IL-6 via H1R activity. This study suggests that a combination of H1R and H4R antagonists should be more effective in blocking the inflammatory allergic response (Peng et al. 2019). In bone marrow-derived macrophages of

Table 1 Effects induced by histamine in microglial cells and monocytes

Cell type	HR	Main effects	Experimental paradigm	Ref.
Microglia	NA	Intrahippocampal injection of histamine inhibited LPS-induced expression of Iba-1 and HMGB1 in the hippocampus	Adult mice, in vivo	Saraiva et al. (2019)
Microglia	NA	Increased phagocytosis and ROS production but inhibited LPS-induced DA degeneration	N9 cell line	Barata-Antunes et al. (2017)
Microglia	H1R H4R	Induced microglial phagocytosis and ROS production; blockade of H1R and phagocytosis protected against DA degeneration	N9 cell line; adult mice, in vivo	Rocha et al. (2016)
Microglia	H1R H2R H3R H4R	Histamine i.c.v. administration induced microglia activation and production of TNF-α, IL-1β, and IL-10	Adult rats, in vivo	Zhang et al. (2020)
Microglia	H1R H4R	Induced microglia activation and production of TNF-α and IL-6	Rat microglia cell cultures	Dong et al. (2014)
Microglia	H2R H3R	Histamine 2/3 receptor agonists inhibited LPS-induced microglial activation, migration, release of TNF-α and IL-1β	Rat microglia cell cultures	Chen et al. (2020)
Microglia	H3R	Inhibited microglial chemotaxis, phagocytosis, and LPS-induced TNF-α and PGE2 production	Mouse microglia cell cultures	Iida et al. (2015)
Microglia	H3R	Blockade of H3R suppressed ATP-induced microglial migration and phagocytosis, reduced the LPS-induced release of pro-inflammatory cytokines, and improved depression-like behavior	Organotypic hippocampal slice cultures; adult mice, in vivo	Iida et al. (2017)
Microglia	H4R	Induced microglia motility and inhibited LPS-stimulated migration and IL-1β release	N9 cell line; cortex explants; organotypic hippocampal slice cultures	Ferreira et al. (2012)
Microglia	H4R	Overexpression of H4R decreased the LPS-induced production of IL-12, IL-6, TNF-α, and IL-1β. Knockdown of H4R enhanced proliferation and	HAPI cell line; adult rats, in vivo	Shan et al. (2019)

(continued)

Table 1 (continued)

Cell type	HR	Main effects	Experimental paradigm	Ref.
		migration in LPS-treated microglia		
Monocytes	NA	Inhibited LPS and/or LPS and TNF-α-induced TF activity, while increasing TF activity in the presence of LPS and PMA	Human peripheral mononuclear cells	Østerud and Olsen (2014)
Monocytes	H1R H4R	Monocytes stimulated with allergen extracts of house dust mite secreted IFN-γ via H4R, and IL-6 via H1R activation	Peripheral monocytes from patients with allergic rhinitis	Peng et al. (2019)
Monocytes	H2R	Induced the expression of MCP-1, CCR2-A and -B in monocytes, and ICAM-1 and VCAM-1 in endothelial cells	THP-1 and U937 cell lines; human aortic endothelial cells; human peripheral mononuclear cells	Kimura et al. (2004)
Monocytes	H2R	Inhibited LPS-induced IL-18 production	Human peripheral mononuclear cells	Takahashi et al. (2004)
Monocytes	H2R	Inhibited chemotaxis, the production of superoxide anions, phagocytosis, and the LPS-induced production of TNF-α and IL-12	Macrophages from peritoneal lavage of adult rats	Azuma et al. (2001)
Monocytes	H2R	Inhibited HMGB1-induced expression of ICAM-1, B7.1, B7.2, and CD40, production of IFN-γ and TNF-α and lymphocyte proliferation	Human monocytes	Takahashi et al. (2013)
Monocytes	H2R	Downregulated AGE-2- and AGE-3-induced expression of adhesion molecules, cytokine production, and lymphocyte proliferation	Human monocytes	Zhang et al. (2010)
Monocytes	H2R	Prevented monocytic apoptosis	Human peripheral mononuclear cells	Soga et al. (2007)
Monocytes	H4R	Induced chemotaxis and phagocytosis	RAW 264.7 cell line; bone marrow-macrophages of mice	Czerner et al. (2014)
Monocytes	H4R	Decreased the IFN-γ and LPS-induced CCL4 expression	Human peripheral mononuclear cells	Mommert et al. (2018)

HR histamine receptor, *NA* not applicable, *Ref* reference

BALB/c mice and on RAW 264.7 cells, the activation of H4R induces chemotaxis and phagocytosis (Czerner et al. 2014).

In human monocytes and macrophages, histamine suppressed LPS-induced pro-inflammatory cytokine secretion (TNF-α, IFN-α, IL-18), whereas it enhanced anti-inflammatory IL-10 (Østerud and Olsen 2014; Frei et al. 2013). Several studies suggest that the activation of H2R is responsible for these effects (Takahashi et al. 2004; Azuma et al. 2001). Inline, histamine decreased the expression of CD14 (cell surface receptor that binds to the LPS-LBP complex) in human monocytes via H2R activation, which may explain the inhibitory effects induced by histamine on LPS-induced TNF-α production (Takahashi et al. 2003). Other studies showed that histamine and the H4R agonist ST-1006 decreased the IFN-γ and LPS-induced CCL4 expression in differentiated M1 macrophages. These data suggest that histamine may counteract inflammatory reactions via H4R activation (Mommert et al. 2018). This dual role of histamine is also observed when an additional stimulus is given in combination with LPS. Accordingly, histamine inhibited LPS or the combination of LPS and TNF-α-induced LPS-induced tissue factor (TF) activity in human monocytes. In contrast, when monocytes were incubated with LPS and PMA, histamine induced a significant rise in TF activity. These data suggest that histamine induces an anti-inflammatory effect on LPS and LPS/TNF-α stimulated monocytes while having a pro-inflammatory effect in the presence of LPS and PMA (Østerud and Olsen 2014). Histamine may also modulate the response of monocytes to other inflammatory stimuli besides LPS. High mobility group box 1 (HMGB1) is a conserved nuclear protein that induces adhesion molecules and inflammatory factors (e.g., IFN-γ, TNF-α) on monocytes. It was shown that histamine inhibited pro-inflammatory effects induced by HMGB1 in human peripheral blood mononuclear cells (PBMCs) via PKA activation (Takahashi et al. 2013). Histamine also inhibited the pro-inflammatory responses induced by advanced glycation end products (AGEs) in human monocytes via H2R activation and the cAMP/PKA pathway (Zhang et al. 2010). Moreover, histamine prevented human monocytic apoptosis induced by serum deprivation, CD95/Fas ligation, or dexamethasone via H2R. Monocytes cultured with anti-IL-10 mAb and histamine did not exhibit an inhibitory effect on apoptosis, suggesting a role for IL-10 in this effect (Soga et al. 2007). Like microglia, histamine may induce pro- or anti-inflammatory reactions in monocytes and tissue-derived cells, depending on the microenvironment. Table 1 summarizes the studies mentioned above supporting the role of histamine and its receptors in monocytes and macrophages.

3 The Role of Histamine in Neurodegenerative Diseases

Accumulating evidence support the relevance of the histaminergic system for several brain diseases, including PD, stroke, Alzheimer's disease, neuropsychiatric disorders, epilepsy, multiple sclerosis, and amyotrophic lateral sclerosis. Histamine and histamine receptor levels change in a disease-specific pattern, explaining the

differential effects of histamine in each context. This review focuses on the impact of histamine in PD and ischemic stroke, as prototypical chronic and acute brain diseases, respectively. There is a substantial amount of data about the role of histamine in these diseases and the putative crosstalk between innate immune cells and neuronal survival and function, which sustain the focus on these two diseases in the following sections.

3.1 Parkinson's Disease

Parkinson's disease is characterized by the progressive degeneration of dopaminergic neurons in the *substantia nigra pars compacta* leading to striatal dopamine depletion and the accumulation of α-synuclein aggregates known as Lewy bodies (Spillantini et al. 1997; Damier 1999). The key symptoms that clinically define PD are rigidity, tremor, bradykinesia, and postural instability, among other non-motor manifestations (e.g., olfactory impairment, gastrointestinal dysfunction) preceding motor symptoms.

The innate immune system plays a crucial role in PD pathology. Increased numbers of microglial cells within the *substantia nigra*, and increased levels of pro-inflammatory mediators (TNF-α, IL-1β, IL-6) were found in the blood, cerebrospinal fluid, and brains of PD patients and animal models of the disease (McGeer et al. 1988; Harms et al. 2013; Watson et al. 2012; Nagatsu et al. 2000). Microglia activation precedes dopaminergic degeneration (Krashia et al. 2019; Sanchez-Guajardo et al. 2010; Gerhard et al. 2006), which may contribute to dopaminergic degeneration in later stages of the disease (Harms et al. 2021). Interestingly, the *substantia nigra* contains a higher density of microglia than other brain regions (Kim et al. 2000), rendering DA neurons more sensitive to an immune challenge. Inline, the intracerebral or systemic administration of LPS induced microgliosis and reduced tyrosine hydroxylase-positive neurons in the *substantia nigra* (Kim et al. 2000; Qin et al. 2007). Therefore, these and other studies raised the notion that microglial activation leads to dopaminergic neuronal degeneration and disease progression. On the contrary, recent studies showed that Cx3cr1-deficiency mice, which display deficient microglia function, had exacerbated dopaminergic degeneration induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and α-synuclein-A53T, suggesting that microglia plays a protective role in PD (Castro-Sánchez et al. 2018; Parillaud et al. 2017). These discrepancies may depend on the experimental models and the stage of development of the disease. Alterations in the peripheral innate immune system, particularly in monocytes, were also shown in PD. Classical monocytes expressing CCR2 and CCL2 are enriched in the blood, and CSF isolated from PD patients (Funk et al. 2013; Wijeyekoon et al. 2020). Monocytes from PD patients have impaired pro-inflammatory cytokine production, impaired phagocytic function, and had high expression of genes related to PD, such as *Snca* or *Lrrk2* (Raj et al. 2014; Grozdanov et al. 2014; Hasegawa et al. 2000; Gardai et al. 2013). On the other hand, other reports showed that monocytes from PD

patients are hyperactive to LPS stimulation and showed increased phagocytic capacity (Grozdanov et al. 2014; Grozdanov et al. 2019; Wijeyekoon et al. 2018). These contradictory data are most likely due to differences in the isolation and culture procedures, cohorts, and methodologies used. Notably, the genetic deletion of CCR2 was neuroprotective, suggesting a deleterious role for infiltrating monocytes in PD (Harms et al. 2018). Taken together, these studies illustrate the critical influence of microglia and peripheral myeloid cell actions on PD pathogenesis.

The histaminergic system is affected in PD. Several reports have shown increased histaminergic fibers and local histamine levels in the *substantia nigra* of PD postmortem human brain and animal models (Panula and Nuutinen 2013; Anichtchik et al. 2000; Rinne et al. 2002; Nowak et al. 2009). Moreover, a Thr105Ile polymorphism of HNMT was shown to be associated with PD, suggesting that lower HNMT activity plays a role in the pathogenesis of PD (Palada et al. 2012). On the contrary, Shan and colleagues showed no alterations in HDC mRNA levels among different clinical or Braak-PD stages, despite the accumulation of Lewy bodies and Lewy neurites in the TMN of PD patients (Shan et al. 2012b). Interestingly, the same authors showed that the mRNA expression of H3R decreased in the SN in PD, while H4R expression increased in the caudate nucleus and putamen. Moreover, increased mRNA levels of HNMT were found in the SN and the putamen in PD patients (Shan et al. 2012c). Altogether these data suggest that changes in the histaminergic system, particularly increased histamine levels, altered histamine metabolism, and expression of histamine receptors, may contribute to PD pathology.

Some studies have been focusing on the role of endogenous histamine in PD pathology. By using HDC KO mice, it was found that histamine deficiency increased amphetamine-induced rotation induced by the neurotoxin 6-hydroxydopamine (6-OHDA) injection in the medial forebrain bundle (MFB) but did not affect levodopa-induced dyskinesia (LID), increased striatal expression of D1 and D2 receptors and H3R mRNA, and increased dopamine release. Therefore, there is an interplay between histaminergic and dopaminergic neurotransmission within the nigrostriatal pathway, impacting motor behavior (Koski et al. 2020). On the other side, the administration of histamine in the *substantia nigra* or systemic administration of histidine (a precursor of histamine) leads to dopaminergic neuronal death and aggravated motor behavior in vivo (Rocha et al. 2016; Vizuete et al. 2000; Liu et al. 2007; Liu et al. 2008). These neurotoxic effects may depend on the activation of microglia phagocytosis and oxidative signaling pathways (Rocha et al. 2016). Moreover, the i.c.v. administration of the specific H4R antagonist JNJ7777120 inhibited microglial activation and TNF-α release, reduced apomorphine-induced rotational behavior, prevented dopaminergic neuron degeneration, and reduced Lewy body-like neuropathology in a rotenone-induced PD rat model (Zhou et al. 2019; Fang et al. 2021). This suggests that histamine may have a detrimental effect on DA survival via H4R activation. In addition, H2R antagonists have also been reported to improve the motor symptoms of PD patients and to exert neuroprotective effects, suggesting that depending on the model, histamine may also induce DA degeneration by H2R activation. Indeed, ranitidine (an H2R antagonist), protected against rotenone-induced apoptosis, inhibiting phosphorylation of JNK and P38,

promoting the phosphorylation of extracellular signal-regulated protein kinase (ERK), and suppressed CASP3 enzyme activity in an human dopaminergic cell line (Park et al. 2009). These studies suggest that histamine may play a major role in inducing DA degeneration via H4R or H2R activation.

Interestingly, dopaminergic neurons are susceptible to LPS-induced inflammatory response, being LPS widely used to mimic PD in rodent models (Qin et al. 2007; Zhao et al. 2018). Noteworthy, we showed that histamine prevented LPS-induced microglial activation and dopaminergic neuronal death (Rocha et al. 2014). Thus, histamine per se induces the activation of microglial responses and dopaminergic degeneration while, when given in combination with other inflammatory stimuli (LPS), triggers an anti-inflammatory and neuroprotective response.

Therapeutic options for PD include levodopa (dopamine precursor), dopamine agonists, and MAO-B inhibitors. The therapeutic choice depends on the stage of the disease (de Bie et al. 2020). MAO-B is involved in the degradation of an extensive range of biogenic and dietary amines, including dopamine and the histaminergic metabolite *N*-methylhistamine (see Sect. 1). Therefore, MAO-B inhibitors increase dopamine and *N*-methylhistamine levels (Riederer and Laux 2011). Increased levels of dopamine improve motor control in patients. The inhibition of histamine metabolism may impact histaminergic neurotransmission and dopaminergic function/survival; however, no studies have been described so far focusing on this putative relation.

Another standard therapeutic option is levodopa (or L-DOPA) which shows high efficacy in the early stage of the disorder. Over time levodopa loses effectiveness and causes dyskinesias and severe psychiatric complications. Several studies have studied the role of the histaminergic system in levodopa-induced dyskinesia (LID). The mechanisms underlying LID in PD may involve H2R. H2R are highly expressed in the input (striatum) and output (globus pallidus, SN) regions of the basal ganglia, particularly in the GABAergic striatopallidal and striatonigral pathways. Several H2R antagonists (e.g., famotidine, ranitidine) could inhibit LID in PD models in vivo (Ahmed et al. 2019; Lim et al. 2015; Yang et al. 2013). This effect may be due to normalized levels of GRK3, reduced ERK activation, and FosB accumulation in the lesioned striatum, and reduced Arc and proenkephalin levels in dyskinetic animals (Ahmed et al. 2019). The ability of famotidine to counteract LID was also observed in MPTP-lesioned macaques but not in clinical trials with PD patients (Mestre et al. 2014; Johnston et al. 2010). Another study focused on the role of H3R agonists immepip or imetit in LID, in rats lesioned with 6-OHDA in the SN or MPTP-lesioned marmoset models for PD. The chronic administration of the H3R agonist immepip alongside L-DOPA decreased LID compared with L-DOPA alone (Gomez-Ramirez et al. 2006; Avila-Luna et al. 2019). Immepip also decreased GABA and glutamate content in the striatum (Avila-Luna et al. 2019).

Deep brain stimulation is also used in some PD patients, in more advanced stages of the disorder, with successful suppression of motor symptoms; however, it does not stop the disease progression. The subthalamic nucleus is an effective therapeutic target for deep brain stimulation, and histamine levels are elevated in the basal ganglia in PD patients. Zhuang et al. demonstrated that histamine levels rise in the

subthalamic nucleus to compensate for abnormal firing patterns. Injection of histamine into the subthalamic nucleus restored normal firing patterns and ameliorated Parkinsonian motor deficits via H2R activation. Moreover, deep brain stimulation regularized neuronal firing through endogenous histamine release under Parkinsonian conditions. These data suggest a role of histamine in the basal ganglia circuitry that regularizes subthalamic nucleus neuronal firing patterns and ameliorates motor dysfunction (Zhuang et al. 2018). Table 2 summarizes the main effects induced by histamine in PD models.

3.2 Stroke

Stroke is characterized by the sudden onset of focal neurological deficits of variable nature and severity caused by cerebrovascular dysfunction. Nearly 85% of strokes are ischemic, meaning that thrombosis or an embolism causes a sudden interruption of blood flow, which may lead to paralysis, impaired speech, and loss of vision, or other neurological signs and symptoms. The remaining percentage of cases is triggered by hemorrhage (Moskowitz et al. 2010).

Innate immune responses mediated by microglia and monocytes play a crucial role in the pathology of ischemic stroke (Schilling et al. 2003; Zrzavy et al. 2018). Both microglia and monocytes trigger pro- and anti-inflammatory roles, which depend on the type and severity of the injury, brain area affected, the window of time post-stroke, and methodologies. Microglial cells became activated within minutes after the onset of ischemic injury, proliferate, migrate to the site of injury, release inflammatory mediators (TNF-α, IL-1β, IL-6, among others) and phagocyte cellular debris (Clausen et al. 2008; Lambertsen et al. 2012). The pharmacological or genetic depletion of microglia induced either protection or toxicity in ischemic injury. Depletion caused by the treatment with colony-stimulating factor 1 (CSF1)/c-kit inhibitor, minocycline, or by using the CX3CR1 KO mice exacerbated inflammation, infiltration of peripheral immune cells, and augmented ischemic brain injury, suggesting endogenous defense mechanism induced by microglia in ischemic stroke (Jin et al. 2017; Szalay et al. 2016; Faustino et al. 2011; Tsuji et al. 2020). On the contrary, Li and colleagues showed that the selective elimination of microglia in the early phases of ischemic injury induced anti-inflammatory and decreased pro-inflammatory factors, decreased ischemic infarct volume, while improved motor performance (Li et al. 2021). These data corroborates that microglia has a detrimental phenotype at the early stages of ischemic injury while at later stages is involved in the repair program post-ischemia. Microglia activation precedes infiltration of peripheral monocytes into the ischemic brain. The leaky BBB allows monocytes to enter into the ischemic injury within the first hours post-ischemia and peaks at 3–7 days (Chu et al. 2014). Monocytes also release several inflammatory mediators and interact with parenchymal cells. The functional role of monocytes has been investigated using CCR2 pharmacological inhibitors or CCR2-deficient mice. Studies using these strategies reveal that CCR2 deficiency reduced angiogenesis and

Table 2 Effects induced by histamine in Parkinson's disease models

PD Model	HR	Main effects	Ref.
Adult rats, in vivo	NA	Intranigral injection of histamine induced microglia activation and DA degeneration	Vizuete et al. (2000)
6-OHDA into the MFB of mice, in vivo	NA	Histamine deficiency increased amphetamine-induced rotation and caused upregulation of striatal dopaminergic neurotransmission	Koski et al. (2020)
Rat microglial cell cultures from the SN, in vitro	NA	Histamine induced nitrite production and iNOS expression. Conditioned medium derived from histamine-treated microglial cells reduced DA survival	Rocha et al. (2014)
Adult mice, in vivo	H1R	Intranigral injection of histamine induced DA death	Rocha et al. (2016)
6-OHDA into the SN and MFB of rats, in vivo	H1R	Blockade of H1R decreased the motor impairment and prevented DA degeneration	Liu et al. (2007)
6-OHDA into the SN and MFB of rats, in vivo	H1R H2R H3R	Blockade of H1R and H2R and the H3R agonist decreased motor impairment	Liu et al. (2008)
SH-SY5Y cell line, in vitro	H2R	Blockade of H2R protected against rotenone-induced DA degeneration	Park et al. (2009)
Rotenone rat model, in vivo	H4R	I.c.v. administration of an H4R antagonist inhibited microglial activation, prevented DA degeneration, and reduced motor impairment	Zhou et al. (2019)
Rotenone rat model, in vivo	H4R	I.c.v. administration of an H4R antagonist inhibited DA degeneration, microglia activation, and motor impairment	Fang et al. (2021)
LID in a hemiparkinsonian mouse model, in vivo	H2R	Blockade of H2R normalized the expression of GRK3, attenuated the ERK and FosB pathways in the striatum	Ahmed et al. (2019)
LID in 6-OHDA and Pitx3 (ak/ak) mutation mouse models, in vivo	H2R	H2R blockade decreased behavioral LID	Lim et al. (2015)
Rat model of LID, in vivo	H2R	H2R blockade decreased LID and improved motor behavior	Yang et al. (2013)
PD human subjects with dyskinesia	H2R	H2R blockade is safe in patients with PD and LID but showed no potential as an antidyskinetic agent	Mestre et al. (2014)
LID in MPTP-lesioned macaques, in vivo	H2R	H2R blockade affected chorea and increased high dose levodopa-induced "good quality" on time	Johnston et al. (2010)
LID in MPTP-lesioned marmosets, in vivo	H3R	H3R agonist with L-dopa reduced dyskinesia. H3R agonist per se increased Parkinsonian disability	Gomez-Ramirez et al. (2006)
LID in rats lesioned with 6-OHDA in the SN, in vivo	H3R	H3R agonist alongside L-Dopa decreased axial, limb, and orolingual abnormal involuntary movements	Avila-Luna et al. (2019)

HR histamine receptor, *NA* not applicable, *Ref* reference

worse behavioral performance suggesting a pro-regenerative action of infiltrating monocytes (Pedragosa et al. 2020; Perego et al. 2016). This effect may be time-dependent, as other studies showed that using CCR2 KO mice and the CCR2 pharmacological inhibitors or neutralizing antibodies resulted in smaller infarct size and lower mortality at 3 days post-stroke while from 5 to 28 days after stroke, treated or KO mice had higher mortality and showed no functional recovery (Fang et al. 2018; Wattananit et al. 2016). These data suggest that monocytes/macrophages mainly polarized to a pro-inflammatory phenotype at the early stage but gradually switched to anti-inflammatory at later stages post-stroke.

Ischemic stroke is caused by a blockage of the cerebral blood supply resulting in death or dysfunction of brain cells, activation of microglia and astrocytes, and mobilization of monocytes (Garcia-Bonilla et al. 2018). Evidence showed that cerebral mast cells releasing histamine also accumulate in the ischemic core and penumbra after injury (Biran et al. 2008). The levels of histamine receptors are also altered, as shown in an ischemia-reperfusion injury model in vivo. In particular, H1R mRNA expression was increased in the caudate-putamen, a decrease in H2R binding densities in the caudate-putamen was observed, H3R mRNA expression was raised in the caudate-putamen of the postischemic brain but was decreased in the globus pallidus and the thalamus; in association with this, H3R binding densities were increased in the cortex, caudate-putamen, globus pallidus, and hippocampus. These data suggest that histamine receptor expression and ligand binding are altered in brain ischemia in distinct areas and may participate in neuroprotection and/or ischemia-associated neuronal damage (Lozada et al. 2005).

The endogenous histamine was found to be essential for hypoxic preconditioning stroke tolerance in mice (Fan et al. 2011). By using HDC KO mice, it was shown that histamine is a critical mediator in hypoxic preconditioning, likely due to enhancing hypoxia-induced VEGF expression (Fan et al. 2011). Moreover, enhancement of histaminergic activity suppresses inflammatory cell recruitment after ischemic events through H2R, which may be a mechanism underlying the protective effect of L-histidine (Hiraga et al. 2007; Motoki et al. 2005; Adachi et al. 2005).

Several contradictory data were reported about the role of histamine receptors in stroke. Regarding the involvement of H3R, it was shown that thioperamide, an H3R antagonist, promotes neurogenesis (SVZ and SGZ) and protects against neuronal death and cognitive impairments in brain ischemic stroke models in vitro and in vivo (Wang et al. 2020). These effects may be due to increased phosphorylation of cAMP-response element-binding (CREB) and upregulation of the expression and release of BDNF (Wang et al. 2020). Another study showed that H3R blockade protects against ischemic/reperfusion injury by histamine-independent mechanisms that involve autophagy mechanisms (Yan et al. 2014). Nevertheless, both studies agree that H3R inhibition is a therapeutic target for cerebral ischemia.

On the other hand, clemastine, an H1R antagonist, reduced cerebral hematoma volume, decreased cerebral edema, lowered rates of neuronal apoptosis, improved behavioral scores in an acute intracerebral hemorrhage murine model. These effects were accompanied by reduced microglia activation and reduced pro-inflammatory

effectors, and increased anti-inflammatory effectors post-lesion (Zhi et al. 2021). Similar results were observed in a hypoxic-ischemic brain injury mimicked by a bilateral common carotid artery occlusion (BCCAO) rat model where clemastine can improve hypomyelination by suppressing the activated microglia and promoting the maturation of oligodendrocyte progenitor cells by restraining the upregulation of IL-1β and NLRP3 in the corpus callosum (Xie et al. 2020). These data suggest that the activation of H1R may trigger detrimental effects in ischemic stroke.

The involvement of H4R has also been suggested to play a crucial role in the modulation of ischemia mechanisms. Chronic intraperitoneal administration with the H4R antagonist, JNJ7777120, protected from the neurological deficit in a rat model of focal ischemia induced by transient MCAo. At short-term (2 days post-lesion), JNJ7777120 reduced granulocyte infiltration in the ischemic area, while at long-term (7 days post-lesion), it was able to reduce the ischemic cortical and striatal lesion, the number of activated microglia and astrocytes in the ischemic cortex, and striatum and decreased the plasma levels of IL-1β and TNF-α, while increased the levels of IL-10. This may suggest that H4R is also a valuable pharmacological target after focal brain ischemia (Dettori et al. 2018).

Administration of H2R antagonists has been reported to produce contradictory results. The administration of H2R antagonists has also shown to be protective in ischemic-induced neuronal lesions in vitro (Malagelada et al. 2004), while in vivo, the administration of ranitidine, an H2R antagonist, antagonized the protective effects mediated by the i.c.v. administration of histamine in transient occlusion of the right middle cerebral artery in rats (Hamami et al. 2004). The last outcome may be due to a suppression of the ischemic release of excitatory neurotransmitters (dopamine, glutamate) (Hamami et al. 2004; Adachi et al. 2004).

All these reports support the role of the histaminergic system in the modulation of ischemic injury. Better comprehension and in-depth analysis of the experimental paradigms and lesion models applied is essential to provide more substantial proofs to proceed into clinical trials. Table 3 summarizes the main effects induced by histamine and its receptors in ischemic stroke.

4 Conclusions/Perspectives

Histamine plays a key role in the modulation of neuronal activities and behavioral functions. It has been shown that it also modulates innate immune cells, both in the brain (microglia) and in the periphery. In turn, the activation of peripheral immune cells can profoundly affect microglia activity, which plays a critical role in the onset and development of brain disorders. Therefore, unraveling the multiple actions of histamine might lead to the development of anti-inflammatory and regenerative therapies for both acute brain pathologies and neurodegenerative diseases. Besides the accumulating evidence supporting the role of the histaminergic system in these mechanisms, there is controversy about the most promising experimental strategy, histamine receptor, and dose to use in the context of brain diseases. The lack of

Table 3 Histamine effects in stroke disease models

Stroke model	HR	Main effects	Ref
Transient occlusion of the MCA of rats, in vivo	NA	L-histidine prevented the development of brain infarction	Motoki et al. (2005)
Hypoxic preconditioning and transient occlusion of the MCA, WT, and HDC KO mice, in vivo	NA	Hypoxic preconditioning improved neurologic function, decreased infarct volume, and increased VEGF expression in WT or HDC KO mice treated with histamine	Fan et al. (2011)
Primary cortical neurons and microglia; acute ICH murine model, in vivo	H1R	H1R blockade reduced neuronal death and inflammatory response and improved behavioral scores	Zhi et al. (2021)
Microglial and oligodendrocyte progenitor cell cultures; bilateral common carotid artery occlusion rat model, in vivo	H1R	H1R blockade reversed hypomyelination	Xie et al. (2020)
Transient occlusion of the MCA of rats, in vivo	H2R	L-histidine decreased inflammatory cell infiltration in the ischemic brain. Blockade of H2R tended to reverse these effects	Hiraga et al. (2007)
Transient occlusion of the MCA of rats, in vivo	H2R	Histidine alleviated brain infarction	Adachi et al. (2005)
Cultured rat cortical neurons, in vitro	H2R	H2R antagonists reduced neuronal cell death induced by OGD	Malagelada et al. (2004)
Transient occlusion of the MCA of rats, in vivo	H2R	I.c.v. administration with histamine suppressed dopamine and glutamate levels and the histologic outcome	Hamami et al. (2004)
Transient occlusion of the MCA of rats, in vivo	H2R	Histidine alleviated ischemic neuronal damage	Adachi et al. (2004)
Cortical neuronal cultures; NE-4C cell line; chronic cerebral hypoperfusion model in mice, in vivo	H3R	Thioperamide had protective effects on OGD-induced cell death, enhanced neurogenesis, and ameliorated CCH-induced cognitive impairments	Wang et al. (2020)
Neuronal cell cultures; mouse model of transient occlusion of the MCA, in vivo	H3R	H3R blockade attenuates I/R injury via histamine-independent mechanisms	Yan et al. (2014)
Transient occlusion of the MCA of rats, in vivo	H4R	H4R blockade protected from the neurological deficit and neuronal damage, inflammatory response, and decreased the plasma levels of IL-1β and TNF-α while increasing the levels of IL-10	Dettori et al. (2018)

CCH chronic cerebral hypoperfusion, *HR* histamine receptor, *ICH* intracerebral hemorrhage, *I/R* ischemia/reperfusion, *MCA* middle cerebral artery, *OGD* oxygen-glucose deprivation, *NA* not applicable, *Ref* reference, *WT* wild-type

consensus about the effects of histamine modulators can be due to the diversity of models and experimental paradigms used. Studies using animal models of disease should use complementary models, mimicking different aspects of the pathology. Choosing experimental models more representative of the human condition is also an upset. More comprehensive analysis, using in vivo and experimental models using human-derived cells (e.g., induced pluripotent stem cells—iPSC), is needed to advance in the knowledge and translational potential of histamine and its receptors. For the experiments using human monocytes, it is also crucial to pay attention to the cohort selection, methods for selecting and cultivating immune cells, which may introduce many variables that impact the effects induced by histamine and histamine receptor modulators.

Brain diseases are accompanied by alterations in histamine levels and the expression of its receptors. Disclosing whether these alterations are a consequence or a cause of neurodegeneration is crucial. Chronic exposure paradigms or histamine depletion (on a temporal and cell-specific basis) before neuronal lesions could help to address this issue. Moreover, additional studies are necessary to correlate the effects of histamine in innate immune cells and the functional consequence for neurons. The use of conditional KO mice targeting the histaminergic system (e.g., HDC, HR) in specific cell populations is relevant to address this question.

The specificity of HR agonists/antagonists is another aspect that hampers robust conclusions. Many HR agonists/antagonists were reported in the literature, but only a few have been studied in humans. Thus, the development of more specific pharmacological modulators is needed. Recent studies showed that H3R forms heteromers with other receptors (D1R, A2A). Thus, it is of utmost relevance to develop novel dual receptor modulators that interact with different neurotransmitter systems, thus exerting more robust effects. The benefits of interacting with dual systems should be further explored in the context of brain diseases. Besides this need to improve a better outcome, there is much evidence supporting more research in this field, which may significantly impact novel therapeutic strategies for brain diseases.

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Part IV
Neuropharmacology: Histamine and Behaviour

The Histamine System in Zebrafish Brain: Organization, Receptors, and Behavioral Roles

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Abstract Three of the four histamine receptors have been identified in zebrafish. Whereas only one histamine receptor 1 gene (*hrh1*) is known, two copies of histamine receptor 2 (*hrh2a* and *hrh2b*) have been identified. Although initially only one gene encoding for histamine receptor 3 (hrh3) was recognized in zebrafish, the genome database contains information for two more *hrh3*-like genes, whereas no genes corresponding for histamine receptor 4 with expression mainly in the immune system have been identified. *Hrh1* and *hrh3* show prominent uneven expression in the zebrafish brain, with the strongest expression in the dorsal telencephalon. Quantitatively significant expression of *hrh1*, *hrh2,* and *hrh3* can also be found in several peripheral organs. Whereas antagonists of hrh1, hrh2, and hrh3 all affect the locomotor activity of zebrafish larvae, interpretation of the data is hampered by a lack of information on receptor binding and signaling characteristics. Zebrafish mutants lacking any of the three histamine receptors have shown modest behavioral phenotypes, possibly due to genetic compensation. None of the receptor mutant fish have shown significant sleep phenotypes. Adult zebrafish lacking *hrh3* display decreased locomotor activity. The zebrafish histamine system shows significant life-long plasticity: presenilin 1 mutant zebrafish develop an abnormally large

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number of histamine neurons and increased thigmotaxis and anxiety-related phenotype. Overexpression of histidine decarboxylase (*hdc*) in larval zebrafish is associated with an increased number of hypocretin neurons, whereas translation inhibition of *hdc* or exposure to α-fluoromethylhistidine leads to decreased numbers of hypocretin neurons. Current pharmacological evidence suggests that this may be mediated by hrh1. Further studies using acute, e.g., pharmacogenetic or optogenetic manipulation of selected components of brain circuits, are required to understand the full range of physiological functions of zebrafish histamine receptors.

Keywords CRISPR/Cas · G protein-coupled receptor · Hypothalamus · Presenilin · Pyrilamine · Sleep · Thioperamide · Zolantidine

1 Zebrafish in Behavioral Neuroscience

Zebrafish were introduced to developmental biology in the 1980s due to the rapid development, high fecundity, and easy maintenance in captivity. Because of the rapid development of transparent embryos, development of many organs can be followed with rather simple equipment. Rapid emergence of genetic manipulation methods ranges from widely used translation inhibition to production of carefully targeted mutants and conditionally regulated models using CRISPR/Cas and other methods. Despite the challenges of both translation inhibition (non-specific targeting, toxicity) to genetic compensation associated with gene modifications (El-Brolosy et al. 2019), a large selection of advanced phenotyping methods has been developed. Advantages of the zebrafish model include excellent possibilities for spatial and temporal analysis of neuronal activity with behavioral outcomes. Behavioral tests available include detailed analysis of larval movements (Burgess and Granato 2007), a range of visual tests (Neuhauss et al. 1999), locomotor analysis of large numbers of individual larvae (Panula et al. 2010), tests for memory, aggression, shoaling behavior, and social interactions (Orger and de Polavieja 2017; Chen et al. 2020). Simultaneous analysis of neuronal activity and tail movements in changing fictive environments (Ahrens et al. 2012) allows whole brain-wide analysis of individual neurons and neuronal groups in a manner that enables identification of neurotransmitter phenotypes (Ahrens et al. 2013). These analyses can be performed in normal fish, gene-modified fish, or under circumstances where selected neurons can be temporarily activated or inactivated. Thus, whole circuits and individual components can be functionally analyzed in experimentally controlled circumstances in exactly reproducible behavioral conditions. These advantages open unprecedented possibilities to analyze the neuronal mechanisms and behavior in animals.

2 Histamine in Fish

With the exception of some groups of fish, including lungfish, the histamine levels in peripheral tissues of most fish are low. This is true, e.g., for the gastrointestinal tract of stomachless fish like carp (Reite 1972), which means that the mammalian-like regulation of acid secretion by histamine and hrh2 does not operate in these species. Furthermore, early studies using o-phthalaldehyde fluorescence and biochemical methods also showed that mast cells in teleost fish generally do not store histamine (Reite 1972). So far, there is no published evidence for the presence of histamine in zebrafish mast cells, and mast cells in most fish do not produce histamine, although they are present in fish (Reite 1972). Histamine is a well-known causative agent in one of the most common food poisoning syndromes caused by the ingestion of rotten fish (Taylor 1986). Due to rapidly activated bacterial activity in fish tissues, this food poisoning is the most commonly known association of histamine and fish.

3 Histaminergic Systems in Fish

3.1 Fish in General

Availability of specific antibodies for histamine (Panula et al. 1984) has enabled detailed studies of the structure of the brain histaminergic system in several fish species. Histamine neurons in jack mackerel *Trachurus trachurus* are found in the posterior hypothalamus around the posterior recess, and fiber projections are directed to the telencephalon, diencephalon, and tegmentum (Inagaki et al. 1991). In the three-spined stickleback, *Gasterosteus aculeatus*, the histamine neurons are located ventrally to the nucleus of the posterior recess and in the nucleus saccus vasculosus, with long projections to the thalamus, habenula, preoptic area, and dorsal telencephalon (Ekstrom et al. 1995), very similarly with zebrafish. Thus, despite the wide variety of fish species, the histaminergic system in its basic layout is essentially similar in those studied species.

3.2 Zebrafish Brain Histamine System

The histaminergic neuron system in the zebrafish brain is organized similarly to most other vertebrates (Anichtchik et al. 2004; Kaslin and Panula 2001), with neuronal cell bodies in the posterior hypothalamus and widespread projections in almost all parts of the brain. A detailed 3-dimensional structure of this region indicates that the same small area harbors neurons that express tyrosine hydroxylase 1 (*th1*), tyrosine hydroxylase 2 (*th2*), markers of dopaminergic neurons, tryptophan hydroxylase, and serotonin (Chen et al. 2020; Kaslin and Panula 2001; Chen et al. 2016; Sundvik and

Panula 2012). Histamine is metabolized by histamine N-methyltransferase, which is widely expressed in the zebrafish brain, including the raphe, preoptic area of the hypothalamus, and periventricular nucleus of the hypothalamus (Norton et al. 2011).

4 Histamine Receptors in Zebrafish

Three G protein-coupled histamine receptors were identified and cloned in 2007 (Peitsaro et al. 2007). Thus, histamine receptor 1 (hrh1), histamine receptor 2 (hrh2), and histamine receptor 3 (hrh3) are all found in zebrafish despite the reported limited expression of *hdc* and histamine levels below the detection limit in, e.g., whole fish without the brain, GI tract, or gills (Eriksson et al. 1998). The first report on histamine receptor genes in zebrafish (Peitsaro et al. 2007) reports on expression of *hrh1* mRNA in the intestine, liver, and spleen, *hrh2* mRNA in gills, heart, and spleen, and *hrh3* in the heart, spleen, eyes, and gills, suggesting that more sensitive methods may reveal expression of *hdc* and synthesis of histamine in small numbers of cells also in peripheral tissues. Even though the full genome information is available, the newer receptor genes are still not yet well analyzed suggesting a more detailed analysis would be relevant.

The zebrafish *hrh1* gene is an intronless gene with 40–48% peptide sequence homology with mammalian *hrh1* (Peitsaro et al. 2007), located in chromosome 11. In 5–7 dpf zebrafish brain, the strongest expression of *hrh1* is found in the dorsal telencephalon in an area that corresponds to the mammalian cortex, amygdala, hippocampus, and in habenula (Sundvik et al. 2011).

A single zebrafish *hrh2* gene was cloned in 2007 as an intronless gene with 43–47% sequence homology with canine, human, and mouse *HRH2* (Peitsaro et al. 2007). Currently, two copies of the *hrh2*-like receptor are recognized in chromosomes 10 and 14. Despite the challenges in showing the gene expression of *hrh2* using in situ hybridization in zebrafish brain, there is a clearly uneven distribution of hrh2 binding sites using $^{[125I]}$iodoaminopotentidine, an hrh2 ligand autoradiography, and the binding can be blocked with tiotidine, an hrh2 antagonist (Peitsaro et al. 2007). The binding sites are more abundant in the optic tectum and central diencephalon compared with adjacent brain regions.

The zebrafish *hrh3* gene in chromosome 7 has three exons (Peitsaro et al. 2007) and is most prominently expressed during the first week of life in the dorsal telencephalon (Sundvik et al. 2011), one of the major targets of caudal hypothalamic histamine neurons (Kaslin and Panula 2001; Kaslin et al. 2004) and caudal hypothalamus, in agreement with its putative role as an autoreceptor (Sundvik et al. 2011). During development, expression of *hrh3* is first clearly detectable in the dorsal telencephalon, caudal hypothalamus, and rostral diencephalon (Puttonen et al. 2018). Thereafter prominent expression in the telencephalon, thalamus, hypothalamus, and optic tectum remains throughout adulthood (Puttonen et al. 2018). The coexpression analysis of telencephalic neurons shows that *hrh3* is expressed mostly in glutamatergic neurons in the superficial pallium, whereas in deeper parts also

GABAergic neurons express *hrh3* (Puttonen et al. 2018). Recently, in zebrafish, two novel *hrh3*-like receptors are identified in the latest GenBank (Release 241.0) by phylogenetic analysis (Fig. 1). *Hrh3b* is located on chromosome 2, and *hrh3b* mRNA is primarily expressed in the lateral subnucleus of the dorsal habenula. *Hrh3c* is located on chromosome 22, and *hrh3c* mRNA is distributed evenly in the left and right habenula (Fig. 2). The function of these two receptors is yet unidentified.

5 Behavioral Roles of Histamine in Zebrafish

Since zebrafish were not initially developed as research tools for behavioral neuroscience, behavioral studies have only been carried out for the past 20 years. Other fish, in laboratory studies mainly goldfish, have been investigated more extensively in the past. Chlorpheniramine, an hrh1 antagonist, has shown memory enhancing effects in active avoidance tests of goldfish (Mattioli et al. 1998; Spieler et al. 1999). The challenge with pharmacological studies on fish histamine receptors is that no comprehensive analysis of ligand specificity is yet available. It is thus difficult to estimate if all effects are mediated through specific histamine receptors.

Since the finding of the brain as the primary source of histamine in zebrafish, the behavioral role of this system has been studied by inhibiting the histamine synthesis using the suicide hdc inhibitor α-fluoromethylhistidine (α-FMH), by exposing live larvae to histamine receptor ligands in swimming water, by inhibiting the translation of *hdc* using morpholino oligonucleotides, and by generating mutant zebrafish lines lacking *hdc* or one of the histamine receptors. Almost 80% reduction in brain histamine levels can be reached with three daily injections of α-FMH (Peitsaro et al. 2003). This treatment reduces hdc activity and reversibly provides a means to regulate histamine levels acutely without genetic manipulation, which is prone to non-specific side effects (translation inhibition) and genetic compensation (genome modifications). In adult zebrafish, a characteristic change in swimming behavior follows the administration of α-FMH. Although the swimming speed is unaffected, the typical swimming pattern along the edges of a round arena (thigmotaxis) is abolished. The fish swim evenly across the arena (Peitsaro et al. 2003), giving an impression of abnormally low anxiety-like behavior. Although injections of L-histidine in adult fish result in a significant increase of approximately 50% in brain histamine, no difference in open field behavior has been reported compared with saline treated fish (Peitsaro et al. 2003). However, adult zebrafish submitted to stress by confinement displayed enhanced learning after intraperitoneal injection of L-histidine (Cofiel and Mattioli 2009). Zebrafish lacking functional presenilin 1 (*psen1*), a component of gamma-secretase complex that regulates, e.g., stem cell populations through notch1, have at the adult stage about 50% more histamine neurons in the hypothalamus than control wild-type fish, and show enhanced thigmotaxis in an open field (Sundvik et al. 2013). Zebrafish mutants with reduced fibroblast growth factor receptor 1a (*Fgfr1a*) function display increased aggressive

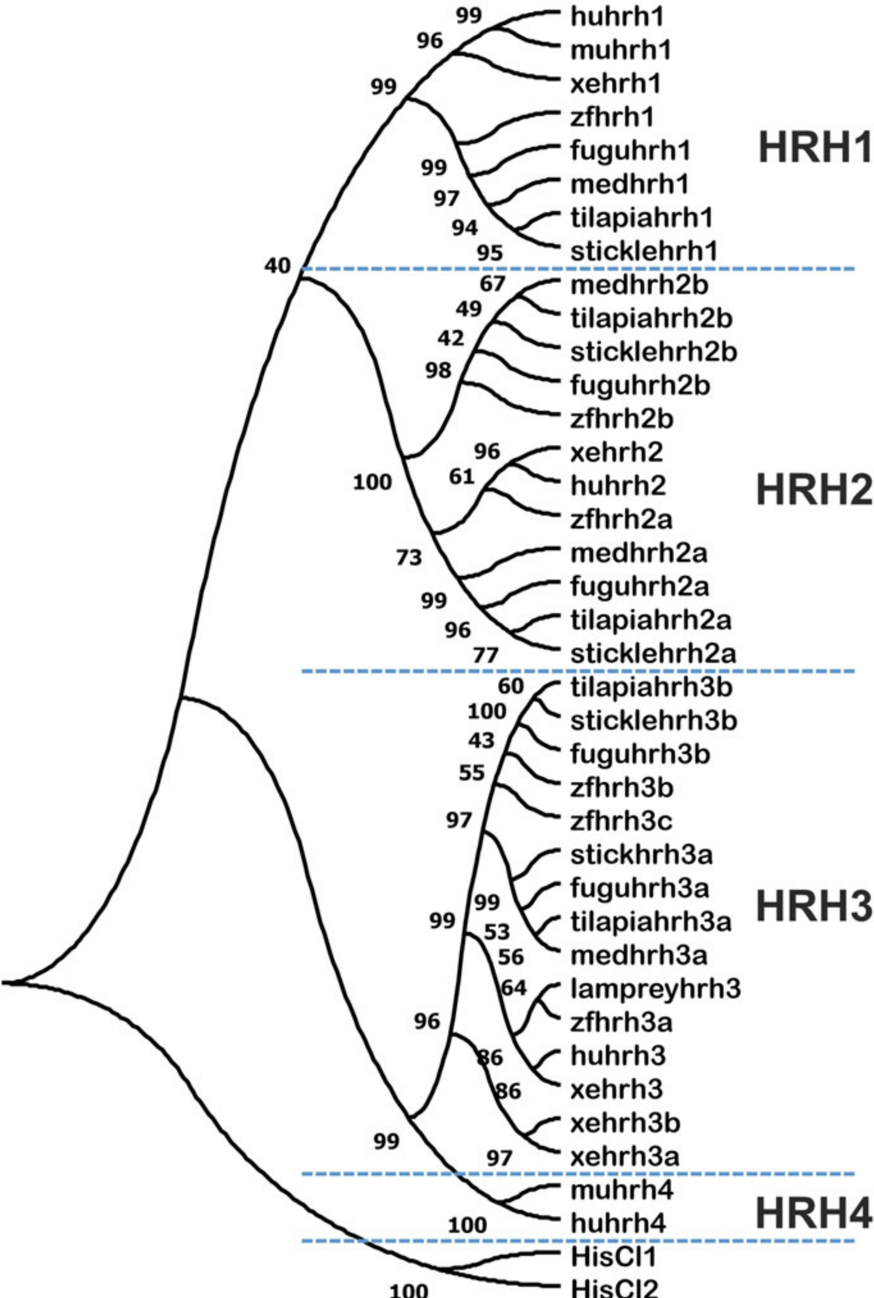

Fig. 1 Phylogenetic tree of histamine receptors based on the full-length open reading frames of deduced amino acid sequences. The tree was constructed using the neighbor-joining method. The genetic distances were calculated using the Kimura's two-parameter method. The bootstrap values on the nodes indicated the percentage of the genes grouped together in 1000 replications. The amino acid sequences were retrieved from GeneBank

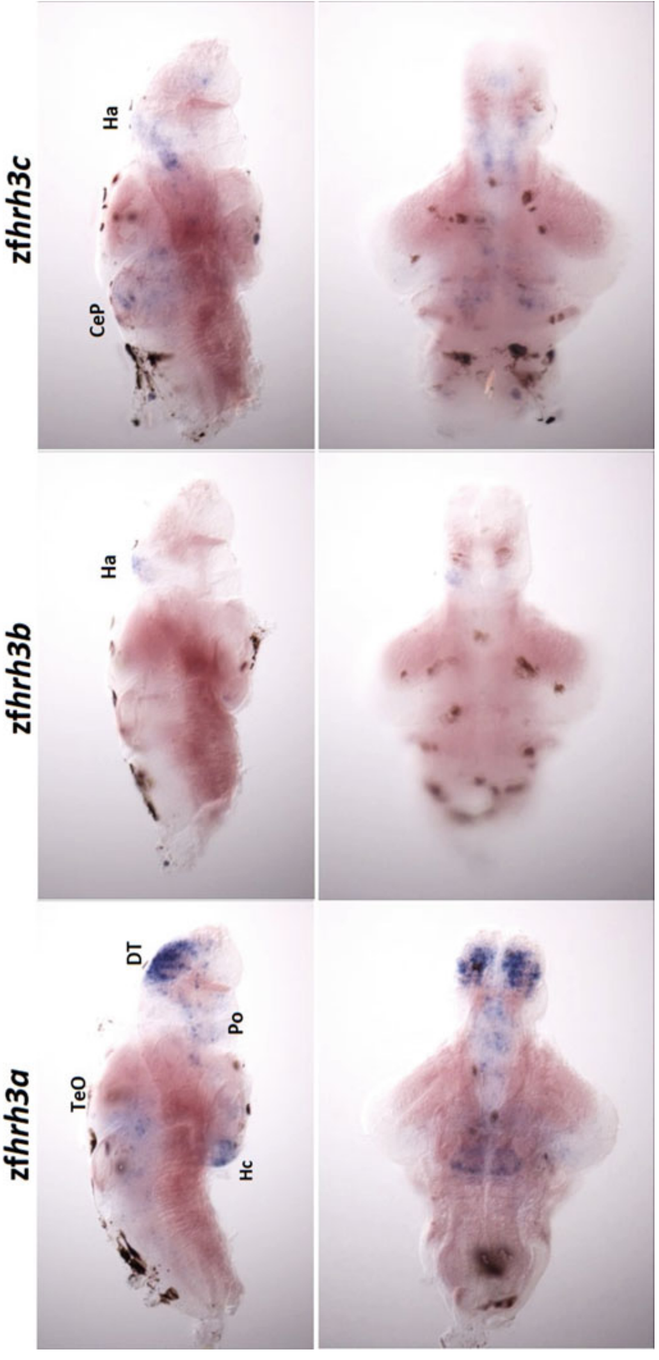

Fig. 2 Expression patterns of zrhrh3a, zfhrh3b, and zfhrh3c in 6-dpf Turku wild-type zebrafish brains by in situ *hybridization*. *Cep* cerebellar plate, *DT* dorsal thalamus, *Ha* habenula, *Po* preoptic region, *TeO* tectum opticum, *Hc* caudal zone of periventricular hypothalamus

and bold behavior. The behavioral phenotype is accompanied by an upregulation of *hnmt*, decreased histamine levels, and higher numbers of neurons expressing the 5-HT transporter gene slc6a4a (*serta*) in the raphe nucleus. Interestingly, hnmt inhibition with tacrine and the agonism of hrh3 with imetit dihydrobromide were able to attenuate the behavioral phenotype displayed by these animals, whereas acute fluoxetine did not produce the same effect (Norton et al. 2011).

The role of histamine in sleep is still not very well understood. In mammals, EEG is a useful and necessary method to quantitatively establish the different stages of wakefulness and sleep, and it has been used widely to assess the role of histamine and histamine receptors in mice (Parmentier et al. 2002; Parmentier et al. 2007; Zecharia et al. 2012). Until recently, no comparable method has been available for zebrafish. Immobility for 1 min has been found a useful correlate of sleep in zebrafish (Prober et al. 2006; Elbaz et al. 2012), initially based on a characteristic posture and other behavioral features during rest (Zhdanova et al. 2001). A thorough analysis of zebrafish *lacking hdc, hrh1, hrh2a, hrh2b, hrh3* or combinations of these has revealed no significant differences between the mutant animals and WT controls (Chen et al. 2017). It is not yet known, if alternative arousal systems compensate possible impairments due to lack of histamine in gene-modified zebrafish. Using optical imaging, two different sleep signatures were recently characterized in zebrafish (Leung et al. 2019). Antagonists of hrh1, mepyramine and promethazine, both had a significant effect on these. Brain-penetrating first generation antihistamines (hrh1 antagonists) have long been used to promote sleep in humans, despite reports of some adverse effects in particularly elderly patients with a tendency to exhibit mental symptoms.

Inverse agonists or antagonists of all three histamine receptors (hrh1: pyrilamine, hrh2: cimetidine, hrh3:thioperamide) all have significant effects on larval motility. At 5 dpf, these drugs at 1–100 μM concentration in the swimming water reduced swimming speed significantly in 6-well plates, in which there is enough space for free swimming (Peitsaro et al. 2007). Surprisingly, immepip, an agonist at the mammalian hrh3, also reduced swimming speed under these conditions. Currently, the binding and signaling properties of zebrafish histamine receptors have not been reported. In addition, the presence of three hrh3-like receptor genes in zebrafish renders it challenging to estimate the mechanisms of ligand effects. Furthermore, larvae exposure to drugs does not allow for estimation of drug availability at the receptors on the cell surface.

An hrh3 mutant zebrafish generated with the CRISPR/Cas method showed no difference compared to wild-type larvae in dark flash responses but shorter period of increased locomotion after sudden darkness (Puttonen et al. 2018), and regular sleep pattern in agreement with an earlier study (Chen et al. 2017). Adult hrh3−/− zebrafish showed lower locomotor activity in the open field compared with wild-type siblings, suggesting that they are hypoactive (Puttonen et al. 2018).

6 Plasticity of the Zebrafish Histamine System

Since normal adult zebrafish show significant thigmotaxis compared with fish treated with α-FMH with low brain histamine (Peitsaro et al. 2003) suggesting abnormally low alertness or anxiety-like behavior, the abnormally high thigmotaxis of presenilin $1^{-/-}$ (*psen*$^{-/-}$, a component of γ-secretase complex) zebrafish suggested that the *psen*$^{-/-}$ zebrafish may have abnormal histamine system (Sundvik et al. 2013). Indeed, quantification of histamine neurons of 12-month-old *psen*$^{-/-}$ zebrafish showed that the number of histamine neurons was significantly higher than in wild-type fish. During larval stages, the *psen*$^{-/-}$ larvae did not react to sudden darkness as strongly as wild-type larvae, suggesting a deficient histamine system. It appeared that at larval stages the number of histamine neurons was indeed abnormally low (Sundvik et al. 2013). One explanation for this may be the abnormally low expression in *psen*$^{-/-}$ fish of *notch 1*, regulated by γ-secretase and known to regulate brain stem cell proliferation and differentiation.

A single gene encodes for zebrafish hypocretin, a neuropeptide involved in the regulation of sleep and narcolepsy (Kaslin et al. 2004). As in mammals, this system is linked with all major aminergic and cholinergic systems in the brain (Kaslin et al. 2004). In mammals, hypocretin is a potent activator of histaminergic neurons through hypocretin receptor 2 (Eriksson et al. 2001), but a reciprocal regulation has been difficult to show experimentally in mammals. Translation inhibition of *hdc* by injection of morpholino oligonucleotides in fertilized eggs strongly reduces the number of developing hypocretin neurons in larval zebrafish, and coinjection of *hdc* mRNA normalizes the number of hypocretin neurons in a dose-dependent manner (Sundvik et al. 2011). In addition, overexpression of *hdc* in developing fish increases the number of hypocretin neurons to about 130% of that in control larvae, suggesting that histamine exerts a bidirectional control the number of hypocretin neurons. Exposure of larvae to α-FMH also reduces the number of hypocretin neurons in developing larvae, as does exposure to pyrilamine, and hrh1 antagonist, suggesting a role for hrh1 in hypocretin neuron development. Nevertheless, one study on *hrh1*$^{-/-}$ zebrafish found no difference between the mutant and control fish (Chen et al. 2017). Further studies on new models are needed to show if the stable mutant fish exhibit genetic compensation (El-Brolosy et al. 2019), or if the translation inhibition with morpholino oligonucleotides and application of suicide enzyme inhibitor α-FMH suffer from non-specific side effects. The possible reciprocal interactions of the hypocretin and histamine systems are particularly important because the number of histamine neurons has been reported to increase concomitantly with the decreasing number of hypocretin neurons in human narcoleptic brains (John et al. 2013; Valko et al. 2013), suggesting significant plasticity in the human histaminergic system, possibly related to the pathological process and degeneration of hypocretin neurons in narcolepsy.

Administration of exogenous histamine through intradiencephalic injection after spinal cord injury induces an enhanced accumulation of activated microglia in the lesion site. Additionally, histamine-treated animals displayed a reactive phenotype

with a multipolar, stellate shape, whereas in the saline treated group, it displayed a resting phenotype with elongated bipolar shape. Furthermore, fish treated with histamine presented a poorer locomotor activity recovery after the lesion (Huang et al. 2017). These results reinforce previous reports that indicate a role for histamine and its receptors in microglial regulation (Rocha et al. 2016; Frick et al. 2016).

Plasticity of the histamine system is also connected to changes in the brain dopamine system. In Parkinson's disease, several neurotransmitter systems undergo gradual degeneration, but the most drastic decline in nigrostriatal dopamine neurons is associated with a significant increase in histamine levels in substantia nigra and putamen (Anichtchik et al. 2000; Rinne et al. 2002). In zebrafish, dopamine neurons are not found in the mesencephalon, but several dopaminergic clusters are located in the diencephalon (Kaslin and Panula 2001; Sallinen et al. 2009). Genome duplication in zebrafish (Postlethwait et al. 1998) has resulted in a number of active duplicated genes, often expressed in a complementary manner. Tyrosine hydroxylase, the rate-limiting enzyme responsible for dopamine synthesis, is duplicated in zebrafish (Candy and Collet 2005) and the two paralogs (*th1* and *th2*), both responsible for dopamine synthesis (Chen et al. 2016), show complementary expression in the zebrafish brain (Chen et al. 2009). Translation inhibition of *th2* leads to an increased number of histamine neurons, and a concomitant increase in the number of hypocretin neurons, in agreement with a potential role of histamine in hypocretin neuron development.

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Different Peas in the Same Pod: The Histaminergic Neuronal Heterogeneity

Gustavo Provensi, M. Beatrice Passani, and Patrizio Blandina

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Abstract The histaminergic neuronal system is recently receiving increasing attention, as much has been learned over the past 25 years about histamine role as a neurotransmitter. Indeed, this amine is crucial in maintaining arousal and provides important contributions to regulate circadian rhythms, energy, endocrine homeostasis, motor behavior, and cognition. The extent to which these distinct physiological functions are operated by independent histamine neuronal subpopulation is unclear. In the rat brain histamine neuronal cell bodies are grouped within the tuberomamillary nucleus of the posterior hypothalamus in five clusters, E1–E5, each sending overlapping axons throughout the entire central nervous system with no strict topographical pattern. These features lead to the concept that histamine regulation of a wide range of functions in the central nervous system is achieved by the histaminergic neuronal system as a whole. However, increasing experimental

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evidence suggesting that the histaminergic system is organized into distinct pathways modulated by selective mechanisms challenges this view. In this review, we summarized experimental evidence supporting the heterogeneity of histamine neurons, and their organization in functionally distinct circuits impinging on separate brain regions and displaying selective control mechanisms. This implies independent functions of subsets of histaminergic neurons according to their respective origin and terminal projections with relevant consequences for the development of specific compounds that affect only subsets of histamine neurons, thus increasing the target specificity.

Keywords *c-fos* · Cognition · Heterogeneity · Histamine · Microdialysis · Stress

1 Introduction

The study of the peripheral effects of histamine started more than 100 years ago (Dale and Laidlaw 1910), and now we know that it is produced and stored by several cell types such as mast cells, basophils, and enterochromaffin-like cells. When released from these cells, histamine triggers allergic reactions and gastric acid secretion, by activating two types of GPCRs, termed H_1R and H_2R, respectively (Ash and Schild 1997; Black et al. 1972; Panula et al. 2015). These findings resulted in the development of antagonists of these receptors that have been successful as blockbuster drugs for treating allergy and gastric ulcers (Leurs et al. 1995; Tiligada and Ennis 2020). Their discoveries were acknowledged with the Nobel prizes to Daniel Bovet in 1957 and Sir James Black in 1988. Conversely, the role of histamine in the central nervous system (CNS) received no consideration until more recently, although suggestions of histamine functional relevance in the brain can be traced back to the 1930s, following the observation that brain-penetrating histamine H_1R antagonists elicited marked sedation. Histamine receptors were not contemplated as sites of action for this effect, in spite of early reports of histamine presence in the brain (Kwiatkowski 1943) and suggestions that this amine has central functions (Green 1964). The reason for neglecting investigation of the neuronal histaminergic system and for the delay in comparison with the exploration of other aminergic neurotransmitters lies on methodological limitations. In the 1960s Arvid Carlsson developed a method based on a fluorescent immunohistochemical analysis with o-phthalaldehyde as a tracer that became crucial to unveil the distribution of the catecholaminergic and serotonergic neurons in the brain (Carlsson et al. 1961), but was not equally suitable for visualizing histamine due to the interference with spermidine, which is ubiquitous in the brain (Green 1970). Therefore, histamine was granted the full status of a neurotransmitter only in the 1980s, when the first direct evidence of the existence of histaminergic neurons occurred with the development of immunohistochemistry using antibodies against histamine (Panula et al. 1984) and histidine decarboxylase (Watanabe et al. 1983). In the same years,

Jean-Charles Schwartz with his group discovered the H_3R that acts as an auto-receptor regulating histamine release and synthesis in the brain (Arrang et al. 1983). These findings gave impetus for studying histamine features in the CNS.

2 Histamine in the Central Nervous System

Brain histamine is synthesized by histidine decarboxylase (Hdc) from L-histidine (Green et al. 1987; Kollonitsch et al. 1978), then packaged into synaptic vesicles by the vesicular monoamine transporter (VMAT2) (Puttonen et al. 2017), in neurons that are scattered in a loose constellation solely in the tuberomamillary nuclei (TMN) of the posterior hypothalamus (Ericson et al. 1987). There are between 65,000–120,000 histamine neurons in the human brain (John et al. 2013; Valko et al. 2013) that project axons to innervate almost the whole CNS from the cortex to the brainstem (Haas et al. 2008; Inagaki et al. 1988). These axons are mostly unmyelinated, present diffuse varicosities that contain synaptic vesicles, and do not form synaptic contacts, with the exception of the mesencephalic trigeminal nucleus (Inagaki et al. 1987; Takagi et al. 1986). As there seems to be no specific high-affinity reuptake system, histamine released into the extracellular space is cleared mostly by histamine *N*-methyltransferase that forms tele-methylhistamine (Green et al. 1987). Nevertheless, some histamine may be taken up by the low-affinity organic cation transporter 3 which is expressed on astrocytes (Yoshikawa et al. 2013). Lack of a high-affinity reuptake system together with mismatches between distribution of histaminergic fibers and histaminergic receptors (Pillot et al. 2002) suggest that histamine may act also as a local hormone influencing not only neuronal but also glial cells. In keeping with this view, glia cells express H1 and H2 and H3 receptors to varying degrees identical to those present on neuronal cells (Iida et al. 2015; Inagaki et al. 1989; Čarman-Kržan and Lipnik-Štangelj 2000). Recently, it has been reported that H_1 receptors on astrocytes play a significant role in anxiety and are involved in the modulation of aggressive behavior, circadian rhythms, quality of wakefulness, but not sleep behavior (Kárpáti et al. 2019). However, not all brain histamine seems to be of neuronal origin, as mast cells may migrate into the brain from extra-neural sources particularly under pathological conditions, e.g., in response to inflammation (Silverman et al. 2000). Also during development mast cells penetrate into the thalamus (Lambracht-Hall et al. 1990) where they reside during adulthood (Goldschmidt et al. 1985). Moreover, report that mouse cultured microglial cells are positive for HDC mRNA suggests that there is a third cell type able to produce histamine in the brain (Katoh et al. 2001). Also microvascular endothelial cells represent a possible source of brain histamine (Yamakami et al. 2000). Noteworthy, the half-life of neuronal histamine is much shorter (no longer than about 1 min) than that of mast cells, where histamine turnover takes hours or weeks (Dismukes and Snyder 1974). Nevertheless, the functional significance of histamine released in the brain by microglia or mast cells in physiology is unknown (Chikahisa et al. 2013; Pham et al. 2021), although the report of an

increase of mast cells number in dove habenula after courtship is intriguing (Silver et al. 1992).

The morphological feature of the histaminergic neuronal system, a compact cell group with widely distributed fibers, only apparently resembles that of other biogenic amine systems such as catecholamines or serotonin. Indeed, dopaminergic, noradrenergic, and serotonergic neuronal cell bodies are restricted to defined cell clusters in the midbrain, locus coeruleus, and raphe nuclei, respectively, with their axons innervating nearly the entire CNS. However, they are distributed in distinct compartments with respect to projection fields, as axons innervating separate brain regions stem from discrete subgroups of dopaminergic (A8–A17), noradrenergic (A1–A7), and serotonergic (B1–B9) neurons (Jacobs and Azmitia 1992; Mason and Fibiger 1979). Based on these features, it can be inferred that specific neurons control independent functions according to their respective origin and terminal projections. Conversely, histamine neurons are grouped in five clusters, E1–E5 (Inagaki et al. 1988), each of which sends overlapping projections throughout the neuroaxis (Ericson et al. 1987). Consistently, retrograde tracers injected into different CNS regions labeled histaminergic cell bodies scattered throughout the TMN without a strict topographical pattern (Inagaki et al. 1990; Köhler et al. 1985).

3 Brain Functions Modulated by Histamine

According to the widespread distribution of its fibers throughout the entire CNS, histamine is a pleiotropic neurotransmitter with diverse roles in the physiology of brain functions. Histamine neurons are best known for their critical role in the regulation of the wake state and all studies strongly emphasize the tight correlation between histaminergic neuronal activity and wakefulness. Indeed, histamine neurons fire fastest during wakefulness, little during non-rapid eye movement (NREM) sleep, and are almost silent during REM sleep (John et al. 2004; Takahashi et al. 2006; Vanni-Mercier et al. 2003). Moreover, histamine levels measured with microdialysis in the hypothalamus and other brain regions of mice and rats are consistently higher during wakefulness than during sleep (Leenaars et al. 2019). In humans, decreased levels of histamine in cerebrospinal fluid of patients with narcolepsy and excessive daytime sleepiness of other origin have been reported, with an inverse correlation between histamine levels and Epworth Sleepiness Scale severity (Bassetti et al. 2010). This suggests a reduced activity of the wake promoting histaminergic neuronal system. Histamine maintains wakefulness through direct projections from the TMN to the thalamus and the cortex and through activation of cholinergic (Cecchi et al. 2001) and aminergic (Korotkova et al. 2005) arousal systems. Orexin neurons are the most likely candidate to activate histamine neurons during wakefulness (Jones 2020). In keeping with this hypothesis, the arousal effect of orexin A depends on the activation of histaminergic neurotransmission and did not occur in mice lacking the H_1R (Huang et al. 2001). On the other hand, impairment of histamine signaling has an opposite effect and promotes NREM sleep (Fujita et al. 2017).

However, this occurred only under acute conditions, as genetically modified mice that do not synthesize histamine (histidine decarboxylase null mice, $Hdc^{-/-}$) have nearly normal amounts of wake (Parmentier et al. 2002). However, these animals fall asleep after a few minutes when placed in a new environment, whereas wild-type ($Hdc^{+/+}$) mice remain awake for 2–3 h (Parmentier et al. 2002). These findings suggest that the histaminergic system is crucial in maintaining the brain in an awake state at moments when high vigilance is required, e.g., when faced with behavioral or cognitive challenges, but alternative arousal systems are likely to compensate its impairments under normal conditions.

Brain histamine plays an important role also in eating behavior as it induces loss of appetite (Clineschmidt and Lotti 1973). Increase of histamine release in the TMN occurs when 24-h fasted rats are fed (Ishizuka and Yamatodani 2012) and when hungry rats try to open a mesh container filled with enticing food (Valdés et al. 2010), thus indicating that this amine regulates both the consummatory and the appetitive phase of feeding behavior. These observations suggest that the histaminergic system represents a potential target for the prevention of obesity and metabolic syndrome (Provensi et al. 2016a). Noteworthy in this regard, oleoylethanolamide, an endogenous messenger that mediates fat-induced satiety, requires an intact neuronal histaminergic system to produce its anorexic effects (Provensi et al. 2014).

In the cerebellar nuclei, histamine selectively depolarizes output projections and improves cerebellar nuclei-mediated motor balance and coordination (Zhang et al. 2016). Other functions of histamine may affect energy metabolism (Tabarean 2016), thermoregulation (Shaw 1971), stress (Taylor and Snyder 1971), and reproduction (Hine et al. 1986).

Since the first report demonstrating that histamine is involved in memory (de Almeida and Izquierdo 1986), many additional studies have confirmed its important role in memory formation of both emotionally charged (Provensi et al. 2020b) and neutral events (Provensi et al. 2020a). Most studies suggest that histamine facilitates learning and memory, and the integrity of the brain histaminergic system is necessary for retrieval (Fabbri et al. 2016) as well as for long-term, but not for short-term memory (Benetti et al. 2015) as tested in the step-down inhibitory avoidance. Consistently, $Hdc^{-/-}$ mice show impairments in novel location recognition (Acevedo et al. 2006b) and non-reinforced episodic object memory (Dere et al. 2003). However, contradictory results were found with $Hdc^{-/-}$ mice that performed better than $Hdc^{+/+}$ mice in the water maze (Acevedo et al. 2006a) and exhibiting better learning and memory in contextual fear conditioning (Liu et al. 2007). Histamine may affect cognitive processes with modalities that differ according to tissue architectural constraints and to the distinct actions exerted by activating its four different G protein-coupled receptors (H_1R, H_2R, H_3R, and H_4R) that are expressed in distinctive patterns and density in the brain. Particular emphasis should be given to the effects mediated by the H_3R, as there are compelling reasons to believe that histamine modulates memory through interactions with other neurotransmitters modulated by H_3R (Passani et al. 2017). In this regard, we demonstrated that intra-basolateral amygdala administration of H_3R antagonists reduced both the freezing time of contextual fear conditioned rats and local release of acetylcholine

(Passani et al. 2001); thus, amnesia may depend on the local modulation of the cholinergic tone. Consistently, H_3R agonists given into the basolateral amygdala ameliorated the expression of fear memory and increased acetylcholine release locally (Baldi et al. 2005; Cangioli et al. 2002). Moreover, the treatment with H_3 receptor inverse agonists induced the recall of object memories even 1 month after training in mice. This effect was mediated by activation of H_2 receptors in the perirhinal cortex. Noteworthy, a human clinical trial revealed that administration of betahistine, an H_3 receptor inverse agonists and weak H_1 receptor agonist, improved memory retrieval for items that are more difficult to remember (Nomura et al. 2019). The H_3R was first described as a histamine auto-receptor (Arrang et al. 1983), and later shown to function also as a heteroreceptor that modulates the release of other neurotransmitters (Blandina et al. 1998). The H_3R regulates signal transduction pathways including $G_{i/o}$-dependent inhibition of adenylyl cyclase, activation of the mitogen-activated kinase (MAPK), protein kinase B (AKT), and glycogen synthase kinase 3 beta (GSK3β) (Bongers et al. 2007; Mariottini et al. 2009; Rapanelli et al. 2016). As stated above, there is good evidence that H_3Rs influence learning and memory by modulating the release of acetylcholine (Blandina et al. 1996; Provensi et al. 2016b; Rani et al. 2021; Toyota et al. 2002). However, this is only one possibility, as H_3Rs modulate the release of other transmitters such as dopamine, glutamate, 5-HT, and noradrenaline (Blandina et al. 1998) that affect performances in several cognitive tests. Hence, histamine may influence cognition in a complex manner, depending on the brain region as well as the nature of the cognitive task involved. Indeed, histaminergic neurons may produce opposing actions by activating receptors with modalities that differ according to the cytoarchitectonics, arrangement, and distribution of histamine receptors in the regions involved in specific learning processes. Since the histaminergic neurons project throughout the CNS with a low level of topographical organization (Ericson et al. 1987; Inagaki et al. 1990; Inagaki et al. 1988), at first it was thought that these neurons formed a homogeneous cell group acting as a functional unit (Wada et al. 1991b). More recently multiple lines of evidence suggest that they consist of discrete subpopulations exhibiting functional heterogeneity at several levels of analysis (Blandina et al. 2012; Scammell et al. 2019).

4 Stress Reveals Diversities Among Histamine Neurons

Analysis of c-fos expression as an index of histamine neurons activation in response to stressful stimuli provided a considerable progress in the characterization of functionally distinct subpopulations of histamine neurons. Histamine release is a sensitive indicator of stress (Westerink et al. 2002), and its turnover is accelerated by acute and chronic restraint and exposure to cold (Ito et al. 1999; Taylor and Snyder 1971; Verdière et al. 1977) as well as to air blast (Ito et al. 1999; Mazurkiewicz-Kwilecki 1980; Verdière et al. 1977). Also, metabolic stress is a potent activator of histamine neurons (Haxhiu et al. 2001). Histamine neuronal cell bodies are

distributed in five clusters, E1–E5, bridged by scattered neurons within the TMN of the rat brain (Inagaki et al. 1988). Overlapping axons originating from all clusters innervate almost the entire CNS with a low level of topographical organization (Ericson et al. 1987; Inagaki et al. 1988, 1990). The brains of other mammals and non-mammalian vertebrates present a similar pattern of distribution (Wada et al. 1991a). In spite of the low level of topographical organization, histamine neurons show clear differences in response to stress stimuli. Indeed, hypercapnic stress (CO_2 exposure) increased c-fos expression only in histamine neurons localized in the E2 cluster (Haxhiu et al. 2001; Johnson et al. 2005). Recordings in rat brain slices revealed that these neurons are excited by acidification within the physiological range (Yanovsky et al. 2012). This effect was mediated by acid-sensing ion channels (ASICs) and metabotropic glutamate receptors (Yanovsky et al. 2012) that were expressed at significantly higher density in E2 cluster than in the remaining clusters. Activation of histamine neurons by increased CO_2 and/or H^+ might affect central respiratory drive through activation of neurons in the nucleus tractus solitarius, a region displaying a dense network of histaminergic fibers (Airaksinen and Panula 1988).

Restraint activated c-fos in up to 36% of histaminergic neurons of E4 and E5 clusters but $<10\%$ of E1, E2, or E3 regions (Miklos and Kovacs 2003). Under stress-free, basal conditions c-fos expression was detected in $<1\%$ of histamine neurons distributed uniformly in the TMN (Miklos and Kovacs 2003). Foot-shock or insulin-induced hypoglycemia activated E4 and E5 histamine neurons but failed to increase c-fos expression in the histamine neurons of the three remaining clusters (Miklos and Kovacs 2003). These observations clearly indicate that histamine neurons were recruited in a subgroup- and stressor-specific manner in the rostral clusters (E4, E5) rather than in the caudal ones (E1–E3).

Previous studies showed an increase in c-Fos expression in histaminergic neurons when hungry rats were presented to a mesh box with enticing food which they can smell and see but they cannot eat (Valdes et al. 2005, 2010). These studies, however, did not describe exactly what subdivisions of TMN became activated. This issue was addressed by Hayato Umehara using a food deprivation under scheduled feeding protocol (Umehara et al. 2011). Rats were habituated to receive food at the same time and for a restrict period of the day (2 h). After habituation, in the experimental day, hungry rats were presented with food, but when they started to eat, food was immediately removed. It was observed a great increase in c-fos expression in the cells of the E3 subdivision whereas few cells were activated in the other subdivisions. These results are in accordance with the role of the histaminergic system in the modulation of motivated arousal. Thus, food deprivation engages in the TMN different neuronal populations as compared with other types of stress (Miklos and Kovacs 2003; Umehara et al. 2012). Figure 1 displays a schematic representation of the different histaminergic clusters activated following exposure to different stressors.

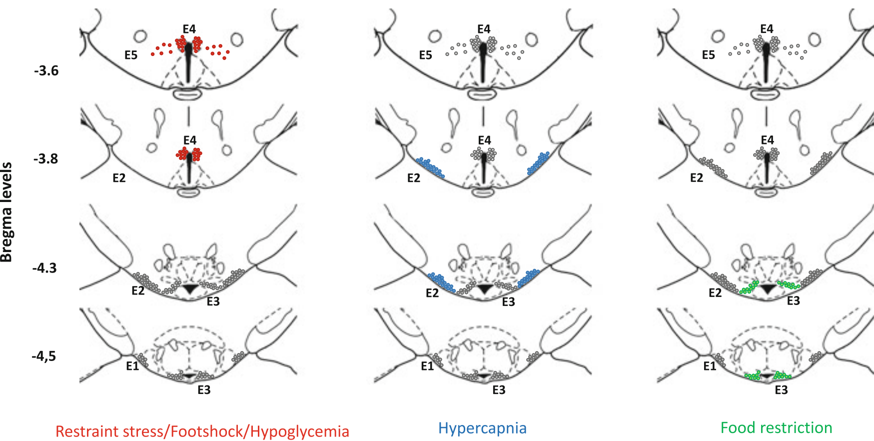

Fig. 1 Different clusters of histaminergic neurons are activated by stressors. By measuring c-fos expression in the rats tuberomammillary nucleus (TMN) following exposure to different stressful stimuli, different patterns of neuronal activation were found across the five histaminergic clusters (E1–E5). Restrain, foot-shock or insulin-induced hypoglycemia activated the rostral E4–E5 subgroups rather than the caudal ones (E1–E3) (Miklos and Kovacs 2003). Hypercapnic stress (CO_2 exposure) increased c-fos expression in histamine neurons exclusively localized in the E2 cluster (Haxhiu et al. 2001; Johnson et al. 2005). Food restriction increased c-fos expression in the E3 subdivision whereas few cells were activated in the other subdivisions protocol (Umehara et al. 2011)

5 Some Histamine Neurons Release GABA

Most TMN histaminergic neurons contain, in addition to Hdc and histamine, also the GABA-synthesizing enzyme, glutamic acid decarboxylase (GAD) and GABA itself (Airaksinen et al. 1992) which is presumably contained in vesicles distinct from those containing histamine (Kukko-Lukjanov and Panula 2003). This observation suggests co-transmission rather than co-release. The mechanism by which TMN neurons release GABA remains unclear. Histamine neurons use the vesicular GABA transporter (vGAT, which is required for packaging GABA into synaptic vesicles for release) to release GABA (Yu et al. 2015). However, the report that GAD is expressed in 85.9 ± 2.6% whereas vGAT only in 7.11 ± 2.05% of histamine neurons (Venner et al. 2019) suggests that Hdc neurons do not require vGAT to release GABA and may use alternative manners. In analogy, GABA is released directly from dopaminergic axons in the striatum independently of vGAT. Instead, GABA release requires activity of the vesicular monoamine transporter vMAT2, which is the vesicular transporter for dopamine, and vMAT2 expression in GABAergic neurons lacking vGAT is sufficient to sustain GABA release (Tritsch et al. 2012). Varicosities on histaminergic axons release histamine by volume transmission, as histaminergic neurons rarely use synapses (Inagaki et al. 1987; Takagi et al. 1986). So it is likely that, similar to histamine, the GABA released from

histamine neurons acts in a paracrine manner, affecting primarily extra-synaptic receptors.

Experiments that used optogenetic stimulation of histaminergic projections indicated that histamine and GABA co-transmission is limited to some brain regions. This is the case for the histaminergic fibers projecting to the caudate-putamen and neocortex where GABA and histamine co-transmission might provide the fine-tuning between excitatory and inhibitory inputs necessary to achieve the optimal arousal state (Yu et al. 2015). However, neither GABAergic transmission nor disruption of GABA synthesis altered hourly sleep–wake quantities (Venner et al. 2019), in keeping with the view that histamine may be important for enhancing arousal in response to challenging circumstances rather than under baseline conditions (Parmentier et al. 2002, 2016). Moreover, histaminergic axons, when stimulated optogenetically, release histamine but not GABA into the ventrolateral preoptic nucleus (VLPO) (Williams et al. 2014). Only 20% of histamine neurons contain histamine and not GABA (Yu et al. 2015), therefore these could be the ones that innervate the VLPO. These observations indicate the existence of two histaminergic neuronal populations that differ for their ability to synthesize and release GABA and form distinct functional circuits impinging on different brain regions. Subpopulations of TMN neurons express also galanin, enkephalins, thyrotropin-releasing hormone (TRH), and substance P (Airaksinen et al. 1992; Köhler et al. 1986) but the physiological impact of these transmitters is not known as yet.

6 Microdialysis Studies

In our laboratory, we have shown differences of histamine release from diverse brain regions in response to pharmacological manipulation of TMN neurons. We used a double-probe microdialysis approach in behaving rats, a powerful technique for outlining the dynamics regulating histamine release in discrete brain regions. Animals were implanted with two probes, one in the TMN, to deliver treatments and to measure histamine release locally, and another one in histaminergic projection areas, to assess histamine release from the dorsal striatum, the nucleus accumbens (NAcc), the nucleus basalis magnocellularis (NBM), or the prefrontal cortex (PFC). Our studies showed that the local, intra-TMN infusion of a specific ligand of receptors expressed on histaminergic neurons affected differently histamine release from diverse brain regions. Figure 2 illustrates the main observations described in the following paragraphs. For instance, the H_3R functions as a presynaptic auto-receptor that restricts histamine synthesis and release in histaminergic terminals (Arrang et al. 1983) and provides a tonic inhibition of firing acting on neuronal somata (Haas and Panula 2003). Hence, blockade of presynaptic and somatic H_3 auto-receptors increases histamine levels in the synaptic cleft as well as histaminergic neuron firing, respectively. Perfusion of the TMN through the microdialysis probe with thioperamide (Giannoni et al. 2009), GSK189254 (Giannoni et al. 2010), or ABT-239 (Munari et al. 2013), three H_3R antagonists/inverse agonists, increased

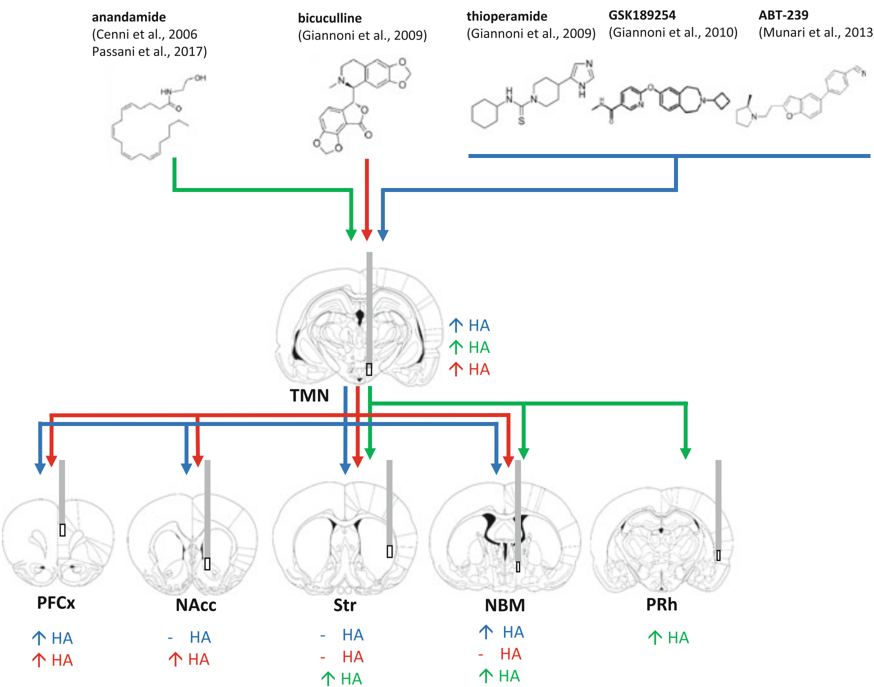

Fig. 2 Dual-probe microdialysis studies revealed the presence of functionally distinct histaminergic pathways impinging on different brain regions and displaying different sensitivity to pharmacological treatments. Rats were implanted with one probe in the tuberomammillary nucleus (TMN) and another probe in a histaminergic projection area: the prefrontal cortex (PFC), the nucleus accumbens (NAcc); the dorsal striatum (Str), the nucleus basalis magnocellularis (NBM) or the perirhinal cortex (PRh). The CB_1 agonist anandamide (Cenni et al. 2006; Passani et al. 2007), the $GABA_AR$ antagonist bicuculline (Giannoni et al. 2009), or H_3R antagonists such as thioperamide (Giannoni et al. 2009), GSK 189254 (Giannoni et al. 2010), and ABT239 (Munari et al. 2013) were delivered locally into the TMN through the microdialysis probe. Histamine release was measured in both the TMN and the projection areas. Although all the drugs increased histamine (HA) release from the TMN itself, they influenced differently the release of histamine from the distinct brain regions (↑ increased, – not affected)

histamine release from the TMN, NBM, and PFC. Conversely, histamine release remained unaltered in the dorsal striatum and NAcc. In the TMN, histamine is released from short projections that innervate the posterior hypothalamus forming extensive axonal arborizations. Increases of histamine release from the PFC or NBM were likely consequent to discharge potentiation of histaminergic neurons sending efferents to these regions, in analogy to the effects of TMN perfusion with orexin A (Huang et al. 2001) or prostaglandin E2 (Huang et al. 2003). On the contrary, TMN perfusion with H_3R antagonists/agonists did not affect histamine release from the dorsal striatum nor from the NAcc, which indicates that histaminergic neurons projecting to these regions (Panula et al. 1989) are insensitive to H_3R blockade. Spatial segregation due to localization of the probe does not justify the contrasting

findings on histamine release, e.g., between the striatum and PFC, as retrograde tracing with dye injections into these regions showed that most histamine somata are within the medial part of the ventral TMN (Köhler et al. 1985). This finding suggests that histamine neurons projecting to the PFC and striatum had the same exposure to H_3R antagonists/inverse agonists but were not affected in the same way. Therefore, as defined by their sensitivity to H_3R antagonists/inverse agonists, histaminergic neurons establish distinct pathways according to their terminal projections and can differentially modulate neurotransmitter release in a brain region-specific means. This implies independent functions of subsets of histamine neurons according to their terminal projections, with relevant consequences for the development of specific compounds that affect only subsets of histamine neurons, thus increasing target specificity. In keeping with these findings, activation of c-fos following GSK189254 administration occurred in cortical areas and the TMN, but not in the striatum (Medhurst et al. 2007). Consistently, systemic as well as intra-TMN administration of another H_3R antagonist ABT-239 increased c-fos expression in the NBM, and cortex, but not in the striatum nor in the NAcc (Munari et al. 2013).

Local perfusion of the striatum or the NAcc with H_3R antagonists/inverse agonists did not alter spontaneous histamine release (Giannoni et al. 2010; Giannoni et al. 2009; Munari et al. 2013), thus indicating that the entire somatodendritic domain of histaminergic neurons projecting to these regions is insensitive to H_3R blockade. It is generally assumed that all histaminergic neurons express H_3Rs, and a response to H_3R ligands is a criterion for their identification. However, several H_3R isoforms have been described, including 6-transmembrane-domain isoforms lacking functional response to H_3R ligands (Bakker et al. 2006). Hence, the lack of response here reported may depend on high expression of particular isoforms. Alternatively, a low H_3R density at the membrane may explain the lack of effects. There is evidence that some histidine decarboxylase-positive cells display low levels of H_3R immunoreactivity (Blandina et al. 2012; Giannoni et al. 2009), although no direct evidence demonstrates that these cells are the ones innervating the NAcc or striatum. TMN perfusion with the cannabinoid receptor 1 (CB1) agonists, methanandamide (mAEA) or ACEA displayed a diversified behavior of the histamine neurons. Administration of these compounds into the TMN augmented histamine release from the TMN, NBM, and striatum (Cenni et al. 2006) but not from the perirhinal cortex (Passani et al. 2007), despite the profuse histamine innervation of this region (Panula et al. 1989). Also, bicuculline revealed a functional heterogeneity of response among TMN neurons with respect to projection fields. Bicuculline is a $GABA_A$-R antagonist and increases histamine neuronal firing through a direct action (Haas et al. 2008). Intra-TMN perfusion with bicuculline augmented histamine release from the TMN, NAcc, and PFC, but not from the striatum (Giannoni et al. 2009). Different subunit composition and stoichiometry of $GABA_A$-Rs on histamine neurons (Sergeeva et al. 2002, 2005) may account for these findings.

7 Differential Genes Expression Distinguishes Functional Subpopulations of TMN Neurons

As the identification of singular cell types is essential to understand circuitry organization and function, anatomical localization, morphology, innervation pattern, or physiology have been used for cell-type classification. More recently, advances in transcriptional profiling methods have enabled classification of cell types also by their gene expression (Northcutt et al. 2019). Indeed, even within a given morphological or physiological class, neurons exhibit heterogeneities that can directly impact on their functionality (Baroni and Mazzoni 2014). To explore the features underpinning neuronal diversity, multidisciplinary approaches have been developed to allow the study of single neurons simultaneously at the morphological, electrophysiological, and gene expression level (Toledo-Rodriguez and Markram 2014). For instance, Olga Sergeeva developed a pipeline consisting of whole-cell patch-clamp recordings combined with single-cell reverse transcription-polymerase chain reaction (scRT-PCR) and morphological measurements to study the heterogeneity of histaminergic neurons (Sergeeva et al. 2002, 2005).

The first study employing such approach aimed to investigate the diversity of $GABA_A$ channels expressed in histaminergic neurons. GABAergic fibers come from several regions, mostly hypothalamic, to suppress histamine neuronal firing through $GABA_AR$ activation. $GABA_AR$ is a protein complex assembled from a family of 19 homologous subunit gene products that form mostly hetero-oligomeric pentamers. The major isoforms contain α, β, and γ subunits and show differential sensitivity to GABA, steroids (Olsen and Sieghart 2009). Histidine decarboxylase transcript was detected in 40 out of 83 neurons isolated from rat TMN (Sergeeva et al. 2002). Major differences regarding the presence of RNA encoding the GABA-synthesizing enzyme glutamate decarboxylases (GAD) as well as all 14 $GABA_AR$ subunits were identified among these cells. The shorter GAD isoform, GAD65, was detected in seven out of 34 Hdc-positive cells, while the longer isoform GAD67 was present in 14 out of 34. RT-PCR analysis showed that among the α-subunits, only α1-, α2-, and α5-subunits were expressed in single TM cells (α1: 23/34; α2: 30/34; α5: 25/34). Among the β-subunits, β3 was most frequently present (26/34), and β1 (8/34) and β2 (11/34) were expressed in some cells. Only few cells (7/34) expressed the ε-subunit. It was also possible to determine the presence of γ1 (14/34) and γ2 (21/34) subunits. The subunits α3, α4, and γ3 were not detected in this cell population. When the expression pattern was correlated with GABA EC_{50} obtained using whole-cell recording three different groups were identified on the basis of their γ subunits expression. The first group, showing the highest GABA potency, presented two variants of the γ subunit. A second group expressing just the γ2 subunit displayed the lowest GABA sensitivity. In the third group, showing an intermediate GABA sensitivity, products of γ-subunit-cDNA amplification were not detected (Sergeeva et al. 2002). Very similar results in terms of subunits expression in TMN Hdc-positive cells and GABA sensitivity were reported also in another work from the same laboratory (Sergeeva et al. 2005).

Purines and pyrimidines are powerful extracellular messengers in both neuronal and non-neuronal cells. Purinergic signaling is mediated by specific receptors (Abbracchio et al. 2009). To date 19 different receptors were cloned and characterized. They are divided into two families: P_1R, sensitive to adenosine, which includes four subtypes; and P_2R sensitive to adenosine 5′-triphosphate (ATP). The P_2R family is further divided in two classes: P_2X ion channel receptors with seven members and the P_2Y G protein-coupled receptors encompassing eight subtypes (Burnstock 2017). These receptors are abundantly expressed in the TMN region (Collo et al. 1996; Kanjhan et al. 1999; Loesch and Burnstock 2001). Accordingly, electrophysiological recordings showed that ATP increased the firing of TMN neurons (Sergeeva et al. 2006; Vorobjev et al. 2003). Single-cell RT-PCR revealed significant differences regarding purinergic receptor expression among histaminergic cells. From the 33 Hdc-positive cells, P_2X receptors were detected in 17 neurons. All of these cells expressed the P_2X_2 receptor type, while the P_2X_7 mRNA expression was not observed. The transcription analysis revealed that the majority of the TMN neurons expressed more than one P_2X receptor type, but they were much less represented: P_2X_1 (2/17), P_2X_3 (5/17), P_2X_4 (4/17), P_2X_5 (6/17), and P_2X_6 (3/17). Such differences seem not to have an important physiological impact, as the individual EC_{50} valued measured for ATP responses in histaminergic neurons ranged from 31–77 μM and no statistical significant differences emerged from cells expressing or lacking the different P_2X receptors (Vorobjev et al. 2003). The same experimental strategy revealed differences in the expression or mRNAs encoding to P_2Y receptors. The subtypes P_2Y_1 (11/23) and P_2Y_4 (14/23) are prevailing isoforms in the population of Hdc-positive neurons analyzed. Transcripts encoding for the P_2Y_{12} (3/14) and P_2Y_{13} (2/14) receptors were also identified. The P_2Y_2 and P_2Y_6 receptors were not detected. From the 23 analyzed cells, four neurons were P_2Y-receptor-negative. Interestingly, semi-quantitative real-time polymerase chain reaction revealed an age-related (from post-natal day 0 to 28) downregulation of mRNA levels for P_2Y_1 and P_2Y_4 receptors. Accordingly, the selective P_2Y_1 agonist 2-methylthioadenosine 5’-triphosphate tetrasodium salt (2meSATP) showed higher potency in cells isolated from 2-week-old with respect to 4-week-old rats (Sergeeva et al. 2006).

The thyrotropin-releasing hormone (TRH) is a tripeptide mainly produced by neurons of the paraventricular nucleus and triggers thyroid-stimulating hormone release from the adenohypophysis. Beyond neuroendocrine function, two TRH receptors, TRH and the TRH-degrading enzyme, are expressed in many brain regions, where they can modulate neuronal activity, suggesting a role of TRH as a neurotransmitter and/or neuromodulator (Fröhlich and Wahl 2019; Gershengorn and Osman 1996; Heuer et al. 2000). There is much evidence of an interaction between TRH and histamine neuronal systems: (1) TRH neurons innervate histaminergic neurons with the densest innervation in the E4 and E5 subdivisions (Airaksinen et al. 1992; Sárvári et al. 2012); (2) TRH-R_2, but not TRH-R_1, is expressed on rat histamine neuronal somata (Gotoh et al. 2007); (3) TMN infusion with TRH increased histamine and t-methylhistamine levels (Gotoh et al. 2007); and (4) TRH-induced hypophagic effect was attenuated in animals lacking histamine

(Gotoh et al. 2007). Consistent with these findings, TRH bath application increased the firing rate of most (over 70%) of TMN neurons measured in mouse or rat slices. After whole-cell voltage-clamp recordings, mouse TMN neurons were isolated for transcriptional analysis. TRH-R_1 and TRH-R_2 were detected in six and nine out of 26 Hdc-positive neurons, respectively. Five cells displayed mRNAs for both receptor types, and six were TRH-R-negative. The distribution of TRH receptors in rat neurons was slightly different. Out of 19 Hdc-positive neurons, eight expressed only the TRH-R_1, one the TRH-R_2 only, and six both receptors. No transcripts were detected in the remaining four neurons. Interestingly, the percentage of neurons unresponsive to TRH in cells electrophysiological experiments is roughly the same percentage of cells showing undetectable amounts of mRNAs encoding for TRH receptors. However, in this study single-cell RT-PCR and electrophysiological recordings were not done in the same cells, therefore the correlation of TRH expression and neuronal excitability cannot be unequivocally determined (Parmentier et al. 2009).

Acutely isolated TMN-Hdc-positive neurons were also subjected to single-cell RT-PCR analysis of dopaminergic markers: the five known dopamine receptors and L-dopa-decarboxylase (DDC, the enzyme responsible for the synthesis of dopamine from L-DOPA). Dopaminergic receptors mRNAs were variably detected in the 29 Hdc-positive cells analyzed (Yanovsky et al. 2011). The most represented were the D_1R and D_5R, present in 13 and 15 neurons, respectively, whereas D_3R and D_4R were found only in eight neurons. Interesting, only transcripts encoding the long isoform of the D_2R (D_2RL) were detected in Hdc-positive neurons. The two D_2R splice variants differ in size, location, and function: the short isoform D_2RS is localized in dopaminergic cells acting as an auto-receptor, whereas the long splice variant (D_2RL) is primarily a postsynaptic receptor (Khan et al. 1998). In keeping with this finding, an increase in the TMN neuronal excitability was observed following exposure to dopamine. Such effect was blocked by sulpiride, a D_2R-selective antagonist. Consistently, the D_2-like receptor agonist quinpirole increased firing rate of TMN neurons and enhances histamine release in the hypothalamus (Yanovsky et al. 2011). A mismatch regarding DDC mRNA and protein levels was observed. DDC amplifiers were found only in three out of 29 Hdc-positive cells, indicating low expression. On the contrary, a large co-localization of DDC and Hdc was observed in TMN ventral region (Yanovsky et al. 2011).

An increase of c-fos expression in the ventrolateral histaminergic TMN neurons in response to systemic hypercapnia was previously reported. Such an effect was region-specific since no differences were observed in other TMN subdivisions (Haxhiu et al. 2001; Johnson et al. 2005). Subsequent studies demonstrated that acidification of the bath solution within the physiological range increased the firing of histamine neurons from rat ventrolateral TMN (Yanovsky et al. 2012). Semi-quantitative PCR performed from mRNA isolated from ventrolateral TMN (containing largely the E2 dense group of neurons) and the ventromedial TMN (comprising the groups E3 and E4 groups) revealed differential expression of classical acid-sensors, such as acid-sensing ion channels (ASICs). The expression of ASIC3 was significantly higher in the lateral compared to the medial TMN

subdivision. ASIC1 and ASIC2 expression was also higher in the TMN lateral part, but the increase did not reach statistical significance. No differences were found between the two subdivisions in terms of ASIC4 expression (Yanovsky et al. 2012). Single-cell RT-PCR analysis performed from 32 isolated histaminergic neurons showed differences in ASICs expression at a single-cell level: ASIC1 transcripts were detected in 23, ASIC2 in 18, ASIC3 in 20, and ASIC4 in 15 TMN-Hdc-positive neurons (Kernder et al. 2014; Yanovsky et al. 2012).

A recent study aiming at elucidating the mechanisms underlying *N*-oleoyldopamine (OLDA)-induced activation of TMN cells shed further light on the heterogeneity of histaminergic neurons (De Luca et al. 2018). OLDA is a product of non-enzymatic conjugation (condensation) between dopamine and oleic acid in catecholaminergic neurons first identified as an endogenous ligand for the vanilloid type 1 receptor (TRPV1) (Chu et al. 2003). Previous studies reported the presence of TRPV1 channels in histamine neurons (Kernder et al. 2014). Consistently, bath application of either OLDA or capsaicin (a TRPV1 activator) depolarized histaminergic neurons (De Luca et al. 2018). However, occurrence of capsaicin-excitation and expression of TRPV1 in TMN declined with brain maturation, and the difference in occurrence of capsaicin-induced excitation between juvenile (77%) and adult histaminergic neurons (25%) was significant (De Luca et al. 2018). Upon maturation, TRPV1 carrying histamine axons may survive only in specific projection areas. Consistently, capsaicin-induced excitation was significantly higher in ventral TMN (E2) histamine neurons traced from nucleus tractus solitarius than in the whole adult population (De Luca et al. 2018), thus suggesting a heterogeneity of histamine neurons in relation to their connectivity.

The presence of other members of TRPV family was also investigated: TRPV2 was identified in nearly half of the neurons investigated (13/24), whereas the TRPV4 was less represented (7/24). Other possible targets of OLDA were also present in histaminergic neurons. For instance, the orphan G-protein coupled receptor GPR119 and peroxisome proliferator activated receptor-alpha (PPARα) were present in six out of 24 Hdc-positive neurons each, but co-expression was never observed. Finally, the presence of both cannabinoid receptors was investigated in the same cells. CB_2R was detected in 12 out of 29 Hdc-positive cells, but none of the individual neurons was CB_1-positive (De Luca et al. 2018). These results are in agreement with previous reports of very few CB_1R-expressing fibers in the E2–E3 subdivisions of the TMN that do not co-localize with Hdc-positive neurons (Cenni et al. 2006).

8 Histamine Neurons Display Electrophysiological Heterogeneity

The electrophysiological signature of putative histaminergic neurons was described a few decades ago. They fire spontaneously in a pacemaker fashion with a pattern that changes across the sleep–wake cycle (Sakai et al. 1990). Histaminergic neurons

have broad action potentials and long-lasting after hyperpolarization (AHP) (Haas and Reiner 1988; Reiner and McGeer 1987). As a unique property among aminergic neurons, agonists of somatodendritic H_3 auto-receptors do not activate an inwardly rectifying potassium channel, rather, they inhibit voltage-dependent calcium channels (Brown et al. 2001).

In a subsequent study, for the first time histaminergic neurons, identified as expressing Hdc, were defined as heterogeneous according to their sensitivity to glycine (Sergeeva et al. 2001).

A comprehensive characterization of TMN neurons was recently described by Fujita et al. (2017). By using a transgenic mouse line expressing Cre recombinase in Hdc-expressing neurons (Hdc-Cre) and a systemic survey of the membrane properties, the authors found electrophysiological diversity between histamine and non-histamine neurons intermingled in the ventral TMN, and among HA neurons themselves. Both passive (e.g., capacitance) and active (e.g., action potential (AP) threshold, peak and amplitude, and after hyperpolarization (AHP) amplitude) were significantly different among the two populations of TMN neurons.

Several differences were also recorded within histamine neuron clusters such as lower input resistance and time constants, greater AHP amplitudes, shorter AP half widths, higher maximum firing rates and faster rise and decay times. These results confirm that diversity, or a continuum of functional properties, does exist among histaminergic neurons within the compact ventral TMN (Fujita et al. 2017).

The authors also determined the impact of acute silencing of histaminergic neuron activity on sleep–wake states in awake mice. Optogenetic acute silencing of histamine neurons in vivo during wakefulness promoted a sleep state that resembles natural slow wave sleep but did not mimic rapid eye movement sleep. The characteristics of light induced sleep were found to be consistent with the effects of selective H_1R antagonists (Ikeda-Sagara et al. 2012; Parmentier et al. 2016), and with the phenotypes of $H_1R^{-/-}$ and $Hdc^{-/-}$ mice showing an inability to maintain vigilance, with decreased sleep latency, in response to behavioral challenges (Parmentier et al. 2002, 2016). This characterization was confined to the ventral TMN. Recently, the electrophysiological properties of histaminergic neurons were further characterized extending the analysis to other subregions of the TMN (Michael et al. 2020). Whole-cell patch-clamp recordings were performed in transgenic mice expressing Cre recombinase in Hdc-expressing neurons. The authors found considerable variability in Hdc-positive neuron passive and active membrane properties. Membrane potential values, input resistance, firing frequency, and active conductance were distributed along a continuum with no segregation of differing Hdc neurons in TMN subregions, consonant with a lack of topographical organization. Furthermore, membrane properties and electrical excitability were similar between Hdc neurons obtained from female and male mice.

Whether all these differences among Hdc cells partition histaminergic neurons in functionally distinct circuits remains a challenge for future investigations.

9 Where Do We Go from Here? Testing the Functional Diversity of Histaminergic Pathways in Learning and Memory

It is indisputable that brain histamine acting in different brain sites is also an important regulator of several cognitive and homeostatic functions; however, it is not known if and how selective activation of histaminergic pathways participate to the unfolding of these different responses. Despite the extensive literature reporting the importance of brain histamine in learning and memory, eating behavior, waking and motivation, a detailed map of histaminergic pathways that are activated at different time points and during different tasks is currently not available. A new neuroanatomical technology that visualizes neuronal activation on a brain-wide scale with cellular resolution by using Fos-TRAP mice is now available (Franceschini et al. 2020). Fos-TRAP mice induces Cre-driven recombination in neurons that express the immediate early gene c-Fos, providing permanent access to a transiently active neuronal population. The association of this technique with histamine immunocytochemistry and ex-vivo electrophysiological recording of activated and inactivated histaminergic neurons, will set the basis for the functional investigation of histaminergic pathways. In our laboratory, we are currently applying these techniques to investigate the selective activation of histaminergic pathways during aversive memory processing. DREADD or optogenetic approaches will be mandatory to substantiate the neuroanatomical findings. This multidisciplinary approach offers a conceptual framework to be implemented in different behavioral settings, e.g. eating behavior, drug addiction, where activation of histaminergic pathways may play a relevant role. These approaches may provide experimentally testable hypotheses to guide future research in humans, offering possible targets for a novel pharmacotherapy to treat dysfunctional behaviors.

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Histamine: A Key Neuromodulator of Memory Consolidation and Retrieval

Hiroshi Nomura, Rintaro Shimizume, and Yuji Ikegaya

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Abstract In pharmacological studies conducted on animals over the last four decades, histamine was determined to be a strong modulator of learning and memory. Activation of histamine signaling enhances memory consolidation and retrieval. Even long after learning and forgetting, it can still restore the retrieval of forgotten memories. These findings based on animal studies led to human clinical trials with histamine H_3 receptor antagonists/inverse agonists, which revealed their positive effects on learning and memory. Therefore, histamine signaling is a

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promising therapeutic target for improving cognitive impairments in patients with various neuropsychiatric disorders, including Alzheimer's disease. While the memory-modulatory effects of histamine receptor agonists and antagonists have been confirmed by several research groups, the underlying mechanisms remain to be elucidated. This review summarizes how the activation and inhibition of histamine signaling influence memory processes, introduces the cellular and circuit mechanisms, and discusses the relationship between the human histaminergic system and learning and memory.

Keywords Histamine · Memory consolidation · Memory retrieval · Neuropsychiatric disorders · Tuberomammillary nucleus

1 Overview

Histamine is a biological amine that functions as a neurotransmitter, regulating sleep and wakefulness, feeding and energy balance, and cognition (Haas and Panula 2003; Haas et al. 2008; Panula and Nuutinen 2013). The brain histaminergic system is active during wakefulness and responsive to motivational stimuli. Many animal studies have revealed that systemic and local injections of histamine receptor agonists and antagonists influence memory performance (Köhler et al. 2011), indicating that histamine is a strong modulator of learning and memory. Based on these findings, chemical compounds modulating histamine signaling have been identified as promising novel therapeutics for cognitive symptoms in patients with neuropsychiatric disorders (Esbenshade et al. 2008; Schwartz 2011; Zlomuzica et al. 2016; Sadek et al. 2016). While the memory-modulatory effects of histamine receptor agonists and antagonists have been confirmed by many studies, the cellular and circuit mechanisms underlying histamine-induced memory modulation are poorly understood. Here, we briefly explain the basics of histamine neurons and receptors, summarize pharmacological and genetic studies analyzing the effects of histamine on learning and memory, and introduce candidate underlying mechanisms. We also review alterations in histamine signaling in several neuropsychiatric disorders and how the modulation of histamine signaling influences learning and memory in humans.

2 Histamine-Producing Neurons and Histamine Receptors in the Brain

The histaminergic system in the brain is composed of approximately 64,000 histamine neurons in humans and 4,600 in rats, with cell bodies located in the tuberomammillary nucleus (TMN) in the hypothalamus and projecting to a wide

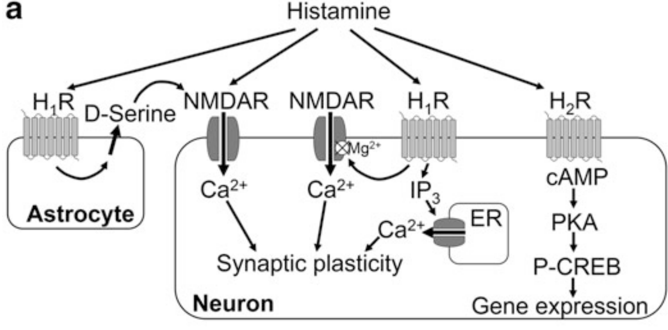
range of regions in the brain (Ericson et al. 1987; Alraksinen et al. 1991). Histamine neurons are grouped in E1-E5 clusters within the TMN (Moriwaki et al. 2015). Originally, the histaminergic system was presumed to be a single functional unit that regulates the activity of the entire brain (Wada et al. 1991). More recently, however, different subsets of histamine neurons have been suggested to separately perform diverse physiological roles (Blandina et al. 2012). Histamine neurons are classified based on different electrophysiological properties (Fujita et al. 2017; Michael et al. 2020) and gene expression patterns (Sergeeva et al. 2002; Vorobjev et al. 2003; Umehara et al. 2012). In addition, several drugs modulate histamine release in multiple brain areas in different ways (Giannoni et al. 2009). These findings imply that histamine neurons are organized into functionally distinct circuits that project to different brain areas, although a histamine neuronal subpopulation responsible for learning and memory remains to be identified. Histamine is synthesized from L-histidine by histidine decarboxylase (HDC), released following action potentials, and mainly methylated by histamine methyltransferase (HNMT) and oxidized by monoamine oxidase B (MAOB) for metabolism (Haas et al. 2008). A mathematical model has been presented to predict histamine synthesis, release, and metabolism (Best et al. 2017). Brain histamine has also been suggested to be produced in mast cells (Nautiyal et al. 2009; Lenz et al. 2018), microglia (Katoh et al. 2001), and microvascular endothelial cells (Yamakami et al. 2000), but the significance of the effect of brain histamine release from nonneuronal cells on learning and memory remains to be determined.

Four types of G protein-coupled histamine receptors (H_1R, H_2R, H_3R, and H_4R) have been identified. H_1Rs and H_2Rs exist in neurons and glial cells and are expressed postsynaptically in most brain regions, including areas involved in learning and memory, such as the cerebral cortex, hippocampus, and amygdala (Martinez-Mir et al. 1990). $G_{q/11}$ and phospholipase C are downstream of H_1R activation, which leads to Ca^{2+}-dependent events and the subsequent excitation of postsynaptic cells. H_2Rs are coupled to G_s, which sequentially activates adenylyl cyclase and protein kinase A (PKA). Although most studies have not examined the contribution of neuronal and astrocytic histamine receptors separately, genetic studies using astrocyte- and neuron-specific conditional knockout mice suggest different roles of H_1R expressed on neurons and astrocytes in various brain functions, including learning and memory (Kárpáti et al. 2019). H_3Rs are present in neurons at both presynaptic and postsynaptic sites. H_3R activation promotes the activation of $G_{i/o}$, which inhibits adenylyl cyclase and subsequently downregulates PKA activation. In addition, histamine suppresses N- and P-type Ca^{2+} channels through H_3R activation (Takeshita et al. 1998). H_3Rs in the axons and somas of histamine neurons negatively regulate histamine release and synthesis (Arrang et al. 1983). H_3Rs are also found in nonhistamine neurons and regulate the release of other neurotransmitters, including γ-aminobutyric acid (GABA), glutamate, acetylcholine, and noradrenaline (Schlicker et al. 1994; Blandina et al. 1996b; Yamamoto et al. 1997). Although H_3Rs are known primarily as presynaptic receptors, they are also located postsynaptically. Postsynaptic H_3Rs have not been studied as extensively as presynaptic H_3Rs (Ellenbroek and Ghiabi 2014), and little is known about the

contribution of postsynaptic H_3Rs to memory processing. H_4Rs are present in several brain regions, including the cerebral cortex, brainstem, thalamus, and amygdala (Strakhova et al. 2009), but the role of H_4Rs seems limited in learning and memory (Sanna et al. 2017).

3 Histamine and Memory Consolidation

The first paper examining the involvement of histamine in learning and memory was published by de Almeida and Izquierdo (de Almeida and Izquierdo 1986). They reported that a posttraining intracerebroventricular (i.c.v.) infusion of histamine enhances the retention of inhibitory avoidance in rats. A local histamine infusion into the hippocampus and amygdala also enhances retention in the same memory task (da Silva et al. 2006; Benetti and Izquierdo 2013). The effect of the intrahippocampal infusion of histamine is blocked by an H_2R antagonist, and an intrahippocampal infusion of an H_2R agonist mimics the histamine-induced enhancement of memory consolidation (da Silva et al. 2006). In addition to the effect of exogenous histamine application, the requirements for endogenous histamine on memory consolidation were tested. Posttraining systemic administration of diphenhydramine, an H_1R antagonist with antagonistic activity to muscarinic receptors, impairs freezing behavior during test sessions of a contextual fear conditioning task (Nonaka et al. 2013). H_1R and H_2R antagonists block memory retention in a novel object recognition task when they are infused into the CA1 30–120 min after training (da Silveira et al. 2013). Depletion of brain histamine via an i.c.v. injection of α-fluoromethylhistidine, an irreversible HDC inhibitor, 1 day before training blocks the retention of long-term but not short-term memory of step-down inhibitory avoidance (Benetti et al. 2015). This memory deficit is rescued by intra-basolateral amygdala (BLA) and intra-CA1 infusions of histamine immediately or 110 min after training. These results indicate that histamine signaling is required for memory consolidation. Based on the findings that H_3R activation inhibits histamine release and synthesis, H_3R agonists and antagonists have been reported to prevent and enhance memory consolidation, respectively. A pretraining systemic injection of H_3R agonists impairs object recognition and the passive avoidance response (Blandina et al. 1996a). More specifically, for memory consolidation, a posttraining, intra-CA1 infusion of an H_3R agonist impairs the retention of long-term memory in a novel object recognition task (da Silveira et al. 2013). Posttraining administration of an H_3R antagonist enhances memory retention in a two-trial delayed comparison paradigm using a Y-maze, which is blocked by the administration of an H_2R antagonist (Orsetti et al. 2001). However, local infusions of H_3R agonists and antagonists into the BLA induce opposite effects. A posttraining intra-BLA infusion of an H_3R antagonist decreases the conditioned fear response (Passani et al. 2001). In contrast, an intra-BLA injection of an H_3R agonist enhances the fear response (Cangioli et al. 2002). Acetylcholine modulation in the BLA might explain the different effects of systemic and intra-BLA administration of H_3R agonists and



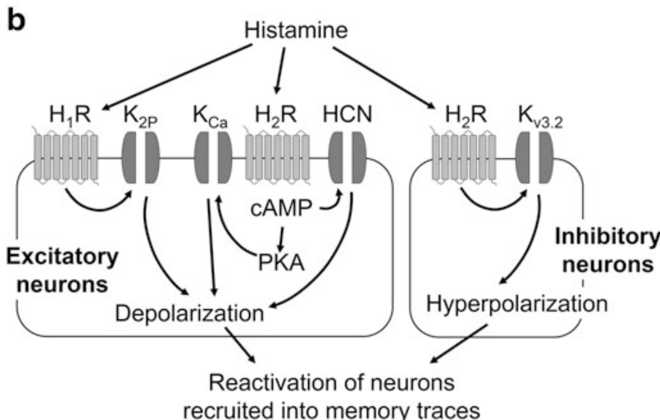


Fig. 1 Possible mechanisms by which histamine enhances memory consolidation and retrieval. (**a**) H_2R activation leads to the phosphorylation of CREB, which is a critical transcription factor for memory consolidation. Histamine increases synaptic plasticity possibly by enhancing NMDA function and/or increasing Ca^{2+} release from the endoplasmic reticulum (ER). (**b**) Histamine increases the excitability of excitatory neurons, possibly through the activation of K_{2P}, K_{Ca}, and/or HCN channels, which are triggered by H_1R and H_2R activation. H_2R activation hyperpolarizes inhibitory neurons through $K_{v3.2}$ channels. Together, the resulting increase in the excitability of the neural circuitry may contribute to memory retrieval through the reactivation of neurons recruited into a memory trace

antagonists (Blandina et al. 2004). The muscarinic receptor activation in the amygdala is critical for consolidation of fear memory (Introini-Collison et al. 1996; Vazdarjanova and McGaugh 1999). The intra-BLA administration of H_3R agonists and antagonists enhances and reduces acetylcholine release in the BLA, respectively (Passani et al. 2001; Cangioli et al. 2002). Therefore, the histamine-acetylcholine interaction may regulate memory consolidation in the BLA.

H_2R-mediated phosphorylation of cAMP-responsive element-binding protein (CREB) is a possible mechanism by which histamine improves memory consolidation (Fig. 1a). CREB is phosphorylated by several protein kinases, including PKA, and is a key transcription factor regulating the synthesis of proteins critical for

memory consolidation (Bourtchuladze et al. 1994; Kida et al. 2002). H_2R is coupled to G_s, which activates adenylyl cyclase and PKA (Haas and Panula 2003). Therefore, H_2R activation is likely to modulate gene expression, which is critical for memory consolidation through the PKA-CREB pathway.

In addition, the histamine-induced modification of synaptic plasticity has been proposed to be a mechanism by which histamine improves memory consolidation (Fig. 1a). Synaptic plasticity is possibly a cellular mechanism of learning and memory (Martin et al. 2000; Neves et al. 2008). Long-term potentiation (LTP) is defined as persistent increases in the synaptic efficacy of excitatory synaptic transmission and is a typical form of synaptic plasticity in the hippocampus that is triggered by Ca^{2+} influx through the N-methyl-D-aspartate receptor (NMDAR) (Bliss and Collingridge 1993; Sakimura et al. 1995). Histamine directly potentiates NMDAR function (Bekkers 1993; Vorobjev et al. 1993; Burban et al. 2010), contributing to the histamine-induced enhancement of LTP (Brown et al. 1995; Kuo and Dringenberg 2008). H_1R activation reduces the Mg^{2+} block of NMDARs, which also increases NMDAR function (Payne and Neuman 1997). In addition, inositol 1,4,5-trisphosphate (IP3)-induced Ca^{2+} release following H_1R activation may promote synaptic plasticity. Researchers have also proposed that H_1R activation triggers D-serine release from astrocytes, leading to enhanced LTP through NMDAR activation (Masuoka et al. 2019). Consistent with these findings, LTP in the hippocampal CA1 region is reduced in H_1R-deficient mice (Dai et al. 2007). However, further studies are needed to determine whether histamine-mediated synaptic plasticity underlies the histamine-induced improvement in memory consolidation because these mechanisms are related to the induction of synaptic plasticity, which contributes to a cellular mechanism underlying memory encoding rather than memory consolidation.

Histamine influences adult neurogenesis, which might modulate memory consolidation. In the hippocampal subgranular zone, new neurons are continuously generated throughout adulthood (Ming and Song 2005; Zhao et al. 2008). Adult-born neurons are presumed to participate in a variety of memory processes, including memory consolidation (Kitamura and Inokuchi 2014). H_1R and H_2R are expressed in neural stem cell niches, H_2R activation promotes neural stem cell proliferation, and H_1R activation induces neuronal differentiation (Molina-Hernández and Velasco 2008; Rodríguez-Martínez et al. 2012; Wasielewska et al. 2017; Liao et al. 2019). Therefore, histamine potentially modulates memory processing by affecting adult neurogenesis. Consistent with this hypothesis, H_1R-deficient mice show impaired spatial learning and reduced adult neurogenesis (Ambrée et al. 2014).

4 Histamine and Memory Retrieval

Memory retrieval is not only a reflection of memory traces in the brain but also a dynamic output process that is modulated by the internal states of subjects (Tarder-Stoll et al. 2020). Compared to memory encoding and consolidation, less is known

about memory retrieval, despite the importance of its deficits in various neuropsychiatric disorders (Beatty et al. 1988; Westmacott et al. 2001; Meeter et al. 2006; Kopelman and Bright 2012; Thomas 2015). Histamine is a candidate key modulator of memory retrieval. Kamei and Tasaka revealed that a pretest i.c.v. infusion of histamine shortens the response latency in an active avoidance task in old rats in an H_1R-dependent manner (Kamei and Tasaka 1993). An i.c.v. administration of histamine and histidine facilitates the retrieval of short-term social memory (Prast et al. 1996). In a radial maze task, histamine (i.c.v.) and histidine (i.p.) administration ameliorated spatial memory deficits induced by MK-801 infusion, which was blocked by both H_1R and H_2R antagonists (Xu et al. 2005). These findings indicate that the exogenous application of histamine facilitates memory retrieval. In addition, the role of endogenous histamine in memory retrieval was examined. A pretest injection of H_1 receptor antagonists blocks the active avoidance response and contextual conditioned fear response (Nishiga et al. 2003; Nonaka et al. 2013). Depletion of histamine 1 day after training impairs the inhibitory avoidance response, which is rescued by a histamine infusion into the CA1 before the retention test (Fabbri et al. 2016). The effect of H_3R antagonists/inverse agonists is consistent with the facilitating effect of histamine on memory retrieval. Systemic administration of an H_3R antagonist prior to the memory test enhances the retrieval of social memory (Prast et al. 1996).

Forgotten memories persist latently in the brain because they are occasionally and spontaneously recollected. A few animal studies have shown that long-term and/or highly invasive manipulation recovers retrograde amnesia. For example, chronic treatment with a histone deacetylase inhibitor and optogenetic activation of memory engram neurons restore forgotten fear memory (Fischer et al. 2007; Ryan et al. 2015). Treatment with H_3R antagonists/inverse agonists is a more clinically applicable method. A single administration of an H_3R antagonist/inverse agonist prevents natural forgetting in a novel object recognition task (Pascoli et al. 2009). Rats discriminate novel and familiar objects after the administration of the H_3R antagonist/inverse agonist in a memory test conducted 24 h following training, while control rats do not discriminate the two objects in the test. The improvement of memory retrieval requires the activation of both H_1R and H_2R. From a clinical perspective, an important goal is to determine whether H_3R antagonists/inverse agonists induce recovery long after learning and forgetting. We examined the effect of H_3R antagonists/inverse agonists (thioperamide and betahistine) on forgotten novel object recognition memories long after learning and forgetting to answer this question (Nomura et al. 2019). While control mice did not discriminate the novel and familiar objects 3 days after training, the mice receiving thioperamide discriminated the two objects 3 days, 1 week, and 1 month after training. Betahistine-treated mice also discriminated the two objects 1 week after the training. Based on these results, H_3R antagonists/inverse agonists recover the retrieval of forgotten memories long after learning. The recovery effect on memory retrieval depends on histamine release and H_2R activation in the perirhinal cortex (PRh) because an i.p. administration of thioperamide promoted histamine release in the PRh, the recovery effect was blocked by a local infusion of H_2R antagonist into the

PRh, and an intra-PRh infusion of thioperamide mimicked the recovery effect. Therefore, we documented that H_3R antagonists/inverse agonists promote the retrieval of forgotten long-term memory through H_2R activation in the PRh (Nomura et al. 2019).

The enhanced retrieval may be due to histamine-induced excitatory effects (Fig. 1b). H_1R activation exerts to an excitatory effect on neurons in most brain regions, including the hippocampus (Selbach et al. 1997; Manahan-Vaughan et al. 1998) and cerebral cortex (Reiner and Kamondi 1994). This excitatory effect involves a decrease in the leak K^+ current (Reiner and Kamondi 1994). H_2R is also involved in histamine-induced excitatory effects through several mechanisms. H_2R activation increases intracellular cAMP and activates PKA, which inhibits afterhyperpolarization by inhibiting Ca^{2+}-dependent K^+ channels, resulting in increased neuronal excitability. In addition, cAMP directly acts on the hyperpolarization-activated cation channel HCN2, leading to depolarization (Pedarzani and Storm 1995). Furthermore, H_2R activation suppresses the activity of inhibitory interneurons through $K_{v3.2}$-containing K^+ channels, and this effect also contributes to histamine-dependent modulation of neural network activity (Atzori et al. 2000). These excitatory effects of histamine may be related to its ability to promote memory retrieval. In fact, the depolarization of PRh neurons mimics the recovery of memory retrieval that is induced by an H_3R antagonist/inverse agonist injection (Nomura et al. 2019). When the excitability of PRh neurons is increased by a Designer Receptors Exclusively Activated by Designer Drug (DREADD) before the memory test, forgotten object memories are recovered by enhancing retrieval. Taken together, these findings suggest that the histamine-induced increase in neuronal excitability through H_1R and/or H_2R activation enhances memory retrieval.

How does the increased neuronal excitability facilitate memory retrieval? According to recent studies, memory retrieval is mediated by the selective reactivation of neuronal populations that were active during learning (Josselyn et al. 2015; Tonegawa et al. 2015). For example, a population of neurons in the BLA that is active during fear conditioning is reactivated during subsequent retrieval of fear memory (Reijmers et al. 2007; Nonaka et al. 2014; Nakayama et al. 2014). Synaptic potentiation occurs specifically in the subpopulation of neurons active during fear conditioning (Nonaka et al. 2014). In addition, optogenetic activation of hippocampal dentate gyrus neurons that were active during fear conditioning triggers memory retrieval (Liu et al. 2012). Different memories appear to be stored in different subsets of neurons because the retrieval of different fear memories activates different subsets of amygdalar neurons (Nomura et al. 2012). These findings have prompted the hypothesis that the retrieval of individual memories requires specific reactivation of the responsible neurons. However, because histamine receptors are not exclusively expressed in neurons that were recruited into a memory trace, histamine may increase neuronal excitability throughout the neural circuit, including both neurons that were and were not recruited into the memory trace, similar to noise added to the neural circuits for memory retrieval. Here, stochastic resonance can explain how adding noise to the circuit enhances memory retrieval. Stochastic resonance is a phenomenon in which the addition of noise to a signal that is

undetectable because it is smaller than a threshold causes the signal to exceed the threshold and become detectable. It has been used to explain various phenomena in biology and physics (Fauve and Heslot 1983; McDonnell and Ward 2011). The explanation of memory retrieval through stochastic resonance is provided below (Fig. 2). When a subject re-encounters a stimulus that the subject memorized in the past, the memory of the stimulus is recalled correctly if neurons recruited into the memory trace are reactivated. However, as time passes after learning, when those neurons become less active and their activity is below the threshold for memory retrieval, the subject does not recall the memory. If histamine is present and increases neuronal excitability throughout the circuit, the activity of some of the neurons recruited into the memory trace will exceed the threshold. The activity of these neurons is presumed to allow the memory to be recalled. In fact, histamine has been shown to specifically promote reactivation of neurons activated during learning (Nomura et al. 2019).

Moreover, gamma oscillations, which are rhythmic activities in local field potentials that span a range of frequencies between 30 and 120 Hz, might link histamine to memory retrieval. Slow gamma oscillations have been proposed to support memory retrieval since place cells in the hippocampus code familiar spatial trajectories during slow gamma oscillations (Zheng et al. 2016). Gamma oscillations are altered in patients with various neurological diseases, including Alzheimer's disease (AD) and in AD mouse models (Herrmann and Demiralp 2005; Van Deursen et al. 2008; Goutagny et al. 2013; Mably et al. 2017; Mondragón-Rodríguez et al. 2018). At a causal level, optogenetic gamma stimulation rescues memory retrieval impairments in an AD mouse model (Etter et al. 2019). The optogenetic stimulation of medial septal parvalbumin neurons at 40 Hz restores slow gamma oscillations in the hippocampus and rescues memory performance in the novel object place recognition task when it was performed during a memory test session. Based on these data, gamma oscillations are linked to memory retrieval. Histamine modulates gamma oscillations in the hippocampus and cortex. In hippocampal slices, histamine promotes gamma oscillations via H_1R activation in a KCNQ channel-dependent manner (Andersson et al. 2017). In a mouse model of Parkinson's disease based on 6-hydroxydopamine (6-OHDA), kainate-induced gamma oscillations are reduced in hippocampal slices. When 6-OHDA-treated mice are injected with H_3R antagonists for 3 days before slice preparation, the slice generates gamma oscillations comparable to sham mice (Masini et al. 2017). The effects of histamine on promoting gamma oscillations have also been confirmed in vivo. A local histamine infusion into the medial entorhinal cortex (MEC) increases gamma power in the MEC, which is blocked by H_1R and H_3R antagonists (Chen et al. 2018). Taken together, these findings suggest that histamine promotes memory retrieval possibly by increasing gamma oscillations.

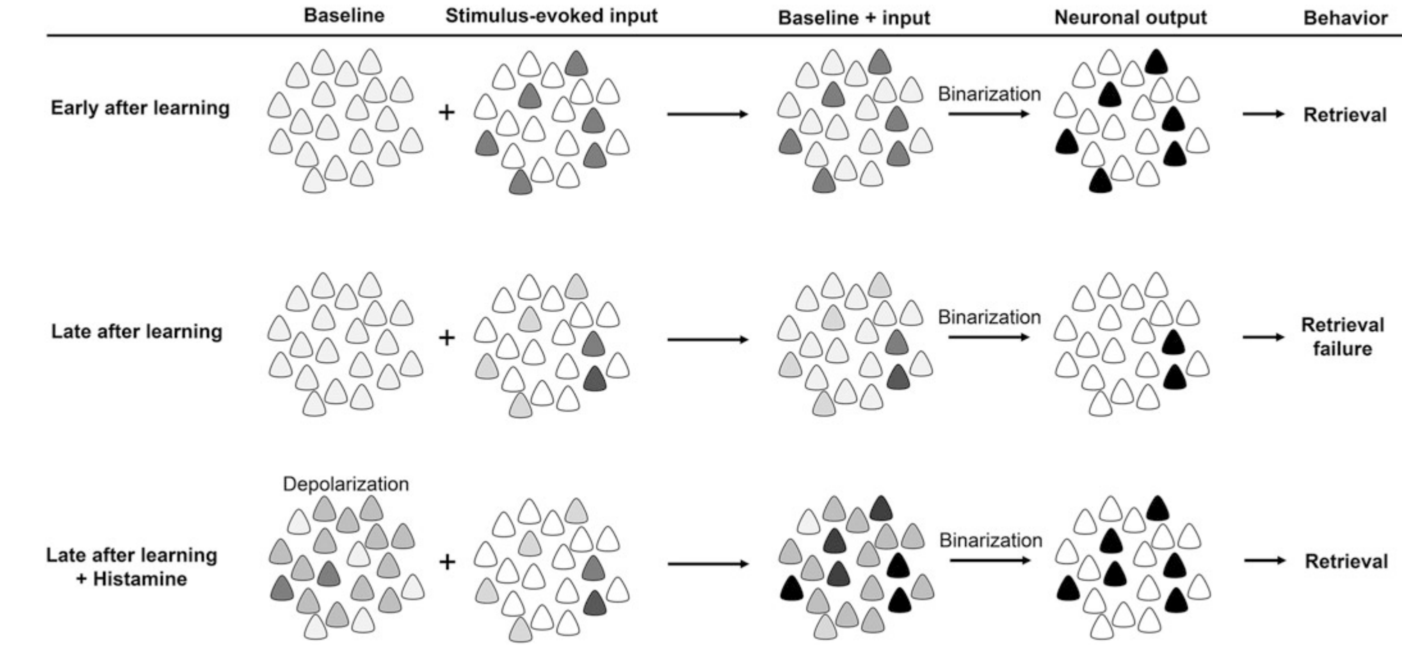


Fig. 2 A stochastic resonance model explaining how histamine enhances memory retrieval. Early after learning, when a subject re-encounters a stimulus that he/she memorized in the past, the stimulus-evoked input is sufficiently large to activate neurons recruited into a memory trace (memory neurons), which leads to memory retrieval. However, as time passes after learning, the stimulus-evoked input is smaller than the threshold and the memory neurons are not activated, which results in retrieval failure. When histamine is present and increases neuronal excitability throughout the neural circuit, the activity of some memory neurons exceeds the threshold, even if the stimulus-evoked input is small. The activity of these neurons induces memory retrieval

5 Histamine and Other Memory Processes

There are other processes that mediate memory storage and expression and are sensitive to drugs. In general, memory consolidation requires cellular and molecular changes that occur within several hours after learning (Hashikawa et al. 2011; Johansen et al. 2011). Blocking these changes leads to a memory deficit 24 h after learning. In addition to rapid changes, delayed molecular changes (e.g., c-Fos and Arc) occur 12–24 h after learning (Bekinschtein et al. 2008; Rossato et al. 2009; Nakayama et al. 2015) and retrieval (Nakayama et al. 2013, 2016). Blocking the delayed molecular changes prevents memory expression 7 days but not 2 days after learning, indicating that the maintenance of long-term memories requires delayed molecular changes following learning. Delayed Arc expression is suggested to induce the elimination of dendritic spines, leading to a refinement of functional memory circuits (Nakayama et al. 2015). Another memory stabilization process occurs after memory retrieval. Memory retrieval renders a consolidated memory labile again, and another round of consolidation and reconsolidation is required for its stabilization (Nader et al. 2000). Reconsolidation is sensitive to many types of drugs (Nader et al. 2000; Nomura and Matsuki 2008; Kindt et al. 2009), and blocking reconsolidation of fear memories has been proposed to be a medical treatment for posttraumatic stress disorder (PTSD). Although brief exposure to a conditioned stimulus (CS) induces reconsolidation in a classical conditioning paradigm, repeated or long-term exposure to CS extinguishes conditioned responses (Myers and Davis 2007). The extinction of conditioned responses is not permanent because CS reappears after the presentation of an unconditioned stimulus and is spontaneously recovered over time (Shen et al. 2013; Hitora-Imamura et al. 2015). Enhancing fear extinction and/or blocking fear reinstatement and spontaneous recovery are important for treating PTSD. Long-term storage of memories over weeks, months, or years requires the reorganization of the brain network at the systems level (Frankland and Bontempi 2005; Klinzing et al. 2019). This long-term consolidation across brain areas is known as systems consolidation. Although the mechanisms of a variety of memory processes partially overlap with those of early consolidation, different mechanisms have also been proposed at the levels of molecules, cells, and circuits (Alberini 2005; Myers and Davis 2007; Nakayama et al. 2015; Tonegawa et al. 2018). Therefore, the effect of histamine on each memory process should be examined separately to elucidate the whole picture of the effects of histamine on learning and memory. The involvement of some neuromodulators in these memory processes has been studied over the past 20 years. Dopamine D1R is involved in delayed steps 12 h after learning, contributing to memory persistence (Rossato et al. 2009). D1R is also critical for fear reinstatement, as blocking prefrontal D1R prevents synaptic depression, changes in amygdala activity, and the reappearance of conditioned fear induced by a reminder shock (Hitora-Imamura et al. 2015). In contrast, a very limited number of studies have analyzed the effects of histamine on memory processes other than initial learning and retrieval. For example, an intra-CA1 infusion of histamine facilitates the consolidation of fear extinction

memory through H_2R-dependent activation of ERK signaling (Bonini et al. 2011). H_3R antagonists reverse the deficit in reconsolidation induced by NMDAR antagonists, although H_3R antagonists alone do not influence memory reconsolidation (Charlier and Tirelli 2011; Brabant et al. 2013). Further studies are needed to understand the overall role of histamine in various memory processes.

6 Effects of the Genetic Manipulation of Histamine Signaling on Learning and Memory

Among studies using genetically modified mice, some reports support the hypothesis that histamine promotes learning and memory, but the opposite results have also been reported. Chronic brain histamine depletion in adulthood via a local infusion of an adeno-associated virus expressing Cre recombinase into the TMN of Hdc flox mice impairs aversive memory (Yamada et al. 2020). Both H_1R- and H_2R-deficient mice show impaired spatial memory in the Barnes maze and impaired object memory in the novel object recognition test (Dai et al. 2007; Zlomuzica et al. 2009; Ambrée et al. 2014). However, both H_1R- and H_2R-deficient mice show greater conditioned fear responses than wild-type mice in the fear conditioning test (Dai et al. 2007). HDC-deficient mice exhibit impaired object memory but enhanced conditioned fear responses in the fear conditioning test (Dere et al. 2003; Liu et al. 2007). In a study using male HDC-deficient mice, spatial memory in the water maze task was shown to be enhanced (Dere et al. 2003), but another study using female mice showed a deficit of spatial memory in HDC-deficient mice (Acevedo et al. 2006). H_3R-deficient mice show enhanced spatial memory in the Barnes maze but comparable object recognition and location memories in the novel location and object recognition tasks compared to wild-type controls (Rizk et al. 2004). The contradictory findings may be due to the long-term manipulation of gene expression in the mutant mice. Conventional genetically modified mice may not be appropriate to analyze the role of histamine signaling in learning and memory because histamine signaling is modified outside of the time of learning and in various brain areas. Future studies using spatial- and/or temporal-specific genetic manipulation of histamine signaling are needed to improve our understanding of the role of histamine in specific memory processes.

7 Activity of Histamine Neurons In Vitro and In Vivo

The activity of histamine neurons during memory processing must be elucidated to understand the contributions of histamine to learning and memory. Histamine neurons show a slow regular firing pattern in vitro and in vivo (Reiner and McGeer 1987; Haas and Reiner 1988). Their action potentials are broad with slow rise and

decay times, followed by a large afterhyperpolarization (Stevens et al. 2001). Recently, the development of genetically modified mice in which histamine neurons are labeled with a fluorescent protein has enabled the performance of electrophysiological recordings specifically from histamine neurons (Fujita et al. 2017; Michael et al. 2020). These studies showed that the electrophysiological properties of genetically identified histamine neurons are broadly consistent with classical observations. These properties are similar across subregions of the TMN and between male and female mice (Michael et al. 2020). In addition, unsupervised hierarchical cluster analysis revealed that histamine neurons are categorized into 2 subclasses, in which histamine type 1 neurons exhibit lower input resistance values, lower membrane time constants, greater afterhyperpolarization (AHP) amplitudes, shorter action potential half-widths, faster rise and decay times, and higher maximum firing rates than type 2 neurons (Fujita et al. 2017).

The activity of histamine neurons in vivo is dynamically modulated by the subject's internal state. Microdialysis studies have shown that extracellular histamine concentrations in the hypothalamus and cortex increase during wakefulness (Strecker et al. 2002; Chu et al. 2004). Electrophysiological analyses revealed that histamine neurons are active during wakefulness, but not drowsiness and NREM and REM sleep (Vanni-Mercier et al. 2003). This histamine activity has been proposed to play an important role in the maintenance of wakefulness. A motivational state may be another key modulator of the activity of histamine neurons. The presentation of inaccessible food to a fasted rat, but not a fed rat, increases c-Fos expression in histamine neurons and histamine release in the hypothalamus (Valdés et al. 2005, 2010). The deprivation of anticipated food under scheduled feeding also induces c-Fos expression in histamine neurons (Umehara et al. 2010, 2011). Therefore, histamine neurons are active during the appetitive phase of feeding. Furthermore, histamine neurons appear responsive to other motivational states. Exposure of male rats to proestrus female rats increases c-Fos expression in the TMN of male rats (Contreras et al. 2016). In contrast, exposure to diestrus female rats has no effect on c-Fos expression. Although water deprivation has no effect on c-Fos expression in the TMN, the presentation of an empty water bottle to thirsty rats increases c-Fos expression in the TMN (Contreras et al. 2016). Taken together, these findings indicate an increase in the activity of histamine neurons when subjects are awake and motivated. The dynamics of arousal and motivation during and after memory tasks might influence memory processing through histamine signaling. Future studies using activity recordings from genetically identified histamine neurons (e.g., calcium imaging, unit recordings from opto-tagged cells (Williams et al. 2014)) will elucidate the activity dynamics of histamine neurons and their effects on learning and memory.

8 Human Histaminergic System and Memory

Based on the findings from the animal studies described above, studies have also assessed whether H_3R antagonists/inverse agonists improve memories in humans (Sadek et al. 2016; Provensi et al. 2020). Because pretest administration of betahistine (H_3R antagonist and weak H_1R agonist) improves the retrieval of 1-week-old forgotten object memory in mice, we conducted a randomized double-blind, placebo-controlled crossover trial to determine whether pretest treatment with betahistine improves object recognition memory 1 week after learning in humans (Nomura et al. 2019). During the learning session, 38 healthy participants studied serial images of 128 objects. Seven and 9 days after learning, we administered 108 mg of betahistine or placebo orally 30 min before the test session started. The participants were asked whether they had seen the target images during the learning phase. Betahistine treatment increased the overall correct ratio. More specifically, betahistine improved the correct rate to a greater extent in subjects with poorer performance after the placebo treatment. On the other hand, a study with healthy participants showed that betahistine (48 mg) had no effect on performance in working memory and paired associates learning tasks (van Ruitenbeek and Mehta 2013). The effects of H_3R antagonists/inverse agonists may depend on the dose, task difficulty, and/or memory type.

Several lines of evidence support the hypothesis that the histaminergic system is altered in several neuropsychiatric disorders, suggesting a possible role of the histaminergic system in cognitive impairments in these disorders (Shan et al. 2017). A positron emission tomography study using a radioligand for H_1R revealed that the binding potential of H_1R is reduced in the frontal and temporal areas of patients with AD (Higuchi et al. 2000). Receptor binding correlated with the severity of AD. The binding of H_2R is not altered in the prefrontal cortex of patients with AD (Perry et al. 1998). The number of HDC-positive neurons in the TMN is reduced in the brains of individuals with AD (Oh et al. 2019), although HDC mRNA expression in the TMN is not altered in patients with AD (Shan et al. 2012). While some studies reported decreased histamine levels in the hippocampus, frontal cortex, and temporal cortex of postmortem brain tissues from patients with AD (Mazurkiewicz-Kwilecki and Nsonwah 1989; Panula et al. 1997), others reported increased histamine levels in the frontal cortex, basal ganglia, and hippocampus (Cacabelos et al. 1989). A study using postmortem brain samples from patients with AD showed that H_3R binding in the frontal cortex correlates with dementia severity, while H_3R binding is not different between the brains of individuals with AD and age-matched controls (Medhurst et al. 2009). In patients with nonsyndromic autosomal recessive intellectual disability, two homozygous HMT mutations (p.Gly60Asp and p.Leu208Pro) have been identified (Heidari et al. 2015). The p.Gly60Asp mutation disrupts the enzymatic activity of HMT, and p.Leu208Pro leads to the instability of HMT. However, HNMT-deficient mice show no deficit in the passive avoidance test (Naganuma et al. 2017).

Clinical trials are currently underway to test whether H_3R antagonists/inverse agonists improve cognitive impairments in patients with AD. A randomized, double-blind, placebo-controlled study with eight patients with mild to moderate AD showed that treatments with GSK239512, an H_3R antagonist, for 4 weeks exert positive effects on memory (Nathan et al. 2013). In addition, a study with 99 placebo-treated subjects and 97 GSK239512-treated subjects revealed that GSK239512 treatments for 16 weeks improved episodic memory, although the treatments had no significant effect on other cognitive domains (Grove et al. 2014). Further studies with larger populations are needed to test whether H_3R antagonists/inverse agonists improve learning and memory in patients with AD.

9 Conclusions and Perspectives

Behavioral pharmacological studies have provided a large amount of evidence supporting the hypothesis that histamine improves memory consolidation and retrieval. Although we introduced candidates for the underlying mechanisms in this review, most of them have not yet been tested in vivo. De novo gene expression is essential for memory consolidation. The mechanism by which histamine modulates gene expression following learning and how the modulation of gene expression regulates the cellular machinery responsible for memory consolidation remains elusive. Although we have provided evidence that histamine augments the reactivation of neurons that were active during learning in slices (Nomura et al. 2019), the mechanism by which histamine modulates neuronal activity in vivo remains to be elucidated. Recently, imaging of activity across large populations of neurons during naturalistic behavior, including learning and memory, has been performed in vivo (Resendez et al. 2016). Optogenetics and DREADDs enable the manipulation of neuronal activities in a cell type-specific manner. Further studies using these imaging and manipulation techniques will elucidate the mechanisms by which histamine improves memory consolidation and retrieval. Few studies have examined the effects of histamine on other memory processes, such as memory maintenance, memory reconsolidation, extinction memory, reinstatement, and systems consolidation. An understanding of these effects will require separate analyses of memory processes, including temporally and spatially restricted genetic manipulation. Because clinical trials of H_3R antagonists/inverse agonists with a small number of participants showed positive effects on memory, histamine likely improves learning and memory in humans. Clinical trials with larger populations are expected to test whether histamine is a novel target for improving cognitive impairments in patients with neuropsychiatric disorders.

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Targeting Histamine and Histamine Receptors for the Precise Regulation of Feeding

Yanrong Zheng and Zhong Chen

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Abstract Histamine has long been accepted as an anorexigenic agent. However, lines of evidence have suggested that the roles of histamine in feeding behaviors are much more complex than previously thought, being involved in satiety, satiation, feeding motivation, feeding circadian rhythm, and taste perception and memory. The functional diversity of histamine makes it a viable target for clinical management of obesity and other feeding-related disorders. Here, we update the current knowledge about the functions of histamine in feeding and summarize the underlying molecular and neural circuit mechanisms. Finally, we review the main clinical studies about the impacts of histamine-related compounds on weight control and discuss insights into future research on the roles of histamine in feeding. Despite the recent progress in

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histamine research, the histaminergic feeding circuits are poorly understood, and it is also worth verifying the functions of histamine receptors in a more spatiotemporally specific manner.

Keywords Feeding behaviors · Feeding circadian rhythm · Feeding motivation · Histamine · Histamine receptors · Satiety · Taste perception

Eating a reasonable diet provides sufficient energy and balanced nutrients for maintaining a healthy body. However, thousands of people are troubled or even tortured by uncontrollable eating. Obsessive eating leads to obesity, which has become a global health concern, while psychiatric eating disorders including anorexia nervosa, bulimia nervosa, and binge eating disorder can even be life threatening. Deciphering the neural and molecular mechanisms behind eating behaviors would profoundly facilitate our understanding of these pathologies and help guide a healthy life.

Eating is a highly dynamic and complicated process, which can be briefly divided into three phases based on both the peripheral and central responses to food over time (Craig 1917; Kringelbach et al. 2012; Sternson and Eiselt 2017). The primary stage of an episode of eating is termed the appetitive phase since eating is primarily driven by the desire for food, motivated by either physical energy demand or pleasure after food rewards (Saper et al. 2002). In addition, the circadian rhythm is another contributor to appetite, setting the schedule for feeding (Asher and Sassone-Corsi 2015; Koch et al. 2020; Segers and Depoortere 2021). Once food is obtained, the appetitive phase ceases and there is a shift to a state of satisfaction (consumption phase), which is mainly maintained by positive reinforcement from food palatability (Sternson and Eiselt 2017). When satisfaction peaks, further ingestive behaviors will be suppressed both peripherally and centrally, which is defined as the termination phase (Sternson and Eiselt 2017; Augustine et al. 2020) (Fig. 1). The termination phase is composed of two distinct ingestion-suppressing processes termed satiation and satiety, respectively. Satiation refers to the sensation of fullness during ingestion, primarily derived from food palatability and/or the distension of stomach (Janssen et al. 2011; Livovsky et al. 2020). Satiation puts an end to the ongoing meal (Higuchi et al. 2020; Li et al. 2020; Klaassen and Keszthelyi 2021), and thus occurs at the interface of the consumption and termination phase (Fig. 1). After the meal ceases, satiation disappears soon as stomach emptying, but the termination phase can be maintained by satiety which describes the postprandial feeling of non-hunger and delays the next eating episode (Janssen et al. 2011; Livovsky et al. 2020; Klaassen and Keszthelyi 2021). Satiety is principally induced by the appetite-suppressing actions of satiety signals, which are the peripheral peptides or hormones released due to the increased nutrients in the intestine or blood plasma (Begg and Woods 2013; Hellstrom 2013; Xu and Xie 2016). Collectively, satiation is usually attributed to the satiating value (e.g., taste, texture, palatability, and total volume) of food before digestion while satiety is more associated with the nutrient composition and total calories consumed. Furthermore, satiation leads to a decreased

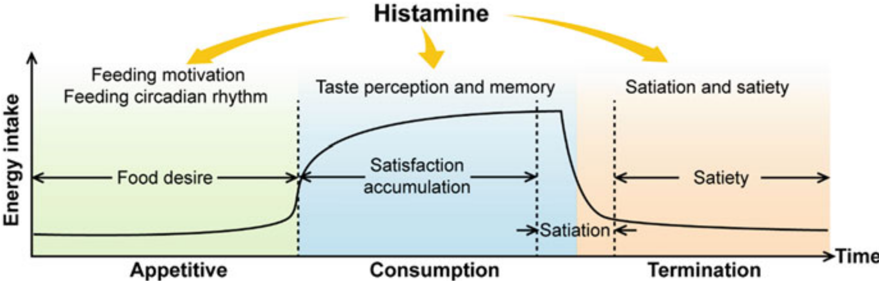

Fig. 1 A schematic overview of the functions of histamine in feeding. Eating can be divided into three phases, namely the appetitive, consumption, and termination phases. The appetitive phase is dominated by the desire for food, motivated by either physical energy demand or pleasure after food rewards. Once the food is obtained, the consumption phase initiates and continues as satisfaction provided by food accumulates. After satisfaction peaks, satiation and satiety suppress food consumption to terminate the meal. Histamine is involved in these phases in different ways, which will be addressed in detail in the following sections

meal size (g or kcal) and shortens meal duration, and satiety, on the other hand, prolongs the inter-meal interval and reduces meal frequency (De Graaf et al. 1999). As time goes by, satiety progressively diminishes and another energy intake cycle initiates.

Histamine is a neurotransmitter and neuromodulator with various functions in the mammalian central nervous system (CNS). Since the 1970s, mounting evidence has revealed that histamine acts as an anorexigenic agent. Acute injection of histamine into the lateral ventricle reduces food intake in cats (Clineschmidt and Lotti 1973), and in rodents continuous central infusion of histamine suppresses feeding (Itowi et al. 1988). Consistent with these observations, increasing central histamine levels, either by boosting histamine synthesis (Sheiner et al. 1985; Orthen-Gambill 1988; Vaziri et al. 1997) or by inhibiting histamine catabolism (Lecklin et al. 1995), also decreases food consumption. Subsequent investigations of histamine-mediated feeding behaviors have revealed that histamine has heterogeneous functions in different feeding phases. Histamine can terminate eating by enhancing both satiation and satiety, while in the appetitive phase it can drive motivated behaviors toward food and engage in the modulation of feeding circadian rhythm. Evidence also shows the involvement of histamine in taste perception during food consumption (Fig. 1). In this review, we first summarize the diverse functions of histamine in feeding behaviors as well as the neural circuit mechanisms behind different functions. Furthermore, we review the main findings regarding the regulation of the histaminergic feeding network by histamine receptors and discuss the insights from clinical feeding interventions targeting histamine receptors.

1 Histamine in Feeding

1.1 Histamine in Satiety and Satiation

Early in the 1990s, it has been shown that histamine is closely associated with satiety. α-fluoromethylhistidine (FMH) is a suicide inhibitor ($IC_{50} = 1.3 \times 10^{-5}$ M in vitro) (Kollonitsch et al. 1978) of histidine decarboxylase (HDC, histamine-synthesizing enzyme) and has been widely used for histamine depletion in vivo. Infusion of α-FMH into the third cerebroventricle of rats fed *at libitum* triggers ingestive behaviors in the early light phase (Ookuma et al. 1993). Interestingly, α-FMH microinfusion into the ventromedial (VMH) or paraventricular hypothalamus (PVH), but not the lateral (LH), dorsomedial (DMH), or preoptic anterior hypothalamus (POAH), recapitulates feeding induced by the depletion of hypothalamic histamine (Ookuma et al. 1993). Given that VMH and PVH serve as satiety centers in the CNS (Becker and Kissileff 1974), these results imply that histamine inhibits feeding by enhancing satiety. Furthermore, continuous automatic detection of daily meal pattern revealed that the inhibition of histamine biosynthesis by α-FMH increased meal frequency in rats fed *at libitum* (Fukagawa et al. 1988; Doi et al. 1994), whereas antagonism of histamine H3 receptors (auto-receptor) by thioperamide decreased it (Machidori et al. 1992), reflecting the involvement of histamine in satiety induction. However, the observations above must be interpreted with caution since the alteration of meal pattern may also result from circadian rhythm derangement (see below for details). By employing an alternative satiety-assessing paradigm (behavioral satiety sequence analysis), Prof. Maria Beatrice Passani and her colleagues found that oleoylethanolamide, a satiety molecule released from the small intestine, induced a reduction in food intake and a shift of behavioral sequence from eating to resting in rats provided with palatable wet mesh for 40 min, which was abolished by α-FMH co-administration (Provensi et al. 2014). These results indicate that histamine is required for oleoylethanolamide-induced satiety. In addition to oleoylethanolamide, inhibition of either histamine biogenesis or the post-synaptic histamine H1 receptor blunts the anorexigenic effects of various satiety signals, including leptin (Morimoto et al. 1999; Yoshimatsu et al. 1999; Yoshimatsu 2008), amylin (Lutz et al. 1996; D'Este et al. 2001), bombesin (Merali and Banks 1994; Kent et al. 1997; Okuma et al. 1997), cholecystokinin (Attoub et al. 2001), glucagon-like peptide-1(Gotoh et al. 2005), and nesfatin-1 (Gotoh et al. 2013), suggesting that histamine relays satiety messages from the periphery to the CNS.

Although it is clear that histamine plays a key role in the transmission of peripheral satiety messages, the mechanisms underlying the peripheral regulation of histaminergic neurons are less clear. It has been shown that leptin receptors are barely expressed in histaminergic neurons (Elmquist et al. 1998; Hakansson et al. 1998) and whether receptors of other satiety molecules residue in histaminergic neurons is unknown, although some of them are present in hypothalamus, and even in the tuberomammillary nucleus (Moody et al. 1988; O'Shea and Gundlach 1993;

Campos et al. 1994; Paxinos et al. 2004; Goebel-Stengel et al. 2011). Evidence to date has tended to support indirect regulation of histaminergic neurons by peripheral satiety signals. Histaminergic neurons receive synaptic input from α-melanocyte stimulating hormone (α-MSH)-containing neurons of the arcuate nucleus (ARC), the main central target of leptin (Fekete and Liposits 2003; Xu et al. 2018). Histaminergic neurons are surrounded by amylin-positive fibers (D'Este et al. 2001), implying a potential synaptic connections between these two kinds of neurons. In addition, corticotropin-releasing hormone neurons and thyrotropin-releasing hormone neurons in the PVH, as well as feeding-related neurons in the nucleus tractus solitarius (NTS), transmit peripheral signals of satiety to histaminergic neurons (Gotoh et al. 2005, 2013; Yoshimatsu 2008; Provensi et al. 2016; Umehara et al. 2016) (Fig. 2).

Although the findings above demonstrate that histamine is required for satiety, histamine itself cannot be classified as a satiety signal. Actually, feeding-induced increase of hypothalamic histamine occurs much earlier (<15 min) than the peripheral release of satiety hormones (Itoh et al. 1991). More importantly, ingestion is the prerequisite of the secretion of endogenous satiety signals. However, the extracellular histamine concentration in the medial hypothalamus of rats fasted for 24 h increases (by 63%) even after the presentation of inaccessible food (in a closed wire mesh box), although ingestion triggers a more dramatic (143%) increase of extracellular histamine (Itoh et al. 1991).

In addition to satiety, histamine also engages in satiation induction. A pilot study conducted by Prof. Toshiie Sakata and his colleagues showed that ad libitum feeding of hard pellet intake, but not intubation of liquid diet with equal calorific value, increased the concentration of tele-methylhistamine (a predominant metabolite of histamine) in hypothalamus and the mesencephalic trigeminal nucleus (Me5) (Fujise et al. 1998). These results indicate that oral sensations during ingestion can affect central histamine turnover. Moreover, depletion of histamine in the hypothalamus by α-FMH not only reduces the latency to eat (due to the loss of satiety) but also enlarges the size of the first meal and prolongs meal duration in the early light phase in rats fed *at libitum* (Sakata et al. 1990; Ookuma et al. 1993). As mentioned above, satiation is a feeling of fullness that occurs during food intake and controls meal size and duration. The evidence above indicates that histamine can suppress feeding by enhancing satiation (Sakata 1995; Sakata et al. 1997). However, the satiation induced by histamine seems to be primarily involved when the rats are in an energy-deficient state, since continuous infusion of α-FMH fails to affect daily intake in rats fed *at libitum* (Doi et al. 1994) but acute α-FMH treatment increases the size of the first meal after 5-h fasting in rats (Fujise et al. 1998) or during the early light phase when nearly 5 h has passed since the last meal (Sakata et al. 1990; Ookuma et al. 1993). Thus, the satiation induced by histamine could be crucial for preventing physical discomfort caused by excessive ingestive behaviors during energy deficiency.

Again, infusion of α-FMH into the VMH merely attenuates satiation in 5-h fasted rats, indicating that there is an overlap in the downstream histaminergic circuits regulating satiety and satiation (Ookuma et al. 1993; Fujise et al. 1998). However, the upstream circuits of histaminergic neurons controlling satiation remain unclear

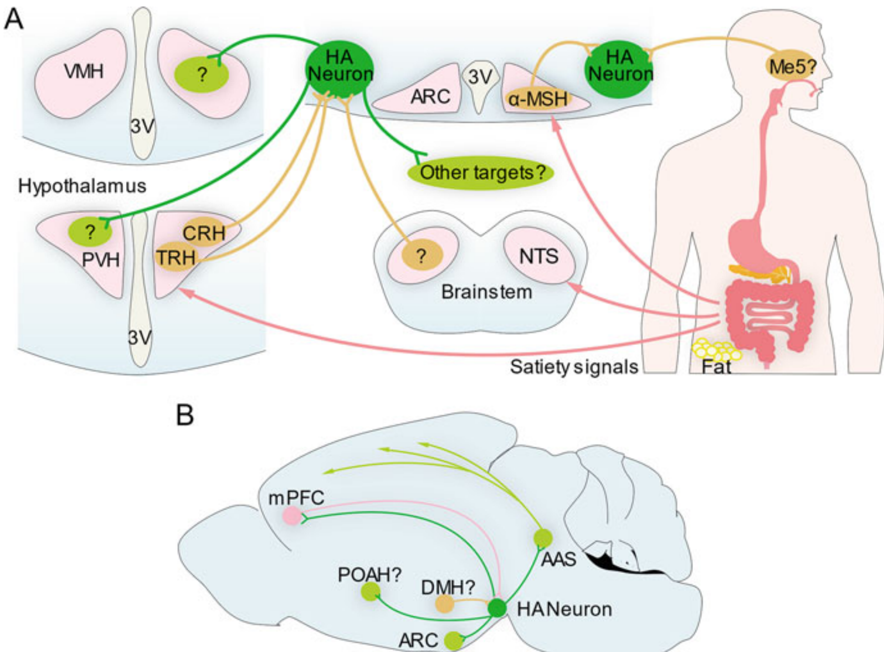

Fig. 2 A schematic diagram of the histaminergic network underlying satiety, satiation, and feeding motivation. (**a**) Histamine is required for the anorexigenic actions of peripheral satiety signals, including leptin, oleoylethanolamide, amylin, bombesin, cholecystokinin, glucagon-like peptide-1, and nesfatin-1. The α-MSH neurons in the ARC, corticotropin-releasing hormone (CRH) neurons, and thyrotropin-releasing hormone (TRH) neurons in the PVH, as well as feeding-related neurons in the NTS can transmit peripheral signals of satiety to histaminergic (HA) neurons. The mesencephalic trigeminal nucleus (Me5) may convey sensation from the oral cavity to histaminergic neurons. The histaminergic neurons further regulate food intake through projections to the VMH and PVH. However, the cell types required in the different nodes of this network are unclear. (**b**) Histaminergic neurons increase arousal to energize feeding motivation through the activation of the ascending arousal system (AAS) and ARC. The histaminergic projections to the POAH might also engage in feeding motivation. Histaminergic neurons and mPFC may form a positive feedback loop to maintain the intensity of the efforts to obtaining food. Moreover, histaminergic neurons also receive input from a food-entrainable circadian oscillator, and DMH might be one candidate for this upstream oscillator

(Fig. 1). Given the fact that the texture of food affects central histamine turnover (Fujise et al. 1998), it is likely that an innervation conveys sensation from the oral cavity to histaminergic neurons directly. Indeed, the mesencephalic trigeminal nucleus, which plays crucial roles in the proprioception of the face and oral cavity, sends projections to histaminergic neurons (Ericson et al. 1989; Ericson et al. 1991; Sakata et al. 2003) (Fig. 2a).

1.2 Histamine in Feeding Motivation

As mentioned above, enticing hungry (24 h of fasting) rats with inaccessible food boosts the release of hypothalamic histamine (Itoh et al. 1991; Valdes et al. 2010), suggesting that histamine may also be involved in food anticipation during the appetitive phase of feeding in addition to terminating a meal through satiety and satiation. Supporting this hypothesis, food-seeking behaviors together with the number of cfos-positive histaminergic neurons increase before the predicted mealtime in rats under a restricted feeding schedule (training for 4 days with food availability from 9:00 to 10:00 h and from 15:00 to 17:00 h) (Inzunza et al. 2000; Meynard et al. 2005). In this paradigm, the activation of histaminergic neurons seems to primarily result from food anticipation rather than circadian rhythm, since few cfos-positive neurons could be observed during the same period of time in rats fed ad libitum (Meynard et al. 2005).

Prof. Fernando Torrealba and his colleagues further advanced the theory that histamine maintains feeding motivation during the appetitive phase (Torrealba et al. 2012). They found that the intense attempts made by 24-h fasted rats to reach food in a closed wire mesh box increased in parallel with the increase of extracellular histamine in the posterior hypothalamus (Valdes et al. 2010). Moreover, when rats were challenged with an instrumental lever press task, in which they had to press a lever enough times to obtain a food reward, 24-h starvation enhanced both the number of lever presses and the extracellular histamine concentration in the medial prefrontal cortex (mPFC) (Riveros et al. 2019). Food reward in both tests induced little interest and histamine release remained unchanged in rats fed ad libitum (Valdes et al. 2010; Riveros et al. 2019). Furthermore, the inhibition of histamine signaling (intracerebroventricular infusion of pyrilamine) decreased the efforts to obtain food in starved (24-h of fasting) rats in a dose-dependent manner (Riveros et al. 2019). The correlation of histaminergic activation with the intensity of endeavor indicates that histamine is fundamental to the maintenance of motivation during the appetitive phase of feeding. In addition to hunger-triggered food-seeking, histamine may also be required for reward-induced feeding since a stronger-tasting food further reinforces TMN activation and strengthens the efforts of hungry rats (24-h of fasting) to obtain food (Valdes et al. 2010). However, histamine was found to be dispensable for the consumption phase; if each level press in the instrumental lever press task was followed by one accessible food pallet, the inhibition of histamine signaling failed to affect the number of level presses and pallets ingested in 24-h fasted rats (Riveros et al. 2019).

The histamine-induced reinforcement of feeding motivation is hypothesized to result from histamine-induced arousal given the fact that the intensity of efforts to obtain food relies on the arousal state and the essential role of histamine in alert and attentive waking (Torrealba et al. 2012). Supporting this hypothesis, food enticement activates several wake-promoting nuclei and leads to increased active waking with suppressed rapid eye movement (REM) and non-REM (NREM) sleep (Valdes et al. 2005). The intense arousal induced by food enticement is characterized by

desynchronized and fast EEG, elevated locomotor activity (behavioral arousal), and increased body core temperature (vegetative arousal), which are blunted by TMN lesions (Valdes et al. 2005; Valdes et al. 2010). In addition, the activation level of the histaminergic system mirrors the arousal state and the intensity of efforts to obtain food in 24-h fasted rats (Valdes et al. 2010; Riveros et al. 2019). These results raise the hypothesis that histamine increases arousal to energize efforts in the appetitive phase of feeding.

The arousal induced by food enticement could also be shown as the general activation of cortex including the mPFC and orbitofrontal, sensory, and motor cortices (Valdes et al. 2010). It is well established that cortical arousal requires a collection of wake-active nuclei in the so-called AAS including the TMN, LH, the ventral tegmental area (VTA), the locus coeruleus (LC), and the dorsal raphe (DR). Interestingly, TMN has been proved to be the earliest activated nucleus in food enticement followed by delayed responses of other AAS nuclei including the LH and DR (Valdes et al. 2010). However, forced wakefulness by noises was found to trigger the release of serotonin rather than histamine in the mPFC, implying the involvement of the LC or VTA in forced arousal (Riveros et al. 2015). These findings suggest that AAS nuclei are hierarchically recruited in response to different external stimuli, and that histaminergic neurons are crucial to arousal induction in feeding motivation (Fig. 2b).

Meal anticipation in restricted-fed (training for 2 weeks with food availability from 22:00 to 24:00 h) rats was found to trigger neural activation in the ARC, which could be abolished by systematic administration of H1 receptor antagonists (diphenhydramine and mepyramine), suggesting that the ARC may also serve as a downstream target of histaminergic neurons in feeding motivation (Umehara et al. 2011). By employing optogenetics and chemogenetics techniques, recent studies have revealed that Agouti-related protein (AGRP) neurons, a group of hunger-activated orexigenic neurons in the ARC, are also required for motivated behaviors (Atasoy et al. 2012; Sternson 2013; Betley et al. 2015). The rapid reduction of AGRP neuron activity by food consumption indicates that they are primarily involved in the appetitive rather than consumption phase (Betley et al. 2015). More importantly, photo-stimulation of AGRP neurons decreases the preference for the flavor favored before conditioning, indicating that the activation of AGRP neurons transmit a negative-valence teaching signal about hunger to maintain the intensity of feeding motivation (Betley et al. 2015; Sternson 2016). Similarly, H1 receptor depletion was found to increase methamphetamine-induced conditioned place preference, while morphine-induced conditioned place preference was stronger in $HDC^{-/-}$ mice (Takino et al. 2009; Gong et al. 2010), implying that histamine may also transmit a negative-valence signal that regulates motivated behaviors. Collectively, these observations suggest that the histamine-induced arousal during food-seeking could also be an outcome of the TMN-ARC axis other than the AAS activation (Fig. 2b).

As mentioned above, increased body core temperature is a characteristic of histamine-induced arousal in feeding motivation (Valdes et al. 2005; Valdes et al. 2010). Histaminergic regulation of thermogenesis heavily relies on projections to the POAH (Yasuda et al. 2004). Recently, the medial preoptic area (MPON), a

subregion within the POAH, was shown to play an essential role in prey-seeking and hunting-like actions (Park et al. 2018). Thus, the histaminergic circuit from the TMN to the POAH may also be related to feeding motivation, although the POAH is dispensable for histamine-mediated satiety (Ookuma et al. 1993).

When it comes to arousal, the histaminergic system is a major output of LH orexinergic neurons for arousal induction (Huang et al. 2001; Mochizuki et al. 2011; Yoshikawa et al. 2021). However, the delayed activation of LH orexinergic neurons after food enticement suggests that LH may not be the upstream input of histaminergic neurons in feeding motivation (Valdes et al. 2010). Given the food anticipation in restricted-fed rats, it is highly possible that a food-entrainable circadian oscillator is involved in the regulation of the histaminergic system in motivated behaviors (Inzunza et al. 2000; Meynard et al. 2005). The DMH, which is thought to be an essential food-entrainable circadian pacemaker, may be a candidate upstream modulator of histaminergic neurons (Gooley et al. 2006; Mieda et al. 2006). The infralimbic (IL) cortical area has been found to mediate the activity of histaminergic neurons involved in the induction of circadian oscillator-independent feeding motivation, as shown by suppressed behavioral arousal and decreased activation of the TMN after generation of IL lesions (Valdes et al. 2006). Since the mPFC, which consists of the prelimbic and IL cortex areas, also serves as a downstream target of histaminergic neurons in feeding motivation (Riveros et al. 2014; Riveros et al. 2015), there possibly exists a positive feedback loop between the TMN and the mPFC, which holds particular significance for survival from starvation by maintaining the intensity of arousal and food seeking (Fig. 2b).

1.3 Histamine in Food Taste Perception and Memory

As mentioned above, the histaminergic system responds differentially to hard and soft diets (Fujise et al. 1998; Ishizuka et al. 2010). In addition to texture, taste also influences histamine release. Aversive tastants such as HCl and quinine elicit the release of histamine in the anterior hypothalamus, whereas the sweeteners induce a delayed reduction of extracellular histamine in the same region (Treesukosol et al. 2003, 2005). After rats are conditioned with a sweet solution paired with an injection of LiCl to produce a taste aversion, re-exposure to sweeteners increases histamine release (Treesukosol et al. 2005; Ishizuka and Yamatodani 2012), indicating that histaminergic activity is modulated by the palatability of tastants rather than merely chemical stimulation.

Nevertheless, the significance of histamine-mediated taste perception is not settled. Given the role of histamine in satiation, the reduction in the release of histamine by sweeteners may prolong the consumption phase of a meal and lead to the overconsumption of sweet food; however, this hypothesis needs further confirmation by abolishing histaminergic signaling and evaluating the effects on the consumption of palatable food. Interestingly, histamine seems not only to decide the ongoing meal but also to affect future food choices. The histaminergic system

was reported to tune the acquisition and retrieval of taste aversive memory through its regulation of cholinergic release in the insular cortex (Puron-Sierra and Miranda 2014). These observations give birth to another assumption whereby the fluctuation in histamine release induced by different foods may serve as a cue for the formation of the corresponding taste memories, and thus may further contribute to food preference and direct food choices.

There is limited knowledge of the neural circuits involved in histamine-mediated taste perception and memory. The chorda tympani, a key oral sensor of chemicals, may be an important source of input to histaminergic neurons involved in taste perception, as its transection attenuates the increase of histamine release elicited by tastants (Treesukosol et al. 2003). On the other hand, the histaminergic projections emanating from the TMN to the nucleus basalis magnocellularis (NBM) engage in taste memory (Puron-Sierra and Miranda 2014).

1.4 Histamine in Feeding Circadian Rhythm

Feeding is under the control of circadian rhythmicity which synchronizes the behaviors and visceral functions to food availability (Segers and Depoortere 2021). Electrophysiological data has shown that the histaminergic neuronal activity correlates with the arousal state with a higher firing rate during the wake than the sleep period (Vanni-Mercier et al. 1984; Szymusiak et al. 1989; Sakai et al. 1990; Krilowicz et al. 1994; Steininger et al. 1999). Thus, histaminergic neurons show higher activity at night in rodents but, in humans, they are more active in the daytime (Haas et al. 2008). Consistent with the circadian pattern of the histaminergic neuronal activity, the activity of hypothalamic HDC peaks at night and decreases during daylight hours (Orr and Quay 1975a, b). Moreover, in the hypothalamus of freely-moving rats, the average extracellular histamine level in the dark phase is significantly higher than that in the light phase (Mochizuki et al. 1992), but the total amount of histamine in the hypothalamus peaks in the early light phase (Orr and Quay 1975a, b), which may result from the high activity of HDC throughout the night. The observation of circadian variation in hypothalamic histamine concentration has led to the assumption that histamine might play a role in feeding rhythm. Supporting this hypothesis, sustained infusion of α-FMH or H1 receptor antagonist chlorpheniramine into the third cerebral ventricle of rats fed ad libitum increases diurnal food intake but suppresses feeding at night, resulting in flattened fluctuation of food intake (Doi et al. 1994). Similarly, depletion of the H1 receptor in aged mice specifically promotes the food consumption in the daytime, leading to the increased ratio of light/night food intake (Masaki et al. 2004). More intriguingly, the disruption of feeding rhythm occurs much earlier than the onset of hyperphagia and obesity in *Hrh1*$^{-/-}$ mice (Masaki et al. 2004; Yoshimatsu 2008). Re-setting the feeding rhythm by scheduled feeding corrects hyperphagia and leads to bodyweight reduction in obese *Hrh1*$^{-/-}$ mice (Masaki et al. 2004; Yoshimatsu 2008), reflecting the fundamental role of histamine-mediated feeding rhythm in obesity.

The hypothalamic suprachiasmatic nucleus (SCN), the master regulator of the mammalian circadian clock, is considered to be one candidate for the downstream target of histamine in feeding rhythm control (Doi et al. 1994). In agreement with this assumption, the SCN is innervated by histaminergic neurons (Watanabe et al. 1984) and infusion of histamine into the SCN reduces daily food consumption in rats fed ad libitum (Itowi et al. 1988). Furthermore, histamine alters the firing rates of SCN neurons (Liou et al. 1983; Scott et al. 1998) and induces a circadian phase-shift of SCN neural activity in rodent hypothalamic slices (Cote and Harrington 1993; Meyer et al. 1998; Biello 2009; Kim et al. 2015). By contrast, intracerebroventricular α-FMH infusion only reduces the amplitude of feeding rhythm in rats fed ad libitum, but fails to shift the circadian feeding cycle as it does in ambulatory rhythm regulation (Doi et al. 1994). In addition, accumulated evidence demonstrates that the SCN is dispensable for the entrainment of daily feeding cycles (Mistlberger 2020; Power and Mistlberger 2020). These results indicate that the SCN may be more involved in the sleep-wake cycle than in feeding rhythm mediated by histamine. Since HDC deletion disrupts the mRNA expression rhythms of clock genes such as Per1/2 and MAL1 in the cortex and striatum rather than in the SCN (Abe et al. 2004), these regions might contain downstream circuits involved in histamine-mediated feeding rhythm. Further investigations are needed to uncover how histaminergic neurons and downstream targets coordinate feeding rhythm.

2 Histamine Receptors in Feeding

Histamine fulfills its functions through the activation of four different histamine receptors (H1–H4 receptors), which belong to the G protein-coupled receptor family. H3 receptors primarily reside in the CNS, while the other three receptors are present both centrally and peripherally. In the brain, the H1 and H2 receptors are predominantly expressed at the post-synapses in almost all brain regions. However, the expression profile of H3 receptors is much more complicated (Panula and Nuutinen 2013). H3 receptors were initially found to serve as auto-receptors in the pre-synapses of histaminergic neurons and to negatively regulate histamine release. Further studies have revealed that H3 receptors are also located pre-synaptically in non-histaminergic neurons where they mediate the release of various neurotransmitters, such as glutamate, γ-aminobutyric acid (GABA), acetylcholine, and noradrenaline (Schlicker et al. 1994; Giorgetti et al. 1997; Yamamoto et al. 1997). H3 receptors also function as post-synaptic receptors in some brain regions such as the cortex and striatum (Ellenbroek and Ghiabi 2014; Yan et al. 2014). The expression pattern of H4 receptors in the brain is still controversial and their functions in the CNS are less clear. In the following section, we summarize the roles of histamine receptors in feeding behaviors (Table 1) and further discuss potential insights into feeding interventions in obesity and other feeding-related disorders.

Table 1 Main findings regarding the roles of histamine receptors in feeding

Receptors	Localization			Roles	Evidence	Ref.
	Nucleus	Neurons	Synapse			
H1	VMH	GRN &?	Post	Satiety	(1) Hyperphagia in H1$^{-/-}$ mice (2) Inhibition or depletion of the H1 receptor attenuates anorexia induced by satiety signals (3) Local H1 antagonism evokes feeding (4) H1 antagonism reduces the discharge rate of GRNs in brain slices	(Garbarg et al. 1980; Sakata et al. 1988a, b, c; Fukagawa et al. 1989; Ookuma et al. 1989; Lecklin et al. 1998; Morimoto et al. 1999; Yoshimatsu et al. 1999; Masaki et al. 2001, 2004; Mollet et al. 2001, 2003; Davidowa 2007; Gotoh et al. 2013)
	PVH	?	Post			
	mPFC	?	Post	Feeding motivation	(1) Food enticement increases exocellular histamine in the mPFC (2) Central H1 antagonism decreases efforts to obtain a food reward	(Valdes et al. 2006; Riveros et al. 2019)
	ARC	?	Post		Systematic H1 antagonism inhibits ARC activation induced by food anticipation	(Umehara et al. 2011)
	?	?	Post	Feeding rhythm	Feeding dysrhythmias in H1$^{-/-}$ mice	(Masaki et al. 2004; Masaki and Yoshimatsu 2006)
	NBM	ChAT	Post	Taste memory	Local H1 antagonism suppresses ACh release and impairs taste aversion memory	(Puron-Sierra and Miranda 2014)
H2	/	/	/	None	(1) Central H2 antagonism fails to alter food intake (2) Food intake	(Sakata et al. 1988c; Fukagawa et al. 1989;

(continued)

Table 1 (continued)

Receptors	Localization			Roles	Evidence	Ref.
	Nucleus	Neurons	Synapse			
					and body weight is unchanged in $H2^{-/-}$ mice	Lecklin et al. 1998)
	?	?	Post	Satiety	Systematic H2 antagonism abolishes the anorexigenic effect of cholecystokinin	(Attoub et al. 2001)
	MPON	Glu	Post	Feeding motivation?	(1) H2 agonism increases the firing rate of glutamatergic neurons in MPON slices (2) Glutamatergic neurons in the MPON facilitate hunting-like behaviors	(Tabarean et al. 2012; Park et al. 2018)
H3	?	HA	Pre	Satiety	Systematic or central H3 antagonism reduces food intake	(Ookuma et al. 1993; Ghoshal et al. 2018; Kotanska et al. 2019; Kumar et al. 2019)
	?	Non-HA	Pre?	Satiety	Systematic H3 agonism reduces food intake but increases central dopamine and norepinephrine metabolites levels	(Yoshimoto et al. 2006)
	Insular cortex	GABA	Post	Taste memory	(1) Local H3 agonism inhibits taste aversion memory and Ach release (2) The impairment of Ach release is alleviated by local $GABA_A$ receptor antagonism	(Giorgetti et al. 1997; Puron-Sierra and Miranda 2014)
H4	?	?	?	?	(1) Hyperphagia in $H4^{-/-}$ mice (2) Systematic H4	(Sanna et al. 2017;

(continued)

Table 1 (continued)

Receptors	Localization			Roles	Evidence	Ref.
	Nucleus	Neurons	Synapse			
					antagonism blunts cisplatin-induced anorexia in mice	Yamamoto et al. 2019)

ChAT cholinergic neurons, *Glu* glutamatergic neurons, *HA* histaminergic neurons, *Non-HA* non-histaminergic neurons, *GABA* GABAergic neurons

2.1 Histamine H1 Receptor: A Putative Downstream Target

A putative molecular mechanism underlying histamine-mediated feeding is the activation of H1 receptors. Central antagonism of H1, but not H2 receptors, elicits feeding (Sakata et al. 1988a, b, c; Fukagawa et al. 1989; Lecklin et al. 1998). Moreover, H1 knockout mice gradually exhibit hyperphagia during aging and develop mature-onset obesity. However, an abnormal feeding rhythm, characterized by the shift of food consumption into the daytime, precedes the phenotype of hyperphagia, highlighting the role of H1-regulated feeding rhythm in the development of obesity (Masaki et al. 2004; Masaki and Yoshimatsu 2006). As the major downstream circuits of histamine-regulated feeding rhythm are still unresolved, the mechanisms underlying feeding dysrhythmias after H1 deletion remain to be elucidated.

The hyperphagia in H1 knockout mice may be an outcome of reduced satiety since the daily meal frequency also seems to be increased by H1 depletion (Masaki et al. 2004). In line with these observations, inhibition or depletion of the H1 receptor attenuates anorexia induced by peripheral satiety signals including leptin (Morimoto et al. 1999; Yoshimatsu et al. 1999; Masaki et al. 2001), amylin (Mollet et al. 2001, 2003; Davidowa 2007), and nesfatin-1 (Gotoh et al. 2013). What's more, microinjection of an H1 antagonist (chlorpheniramine) into the hypothalamic satiety center (VMH or PVH) evokes feeding, which cannot be recapitulated by the inhibition of H1 receptors in other hypothalamic subregions including the LH, DMH, or POAH (Ookuma et al. 1989). The H1 antagonist chlorpheniramine reduces the discharge rate of glucose-responding neurons in the VMH (Fukagawa et al. 1989). Since glucose-responding neurons are crucial for energy-sensing and glucose homeostasis regulation by the VMH (Chan and Sherwin 2013), these results indicate that the H1 receptor may regulate satiety by affecting energy-sensing in the VMH (Fukagawa et al. 1989), which is in agreement with our previously stated assumption that the role of histamine in satiety and satiation relies on the energy state.

H1 receptors are also the main drivers of histamine-mediated feeding motivation, as shown by the diminished efforts to obtain a food reward after the infusion of H1 antagonist (pyrilamine) into lateral ventricles of 24-h fasted rats (Riveros et al. 2014). The mPFC may be where H1 receptors work since food enticement but not loud noise awakening specifically increases histamine concentration in the mPFC of 24-h fasted rats (Riveros et al. 2015). In addition, H1 antagonism by

diphenhydramine or mepyramine inhibits ARC activation induced by food anticipation in rats under a restricted feeding schedule (Umehara et al. 2011), indicating that H1 receptors in the ARC may also be involved in feeding motivation.

Local infusion of the H1 receptor antagonist pyrilamine into the NBM suppresses acetylcholine (Ach) release in the insular cortex and simultaneously impairs taste aversion memory (Puron-Sierra and Miranda 2014), indicating that histamine mediates taste memory through the activation of H1 receptors in the NBM.

2.2 Histamine H2 Receptor: A Dispensable Receptor for Feeding?

H2 receptors are presumed to be dispensable for feeding behaviors because there are several lines of evidence showing that central antagonism of the H2 receptor (intracerebroventricular infusion of famotidine or cimetidine) fails to affect food consumption (Sakata et al. 1988c; Fukagawa et al. 1989; Lecklin et al. 1998). Similarly, neither food intake nor body weight was found to be altered by H2 depletion in mice (Kobayashi et al. 2000). However, systematic H2 receptor antagonism by ranitidine abolishes the anorexigenic effect of cholecystokinin in the restricted-fed rats (with food availability from 10:00 to 17:00 h), indicating that the H2 receptor may be involved in histamine-induced satiety (Attoub et al. 2001). More surprisingly, another H2 antagonist, cimetidine, has been reported to suppress appetite and induce body weight loss in overweight adults (Stoa-Birketvedt 1993; Stoa-Birketvedt et al. 1998). Thus, after excluding the unperceived pharmacological effects of the H2-targeting compounds, the functions of the H2 receptor could be much more complicated than originally supposed. As discussed above, the MPON may be orchestrated in the downstream histaminergic circuits underlying feeding motivation. In the MPON, histamine seems to selectively activate H2 receptors rather than H1 receptors to induce hyperthermia (Tabarean et al. 2012). Interestingly, H2 receptors influence the activity and firing of glutamatergic neurons, but not GABAergic neurons, in the MPON during thermoregulation (Tabarean et al. 2012). Similarly, the photo-stimulation of a subpopulation of glutamatergic neurons in the MPON has been reported to facilitate hunting-like behaviors without the requirement for activity of GABAergic neurons in the same area (Park et al. 2018). In light of the finding that histamine induces vegetative arousal during food anticipation, it is likely that H2 receptors participate in feeding motivation in a cell type-specific manner (Table 1). Given these findings, it will be of great significance to re-examine the feeding-related roles of H2 receptors in the scale of a single cell type.

2.3 Histamine H3 Receptor: A Unique Mechanism Involved?

Given the roles of H3 receptor as an auto-receptor, it is reasonable to believe that it participates in feeding behaviors through the regulation of histamine release and subsequent activation of post-synaptic H1 receptors; this notion is supported by the observation of reduced food consumption after H3 receptor antagonism (Ookuma et al. 1993; Ghoshal et al. 2018; Kotanska et al. 2019; Kumar et al. 2019). However, in contrast with previous studies, systematic administration of the H3 receptor agonist imetit was also reported to decrease daily food intake (Yoshimoto et al. 2006) and depletion of the *Hrh3* gene was found to lead to hyperphagia and obesity (Takahashi et al. 2002). Moreover, the hyperphagia phenotype of *Hrh3*$^{-/-}$ mice, characterized by an increase in nocturnal food intake, was found to occur earlier than that in *Hrh1*$^{-/-}$ mice who consume more food during the daytime (Takahashi et al. 2002; Masaki et al. 2004). These findings have suggested the possibility of other molecular mechanisms underlying H3 receptor-mediated feeding besides regulation of histamine release.

Indeed, H3 receptors are abundantly expressed outside the TMN as either heteroreceptors or post-synaptic receptors. It has been reported that imetit-induced anorexia in diet-induced obese mice (*at libitum* fed) is not correlated with histamine release (Yoshimoto et al. 2006). By contrast, imetit suppresses feeding simultaneously with the fluctuation of central dopamine and norepinephrine metabolites levels (Yoshimoto et al. 2006), implying a potential heteroreceptor-related mechanism. Local agonism means selective activation of H3 receptors of insular cortex by only injecting the agonist in this area rather than systematic administration (Puron-Sierra and Miranda 2014). Based on the observations that H3 receptors are mainly expressed in the GABAergic neurons of the insular cortex and that the impairment of Ach release could be alleviated by local $GABA_A$ receptor antagonism (Giorgetti et al. 1997), H3 receptors may serve as post-synaptic receptors when modulating taste memory. At post-synapses, H3 receptors also heterodimerize with both the dopamine D1 and D2 receptors and alter dopaminergic signaling transduction (Ryu et al. 1994; Ferrada et al. 2009; Moreno et al. 2011). Given that dopamine determines the reward value of food, the post-synaptic H3 receptors may be required for feeding motivation. Thus, extensive investigations are encouraged to illuminate the feeding-related roles of the H3 receptor in non-histaminergic neurons (Table 1).

2.4 Histamine H4 Receptor: A Receptor Awaiting Exploration

Limited evidence to date has suggested the potential anorexigenic actions of the H4 receptor. H4 receptor deficiency increases 1-h food consumption after 4-h food deprivation in mice (Sanna et al. 2017) and subcutaneous injection of the H4 receptor antagonist JNJ7777120 blunts cisplatin-induced anorexia in mice fed at

libitum (Yamamoto et al. 2019). Nevertheless, the detailed characteristics of H4-mediated feeding behaviors and the underlying mechanisms still remain to be determined (Table 1).

2.5 Clinical Trials of Chemicals Targeting Histaminergic Receptors

Weight gain has been identified as a major adverse effect of second-generation antipsychotic drugs (SGA), such as risperidone, clozapine, and olanzapine. The weight gain induced by these drugs is highly correlated with their binding affinity for the H1 receptor (He et al. 2013; Luo et al. 2019), highlighting the possibility of weight control in human beings by targeting the histaminergic system. Supporting this hypothesis, betahistine, a histamine analog with both H1 receptor agonistic and H3 receptor antagonistic effects, has been shown to be effective in preventing weight gain in schizophrenic patients prescribed with SGA drugs (Table 2). Moreover, betahistine has an impressive safety profile when used as a therapy for vestibular disorders such as Ménière's disease and the symptomatic treatment of vertigo (James and Burton 2001; Jeck-Thole and Wagner 2006).

However, in non-schizophrenic populations with/without a high body mass index (BMI), betahistine together with other histamine-related agents fails to induce a weight change in most clinical trials (Table 2). Although the unsatisfactory outcomes may result from the poor blood-brain barrier penetration of H1/H2 receptor-targeting compounds, numerous clinical trials assessing anti-obesity pharmacological actions of H3 antagonists, which show higher CNS availability, have also been aborted and ended up without results disclosed (Provensi et al. 2016). The heterogeneous phenotypes caused by unhealthy eating may explain the varying outcomes in human beings. Some obese patients show a general reduction in satiety with higher susceptibility to hunger while others encounter uncontrollable episodes of compulsive eating even when they feel full. In addition, a portion of the population shows an overwhelming attraction to energy-dense foods such as high-fat foods and dessert (Hebebrand et al. 2014). These hyperreactions to certain kinds of food share some similarities with addiction. Consistent with these similarities, food addiction occurs more often in patients with obesity and binge eating disorder (Pedram et al. 2013; Albayrak et al. 2017). Feeding dysrhythmias also contribute along with dietary structure to high BMI in humans (Muscogiuri et al. 2020). Taken together, results from previous studies suggest that abnormal changes in body weight can stem from distinct eating habits and that effective body weight management must be based on the precise regulation of various feeding behaviors. Despite the multiple functions of histamine in feeding, the best strategy to achieve the precise regulation of certain feeding behaviors is still not clear. Thus, extensive investigations are needed to accelerate the clinical transformation of histamine receptor-related compounds.

Table 2 Main clinical studies regarding the impacts of histamine-related compounds on weight control

Drug	Target	Population	Characteristics	Duration	Treatment	Food intake	BW vs. baseline	ΔBW vs. placebo	BMI vs. baseline	ΔBMI vs. placebo	Ref.
Betahistine	H1&H3	Diagnosed with schizophrenia or bipolar disorder	18–55 years ♀ 17 ♂25 BMI = 25.23 ± 2.33	12 weeks	Placebo + SGA ($n = 29$) Betahistine (36 mg/day) + SGA ($n = 13$)	/	/	Less**	/	Less**	(Kang et al. 2018)
Betahistine	H1&H3	Treated with antipsychotic medications	30 ± 12.8 years ♀ 27 ♂24 BMI = 32.9 ± 6.0	12 weeks	Placebo + Olan/Cloz ($n = 22$) Betahistine + Olan/Cloz ($n = 29$) 0–2 weeks: 8–48 mg/day 2–12 weeks: 48 mg/day (US) 0–2.5 weeks: 8–36 mg/day 2.5–12 weeks: 36 mg/day (China)	/	/	Less**	/	Less**	(Smith et al. 2018)
Betahistine	H1&H3	Diagnosed with schizophrenia, schizoaffective disorder, schizophreniform disorder, or a psychotic disorder	16–45 years ♀ 10 ♂25 18.5 < BMI < 35	16 weeks	Placebo + Olan ($n = 20$) Betahistine (48 mg/day) + Olan ($n = 15$)	/	/	NS	/	/	(Barak et al. 2016a)
Betahistine	H1&H3	Healthy females	18–45 years ♀46 16.8 < BMI < 27	4 weeks	Days 1–7: Placebo ($n = 22$) Betahistine (144 mg/day) ($n = 24$) Days 8–14: Placebo + Olan Betahistine (144 mg/day) + Olan Days 15–28: Olan only	/	/	Less*	/	/	(Barak et al. 2016b)

Betahistine	H1&H3	Diagnosed with schizophrenic disorder	16–45 years ♀8 ♂35 18.5 < BMI < 35	6 weeks	Placebo + Olan ($n = 14$) Betahistine (144 mg/day) / Reboxetine (8 mg/day) + Olan ($n = 29$)	/	/	Less**	/	Less**	(Poyurovsky et al. 2013)
Betahistine	H1&H3	Obese female	18–70 years ♀76 30 < BMI < 40	1 day	Placebo ($n = 19$) Betahistine (48 mg/day) ($n = 19$) Betahistine (96 mg/day) ($n = 17$) Betahistine (144 mg/day) ($n = 21$)	NS	/	/	/	/	(Ali et al. 2010)
Betahistine	H1&H3	Obese adults	18–65 years ♀ + ♂ = 234 30 < BMI < 40	12 weeks	Placebo ($n = 63$) Betahistine (16 mg/day) ($n = 55$) Betahistine (32 mg/day) ($n = 58$) Betahistine (48 mg/day) ($n = 58$)	/	/	NS	/	NS	(Barak et al. 2008)
Betahistine	H1&H3	Hospitalized for a first episode of schizophrenic disorder	22 ± 1.7 years ♂3 BMI = 22.2 ± 4.0	6 weeks	Betahistine (144 mg/day) + Olan ($n = 3$)	/	<7%	/	/	/	(Poyurovsky et al. 2005)
Ranitidine	H2	Diagnosed with a first episode of schizophrenic disorder	18–60 years ♀8 ♂67 BMI < 30	8 weeks	Placebo + Olan ($n = 25$) Ranitidine (150 mg/day) + Olan ($n = 25$) Ranitidine (300 mg/day) + Olan ($n = 25$)	/	/	NS	/	NS	(Mehta and Ram 2016)

(continued)

Table 2 (continued)

Drug	Target	Population	Characteristics	Duration	Treatment	Food intake	BW vs. baseline	ΔBW vs. placebo	BMI vs. baseline	ΔBMI vs. placebo	Ref.
Nizatidine	H2	Diagnosed with schizophrenia, schizoaffective disorder, or schizophreniform disorder	18–65 years ♀22 ♂32 BMI < 40	12 weeks	Placebo + Olan ($n = 27$) Nizatidine (300 mg/day) + Olan ($n = 27$)	/	/	NS	/	NS	(Assuncao et al. 2006)
Famotidine	H2	Hospitalized for a first episode of acute psychosis	40–65 years ♀5 ♂9 BMI < 30	6 weeks	Placebo + Olan ($n = 7$) Famotidine (40 mg/day) + Olan ($n = 7$)	/	/	NS	/	NS	(Poyurovsky et al. 2004)
Nizatidine	H2	Diagnosed with schizophrenia	28.7 ± 8.8 years ♀14 ♂21 BMI = 26.8 ± 1.7	8 weeks	Placebo + Olan ($n = 17$) Nizatidine (300 mg/day) + Olan ($n = 18$)	/	Less*	Less*	Less*	Less*	(Atmaca et al. 2003)
Nizatidine	H2	Diagnosed with schizophrenia, schizoaffective disorder, or schizophreniform disorder	18–65 years ♀ + ♂ = 169 BMI < 40	16 weeks	Placebo + Olan ($n = 56$) Nizatidine (300 mg/day) + Olan ($n = 56$) Nizatidine (600 mg/day) + Olan ($n = 57$)	/	/	NS	/	NS	(Cavazzoni et al. 2003)

Cimetidine	H2	Overweight adults with type 2 diabetes	18–65 years ♀14 ♂29 $27.2 < \text{BMI} < 48.2$	12 weeks	Placebo ($n = 24$) Cimetidine (1,200 mg/day) ($n = 19$)	/	Less*	Less*	Less*	/	(Stoa-Birketvedt et al. 1998)
Cimetidine	H2	Overweight adults	18–59 years ♀55 ♂5 $25 < \text{BMI} < 37$	8 weeks	Placebo ($n = 30$) Cimetidine (600 mg/day) ($n = 30$)	Reduced hunger	/	Less***	/	Less***	(Stoa-Birketvedt 1993)

BW body weight, *BMI* body mass index, *ΔBW* body weight change, *ΔBMI* body mass index change, *Ref* references, *SGA* second-generation antipsychotic drugs, *Olan* olanzapine, *Cloz* clozapine, ♀: female, ♂: male, /: not investigated in the trial, *NS* not significant compared with the indicated group
$^*p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$

3 Functional Diversity of Histamine: What Shall We Do Next?

3.1 *Diverse Functions of Histamine in Different Phases of Feeding*

Evidence so far has supported the notion that histamine plays more important roles in the appetitive and termination phases of feeding. On the one hand, histamine can suppress feeding by promoting satiation and satiety. On the other hand, when feeding is highly motivated (e.g., in the energy-deficient state), histamine also serves as an arousal inducer to drive motivated behaviors toward food rewards as it does for other motivated behaviors such as drinking, mating, or drug seeking (Torrealba et al. 2012; Contreras et al. 2016). In the physical conditions, however, histamine does not seem to participate in drinking regulation (Ookuma et al. 1993; Lecklin et al. 1998). Collectively, histaminergic system goes through dynamic functional switching in response to food-related cues (Fig. 3a).

Compared to the other two phases, the contribution of histamine to the consumption phase is less clear (Riveros et al. 2019). Given the role of histamine in taste perception and memory, it is reasonable to assume that histamine also engages in the consumption phase. However, pharmacological inhibition of histamine synthesis (α-FMH) or inhibition of H1 receptors (chlorpheniramine) in the LH, a putative driver of the consumption phase (Betley et al. 2015; Sternson 2016), fails to affect feeding (Ookuma et al. 1989; Ookuma et al. 1993). Interestingly, the cell types in the LH are highly heterogeneous and cell type-specific activation of inhibitory neurons, but not the entire neural population in the LH, evokes feeding (Jennings et al. 2013, 2015). Thus, it is possible that the effects of histamine on different LH neurons counteract each other. Taken together, the functions of histamine in different phases of feeding may be worth re-verifying using cell type-specific neural circuit tracing and manipulating techniques, such as optogenetics and chemogenetics (Fig. 3b).

3.2 *Circuit Basis for the Functional Switching of Histamine in Feeding*

Exhaustive studies have emphasized the functions of histaminergic projections to VMH and PVH in feeding, however, the limited outputs mismatch the functional diversity of histamine. Morphological evidence shows that histaminergic neurons in the TMN are divided into five subgroups (E1–E5). Food anticipation in restricted-fed rats was found to specifically induce the activation of E3 subgroups (Umehara et al. 2011), while E2 histaminergic neurons seemed to be more related to food consumption during the dark phase (Ujita et al. 2016). Stress challenges, such as restraint and foot shook, exclusively activate the E4–E5 subgroups (Miklos and Kovacs 2003). Moreover, the histaminergic projections to the mPFC and dorsal

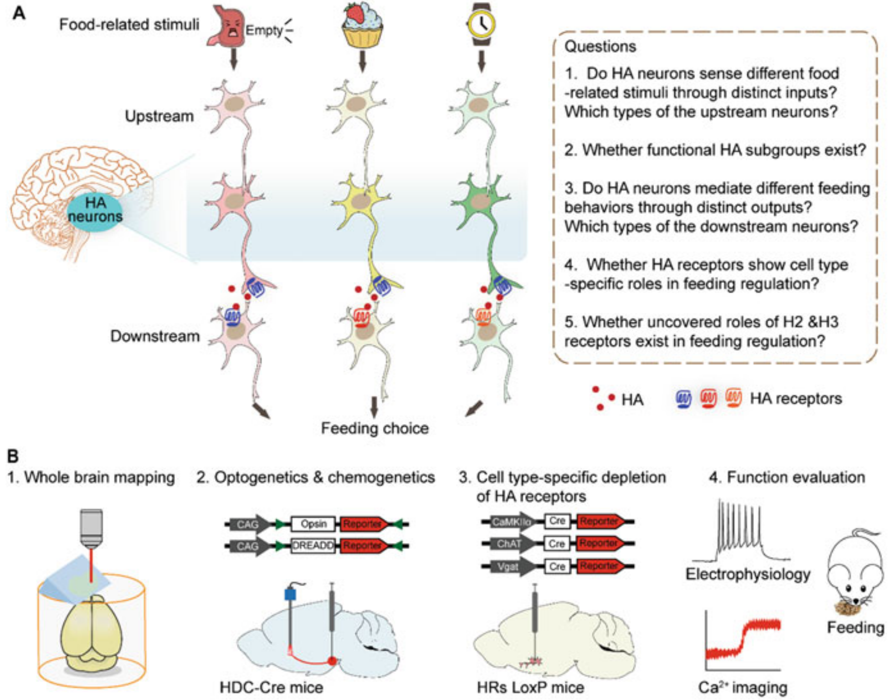

Fig. 3 Perspectives on future research into the role of histamine in feeding. (**a**) Evidence to date implies the existence of functional subpopulations of histaminergic neurons. These subgroups may sense distinct stimuli through discrete upstream inputs and respond to food cues by projecting to different brain areas. To verify this assumption, many questions need to be answered. (**b**) For addressing these issues, the following attempts are encouraged: (1) high-resolution visualization of three-dimensional histaminergic circuits in the whole brain with novel microscope technologies such as fMOST, (2) dissection of single histaminergic circuits with optogenetics or chemogenetics in mice expressing opsin or DREADD in histaminergic neurons. (3) examination of the roles of histamine receptors after selective depletion of histamine receptors in different neural types (for example, CaMKIIα: glutamatergic neurons, ChAT: cholinergic neurons, Vgat: GABAergic neurons) with the Cre-LoxP system, (4) evaluation of behavioral phenotypes and detection of neuronal activities using electrophysiology or Ca^{2+} imaging based on the manipulations above. DREADD, designer receptors exclusively activated by designer drugs, HA: histamine, HA receptors: histamine receptors, HR LoxP mice: transgenic mice with LoxP sites inserted around the gene encoding a particular histamine receptor

striatum produce disparate effects on locomotor and repetitive behaviors (Rapanelli et al. 2017). Collectively, there possibly exist the histaminergic subgroups sensing different food-related cues and mediating discrete feeding behaviors through separate outputs (Fig. 3a). However, morphological data to date doesn't support the biased projections of histaminergic subpopulations (Kohler et al. 1985; Ericson et al. 1987; Inagaki et al. 1990). A higher-resolution visualization of three-dimensional histaminergic circuits in the whole brain with novel microscope technologies such as fluorescent micro-optical sectioning tomography (fMOST) may allow the

visualization of histaminergic connections in more detail and shed light on the uncovered circuit mechanisms underlying the functional switching of histamine in feeding (Fig. 3b).

3.3 Precise Regulation of Feeding Behaviors Through Histamine Receptors

The functional diversity of histamine makes it a viable target for feeding behavior regulation in treatment of obesity and other feeding-related disorders. However, targeting histamine receptors generally in the brain does not seem to be a wise choice, as the functional diversity of histamine also appears to be a "double-edged sword" and the disparate histaminergic circuits could interplay with each other resulting in the net energy intake remaining unchanged. Illuminating the cell type-specific roles of histamine receptors through a combination of spatiotemporally specific gene-editing technologies and various functional analyses will help to uncover novel biological and pathological functions of histamine receptors (Cheng et al. 2021; Jiang et al. 2021) (Fig. 3b) and provide insight into the development of compounds or dosage forms selectively targeting certain histamine receptors in specific cells.

4 Conclusions

In summary, histamine is undoubtedly a crucial mediator of feeding with a wide range of functions. In the termination phase, histamine is required for both satiation and satiety and prevents further eating. As satiety diminishes, histamine switches its role to driving motivated behaviors geared toward obtaining food in the appetitive phase and organizing rhythmic food intake. In addition, histamine also participates in taste perception and memory during food consumption. However, the circuit basis for functional switching of histamine is unclear and the mechanisms of histamine receptors in feeding are still murky. Employing cutting-edge technologies, dissecting histaminergic circuits, and manipulating histamine receptors in a more spatiotemporally selective manner will help to address these issues and shed light on clinical strategies for the precise regulation of feeding behaviors.

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Conflict of Interests The authors declare that there are no conflicts of interest.

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A Duet Between Histamine and Oleoylethanolamide in the Control of Homeostatic and Cognitive Processes

Gustavo Provensi, Alessia Costa, Barbara Rani, Patrizio Blandina, and M. Beatrice Passani

This article is dedicated to Ivan Izquierdo to whom we owe immense gratitude for his guidance in science and life.

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Abstract In ballet, a *pas de deux* (in French it means "step of two") is a duet in which the two dancers perform ballet steps together. The suite of dances shares a common theme of partnership. How could we better describe the fine interplay between oleoylethanolamide (OEA) and histamine, two phylogenetically ancient molecules controlling metabolic, homeostatic and cognitive processes? Contrary to the *pas de deux* though, the two dancers presumably never embrace each other as a dancing pair but execute their "virtuoso solo" constantly exchanging interoceptive messages presumably via vagal afferents, the blood stream, the neuroenteric system. With one exception, which is in the control of liver ketogenesis, as in hepatocytes, OEA biosynthesis strictly depends on the activation of histaminergic H_1 receptors. In this review, we recapitulate our main findings that evidence the interplay of

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histamine and OEA in the control of food consumption and eating behaviour, in the consolidation of emotional memory and mood, and finally, in the synthesis of ketone bodies. We will also summarise some of the putative underlying mechanisms for each scenario.

Keywords Appetite · Ketogenesis · Memory

1 Introduction

Nature selects physiological mechanisms that optimise homeostatic processes and behavioural responses to ensure survival under changing environmental conditions. As an example, multiple lipid-sensing mechanisms exist throughout the mammalian body to convey information to the central nervous system on the energetic status and food palatability. At the other end, brain circuits originating in the ancestral part of the brain, the hypothalamus, and involving several neuromodulators orchestrate the appropriate behaviour to secure the appropriate energy balance in abundance and scarcity of food. For animals, and our ancestors, foraging in the wild is advantageous to remember contextual cues associated with food sources, such as their exact location and safety of access (Piomelli 2013). This requires a state of arousal that may enhance memory consolidation of aversive (encounter with a predator) or rewarding (palatable meal) experiences. This theory raised the possibility that hormonal and neural signals elicited by feeding might also enhance the consolidation of recent experiences.

The complex communication between the periphery and the central nervous system constitutes the gut-brain axis, linking emotional and cognitive brain centres with peripheral functions. Oleoylethanolamide (OEA) is one of the gut-derived lipid satiety factors relaying signals not only to brain structures, such as the hypothalamus to regulate feeding (Fu et al. 2003), but also to other brain structures to strengthen memory consolidation (Campolongo et al. 2009). OEA is also found in various tissues including the brain, immune cells, white adipose cells, hepatocytes and exerts its functions by binding to the nuclear peroxisome proliferator activated receptors (PPAR-α), cell-surface receptors such as the transient receptor potential cation channel vanilloid-1 (TRPV1) (Ahern 2003) and G-protein coupled receptor 119 (GPR119) (Overton et al. 2006). Some of OEA's functions in these districts have been described recently and will be addressed in the following chapters.

Histamine is one of the main actors in the allergic and inflammatory responses which have been described over a century ago when Lewis described the triple cutaneous response that now goes under his name. The central effects of hypothalamic histaminergic neurons activity, as well, are manifold and most likely depend on the selective activation of specific neuronal pathways (Blandina et al. 2012). Homeostatic functions such as thermoregulation, circadian rhythms, neuroendocrine

secretion are regulated by brain histamine. Neuronal histamine induces loss of appetite and has long been considered a satiety signal that is released during food consumption (Provensi et al. 2016). Since the pivotal work by de Almeida and Izquierdo in the 1980s (de Almeida and Izquierdo 1986) it has been unequivocally demonstrated that histaminergic brain circuits modulate the formation and retrieval of different types of memories, such as those associated with aversive events (Izquierdo et al. 2016; Provensi et al. 2020b) and is implicated with social (Garrido Zinn et al. 2016) (Rani et al. 2021b) and object recognition (da Silveira et al. 2013; Provensi et al. 2020a). Hence, there is abundant overlap of localisation and/or physiological functions in the brain and peripheral organs which are controlled or modulated by OEA and histamine.

With all these considerations in mind, we hypothesised that somehow histamine and OEA may work in a coordinated fashion, not only to organise specific behavioural responses that depend on the homeostatic state of a subject, e.g., stop eating when feeling satiated, but also to allocate the appropriate emotional value to different experiences. In the following chapters we provide evidence that indeed OEA and histamine are a molecular pair performing elaborate *movements* along with *virtuoso solo*. Our main interest is focused on the central actions of the two systems.

2 Virtuoso Solo of Brain Histamine

Histamine neurons reside in the tuberomammillary nucleus (TMN) of the hypothalamus, and it is becoming clear that the TMN acts as a hub for key circuitries that integrate sensory and homeostatic inputs; together with other neurotransmitter systems, the TMN contributes to comparing these inputs to "set points" for body temperature and energy homeostasis (Tabarean 2016), thirst (Magrani et al. 2006), sleep–wake cycle (Takahashi et al. 2006; Venner et al. 2019; Yoshikawa et al. 2021), energy expenditure (Yasuda et al. 2004), appetite and satiation (Masaki and Yoshimatsu 2006). Thermoregulation is a fundamental function of histamine signalling in the CNS that has been described in most organisms from invertebrates (Hong et al. 2006) to mammals (Tabarean et al. 2012) and involves H_1, H_2 and H_3 receptors. Other homeostatic functions of brain histamine inherent to the regulation of energy intake and expenditure include stimulation of the sympathetic nervous system to increase lipolysis in the adipose tissue (Bugajski and Janusz 1981). Furthermore, the adipocytokine leptin regulates feeding and obesity, partially through brain histamine and its H_1 receptor (Masaki and Yoshimatsu 2006).

The activity of histaminergic neurons is tightly regulated during the wake–sleep cycle (Anaclet et al. 2009; Fujita et al. 2017; Takahashi et al. 2006). Generally, wakefulness is inhibited by antagonists of the H_1 receptor, as patients suffering from allergic reaction experience when using first-generation antihistamines. The sedative effect of these compounds may be accompanied by weight gain; according to the National Health Examination Survey, prolonged use of H_1 receptor antagonists such as cetirizine, fexofenadine and desloratadine increases the risk of obesity (Ratliff

et al. 2010). The authors of the survey found that adult users of antihistamines had significantly greater weight, waist circumference, body mass index and showed insulin resistance as compared with matched, healthy controls. Blockade of hypothalamic H_1 receptors is responsible also for the obesogenic effect of atypical antipsychotic drugs such as olanzapine and clozapine (Kim et al. 2007; Kroeze et al. 2003). The mechanism involves activation of hypothalamic AMP-kinase, which has been linked to the regulation of food intake (Minokoshi et al. 2004) and is lost in H_1 receptor deficient mice (Kim et al. 2007).

The first report of the anorexiant effect of histamine dates back to the 1970s, when it was demonstrated that histamine infusion in rats' lateral ventricles or the hypothalamic suprachiasmatic nucleus caused a long-term suppression of food intake (Clineschmidt and Lotti 1973; Lecklin et al. 1998). Several other studies followed which, by using different types of pharmacological manipulations, selective brain region lesions, and use of genetically modified mice, confirmed that brain histamine participates in the control of food intake and body weight. These studies also demonstrated that the anorexic effect is mediated by H_1 receptors activation or H_3 receptors blockade in the hypothalamic paraventricular (PVN) and ventromedial nucleus (Provensi et al. 2016).

The histaminergic system is also necessary for motivated behaviours as it plays a prominent role in the regulation of the arousal state during goal-directed behaviours (Contreras et al. 2016; Torrealba et al. 2012). These authors showed that increased arousal associated with appetitive behaviours such as drug- and water seeking, sexual motivation, appetite for food caused an early activation of the TMN, strongly suggesting the involvement of histaminergic neurons in the arousal that gives the appropriate intensity to these goal-directed behaviours (Contreras et al. 2016). The histaminergic neurotransmission is indispensable also to generate the neuronal activation of specific brain areas necessary for different components of learning and memory. In the last 30 years, thanks to the pioneering work of Ivan Izquierdo, to whom this review is dedicated, brain histamine is now recognised as one of the actuators of fear memory acquisition, consolidation, retrieval and extinction (Izquierdo et al. 2016) by activating different histamine receptors in a spatio-temporal coordinated fashion (Benetti et al. 2015; Fabbri et al. 2016). Brain histamine is necessary for the recognition and memorisation of environmentally salient stimuli devoid of strong emotional value (Provensi et al. 2020a). Activation of brain histaminergic receptors is also required for social recognition memory which is crucial for reproduction, for social bonding and species survival (Garrido Zinn et al. 2016; Rani et al. 2021a). Hence, we can rightly include the histaminergic neuronal system in the *gut-brain* axis (see Box 1).

Box 1 Virtuoso solos of brain histamine

• Sleep-wake cycle	Takahashi et al. 2006; Yoshikawa et al. 2021
• Appetite and satiation	Masaki and Yoshimatsu 2006
• Thermoregulation	Hong et al. 2006; Tabarean et al. 2012
• Lipolysis in the adipose tissue	Bugajski and Janusz 1981
• Arousal state	Contreras et al. 2016; Torrealba et al. 2012
• Learning and memory	Izquierdo et al. 2016; Fabbri et al. 2016; Benetti et al. 2015

3 Virtuoso Solo of Oleoylethanolamide

OEA, as other N-acylethanolamides, is found in various tissues including adipocytes where it accelerates lipolysis (Jung et al. 2021), in immune cells where it exerts anti-inflammatory and pain relieving effects (Pontis et al. 2016), in hepatocytes where it promotes glycogen synthesis and gluconeogenesis suppression (Ren et al. 2020) and attenuates diabetes-induced encephalopathy in mice (Ren et al. 2019). In the brain, OEA modulates the firing rate of midbrain neurons in rats through a fast action on nicotinic receptors (Melis et al. 2008) and excites histaminergic neurons isolated from the TMN (De Luca et al. 2018). The physiological implications of the latter observations are not clear yet; in fact, it is not known if and in which circumstances neurons synthesise and release OEA.

OEA has a prominent role in gut physiology, it controls intestinal motility (Capasso et al. 2005), increases intestinal epithelial cells resistance (Karwad et al. 2017), affects the polarisation of T_H lymphocytes in Peyer's patches towards an anti-inflammatory profile (Di Paola et al. 2018) and exerts protective and anti-inflammatory actions in experimental ulcerative colitis (Lama et al. 2020). Also, OEA treatment in mice changes the microbiota composition in a way that simulates the effect of a diet low in fat and high in polysaccharides content (Di Paola et al. 2018).

In the small intestine (duodenum and jejunum), the levels of OEA change according to the nutrient status as they decrease during food deprivation and increase upon refeeding (Astarita et al. 2006; Rodríguez de Fonseca et al. 2001). Duodenal infusion of individual nutrients revealed that fat, in particular oleic acid, is a potent stimulus for OEA synthesis, whereas sugar and protein do not alter OEA levels (Igarashi et al. 2015; Schwartz et al. 2008). More recent studies demonstrated that prolonged consumption of a high-fat diet even for short periods of time (1 week) is

sufficient to suppress jejunal OEA mobilisation (Igarashi et al. 2015). This observation raises the possibility that fat enriched diets might promote overeating, at least in part, by suppressing the satiating effects of gut-derived OEA (Brown et al. 2017; Piomelli 2013).

Overfeeding of dietary fats is known to diminish brain dopaminergic function, which might exacerbate obesity by provoking compensatory food consumption to restore reward sensitivity (Volkow et al. 2011). An elegant work by de Araujo and colleagues demonstrated that the administration of OEA to high-fat–fed mice was sufficient to restore dopamine release (Tellez et al. 2013). Furthermore, the authors showed that OEA eliminated motivation deficits during flavourless intragastric feeding and stimulated ingestion of low-fat food. Hence, these results strongly suggest that the restored extraintestinal lipid signalling afforded by OEA increases the reward value of less palatable or caloric, yet healthier, nutrients. These findings have several implications for the understanding of mechanism that underly obesity and open the venue for yet unexplored weight-loss strategies.

In this regard, bariatric surgery is the ultimate treatment strategy for long-lasting weight loss in patients with morbid obesity. In a rat model of bariatric surgery, the group of Fenske showed that ingested fat mobilised OEA production, which was associated with vagus nerve-dependent increase in striatal dopamine release and dopamine D1 receptor expression (Hankir et al. 2017). The clinical implications of these findings are beginning to appear in the scientific literature. For instance, a recent clinical study reported the beneficial effects of OEA in morbid obese patients (Montecucco et al. 2015) and in obese patients diagnosed with non-alcoholic fatty liver disease (Tutunchi et al. 2020; Tutunchi et al. 2021). These findings add to the notion that OEA is not only a fundamental player in gut physiology and energy balance but is a key factor in improving eating behaviour by attributing a hedonic value to nutrients.

As mentioned before, the ability of animals to remember cues associated with food sources and safety of access has tremendous advantages for foraging in the wild. In this context emotional arousal during aversive and rewarding experiences enhances memory consolidation. Therefore, it is plausible that hormonal and neural signals elicited by feeding might promote the memorisation of recent experiences. Campolongo and colleagues proved this hypothesis to be true (Campolongo et al. 2009). In the classical animal memory tests to evaluate emotional and spatial memory, the inhibitory avoidance and the Morris water maze, the authors found that post-training administration of OEA ameliorated memory in a PPAR-α dependent manner. They also demonstrated that the promnesic effects of OEA necessitate the activation of the nucleus tractus solitarius (NTS; the relay station of the vagus nerve) and noradrenergic activity in the basolateral amygdala (BLA). These findings strongly suggest that peripheral OEA reaches the brain via afferent vagal fibres and improves memory consolidation by indirectly stimulating the amygdala

(Campolongo et al. 2009). The beneficial effects of OEA were also demonstrated in a model of cognitive deficit induced by 3,4-methylenedioxymethamphetamine (MDMA) (Plaza-Zabala et al. 2010) (see Box 2).

Box 2 Virtuoso solos of oleoylethanolamide

• Lipolysis	Jung et al. 2021
• Anti-inflammatory and pain-relieving effects	Pontis et al. 2016
• Glycogen synthesis and gluconeogenesis suppression	Ren et al. 2020
• Intestinal motility	Capasso et al. 2005
• Protective and anti-inflammatory actions in experimental ulcerative colitis	Lama et al. 2020
• Changes the microbiota composition towards a lean-like phenotype	Di Paola et al. 2018
• Satiating effects	Reviewed in Piomelli 2013
• Memory amelioration	Campolongo et al. 2009; Plaza-Zabala et al. 2010

4 Histamine and OEA Partnership in Eating Behaviour

OEA is one of the several endogenous molecules that contribute to the assembling of complex networks of neural and hormonal signals that coordinate food intake and energy expenditure. OEA causes a state of satiety, the feeling of fullness that persists after eating, characterised by prolonged inter-meal intervals (Piomelli 2013). The most accredited mechanism of action of OEA is the activation of PPAR-α in enterocytes which send signals to the NTS in the hindbrain by activating sensory fibres of the vagus nerve (Fig. 1). Cerebral histamine, on the other hand, is a satiety factor that works by activating H_1 receptors in specific hypothalamic nuclei (Masaki and Yoshimatsu 2006; Provensi et al. 2016). Given the prominent role of neuronal histamine in feeding behaviour, we hypothesised that OEA might engage histamine signalling in the brain to fully exert its hypophagic effect. To test our assumption, we administered single injections of OEA to mice deficient in the histamine-synthesising enzyme histidine decarboxylase (*Hdc*$^{-/-}$) and to wild-type congeners (*Hdc*$^{+/+}$), or to mice acutely depleted of histamine via intracerebroventricular (i.c.v.) infusion of the Hdc suicide blocker α-FMH. As expected, OEA reduced food consumption in histamine-deprived mice when compared with food consumed by controls. However, the anorexiant effect of OEA was significantly attenuated in *Hdc*

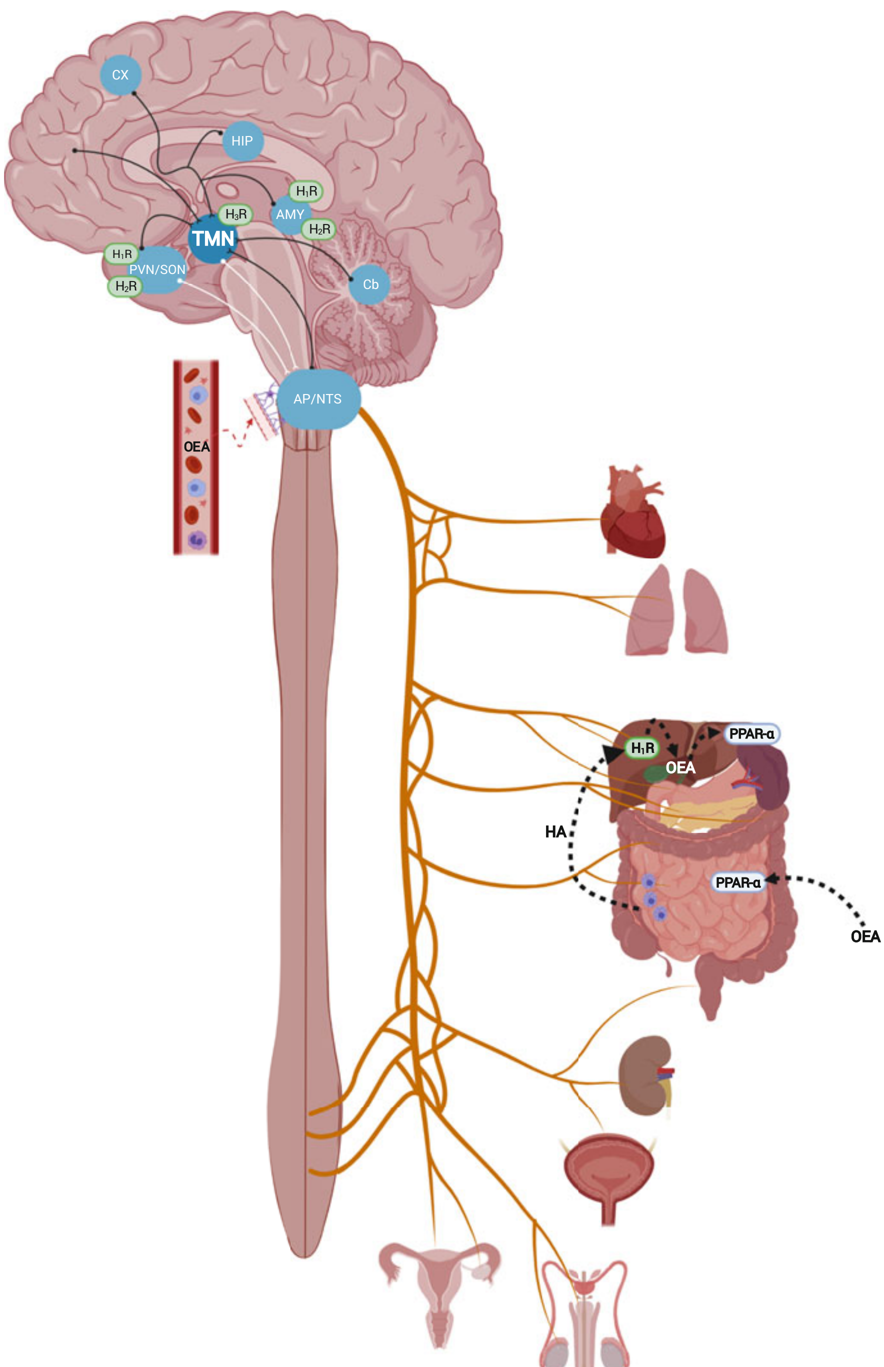

Fig. 1 OEA is released by enterocytes and locally activates peroxisome proliferator activated receptor-α (PPAR-α) which in turn sends signals through the vagus nerve to the nucleus tractus solitarius (NTS) in the hindbrain. From the NTS the signal is relayed to the magnocellular neurons

$^{-/-}$ mice or animals pharmacologically deprived of histamine (Provensi et al. 2014). Hence, OEA caused a profound reduction in the total amount of food consumed by mice with normal histaminergic transmission, whereas such an effect was significantly less pronounced in histamine-deprived mice. The tight connection between OEA and brain histamine was further confirmed by measuring food consumption after coadministration of OEA and ABT-239, an H_3R antagonist that blocks both auto- and heteroreceptors and transiently increases histamine release (Munari et al. 2013). Indeed, we proved that the hypophagic effects of ABT-239 and OEA converge onto a common pathway, as suggested by the isobolographic analysis of feeding behaviour (Provensi et al. 2014). As a further support to our hypothesis, microdialysis experiments showed that OEA increased histamine release in the brain of fasted mice within a time window compatible with its hypophagic action. It is known that OEA stimulates oxytocin expression in magnocellular neurons of the PVN and supraoptic nucleus (SON) of the hypothalamus (Gaetani et al. 2010; Romano et al. 2013) and the release of oxytocin at the nerve endings in the neurohypophysis (Romano et al. 2013). As an anatomical correlate of the feeding behaviour, we found that OEA increased c-Fos expression in oxytocic neurons of the PVN and SON of *Hdc*$^{+/+}$, but not in the PVN of *Hdc*$^{-/-}$ mice. Furthermore, oxytocin-immunostaining was markedly increased in the neurohypophysis of *Hdc*$^{+/+}$, but not *Hdc*$^{-/-}$ mice. c-Fos density of immunoreactive neurons in the brain regions that receive histaminergic innervation and partake in the expression of feeding behaviour though was similar in OEA-treated *Hdc*$^{-/-}$ and *Hdc*$^{+/+}$ mice (Umehara et al. 2016). These results argue in favour of a selective activation of histaminergic pathways according to the internal milieu and environmental challenges. Furthermore, OEA increased c-Fos expression in the NTS of both genotypes, suggesting that OEA-induced activation of the NTS precedes the stimulation of histaminergic neurons, hence in *Hdc*$^{-/-}$ mice the signalling relayed to the NTS is interrupted further down the line (see Box 3).

Fig. 1 (continued) of the paraventricular (PVN) and supraoptic (SON) nuclei of the hypothalamus, stimulating oxytocin neurotransmission. The signal reaches also the tuberomammillary nucleus (TMN, white lines) where the histaminergic neurons are located. The TMN sends histaminergic projections to several brain areas including the hippocampus (HIP), frontal cortex (CX) and amygdala (AMY). Histaminergic projections to the AMY determine the activation of H_1R and H_2R to induce a promnesic effect, whilst projections to the SON and PVN (black lines) lead to H_1R and H_2R activation to produce the hypophagic effect. *AP* area postrema, *Cb* cerebellum, H_1R H_1 receptor, H_2R H_2 receptor

Box 3 A duet between histamine and oleoylethanolamide

• OEA hypophagic effect is attenuated in $Hdc^{-/-}$ or α-FMH treated mice	Provensi et al. 2014
• ABT-239 (H_3 antagonist) and OEA coadministration further decrease food consumption in normal mice	
• OEA increased histamine release in the prefrontal cortex of fasted $Hdc^{+/+}$ mice	
• OEA does not increase c-Fos expression in PVN oxytocic neurons of $Hdc^{-/-}$ mice	
• α-FMH i.c.v. injection abolishes the OEA promnesic effect in the CFC test • H_1R and H_2R antagonists, pyrilamine and zolantidine, intra BLA infused prevent the OEA effect • OEA increases histamine release from the BLA	Provensi et al. 2017
• Chronic or acute histamine deprivation prevents OEA-induced reduction of the immobility time in TST • OEA-induced hippocampal and cortical CREB phosphorylation is not observed in histamine deprived mice	Costa et al. 2018
• Beneficial effects of OEA against stress-induced alteration are not present in $Hdc^{-/-}$ mice • OEA prevents stress-related behavioural complexity in normal mice only • OEA-induced increase in PVN oxytocin expression is reduced in $Hdc^{-/-}$ mice	Rani et al. 2021a, b
• H_1-receptor activation triggers OEA biosynthesis in liver • Histamine-dependent OEA signalling enhances fasting induced ketogenesis • A disabled histaminergic signalling reduces ketogenesis and hepatic OEA synthesis	Misto et al. 2019

5 OEA Requires Histaminergic Neurotransmission to Promote Its Procognitive Effects

A preamble is necessary to strengthen the relevance of histamine and OEA as the "dancing pair" that controls several aspects of cognitive processes and the translational relevance. Memory determines the uniqueness of our personal history and is decisive for each individual to survive and prosper. It is a multistate process that includes acquisition, consolidation and retrieval. Impairment of memory processing may result in intrusive ideation, triggering maladaptive responses that are key symptoms of psychiatric disorders such as generalised anxiety, obsessive-compulsive disorders, post-traumatic stress disorder and phobias. Insights leading to better treatments of these diseases can be gained by understanding the neurobiology of emotional memory. It is indisputable that several neurotransmitter systems

may contribute to memory consolidation within the same or other brain region and as mentioned before, the histaminergic system plays a primary role. We therefore speculated that OEA might engage the brain histaminergic system to unfold its promnesic actions. We tested our hypothesis challenging rats to remember an aversive event by using the contextual fear conditioning paradigm, where the animal learns to avoid a threatening compartment of the arena. In agreement with the findings of Campolongo and co-authors (Campolongo et al. 2009), we found that OEA administered i.p. ameliorated the expression of the aversively motivated memory (Provensi et al. 2017). In addition, the promnesic effect of OEA was abolished by the pharmacological depletion of releasable brain histamine via i.c.v. injection of α-FMH. The same results were obtained with intra-BLA injections of pyrilamine or zolantidine, an H_1 and an H_2 receptor antagonist, respectively, during emotional memory consolidation. As a further argument in favour of our hypothesis, we found that exogenous OEA increased histamine release from the BLA when administered at the same dose that affected rat's memory (Provensi et al. 2017). It is worth remembering that OEA at the concentration used in our study does not readily pass the blood brain barrier (Campolongo et al. 2009). Presumably, then, OEA engages the vagus nerve by activating peripheral PPAR-α and consequently activates the NTS that in turn provides the BLA, together with the locus coeruleus, with a dense supply of norepinephrine. It is known that both the NTS (Clayton and Williams 2000) and locus coeruleus (Rosa et al. 2014) contribute to memory processing by affecting noradrenergic neurotransmission in the amygdala. We think that the emotional arousal which is generally considered indispensable for good memory consolidation of fear tasks is provided by both the noradrenergic and histaminergic transmission in the BLA. The histaminergic system, therefore, appears to have a "permissive" function on the memory enhancing effects of OEA and to allow the full unfolding of its central effects.

An intriguing finding adds to the complexity of the interactions between OEA and histamine. Some of the TMN neurons express PPAR-α and TRPV (De Luca et al. 2018), hence they may respond to locally released OEA during the unfolding of disparate behaviours. These is a completely unexplored field that deserves further analysis.

In the context of evolutionary relevance of these results, we believe that OEA produced in the gut after consuming a fat-rich meal initiates an integrated response via vagal afferents or other routes, reaching satiety centres to control feeding behaviour, which may coincide temporarily with memory consolidation of salient information about the spatial and emotional context in which the meal was consumed (see Box 3).

6 Histamine and OEA Partnership in Alleviating Stress and Depression

The literature illustrating the role of OEA in humans is still scant and sometimes controversial. The few published human studies indicate a homeostatic function of OEA to counteract cognitive and eating maladaptive behaviours and attenuate dysmetabolic diseases. Even less is known of the participation of OEA in mood disorders. For instance, the blood concentrations of N-acylethanolamides, among which OEA was tested in 71 healthy volunteers and it was found to be increased in response to acute stress (Dlugos et al. 2012). Subjects affected by post-traumatic stress disorder (PTSD) have significantly higher plasma concentrations of OEA (Hauer et al. 2014; Schaefer et al. 2014), and changed levels of OEA were found in the cerebrospinal fluid of patients suffering from several disorders, ranging from sleep deprivation (Koethe et al. 2009) to eating disorders (Gaetani et al. 2008; Hansen 2010)]. In a recent multicentre, double-blind, placebo-controlled study, 149 subjects with social anxiety disorder were randomly assigned to 12-week treatment with either JNJ-42165279, a selective inhibitor of fatty acid amide hydrolase (FAAH), the enzyme responsible for the degradation of fatty acid amides including OEA (Schmidt et al. 2021). The study found that treatment with JNJ-42165279 was associated with increased fatty acid serum concentration and a moderate, but significant anxiolytic effects. In another study, though, depressed patients recruited at a primary care setting with current selective serotonin reuptake inhibitors (SSRI) treatment were found to have increased plasma levels of OEA that correlated with somatic symptoms of depression (Romero-Sanchiz et al. 2019).

In the last years, animal models predictive of antidepressant efficacy have been used to assess the effect of chronic OEA treatment, by using different stress protocols, such as the tail suspension (Yu et al. 2015), a test that evaluates stress-coping behaviour of mice, the unpredictable mild stress (Jin et al. 2015; Yu et al. 2015), or by inducing a depressive-like behaviour after ethanol binge administration (Antón et al. 2018). In all circumstances, OEA dampened the depressive-like behaviours. Furthermore, it was suggested that OEA decreased frustration stress induced by binge-like eating in female rats (Romano et al. 2020).

The role of neuronal histamine in mood disorders is not completely understood. Preclinical studies evaluated the antidepressant-like activity of different H_3 receptors in different animal models (Bahi et al. 2014; Gao et al. 2013; Pérez-García et al. 1999; Femenía et al. 2015). Early work by Yanai's group showed reduced H_1R density in the brain of depressed patients, assessed with positron emission tomography, that positively correlated with the severity of clinical profile (Kano et al. 2004). More recently, we reported that the selective serotonin reuptake inhibitors (SSRIs) paroxetine and citalopram necessitate the integrity of the central histaminergic system to reduce immobility in the tail suspension test (Munari et al. 2015). In other words, we hypothesise that the physiological release of histamine is necessary for SSRI to express their therapeutic effect. An excitatory loop exists between the histaminergic TMN and the serotonergic raphe nuclei (please refer to Fig. 7 in

Munari et al. 2015 for details) serotonin depolarises histaminergic neurons by activating 5-HT2C receptors (Eriksson et al. 2001) and in turn activation of H1 receptors on dorsal raphe neurons increases the serotonergic neuron firing rate (Brown et al. 2002; Bárbara et al. 2002). If this loop is disrupted in histamine-deprived mice or H1 receptor density is decreased as in a cohort of depressed patients (Kano et al. 2004), SSRIs may be ineffective. This profile in the depressive population may indeed contribute to individual differences in the response to antidepressant and may prove a good predictor of better treatments.

It is known that acute stress of various nature activates the brain histaminergic system (Westerink et al. 2002; Taylor and Snyder 1971; Haxhiu et al. 2001; Miklós and Kovács 2003) in a stressor- and neuron subgroup-specific manner. Increased histamine release was observed in the TMN of hungry rats enticed with food enclosed in a wire mesh that they cannot reach (Valdés et al. 2010).

Following these premises, we evaluated if OEA engages histaminergic neurons to exert its antidepressant-like effect (Costa et al. 2018). To answer our queries, we used $Hdc^{-/-}$ and wild-type $Hdc^{+/+}$ mice, or pharmacologically deprived of histamine with i.c.v. injection of α-FMH. In the tail suspension test, OEA considerably reduced the immobility time of $Hdc^{+/+}$ mice. However, such effect was not observed following either acute or chronic histamine deprivation.

CREB signalling pathways are relevant for the pathogenesis and therapy of depression (Gass and Riva 2007). Indeed, the behavioural effect of OEA was accompanied by increased hippocampal and cortical CREB phosphorylation which was not observed in histamine-deprived mice. In the same paradigm, other classical tricyclic antidepressant such as imipramine increased CREB phosphorylation and reduced immobility time in both wild-type and histamine-deficient mice (Costa et al. 2018). Hence, OEA behaved exactly like SSRIs (but not TCAs (Munari et al. 2015)), as it necessitates the integrity of the histaminergic neurotransmission to unfold its central effects.

Despite being a valuable tool in drug discovery for high-throughput screening of future antidepressants, the tail suspension test is inadequate to investigate the neurobiological mechanisms of chronic stress and the pathogenesis of mood disorders. Chronic social defeat stress (CSDS) is a preclinical paradigm that more closely reproduces some of the symptoms observed in depression (Menard et al. 2017) and represents exposure to stress stimuli in adult humans. Indeed, chronic uncontrollable stress is a major risk factor for the development of psychiatric and metabolic disorders. The CSDS protocol consists of introducing an experimental mouse of either genotype in the cage of an aggressive mouse until the first attach occurs, followed by 2 h of visual and olfactory, but not physical contact. The protocol is repeated for 20 days, after which mice are engaged in behavioural tests. We therefore used the CSDS to investigate the relationship between the histaminergic system and OEA on CSDS behavioural outcomes both in $Hdc^{-/-}$ and $Hdc^{+/+}$ mice (Rani et al. 2021a). CSDS caused cognitive and social behaviour impairments in both genotypes when compared to non-stressed congeners; however, only stressed $Hdc^{+/+}$ mice responded to the beneficial effects of OEA. Furthermore, we used an advanced multivariate approach known as T-pattern to detect subtle behavioural features.

The T-pattern analysis permits the detection of events in time-ordered sequences ordered according to statistically significant constraints among them (Casarrubea et al. 2015; Santangelo et al. 2017). We observed numerous differences between non-stressed *Hdc*$^{+/+}$and *Hdc*$^{-/-}$ mice and dissimilarities in the impact of stress and OEA on the two genotypes (Rani et al. 2021a). Non-stressed *Hdc*$^{-/-}$ mice showed a more complex pattern of time-locked behaviours with respect to wild-type mice, with marked repetitive sequences. This phenotype was also observed in α-FMH-treated wild-type mice, that was unaffected by OEA (Santangelo et al. 2017). The group of Pittenger (Baldan et al. 2014; Pittenger 2020) was the first to report that *Hdc*$^{-/-}$ mice reproduce a mutation associated with Tourette's syndrome and we suggested that lack of brain histamine may represent a predisposing behavioural phenotype causing the enhanced stereotypical tic-like behaviours of Tourette's syndrome (Santangelo et al. 2017). Stressed mice of both genotypes displayed increased behavioural complexity that was prevented by OEA which seemed to alleviate the anxiety-like response induced by repeated social stress, but only in *Hdc*$^{+/+}$ mice. A plausible explanation for *Hdc*$^{-/-}$ mice behaviour is the incapacity of these animals to elaborate appropriate patterns which are unlocked from their stereotypical repertoire.

Overall, our data corroborate our hypothesis that brain histamine has a permissive role in the behavioural effects of OEA. In this regard, histamine receptor antagonists are among the most used drugs worldwide; therefore, understanding the impact of potential treatments or endogenous mediators on stress-induced behavioural and metabolic consequences may help unravel unexplored therapeutic applications (see Box 3).

7 Histamine Controls Liver Ketogenesis Via Oleoylethanolamide Signalling

The duet between histamine and OEA unfolds also in peripheral organs, not only along the gut-brain axis but also in organs such as the liver where both "dance in close proximity".

Mammals adapt to prolonged periods of food scarcity by releasing free fatty acids from adipose tissue and transforming them into ketone bodies that are used as energy supply (Kersten 2014). Ketogenesis is a crucial metabolic response to prolonged periods of food scarcity and is initiated by the stimulation of PPAR-α which depends primarily on lipolysis-derived fatty acids (Dubois et al. 2017; Kersten 2014). Contrary to what occurs in the gut, hepatic OEA levels increase during fasting and fall after feeding (Fu et al. 2007; Izzo et al. 2010). The newly formed OEA cooperates with lipolysis-derived free fatty acids to activate PPAR-α, the ultimate transcriptional regulator of ketogenesis. We recently described a novel paracrine signalling system that enhances ketogenesis during fasting (Misto et al. 2019). We believe that the mechanism is based on extrahepatic mast cells secretion of histamine

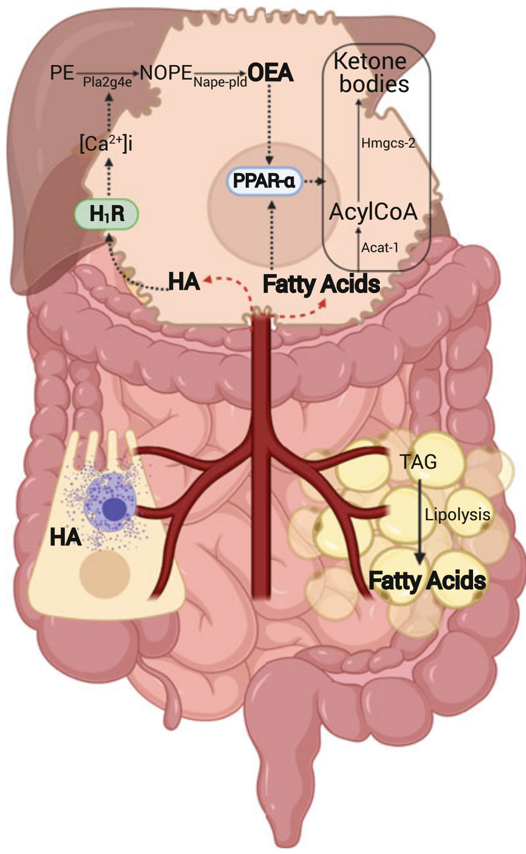

Fig. 2 In our model, fasting stimulates extrahepatic mast cells to secrete histamine (HA) into the portal circulation. HA enters the liver where it triggers OEA biosynthesis by interacting with the H1R, which activates the N-oleoyl-PE (NOPE)-synthesising enzyme via intracellular calcium mobilisation. Nape-pld converts N-oleoyl-PE into OEA. Newly formed OEA cooperates with lipolysis-derived free fatty acids to activate PPAR-α, the ultimate transcriptional regulator of ketogenesis Broken lines indicate pathways inferred from the literature (Leurs et al. 1995; Romano et al. 2015). *Acat-1* acetyl-CoA acetyltransferase-1, *HA* histamine, *Hmgcs*-2b-hydroxy-b-methylglutaryl-CoA synthase-2, *Nape-pld* N-acyl-PE phospholipase D, *Pla2g4e* N-acyltransferase Pla2g4e, *TAG* triacylglycerol

into the portal circulation, stimulation of liver H_1R, and local biosynthesis of the high-affinity PPAR-α agonist, OEA (Fig. 2). It is not known though how fasting affects histamine release from mast cells. Genetic and pharmacological manipulation that disabled the histaminergic signalling reduced ketogenesis and hepatic OEA synthesis as well (Misto et al. 2019).

These newly identified signalling pathways broaden histamine contribution to the peripheral control of energy balance and lipid metabolism. In particular, the observations that in mice, genetic H_1 receptor deletion increases abdominal adiposity and glucose intolerance (Masaki et al. 2001) whereas H_1 receptor antagonism aggravates high-fat diet-induced hepatic steatosis (Raveendran et al. 2014) is of translation value. In this regard, our finding that the H_1 receptor antagonist fexofenadine disables histamine-dependent signalling and impairs ketogenesis suggests a possible explanation of the mechanisms implicated in other dysmetabolic diseases. As mentioned before, H_1 receptor antagonism has been associated with dyslipidaemia and weight gain that often accompany the protracted use of atypical antipsychotic drugs (Kim et al. 2007; Kroeze et al. 2003). As mentioned before, chronic use of

prescription H_1R antihistamine commonly prescribed to alleviate allergy symptoms is associated with increased weight gain and insulin resistance (Ratliff et al. 2010). Hence, deranged OEA synthesis and release in different organs may be the cause of the onset of antihistamine unwanted effects (see Box 3).

8 Conclusions

OEA and histamine presumably co-evolved to partake in the vertebrate physiology. The behavioural effects of OEA have been described in lesser vertebrate species as well as in humans. The physiological role of brain histamine has been described in several species as well, ranging from Drosophila and humans, reflecting the importance of these two molecules in many aspects of behaviour and physiology. Our studies strongly support the hypothesis that OEA and histamine are interdependent in regulating homeostatic responses and cognitive functions. Clearly, further work is required to clarify all the mediators and to exhaustively describe the neuronal circuitry involved in this *pas de deux*. Hopefully, the understanding of complex, integrated circuits will help developing new therapeutical approaches for the treatment of metabolic and cognitive disorders that often go hand-in-hand. Quoting Maria Lindskog (Lindskog 2017) *The identification of signalling pathways connecting the periphery with the central nervous system is fascinating and holds great promise for the development of new therapeutics, since the periphery is much more accessible for pharmaceutical treatment compared with the brain.*

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Part V
Neuropharmacology: Histamine and Sleep

Histamine as an Alert Signal in the Brain

Takatoshi Mochizuki

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Abstract Sleep-wake behavior is a well-studied physiology in central histamine studies. Classical histamine H1 receptor antagonists, such as diphenhydramine and chlorpheniramine, promote sleep in animals and humans. Further, neuronal histamine release shows a clear circadian rhythm in parallel with wake behavior. However, the early stages of histamine-associated knockout mouse studies showed relatively small defects in normal sleep-wake control. To reassess the role of histamine in behavioral state control, this review summarizes the progress in sleep-wake studies of histamine-associated genetic mouse models and discusses the significance of histamine for characteristic aspects of wake behavior. Based on analysis of recent mouse models, we propose that neuronal histamine may serve as an alert signal in the brain, when high attention or a strong wake-drive is needed, such as during exploration, self-defense, learning, or to counteract hypersomnolent diseases. Enhanced histaminergic neurotransmission may help performance or sense of signals concerning internal or environmental dangers, like peripheral histamine from mast cells in response to allergic stimuli and inflammatory signals.

Keywords Clock gene · Cre-loxP · Knockout mouse · Narcolepsy · Vigilance

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Abbreviations

AAV	Adeno-associated viral vector
Arc	Arcuate
CCx	Cerebral cortex
CNO	Clozapine N-oxide
EEG	Electroencephalogram
H1R	H1 receptor
H2R	H2 receptor
H3R	H3 receptor
HDC	Histidine decarboxylase
Hip	Hippocampus
hM3Dq	Human M3 mutant muscarinic Gq-coupled receptor
hM4Di	Human M4 mutant muscarinic Gi-coupled receptor
HNMT	Histamine N-methyltransferase
hRPE	Human retinal pigment epithelium
ILC	Infralimbic cortex
LS	Lateral septum
NREM	Non-rapid eye movement
OX2R	Orexin receptor 2
REM	Rapid eye movement
TMN	Tuberomammillary nucleus
VMH	Ventromedial hypothalamus
WT	Wild-type

1 Introduction

Since the discovery of histaminergic neurons in the brain (Watanabe et al. 1984; Panula et al. 1984), researchers have shown that histamine is involved in basic, fundamental functions such as control of sleep-wake behavior, circadian rhythm, thermoregulation, and feeding (Haas et al. 2008). Sleep-wake behavior is a well-studied physiology of central histamine studies because classical histamine H1 receptor (H1R) antagonists promote sleep in animals and humans (Lin 2000). Histamine neurons receive afferent inputs from many brain regions associated with circadian and homeostatic control (Ericson et al. 1991; Sherin et al. 1998), and project fibers to many brain areas including the hypothalamus, the cerebral cortex, and the basal forebrain (Inagaki et al. 1988), then release histamine preferentially during the wake/active period (Mochizuki et al. 1992; Chu et al. 2004). These findings strongly suggest the importance of histamine neurotransmission for sleep-wake control.

For the last three decades, the genetic approach of generating mutant mouse models has been developed. For histamine studies, two lines of histamine-associated

Table 1 Sleep-wake and other behavioral phenotypes of histamine-associated genetic mouse models

Model	Changes in histaminergic system	Changes in sleep-wake behavior	Other behavioral phenotypes	References
H1R KO	No H1R binding in the brain	Nearly normal, but fewer brief awakenings during sleep	Less exploratory activity in the open field test	Inoue et al. (1996) Huang et al. (2006)
H1R conditional KO	Glial (astrocytic) H1R reduced by 47%	Nearly normal, but slightly increased EEG delta activity during wakefulness	Increased aggressive behavior	Kárpáti et al. (2019)
HDC KO	No histaminergic immunoreactivity in the brain	Nearly normal, but wakefulness reduced at dark onset	Earlier sleep entry after behavioral challenge	Parmentier et al. (2002)
HDC conditional KO	Hypothalamic histamine content reduced by 50%	NREM sleep increased by 15–33%	Bad score in the passive avoidance task	Yamada et al. (2020)
HDC::Cre	Activated by AAV-hM3Dq	No change after CNO injection	Awake more after CNO injection and cage change	Venner et al. (2019)
HDC::Cre	Suppressed by AAV-hM4Di	NREM sleep increased by 40%	–	Yu et al. (2019)
HDC::Cre	Cells ablated by AAV-caspase 3	Normal sleep-wake amount, but fragmented	–	Yu et al. (2019)
HNMT KO	Tissue content increased by five-fold	Wakefulness increased by 27% at light onset	Increased aggressive behavior	Naganuma et al. (2017)

knockout (KO) mice have been generated: histidine decarboxylase (HDC) and H1R KO mice (Inoue et al. 1996; Parmentier et al. 2002). Many researchers expected these KO mice to show defective sleep-wake behavior; however, they surprisingly showed nearly normal phenotypes of sleep-wake behavior and circadian rhythms (see next chapter and Table 1). Specifically, no apparent abnormality was found in baseline sleep-wake behavior of these KO mice, but some behavioral changes were observed when they were placed in unusual situations or exposed to stressful handlings, which suggests that the histamine signaling may be more important when the mice are attentive to environmental cues or are in a highly vigilant state.

Interestingly, such an idea was also supported by the results from a series of excellent electrophysiological studies using non-anesthetized head-restrained mice. Takahashi et al. demonstrated that histamine neurons in the tuberomammillary nucleus (TMN) showed a different rate of spontaneous discharge during wakefulness, with the lowest rate in quiet wakefulness, moderate in active wakefulness, and highest in attentive wakefulness (Takahashi et al. 2006). More importantly, all

histamine neurons recorded were specifically wake-active, showing an increased firing rate after the onset of wake episodes, with a delay of 0.8–3.8 s. Conversely, noradrenergic neurons in the locus coeruleus also have a wake-specific firing profile but start firing 0.36–0.98 s before the onset of wake episodes (Takahashi et al. 2010). These results suggest that histamine neurons have a limited role in the initiation of wake episodes but a substantial role during sustained wakefulness, especially when a high level of arousal is needed (Takahashi et al. 2006).

All these findings strongly suggest that the strategy of KO mice studies should be re-considered to address more these behavioral challenges than basic circadian control of sleep-wake behavior. For this purpose, this review summarizes the progress in behavioral studies of histamine-associated genetic mouse models and discusses the significance of histamine for characteristic aspects of wake behavior.

2 Sleep-Wake Behavior of Genetic Mouse Models

Table 1 summarizes a variety of histamine-associated genetic mouse models for sleep-wake and other behavioral phenotypes. The first genetic model of the histamine system was the H1R KO mouse, which is constitutively devoid of H1R throughout the body (Inoue et al. 1996). Behavioral tests showed that compared with wild-type (WT) mice, H1R KO mice exhibited reduced amplitudes of circadian variation in locomotor activity in a home cage. In the open field test, H1R KO mice showed reduced exploratory behavior and rearing, though general motor coordination and grasp reflexes were normal. These results suggest that histamine (through H1R) may control vigilance and locomotor activity in some circumstances. To better understand the role of H1R in sleep-wake control, my group examined H1R KO mice using electroencephalograph (EEG)/electromyogram recordings to characterize their sleep-wake phenotype (Huang et al. 2006). Surprisingly, amounts of wakefulness, non-rapid eye movement sleep (NREM) sleep, and rapid eye movement (REM) sleep were normal in these mice, although they had fewer brief awakenings during NREM sleep episodes. Brief awakenings describe a short-term (<16 s) wake period with desynchronized EEG and muscle movements that occur during NREM sleep episodes (Tobler et al. 1997). H1R KO mice showed a 40–50% reduction of brief awakenings compared with WT mice (Huang et al. 2006) and pyrilamine treatment (an H1R antagonist; 5 mg/kg, intraperitoneally) caused a similar reduction of brief awakenings in WT mice. A brief awakening interrupts NREM sleep episodes, thereby disrupting sleep continuity and deep sleep, which may be of importance for small animals to be ready for waking upon environmental changes and danger. The above results suggest that H1R signaling helps, at least in part, to arouse animals in case of an emergency.

Soon after, HDC KO mice were generated and their sleep-wake phenotype examined (Parmentier et al. 2002). These mice are constitutively devoid of HDC and show no histamine immunoreactivity in the brain. Similar to H1R KO mice, HDC KO mice have a nearly normal amount of wake and NREM sleep, but their

wake was decreased in a particular daily time window, specifically for 4 h around the onset of the dark period (Parmentier et al. 2002). In general, this time window includes most wake-driving periods for nocturnal laboratory animals, and the loss of histamine may have the biggest impact on arousal maintenance during this period. Outside of this time window, HDC KO mice showed normal sleep-wake behavior, except for slightly more REM sleep in the light period. Interestingly, in contrast to baseline sleep-wake behavior, HDC KO mice showed a remarkable reduction of wakefulness in response to behavioral/environmental stimuli (Parmentier et al. 2002). When HDC KO mice were transferred to a new cage, they did not explore the new environment for as long as WT mice and fell asleep much earlier and slept more than WT mice. A similar short latency to sleep after behavioral challenge was demonstrated after intraperitoneal injection or littermate change handlings, which suggests that HDC KO mice are insensitive to such behavioral challenges or cannot stay awake normally under stressful conditions. Furthermore, a similar short latency to sleep was also observed in H1R KO mice after intraperitoneal injection handling (Huang et al. 2006). These results may best describe an important role of histamine/H1R in sleep-wake control, especially under emergency or stressful situations.

A lack of a clear deficit in normal sleep-wake in constitutive HDC or H1R KO mice could be the result of functional compensation by other wake-active neuronal systems during development. To avoid this compensatory issue, a variety of conditional KO (cKO) mouse models have been developed in the last decade using Cre-loxP and Flp-FRT gene switch systems. Recently, flox HDC (Yamada et al. 2020) and flox H1R (Kárpáti et al. 2019) mice were examined for a sleep-wake phenotype. Using flox HDC mice at 8 weeks of age, Yamada et al. eliminated HDC expression in the posterior hypothalamus including the ventral TMN by introducing Cre recombinase encoded in an adeno-associated viral vector (AAV). Consequently, hypothalamic histamine content decreased in cKO mice by half compared with the control group, and their amount of wakefulness was significantly suppressed in both the light and dark periods (Yamada et al. 2020). These results better indicate the contribution of histamine to baseline sleep-wake control than the constitutive HDC KO mice studies, although the wake deficit still seems limited or mild. For cell-type specific elimination of H1R, Kárpáti et al. crossed flox H1R mice with either GFAP-Cre- or CaMKII-Cre-transgene expressing mice to eliminate H1R specifically in astrocytes or neuronal cells, respectively. They did not observe a significant change in baseline sleep-wake behavior in either line of cKO mice but instead found an abnormal elevation of EEG delta activity during wakefulness in astrocytic H1R KO mice (Kárpáti et al. 2019). These results suggest that astrocytes, as a target of histaminergic neurotransmission, may facilitate cortical neuronal activity during wakefulness via astrocytic H1R.

Another approach uses Cre recombinase-expressing mice to temporarily stimulate or inhibit Cre-expressing neurons specifically by optogenetic or pharmacogenetic techniques. Using HDC-Cre mice (Walker et al. 2013), we have pharmacogenetically stimulated histamine neurons using AAV-hM3Dq and clozapine N-oxide (CNO) administration and measured sleep-wake behavior (Venner et al. 2019). Although CNO injection induced no instant behavioral effect or EEG

arousal in these mice compared with the control injection day, these mice showed more wakefulness when they were transferred to a new cage after CNO injection. The results again suggest that activation of histaminergic transmission may be more important in a situation of needed high arousal than the baseline condition. Conversely, Yu et al. performed pharmacogenetic inhibition of histamine neurons using AAV-hM4Di in a different line of HDC-Cre mice and successfully demonstrated increased NREM sleep for a few hours in the middle of dark (active) period (Yu et al. 2019). Using the same HDC-Cre mice, Yu et al. also generated histaminergic neuron-ablated mice by injecting AAV-caspase 3 (causing apoptosis) into the TMN area. These mice, however, did not show a clear sleep-wake deficit, except for a slight shortening in duration of wake episodes (Yu et al. 2019). Thus, these findings together suggest that histaminergic transmission may be necessary when the animals are in a high arousal state but may have limited effect on regular circadian or homeostatic control of sleep-wake behavior.

Knocking out histamine N-methyltransferase (HNMT), a major histamine metabolizing enzyme in the brain, is another way to activate histaminergic transmission. Indeed, we have analyzed sleep-wake behavior of constitutive HNMT KO mice (Naganuma et al. 2017). Although, in the brain of these mice, both the tissue content and extracellular concentration of histamine is much higher compared with WT mice, changes in sleep-wake behavior were relatively small. HNMT KO mice had more wakefulness in the first half of the light (rest) period and a subsequent reduction of wakefulness in the first half of the dark (active) period. This sleep-wake phenotype was unexpected and interestingly, it was associated with hyperaggressive behavior. Compared with WT mice, HNMT KO mice showed significantly increased aggressive behavior in the resident-intruder test, with a higher attacking number and higher intensity of biting to an intruder (Naganuma et al. 2017). One possibility is that because of the chronic increase of brain histamine, HNMT KO mice were in a state of high alert or cautious about the environment and thus felt unpleasant because of the sleep deficit, especially during the light period, which resulted in rebound sleep during the dark period. Moreover, it was surprising that brain histamine induces hyperaggressive behavior through activation of H2 receptors (H2R) in the brain, independently of the waking action through H1R (Naganuma et al. 2017). Histaminergic signaling through H2R may also serve as an alert signal in the brain.

3 Narcolepsy and Histaminergic Neurons

Orexins (also known as hypocretins) are neuropeptides produced by neurons in the lateral hypothalamus/perifornical area; they play important roles in sleep-wake control, feeding, and energy expenditure (Sakurai 2007). Orexin neurons project widely in the brain and notably innervate wake-promoting neurons including the monoaminergic and forebrain/brainstem cholinergic nuclei (Peyron et al. 1998). Orexin neurons and histaminergic neurons are both located in the hypothalamus.

The histaminergic neurons express orexin receptor 2 (OX2R) (Marcus et al. 2001) and project widely throughout the brain, forming an extensive output pathway for arousal signaling in the brain. Using H1R KO mice or OX2R rescue mouse models, we have demonstrated that the orexin > OX2R > histamine > H1R signaling pathway is responsible for sustaining wakefulness (Huang et al. 2001; Mochizuki et al. 2011).

Lack of orexin signaling is well recognized as a major cause of narcolepsy/cataplexy, a hypersomnolence disorder characterized by excessive daytime sleepiness and abnormal occurrence of REM sleep in NREM sleep episodes which causes sleep paralysis and hypnopompic hallucinations. Cataplexy is a symptom of sudden muscle atonia typically triggered by strong positive emotion (Nishino and Mignot 1997; Scammell 2003). Orexin deficient mouse models and orexin receptor mutant dogs showed many of these narcoleptic symptoms (Chemelli et al. 1999; Lin et al. 1999; Hara et al. 2001; Mochizuki et al. 2004). Indeed, people with narcolepsy/cataplexy have low levels of orexin in cerebrospinal fluid (CSF) (Nishino et al. 2001b). The pathophysiological relevance of histamine in narcolepsy is not well understood, but Nishino et al. reported that brain histamine content and histamine concentration in CSF were significantly lower in narcoleptic dogs and patients with narcolepsy, respectively (Nishino et al. 2001a, 2009). Loss of orexin signaling may result in less activity of histaminergic neurotransmission which results in sleepiness. However, John et al. reported that histaminergic neurons had normal electrophysiological properties in narcoleptic dogs across the sleep-wake state (John et al. 2004). Surprisingly, Valko et al. and John et al. independently reported that the number of histaminergic immunoreactive neurons increased in postmortem brain from patients with narcolepsy (John et al. 2013; Valko et al. 2013). We do not fully understand how such an increase in histaminergic neurons occurs (Scammell et al. 2019), but it is possible that neurons adjacent to the TMN area may preserve a similar neuronal origin and/or properties as histaminergic neurons, thereby inducing HDC to compensate or counterbalance for the loss of orexin signaling and sleepiness. In this respect, one could speculate that histaminergic neurons might warn people with narcolepsy of a defect in the wake-maintaining system of the brain. Interestingly, in contrast to noradrenergic and serotonergic neurons, histaminergic neurons continued firing during cataplexy episodes in narcoleptic dogs (John et al. 2004), which suggests a unique role of histaminergic neurons in the pathophysiology of narcolepsy/cataplexy.

In the last decade, clinical development of H3 receptor (H3R) antagonists/inverse agonists, which regulate the release of neuronal histamine and other monoamines, has proceeded in European countries (Schwartz 2011; Szakacs et al. 2017). For the first time in this class, pitolisant has been approved by the European Medicines Agency and the US Food and Drug Administration, for the treatment of excessive daytime sleepiness in narcolepsy/cataplexy. Considering the increase in number of histaminergic neurons in the brain of patients with narcolepsy, one could wonder why people with narcolepsy could benefit from H3R blockers to increase the histamine signal. One possibility is that the increased number of histaminergic neurons may still not release enough histamine to compensate for the sleepiness

produced by the lack of orexin. Alternatively, enhancement of the release of other monoamines, such as noradrenaline and serotonin (Kathmann et al. 1998; Threlfell et al. 2004), may be a major action of pitolisant for improving severe sleepiness in narcolepsy (Scammell et al. 2019).

4 Clock Gene Expression

Circadian rhythms in mammals are controlled by neurons in the suprachiasmatic nucleus (SCN) of the hypothalamus. Because histaminergic neurons send dense innervation to the rostral hypothalamic region, including the medial preoptic area and SCN (Inagaki et al. 1988), participation of histamine signaling in circadian clock control has long been hypothesized. In support of this model, an electrophysiological study using rat hypothalamic slices demonstrated that SCN neuronal activity was modified by histamine administration; approximately 34% of SCN neurons were inhibited by histamine via H2R, while approximately 17% were excited via H1R (Liou et al. 1983). In addition, a behavioral study showed that intracerebroventricular administration of histamine in rats caused a circadian phase shift in locomotor activity (Itowi et al. 1991). These results support the idea that histamine may have a direct effect on the circadian control system.

Nevertheless, KO mouse studies have not provided supportive results. Although both H1R KO mice and HDC KO mice have less locomotor activity during the dark period (Inoue et al. 1996; Abe et al. 2004), the overall circadian rhythmicity was nearly normal in these mice. HDC KO mice had a slightly prolonged free-running circadian period under the constant dark condition, but this defect was possibly caused by insufficient behavioral reinforcement by the low locomotor activity (Abe et al. 2004). Furthermore, the circadian expression pattern of clock genes such as *Per1, Per2,* and *Bmal1* in the SCN was normal in HDC KO mice, which indicates that histaminergic input to the SCN was not critical to circadian oscillatory activity (Abe et al. 2004). Interestingly, the expression levels of *Per1* and *Per2* in other brain areas, such as the cerebral cortex and striatum, were significantly suppressed in HDC KO mice, which suggests that histamine may be indirectly involved in circadian control through brain areas outside the SCN (Abe et al. 2004).

It is particularly interesting to note that histamine may affect clock gene expression in many brain areas outside the SCN, in other words, peripheral clocks. Although the detailed mechanisms of how the SCN (known as the circadian master clock) governs the expression of peripheral clock genes are not well understood, it is intriguing to hypothesize that histaminergic neurons may function as an activator for peripheral clock gene expression and modulate regional and/or global brain activity widely along their fiber projections. Recently, Morioka et al. examined this hypothesis in vitro using a cell line originating from the human retinal pigment epithelium (hRPE). These cells were considered to be a peripheral clock model with circadian rhythmicity shown by Bmal1–luciferase transcription activity. Histamine significantly shifted the circadian phase of Bmal1–luciferase transcription in hRPE cells

through activation of H1R (Morioka et al. 2018). A similar inductive action of noradrenaline on expression of the clock gene, *Per1*, was found in rat C6 glioma cells and a spinal astrocyte culture through α1 and β2 adrenoceptors (Morioka et al. 2010; Sugimoto et al. 2011). Thus, monoaminergic systems, with broad fiber projections throughout the brain, may play a critical role in regulating the circadian phase of peripheral clock gene expression.

5 Conclusions

It is well recognized that histamine in the periphery serves as an alert signal; for example, histamine is released from mast cells and basophils in response to allergic stimuli and inflammatory signals (Parsons and Ganellin 2006; Thurmond et al. 2008). Central histamine may also serve as an alert signal in the brain, when high alert or a strong wake-drive is needed, such as during exploration, self-defense, learning, or to counteract hypersomnolent diseases.

A simplified diagram of the histaminergic alert system is shown in Fig. 1. Histamine neurons receive afferent inputs from wake-active orexin neurons and sleep-active GABA/galanin neurons in the hypothalamus, as well as from forebrain regions such as the infralimbic cortex (ILC) and lateral septum (LS) (Ericson et al. 1991). The ILC is associated with working memory, attention, and emotion (Heidbreder and Groenewegen 2003), whereas the LS is associated with mood and motivation (Sheehan et al. 2004). These forebrain signals can also reach histamine neurons through orexin neurons (Oishi et al. 2013; Burgess et al. 2013). Histamine neurons may integrate these excitatory and inhibitory signals, then output an alert signal to many brain regions, such as the cerebral cortex, the hippocampus, ventromedial hypothalamus, and arcuate nucleus to handle environmental stimuli, behavioral challenges, or higher functions. Interestingly, Ishizuka and Yamatodani also

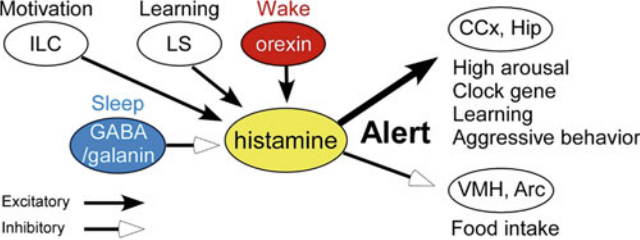

Fig. 1 Schematic of neuronal inputs and outputs of the histaminergic system. Histamine neurons receive afferent inputs from wake-active orexin neurons and sleep-active GABA/galanin neurons in the hypothalamus, as well as from forebrain regions such as the infralimbic cortex and lateral septum (Ericson et al. 1991). Histaminergic neurons may integrate these excitatory and inhibitory signals, then output an alert signal to many brain regions, including the cerebral cortex, hippocampus, ventromedial hypothalamus, and arcuate nucleus to handle environmental stimuli, behavioral challenges, or higher functions

suggested that histamine suppresses feeding behavior through H1R, not only when the animals felt satiety but also when they received aversive and hazardous taste stimuli (Ishizuka and Yamatodani 2012). This anorectic effect of histamine may also be a part of an alert system to arouse and remember dangerous food.

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Brain Mast Cells in Sleep and Behavioral Regulation

Seiji Nishino, Noriaki Sakai, Naoya Nishino, and Taisuke Ono

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Abstract The function of mast cells in the brain for the mediation of neurobehavior is largely unknown. Mast cells are a heterogeneous population of granulocytic cells in the immune system. Mast cells contain numerous mediators, such as histamine, serotonin, cytokines, chemokines, and lipid-derived factors. Mast cells localize not only in the periphery but are also resident in the brain of mammalians. Mast cells in the brain are constitutively active, releasing their contents gradually or rapidly by anaphylactic degranulation. Their activity is also increased by a wide range of stimuli including both immune and non-immune signals. Brain mast cell

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neuromodulation may thus be involved in various neurobehavior in health and diseases.

Using *Kit* mutant mast cell deficient mice (*Kit*^{W}/*Kit*$^{W\text{-}v}$), we obtained results indicating that brain mast cells regulate sleep/wake and other behavioral phenotypes and that histamine from brain mast cells promotes wakefulness. These findings were also confirmed using a newer inducible and *Kit*-independent mast cell deficient Mas-TRECK (toxin receptor knockout) mouse. Injections of diphtheria toxin (DT) selectively deplete mast cells and reduce wakefulness during the periods of mast cell depletion.

We recently introduced a mouse model for chronic sleep loss associated with diabetes. The mice reared on the wire net for 3 weeks (i.e., mild stress [MS]) showed decreased amount of non-rapid eye movement (NREM) sleep, increased sleep fragmentation, and abnormal glucose tolerance test [GTT] and insulin tolerance test [ITT], phenotypes which mirror human chronic insomnia. Interestingly, these mice with insomnia showed an increased number of mast cells in both the brain and adipose tissue. Mast cell deficient mice (*Kit*^{W}/*Kit*$^{W\text{-}v}$) and inhibition of mast cell functions with cromolyn or a histamine H1 receptor antagonist administration ameliorated both insomnia and abnormal glycometabolism. Mast cells may therefore represent an important pathophysiological mediator in sleep impairments and abnormal glycometabolism associated with chronic insomnia.

Keywords Brain · H1 antagonists · Mas-TRECK · Mast cells · Sleep

1 Introduction

The aim of this review article is to dissect the roles of brain mast cells in sleep and behavioral controls. Mast cells are a heterogeneous population of granulocytic cells in the immune system (Nautiyal et al. 2008; Marshall 2004; Galli et al. 2011, 2012). Mast cells contain numerous mediators, such as histamine, serotonin, cytokines, chemokines, and lipid-derived factors (Galli et al. 2011, 2012; Johnson and Krenger 1992; Marshall 2004; Nautiyal et al. 2008) (Fig. 1). Mast cells localize not only in the periphery but are also resident in the brains of mammalians (Silver et al. 1996). Mast cells in the brain are constitutively active, releasing their contents gradually or rapidly through anaphylactic degranulation (Dvorak et al. 1992). Their activity is also increased by a wide range of stimuli including both immune and non-immune signals (Florenzano and Bentivoglio 2000). Brain mast cell neuromodulation may thus be involved in various neurobehavior in health and diseases.

However, the function of mast cells in the brain for the mediation of neurobehavior is largely unknown. Using *Kit* mutant mast cell deficient mice *Kit*^{W}/*Kit*$^{W\text{-}v}$, and a newer inducible and *Kit*-independent mast cell deficient, Mas-TRECK

Brain Mast Cells are involved Sleep regulation?

Fig. 1 Mast cells and their chemical mediators. Characteristics of mast cells differ depending on the existing tissues, developmental stages, immune reactions. This figure shows the potential range of stimuli and secretory responses of mast cells. Not all mast cells secrete all these mediators, and not all mast cells respond to these stimuli. The exact phenotype of a particular mast cell is influenced largely by tissue location, developmental stage, and immune activation. The figure was adapted from the figure in a review article by Johnson and Krenger (1992). Adrenocorticotropic hormone (ACTH); antibody (Ab); basophil chemotactic factor (BCF); calcitonin gene-related peptide (CGRP); mast/stem cell growth factor receptor (c-kit); concanavalin A (ConA); connective-tissue type mast cell (CTMC); delayed-type hypersensitivity (DTH); diacylglycerol (DAG); eosinophil chemotactic factor (ECF), high-affinity receptor for IgE (Fc epsilon RI); granulocyte-macrophage colony-stimulating factor (GM-CSF); histamine releasing factor (HRF); immunoglobulin E (IgE); interferon (IFN); interleukin (IL); lactate dehydrogenase (LDH); leukotriene (LT); myelin basic protein (MBP); nerve growth factor (NGF); neurokinin (NK); neuropeptide Y (NPY); neurotensin (NT); neutrophil chemotactic factor (NCF); platelet activating factor (PAF); phytohemagglutinin (PHA); prostaglandin (PG); somatostatin (Som); substance P (SP); tumor necrosis factor (TNF); vasoactive intestinal peptide (VIP)

mouse, we have recently observed that brain mast cells are likely involved in physiological wakefulness and arousal responses (Chikahisa et al. 2013; Sakai et al. 2019) and abnormal glycometabolism associated with chronic sleep loss (Chikahisa et al. 2017). We have introduced these results and will extend our hypothesis and discussions in this review article.

2 Brain Mast Cells Are Pluripotent Cells That Have Multiple Interacting Chemical and Neural Systems

Factors affecting mast cell numbers in the brain are likely to be neurophysiologically important, since a majority of brain mast cells are active in the basal state (Florenzano and Bentivoglio 2000), Additionally, their activity is increased by a wide range of stimuli including both immune and non-immune signals via behavioral manipulations (Nautiyal et al. 2008; Paus et al. 2006). Many apparently unrelated manipulations, including handling, sex, and stress, increase the number of brain mast cells (Nautiyal et al. 2008). Interestingly, all of these manipulations increase central nervous system (CNS) arousal (Nautiyal et al. 2008).

Of the over 50 mediators of mast cells, some are synthesized upon activation (e.g., substance P, somatostatin, cytokines) while others are preformed and stored in granules, allowing for very fast release (e.g., histamine, serotonin) (Marshall 2004; Johnson and Krenger 1992; Galli et al. 2011, 2012). Mast cells can act via autocrine and paracrine mechanisms (Boyce 2007), and their secretions can reach a large spatial volume. The residence of mast cells in the meninges and perivascular locations on the brain side of the blood–brain barrier (Khalil et al. 2007), primarily in thalamic and hippocampal regions (Hendrix et al. 2006; Taiwo et al. 2005), indicates that they are strategically situated to initiate neural and vascular responses. However, the function of mast cells in the brain is still largely unknown.

3 Brain Mast Cells and Sleep and Behavioral Regulations

Of the known mast cell mediators, many have been individually implicated in the modulation of sleep/wake and behavior. Histamine is one mediator that has been implicated in the regulation of the sleep–wake cycle (Brown et al. 2001; Haas and Panula 2003). Histamine neurons are located exclusively in the tuberomammillary nucleus (TMN) of the hypothalamus, from where they project to practically all brain regions, including areas important for vigilance control such as the basal forebrain, thalamus, cortex, and brainstem structures (Brown et al. 2001; Haas and Panula 2003). Histaminergic neurons fire maximally during waking and slow down during light slow-wave (SWS) sleep and are silent during deep SWS and rapid eye movement sleep (REM) sleep (Thakkar 2011). The sedative-hypnotic effects of histamine H1 (H1) antagonists are well recognized, the result consistent with the wake-promoting role of central histamine. Histamine is also involved in other arousal-related systems, including satiation, sexual behavior, and anxiety (Donoso and Broitman 1979; Ikarashi and Yuzurihara 2002). Histamine reduces appetite, but histamine turnover is paradoxically increased during fasting. It is unknown if mast cell derived histamine is involved in these behaviors.

Mast cell derived cytokines act as neuromodulators having effects on sleep: Tumor necrosis factor-α (TNF-α), interleukin-1, and interleukin-6 all enhance

SWS in experimental animals (Krueger et al. 2001). Lipid-derived factors like prostaglandin D2 also have known roles as neuromodulators, contributing to the regulation of sleep, pain, and body temperature (Hayaishi and Urade 2002; Ueno et al. 1985).

Therefore, mast cells most likely have multifaceted interactions with brain systems controlling sleep and behavior.

4 Neuroimmune Involvement in Sleep and Psychiatric Diseases

There is evidence for dynamic interactions between the immune system and central nervous system (CNS) (Steinman 2004). While it is known that some immune cells, such as microglia, are resident in the brain for surveillance and clearance (Nimmerjahn et al. 2005), the roles of other immune cells, including mast cells, are underexplored.

While much of the evidence for immune system effects on the brain has come from disease states, other evidence also points to the role of neuroimmune interactions in normal physiology. Cytokines released in the periphery during an immune response gain access to the brain and modulate many brain systems, including sleep and behavioral effects, cognition, and pain processing (Maier 2003).

There is also a growing number of investigations on the role of immune cells in the healthy brain. CNS-specific T-cells contribute to hippocampal neurogenesis in adults with consequences for the formation of spatial memories (Ziv et al. 2006). In addition, major histocompatibility complex molecules (expressed in dendritic cells, T-cells, microglia, and mast cells in the brain) are implicated in neuronal synapse development (Huh et al. 2000) and play a role in synaptic plasticity (Oliveira et al. 2004). Given that brain mast cells can change the signaling milieu of the brain, the brain mast cells provide a functional link through which the immune system interacts with the brain and mediates sleep and behavioral effects.

5 Mast Cell Deficient Mice Exhibit Altered Sleep Changes at Baseline and After Sleep Deprivation

We have explored the possibility that brain mast cells might contribute to sleep regulation, using the Kit mutant mast cell deficient ($Kit^{W}/Kit^{W\text{-}v}$) and wildtype (WT) littermate mice. KIT is a receptor tyrosine kinase type III, expressed on the surface of hematopoietic stem cells as well as other cell types. KIT binds to stem cell factors, a substance that causes certain types of cells to grow, and signals through KIT play a role in cell survival, proliferation, and differentiation (Chabot et al. 1988).

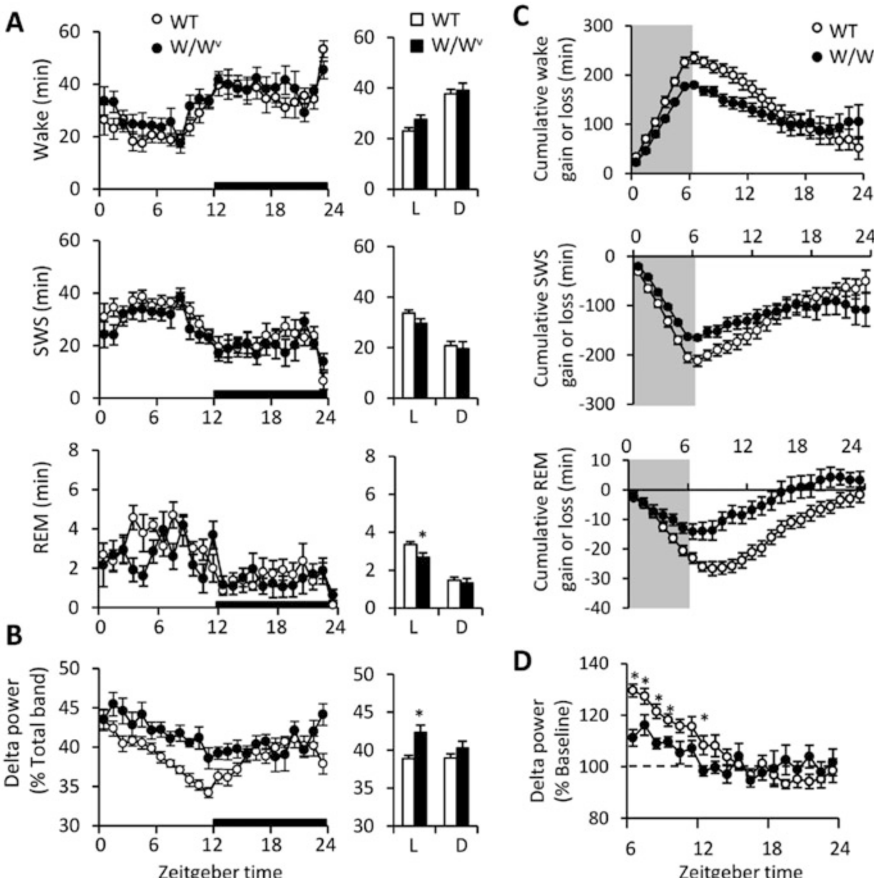

Fig. 2 Baseline sleep/wake characterizations of WT and W/Wv mice. (**a**) Time course for amount of wake (top) and SWS (middle) was not different between the two genotypes. The amount of REM (bottom) was slightly decreased in Kit^{W}/Kit^{W-} (W/Wv) mice during the light phase (L; ZT0-12) but not during the dark phase (D; ZT12-24). (**b**) EEG delta power in SWS was significantly higher in W/Wv mice during the light phase (L; ZT0-12). The bar graphs indicate the averaged data for each 12-h period across ZT0-12 (L) and ZT12-24 (D). (**c**) Cumulative sleep/wake loss and gain compared with baseline conditions for the sleep deprivation experiment. Sleep deprivation began at ZT0 and ended at ZT6 (the shadow areas). (**d**) The rebound response of EEG delta power in SWS after sleep deprivation was attenuated in W/Wv mice. Data is expressed as the percentage change from the baseline value (dotted line) at the same time. Amount of sleep/wake and EEG delta power was averaged at hourly intervals. $*p < 0.05$, $**p < 0.01$, WT vs. W/Wv. All data is expressed as mean ± SEM (n = 8/group). The figure was adapted from the figure in a review article by Chikahisa et al. (2013)

We first examined sleep patterns at baseline sleep over 24 h (LD 12: 12 cycle) and found that mast cell deficient mice spent slightly more time in wake and were slightly more active, but the differences between genotypes were not statistically significant (Fig. 2) (Chikahisa et al. 2013). However, we found an increase in EEG

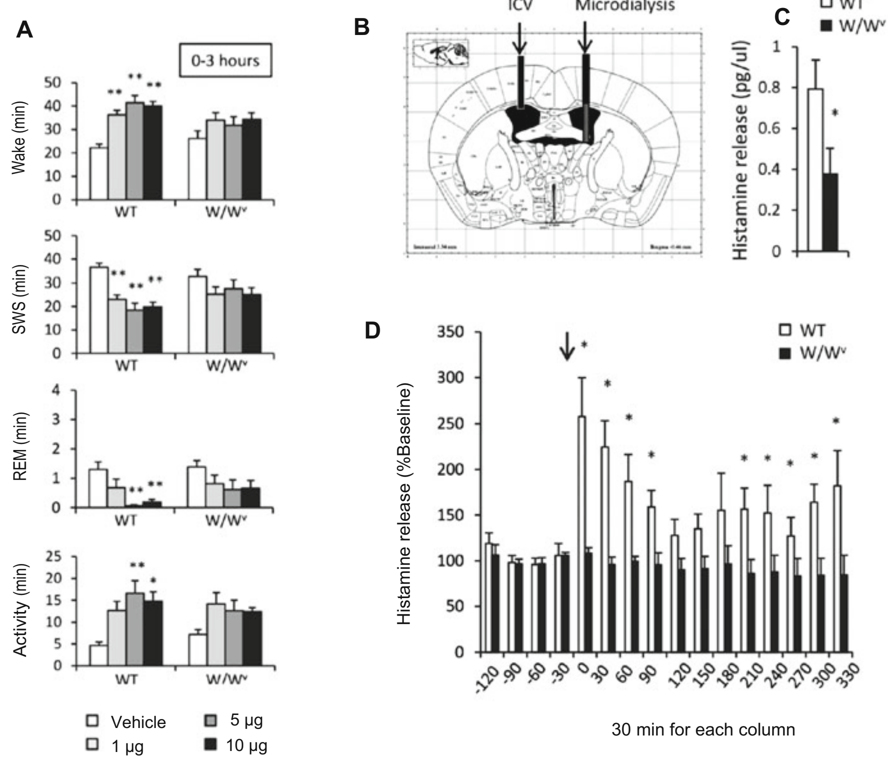

Fig. 3 The effects of ICV injection of compound 48/80 (C48/80) on sleep/wake and locomotor activity in WT and in Kit^{W}/Kit^{W-} (W/Wv) mice. ICV injection of C48/80 promoted wakefulness for both (**a**) 0–3 h after the injection in WT, but not in W/Wv mice. The amount of sleep/wake and locomotor activity was averaged at hourly intervals. $*p < 0.05$, $**p < 0.01$, vs. vehicle; $\#\#p < 0.01$, vs. 1 μg. Data is expressed as mean ± SEM (n = 8/group). (**b**) A schematic representation of the lateral ventricle sections adopted by Franklin and Paxinos (1997). Black bars indicate the placement of the guide cannulae for ICV injection of C48/80 (5 μg) and microdialysis probe. Microdialysis membranes, indicated as gray bars, were inserted into the lateral ventricle. (**c**) Baseline histamine levels in the lateral ventricle of WT mice were higher than that of W/Wv mice (WT: 0.792 ± 0.174 pg/μl, W/Wv: 0.378 ± 0.056 pg/μl). (**d**) Histamine levels in the lateral ventricle increased by C48/80 stimulation in WT mice, while it did not change in W/Wv mice. Data is expressed as the percentage change from the baseline value (average value for 90 min before the injection) of each group. $*p < 0.05$, vs. WT mice. Histamine levels are expressed as mean ± SEM (n = 6–7/group). Each column represents the histamine level for 30 min. The arrow (↓) indicates the time of the C48/80 injection. The figure was adapted from the figure in a review article by Chikahisa et al. (2013)

delta power in mast cell deficient mice (Fig. 2, bottom). We also evaluated sleep recovery after 6-h sleep deprivation (starting from ZT 0: light on) on these animals and found that mast cell deficient mice exhibited less profound sleep recovery after sleep deprivation compared to WT mice (Fig. 3) (Chikahisa et al. 2013). This result suggests that sleep homeostasis (arousal response during sleep deprivation/recovery

sleep) of mast cell deficient mice may be altered (Chikahisa et al. 2013). It is important to emphasize that sleep parameters, such as baseline amounts of sleep, are often compensated in congenital genetic engineered animals, and sleep changes in these animals sometimes can only be seen with certain manipulations, and so further experiments are needed to examine if brain mast cells are involved in physiological sleep/wake regulations.

6 Arousal Response During Food Deprivation Was Blunted in Mast Cell Deficient Mice

It is well demonstrated that food deprivation enhances wakefulness in rodents due to the arousal response through increased food seeking behavior (Challet et al. 1997). In WT mice, significant increases in time spent in wakefulness were seen during the initial active period of food deprivation, while this enhancement of wakefulness was completely blunted in mast cell deficient mice (Chikahisa et al. 2013). This suggests that mast cells may be activated during fasting and substances released from mast cells may possibly be involved in the arousal response during fasting.

7 A Histamine Release Enhancer, Compound 48/80, Enhances Wakefulness in WT Mice, But Not in Mast Cell Deficient Mice

In order to further evaluate the role of brain mast cells in sleep regulation, we evaluated the effects of intracerebroventricular (ICV) administration of compound 48/80 on sleep and wake in mast cell deficient and WT mice (Chikahisa et al. 2013). Compound 48/80 is a polymer produced by the condensation of N-methyl-p-methoxyphenethylamine with formaldehyde. It promotes mast cell degranulation and enhances histamine release (Challet et al. 1997). We found that ICV administration of compound 48/80 significantly enhances wakefulness in WT mice, but not in mast cell deficient mice (Fig. 3).

We also measured histamine release in the thalamus and the area over lateral ventricle (Fig. 3b–d) after ICV administration of compound 48/80 in WT mice (Chikahisa et al. 2013). The baseline histamine content in the lateral ventricle of WT mice was twice higher than that of W/Wv mice (Fig. 3c). In the pilot study, we found there was no increase in the histamine release in the thalamus, but a rapid increase was found in the lateral ventricle in these mice. Therefore, histamine release in the lateral ventricle was compared between mast cell deficient and WT mice, and we found that an increase in histamine release was completely blunted in the mast cell deficient mice (Fig. 3d).

This result suggests that histamine derived from brain mast cells is wake promoting. The reason that there was no increase in histamine release in the thalamus may possibly be (1) ICV injection of the compound does not reach the thalamus, and/or (2) volume transmission is mainly involved in brain mast cell mediated effects, as brain mast cells are enriched in the choroid plexus and meninges.

8 Mast Cell Deficient Mice Showed Attenuated Responses to Sleep-Inducing Histamine H1 Antagonists

In order to test if histamine release from mast cells is involved in sleep/wake regulation, we evaluated if the sleep enhancing effects of H1 receptor antagonists (H1RAs) were altered in mast cell deficient mice. (Chikahisa et al. 2013). Two H1RAs, mepyramine (0.25, 1 and 4 mg/kg, i.p.) and triprolidine (5, 10, 20 mg/kg, i.p.) were used, and the drugs were injected at ZT 14. We found that both mepyramine and triprolidine dose-dependently enhance SWS and reduce wakefulness, but the effects were blunted or attenuated in mast cell deficient mice (Fig. 4). These results suggest that histamine release from the mast cell may also mediate (physiological) wakefulness in normal mice.

9 A New Inducible and *Kit*-Independent Mast Cell Deficient, Mas-TRECK (Toxin Receptor Knockout) Mouse

One of the limitations of our studies, however, was the specificity of the mast cell deficient mouse model. *Kit* mutant mice ($Kit^{W}/Kit^{W\text{-}v}$) possess pleiotropic defects in pigment-forming cells, germ cells, RBCs, and mast cells (Grimbaldeston et al. 2005). These mice lack intermediate cells derived from melanoblasts in the stria vascularis resulting in endocochlear degeneration, loss of endocochlear potential, and hearing impairment (Grimbaldeston et al. 2005). Another Kit-mediated mast cell deficient mouse model, $Kit^{W\text{-}sh/W\text{-}sh}$ ($sash^{-/-}$) mice, has recently become available (see (Nautiyal et al. 2008)). Germ cells and erythrocytes are not affected in these mice, but other *Kit*-mediated abnormalities, abnormalities in melanogenesis, and hearing impairment are seen in these mice (Nautiyal et al. 2008). Since *Kit* is also expressed in the CNS (Yarden et al. 1987; Qiu et al. 1988; Geissler et al. 1988), *Kit* mutant mice may have significant influences on CNF functions with mast cell independent manner (see also (Galli et al. 1993)).

Dr. Kubo's lab at Tokyo University of Science recently produced a new inducible and *Kit*-independent mast cell deficient, Mas-TRECK (toxin receptor knockout) mouse, namely, a diphtheria toxin (DT)-based conditional deletion system using *Il4* enhancer elements previously shown to be specific for IL-4 production in mast

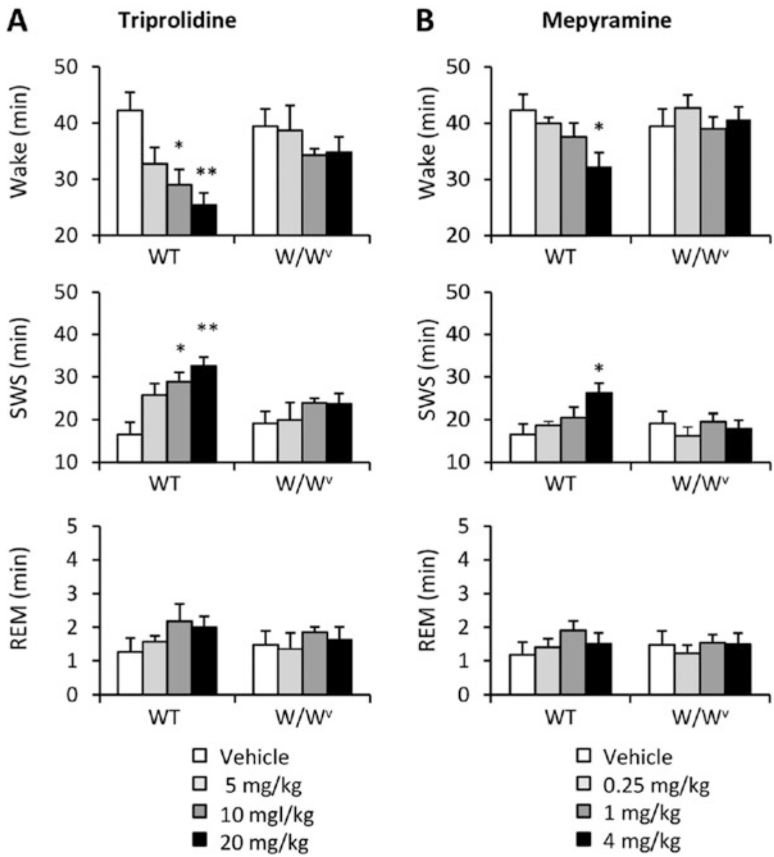

Fig. 4 Changes in sleep and wake amount after administration of H1RAs, mepyramine, and triprolidine (at ZT 14) in WT and W/Wv mice. (**a**) Triprolidine and (**b**) mepyramine increased SWS only in WT mice. $*p < 0.05$, $**p < 0.01$, vs. vehicle. All data is expressed as mean ± SEM (n = 7–8/group). The figure was adapted from the figure in a review article by Chikahisa et al. (2013)

cells and basophils (Mas-TRECK and Bas-TRECK mice), respectively (Sawaguchi et al. 2012). DT treatment of Bas-TRECK mice resulted in specific deletion of basophils, whereas both mast cells and basophils were deleted in Mas-TRECK mice (Sawaguchi et al. 2012). In Mas-TRECK mice, injections of DT selectively deplete mast cells and basophiles, whereas the numbers of other hematopoietic cell populations exhibit no changes (Sawaguchi et al. 2012). Contrary to congenital Kit^{W}/$Kit^{W\text{-}v}$ mast cell deficient mice, Mas-TRECK mice are inducible and recoverable, and thus we could correlate the sleep and behavioral changes to the degrees and periods of the mast cell deficiency induced by DT injection, confirming that the mast cell deficiency indeed contributes to the sleep and behavioral changes observed.

Using the Mas-TRECK mice, we have observed that significant declines in the whole brain histamine levels were seen on day 5 to day 15 (about 60–70%), at day

45 (30%), and the decline became non-significant at day 90 (20%) (Sakai et al. 2019).

We observed significant reductions in wake associated with reduction in locomotor activity in light periods. Thirty days after the toxin injection, the amount of wakefulness and locomotor activity roughly returned to the baseline levels, with the results strongly suggesting that mast cells mediate wakefulness, and the loss of mast cells reduces wake amounts and locomotor activities mostly during the day 5 to day 15 period (Sakai et al. 2019). It is of importance as these changes were observed in the inducible mast cell deficient mouse model, and the changes were reversed when restoration of mast cells occurred. Contrary to the mast cells, basophiles do not exist in the brain, and we also evaluated effects of depletion of basophiles with BAS-TREAK mice, but no sleep and behavioral changes were observed in these mice, suggesting that peripheral depletions of basophiles do not affect sleep and behavior (Sakai et al. 2019).

10 Brain-Resident Mast Cells and Neurobehaviors

Brain-resident mast cells have also been reported to affect higher brain function in rodents, but the role of mast cells in the regulation of emotionality and social behavior was not well elucidated. We therefore examined the relationship between mast cells and social behavior and investigated the underlying mechanisms (Tanioka et al. 2021). WT male mice intraventricularly injected with a degranulator of mast cells (Compound 48/80; 10 μg dissolved in 1.0 μl saline) exhibited an increase in total distance and social preference levels compared to the saline group and cromolyn-injected group in a three-chamber sociability test (Tanioka et al. 2021). In addition, we also observed that inducible Mas-TRECK mice exhibited reduced social preference levels in a three-chamber sociability test without other behavioral changes, such as anxiety-like and depression-like behavior (Tanioka et al. 2021). Mas-TRECK male mice also had reduced serotonin content and serotonin receptor expression and increased oxytocin receptor expression in the brain (Tanioka et al. 2021). These results suggest that mast cells may contribute to the regulation of social behavior in male mice. This effect may be partially mediated by serotonin derived from mast cells in the brain.

11 Chronic Sleep Loss and Abnormal Glycometabolism and Mast Cell Involvements

A series of human and animal studies clearly demonstrated that insufficient sleep is associated with a variety of metabolic diseases including type 2 diabetes and obesity (Spiegel et al. 2009). Despite the high prevalence of these conditions, the molecular

mechanisms underlying the interaction between sleep loss and metabolic impairments are still largely unknown. This is partially due to the lack of valid animal models for chronic sleep loss that is analogous to chronic insomnia in humans that can be used for studying the mechanical links between insomnia and metabolic diseases.

With the collaboration of Drs. Chikahisa and Sei, Tokushima University, we have recently succeeded in introducing a mouse model of chronic sleep loss associated with signs of diabetes (abnormal glucose tolerance test [GTT] and insulin tolerance test [ITT]) (Chikahisa et al. 2017). The mice were placed in the wire net cage (i.e., mild stress [MS]), with the same size and dimensions as a regular cage), and sleep was monitored before and after placement in the wire net cage. Rearing on wire net for 1-week disturbed sleep, namely an increase in wake amounts mostly during active periods and a decrease in slow-wave activity (SWS) during NREM sleep in both resting and active periods, but did not impair GTT or ITT (Fig. 5) (Chikahisa et al. 2017). However, we found that the mice reared on the wire net for 3 weeks showed decreased amounts of non-rapid eye movement (NREM) sleep, attenuated SWA during NREM sleep, and increased sleep fragmentation, compared with that of the control (CNT) group (Fig. 6) (Chikahisa et al. 2017). Interestingly, these mice showed impaired GTT and an increased plasma noradrenaline. Plasma insulin response to glucose was also disrupted in the wire net group. The GTT abnormalities we found were mild, sleep loss was rapidly recovered after we returned the mice to the control cage and the impaired glucose tolerance was also recovered (6 days after returning to the sawdust cage). We therefore believe that this model is useful to study the mechanisms of abnormal glycometabolism associated with sleep loss.

Inhibitions of mast cell degranulation with ICV administration of cromolyn (30 μg) and deletion of mast cells (i.e., $Kit^{W}/Kit^{W\text{-}v}$ mice) ameliorated the sleep loss and impairment of glucose tolerance induced by chronic mild stress (MS) (Chikahisa et al. 2017), suggesting that mast cells play central roles for sleep loss and abnormal glycometabolism associated with MS.

Basal histamine contents (in the cortex and thalamus) and release (measured in the lateral ventricle via microdialysis) in MS mice were higher than the levels in CNT mice (Fig. 7) (Chikahisa et al. 2017). However, the expression of histidine decarboxylase (HDC) mRNA in the posterior hypothalamus was not different between the two groups (Fig. 7). C-fos expression in the histamine neurons in the posterior hypothalamus of MS mice was also not significantly higher than in CNT mice (Fig. 7), suggesting that an increase in histamine levels observed in MS mice is largely due to brain-resident mast cells, rather than TMN neuronal activity.

Histological examinations in the brain and peripheral white adipose tissue (WAT) revealed that MS mice showed an increased number of mast cells in both WAT and in the periventricular organs around the hippocampus and thalamus in the brain, while no difference in mast cell number in the volar skin of the lower legs from CNT and MS mice was observed (Fig. 8) (Chikahisa et al. 2017).

Increased mast cells in WAT in MS mice may mediate the changes in glucose homeostasis seen in MS mice. A recent study has reported that the number of mast cells in the WAT of obese mice was higher than in that of their lean counterparts (Liu

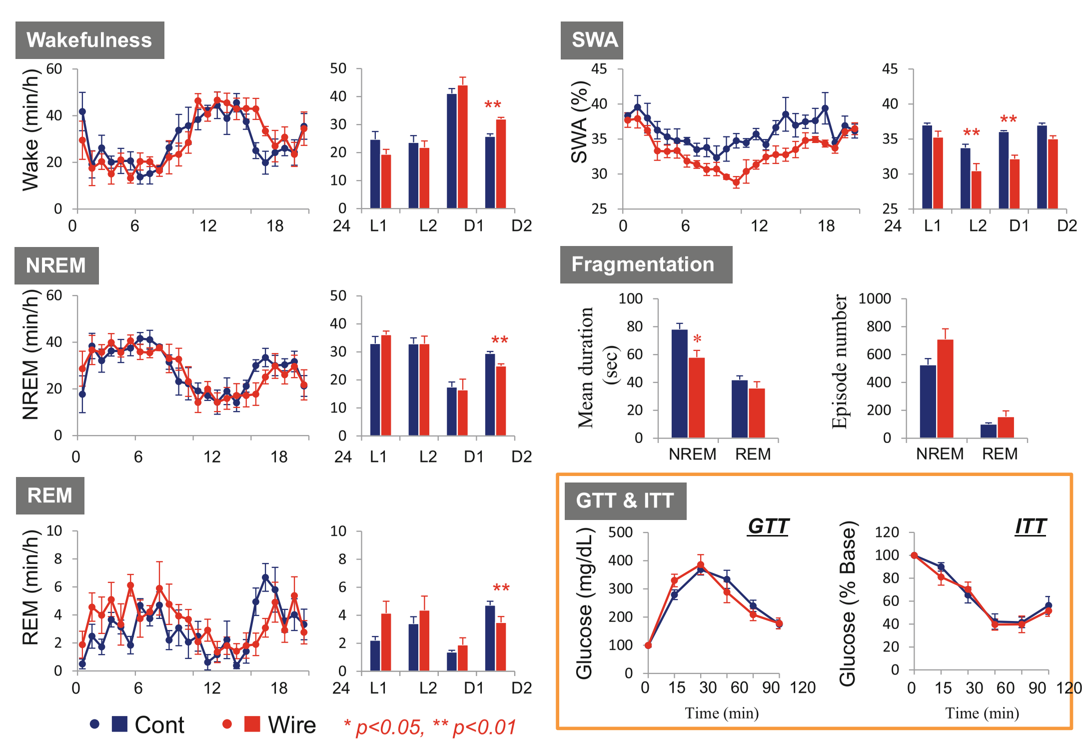

Fig. 5 Rearing on a wire net for 1 week disturbed sleep but did not impair glucose tolerance. Hourly time course (left panels) and 6-h bins (right panels; ZT0-6 (L1), ZT6-12 (L2), ZT12-18 (D1), and ZT18-24 (D2)) for wakefulness (a), non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep, and slow-wave activity (SWA) in NREM sleep after rearing on a wire net for 1 week. Mean duration of bouts and episode number of NREM and REM sleep across 24 h. An intraperitoneal glucose tolerance test (GTT) (g) and an insulin tolerance test (ITT) (h) were performed in control (CNT) and chronic mild stress (MS) mice. All data are expressed as mean ± SEM (n = 5/group). *$p < 0.05$, CNT vs. MS mice. The figure was adapted from the figure in a review article by Chikahisa et al. (2017).

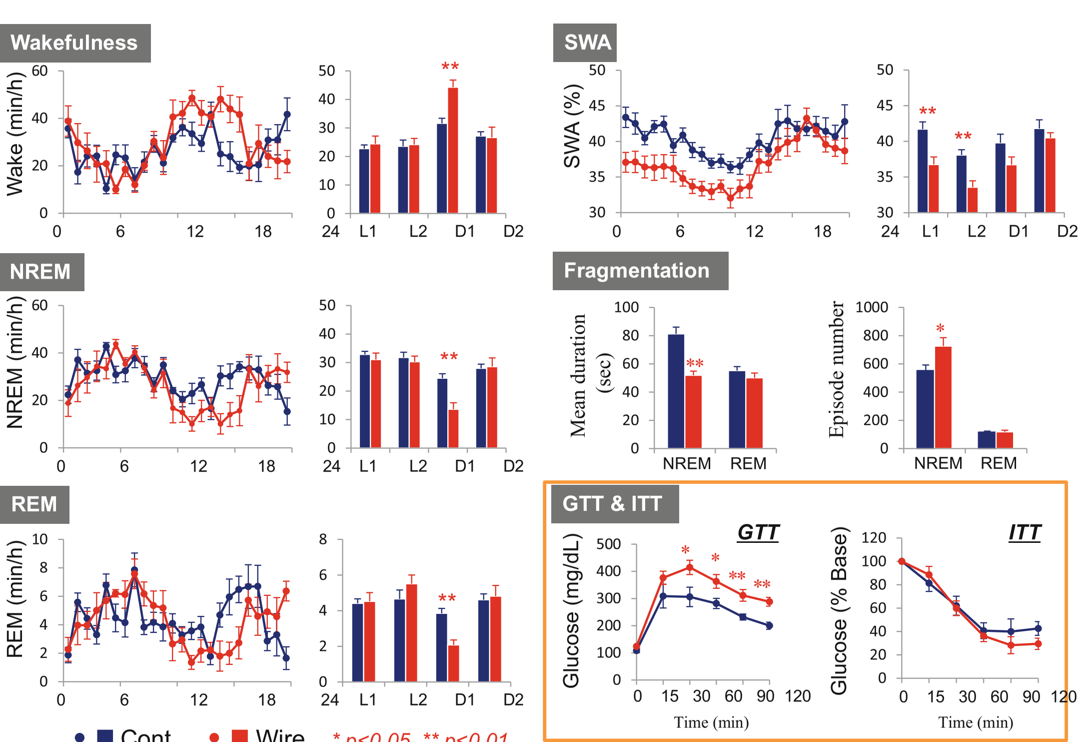

Fig. 6 Effects of chronic mild stress (MS) on sleep in mice. Hourly time course (left panels) and 6-h bins (right panels; ZT0-6 (L1), ZT6-12 (L2), ZT12-18 (D1), and ZT18-24 (D2)) for wakefulness, non-rapid eye movement (NREM) sleep, rapid eye movement (REM) sleep, and slow-wave activity (SWA) in NREM sleep. Mean duration of bouts and episode number of NREM and REM sleep across 24 h. An intraperitoneal glucose tolerance test (GTT) (g) and an insulin tolerance test (ITT) were performed in control (CNT) and chronic mild stress (MS) mice. Blue circles and bars indicate control (CNT) mice, and red circles and bars indicate MS mice. All data are expressed as the means ± SEM (n = 7/group). *$p < 0.05$, **$p < 0.01$, CNT vs. MS mice. The figure was adapted from the figure in a review article by Chikahisa et al. (2017)

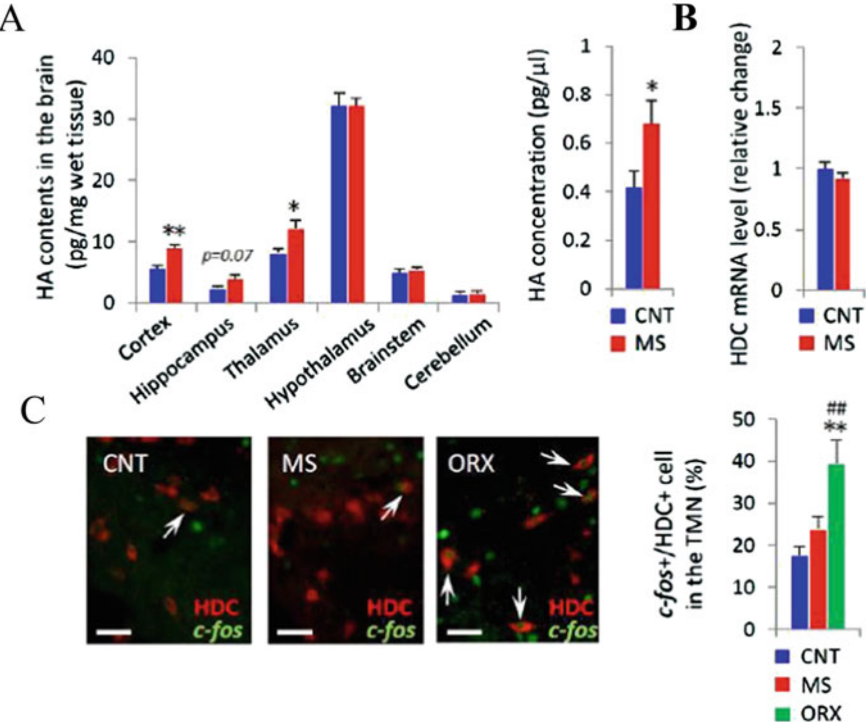

Fig. 7 Increased histamine (HA) levels in chronic mild stress (MS) mice. HA content in each region of the brain (left panel) and HA release (measured in the lateral ventricle via microdialysis) (right panel) in the control (CNT) and MS mice (**a**). Histidine decarboxylase (HDC) mRNA expression in the hypothalamus (**b**). Coronal section through mouse tuberomammillary nucleus (TMN) region showing c-fos-positive histaminergic neurons (**c**). Immunoreactivity for HDC (red) and c-fos (green) is localized in the TMN of control, MS, and orexin B-injected (ORX, 1 nmol, i.c.v.) mice (left figures). The merged image shows c-fos-positive HDC-immunoreactive cell bodies (shown by arrows). Cell numbers of c-fos-positive HDC cells are expressed as a percentage of the total HDC-immunoreactive cell numbers (right panel). Scale bar, 100 µm. Blue bars indicate control mice, red bars indicate MS mice, and green bars indicate orexin B-injected mice. All data are expressed as mean ± SEM (n = 6–8/group). $*p < 0.05$, $**p < 0.01$, vs. CNT; $\#p < 0.05$, $\#\#p < 0.01$, vs. MS. The figure was adapted from the figure in a review article by Chikahisa et al. (2017)

et al. 2009). In addition, mast cell-deficient (*Kit*$^{W\text{-}sh}$/*Kit*$^{W\text{-}sh}$) mice and WT mice receiving a mast cell stabilizer showed a lower rate of diet-induced obesity and diabetes than WT control mice (Liu et al. 2009). The mast cell stabilizer also reduced fasting blood glucose, HbA1c, low-density lipoproteins, and triglycerides in diabetic patients (El-Haggar et al. 2015). These results are in agreement with our results that MS resulted in normal glucose tolerance of mast cell-deficient mice.

To examine if sleep-inducing compounds improve sleep loss and abnormal GTT, we injected an H1 receptor antagonist (pyrilamine 5 mg/kg/day, i.p.) and diazepam, benzodiazepine hypnotics (BZD, 2 mg/kg/day, i.p.) for 1 week in the 3rd week after

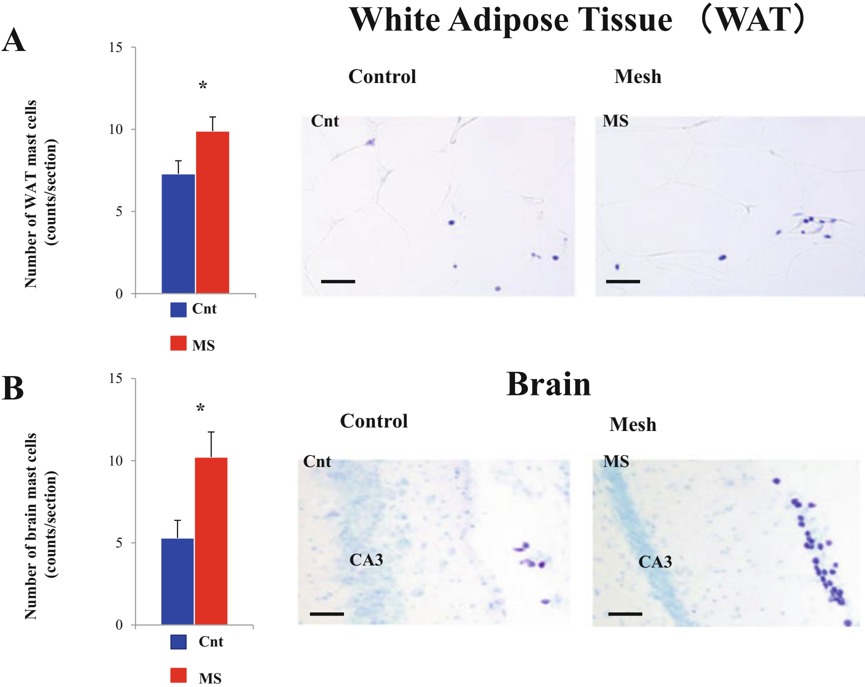

Fig. 8 Chronic mild stress (MS) for 3 weeks increased the number of mast cells. Toluidine blue staining detected mast cell numbers in the white adipose tissue (WAT) (**a**), and brain (**b**) from control (CNT) and MS mice. Scale bar, 50 μm (**a**) and 100 μm (**b**). Blue bars indicate CNT mice, and red bars indicate MS mice. All data are expressed as mean ± SEM (a, b: n = 6/group, c: n = 13/ group). *$p < 0.05$, vs. CNT. Abbreviations: field CA3 hippocampus (CA3). The figure was adapted from the figure in a review article by Chikahisa et al. (2017)

mice were moved to wire net (Chikahisa et al. 2017). We found that one-week treatment with H1RA decreased the amounts of wakefulness and increased NREM sleep amounts in both CNT and MS mice (Fig. 9a, b). Treatment with H1RA enhanced SWA during NREM sleep in both groups. The SWA in H1RA-treated MS mice recovered to the level of that in vehicle-treated CNT mice. Interestingly, H1RA treatment also normalized the GTT abnormality. A BZD treatment also increased the amount of NREM sleep in CNT and MS groups and rescued the chronic sleep loss in the MS group. Interestingly, SWA was reduced by BZD treatment and GTT was rather worsened in the MS group. Neither H1RA nor BZD affected body weight, food intake, or the plasma concentrations of glucose, triglycerides, free fatty acids, or cholesterol in both CNT and MS mice. These data suggest that H1RA treatment ameliorated impaired GTT and sleep loss observed in MS mice and that histamine-mediated function is associated with stress-induced GTT abnormality and sleep loss.

H1RA treatment may also normalize glucose tolerance through peripheral mechanisms, since chronic treatment with H1RA (cetirizine, a second generation H1RA

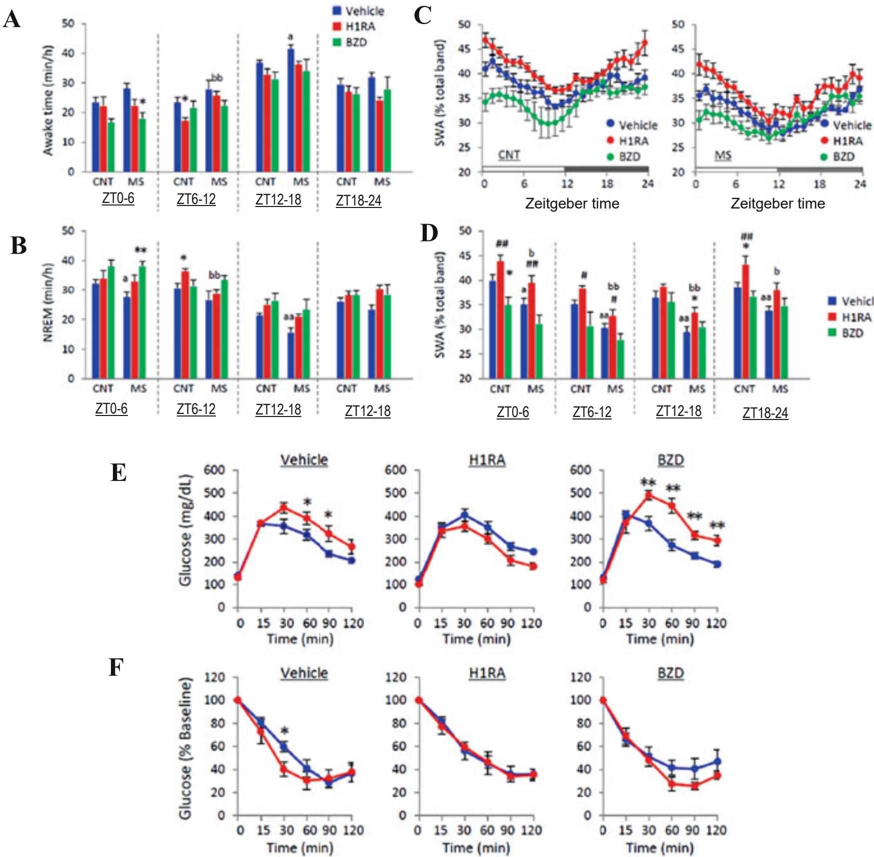

Fig. 9 Effects of pyrilamine (H1ARA) and diazepam (BZD) on sleep and glucose tolerance in control (CNT) and chronic mild stress (MS) mice. Time course for 6-h bins (ZT0-6, ZT6-12, ZT12-18, and ZT18-24) of wakefulness (**a**), non-rapid eye movement (NREM) sleep (**b**), and slow-wave activity (SWA) in NREM sleep (**c**, **d**) in mice injected with vehicle, histamine H1 receptor antagonist (H1RA) or benzodiazepine (BZD). Hourly time course for SWA during NREM sleep (**c**) across 24 h after injection of each drug. Blue circles and bars indicate mice injected with vehicles, red circles and bars indicate H1RA administration (5 mg pyrilamine/kg body weight, i.p.), and green circles indicate BZD administration (2 mg diazepam/kg body weight, i.p.). All data are expressed as mean ± SEM (n = 6/group). *$p < 0.05$, **$p < 0.01$, vs. vehicle; #$p < 0.05$, ##$p < 0.01$, vs. BZD. ap < 0.05, aap < 0.01, vehicle-treated CNT vs. vehicle-treated MS; bp < 0.05, $p < 0.01$, H1RA-treated CNT vs. H1RA-treated MS. An intraperitoneal glucose tolerance test (GTT) (**e**) and an insulin tolerance test (ITT) (**f**) were performed in mice injected with vehicle (left panels), a histamine H1 receptor antagonist (H1RA, 5 mg pyrilamine/kg body weight, i.p.) (middle panels), or a benzodiazepine (BZD, 2 mg diazepam/kg body weight, i.p.) (right panels). Blue circles and bars indicate CNT mice, and red circles and bars indicate MS mice. All data are expressed as mean ± SEM (n = 6/group). *$p < 0.05$, **$p < 0.01$, CNT vs. MS mice. The figure was adapted from the figure in a review article by Chikahisa et al. (2017)

with low central penetration) has been recently reported to ameliorate glucose intolerance in high-fat diet mice (Anvari et al. 2015). It is not known whether histamine released from peripheral mast cells affects sleep or not, but it is known that peripheral histamine does not cross the blood–brain barrier.

The complexity of functional links between sleep and glycometabolism should also be emphasized as the dissociation between chronic sleep loss and abnormal glycometabolism can be seen with a BZD treatment. It should also be emphasized that BZD increases NREM sleep, but SWA was reduced. It is thus of interest to examine other types of hypnotics to explore whether increased SWA can moderate GTT abnormalities.

Although the relationship between central and peripheral mast cell function should be further clarified, the results of our experiments suggest for the first time that mast cells mediate sleep loss and abnormal glycometabolism associated with mild stress, and activated brain mast cells may contribute to sleep loss, while activated mast cells in WAT mediate abnormal glycometabolism, and further studies are warranted.

12 Conclusions

Our results showed for the first time that brain mast cells are likely involved in physiological wakefulness and arousal responses to various behavioral manipulations. We also found that the availability of mast cells influences fundamental neuropsychiatric symptoms, including social behavior, suggesting brain mast cells may play significant roles in the pathophysiology of some neuropsychiatric diseases.

Most importantly, we found that histamine from brain mast cells may mediate chronic insomnia associated with mild stress. Interestingly, activation of peripheral mast cells in the WAT concomitantly occurs, and this may mediate abnormal glycometabolism, and thus resulting in chronic insomnia associated with general inflammation and mast cells. Their chemical mediators are some of the important facilitators for this pathophysiology.

The knowledge obtained from these experiments will likely bring new concepts of how sleep and behavior is regulated by non-neuronal cells in normal and pathophysiological conditions. Since known chemicals and substances released from the mast cell are likely involved in the mediation of the effects, these systems can be targeted by pharmacological treatments for various sleep and behavioral disorders, and results from the proposed study will be very useful for further translational research.

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The Role of the Central Histaminergic System in Behavioral State Control

Elda Arrigoni and Patrick M. Fuller

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Abstract Histamine is a small monoamine signaling molecule that plays a role in many peripheral and central physiological processes, including the regulation of wakefulness. The tuberomammillary nucleus is the sole neuronal source of histamine in the brain, and histamine neurons are thought to promote wakefulness and vigilance maintenance – under certain environmental and/or behavioral contexts – through their diffuse innervation of the cortex and other wake-promoting brain circuits. Histamine neurons also contain a number of other putative neurotransmitters, although the functional role of these co-transmitters remains incompletely understood. Within the brain histamine operates through three receptor subtypes

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that are located on pre- and post-synaptic membranes. Some histamine receptors exhibit constitutive activity, and hence exist in an activated state even in the absence of histamine. Newer medications used to reduce sleepiness in narcolepsy patients in fact enhance histamine signaling by blunting the constitutive activity of these histamine receptors. In this chapter, we provide an overview of the central histamine system with an emphasis on its role in behavioral state regulation and how drugs targeting histamine receptors are used clinically to treat a wide range of sleep-wake disorders.

Keywords Arousal · Co-transmission · Inverse agonists · Sleep

1 The Anatomic Tuberomammillary Hypothalamus (TMN)

Enabled in the early 1980s by the development of antibodies against histamine and histamine producing enzymes the Panula and Watanabe groups independently determined the anatomic location and projections of central histamine neurons (Panula et al. 1984, 1989; Watanabe et al. 1984). They specifically found that histamine producing neurons were restricted to the posterior hypothalamus, a region otherwise known as the tuberomammillary nucleus (TMN). The number of histamine cells within the TMN was limited, e.g., 4,000 to 5,000 neurons in rats and >65,000 in humans across both sides of the mammillary recess (John et al. 2013). More remarkable however – given the limited number of histamine cells within the TMN – was the finding that these neurons provided innervation of nearly the entire brain, including portions of the spinal cord. Since this seminal discovery, the anatomic TMN has been conventionally subdivided into either three (medial, ventral, and diffuse) (Ericson et al. 1987) or five (E1–E5) subgroups (Inagaki et al. 1988) and this anatomical organization appears to be conserved across most mammals and non-mammalian vertebrates (Wada et al. 1991a).

2 Histamine Synthesis, Storage, Release, Degradation, and Reuptake

Histamine is synthesized (via oxidative decarboxylation) from the essential amino acid L-histidine by the enzyme histidine decarboxylase (HDC). Within the brain, expression of the HDC enzyme is restricted to histaminergic neurons of the TMN and non-neuronal mast cell and microglia (Iida et al. 2015; Silver et al. 1996). Given its pivotal role in histamine synthesis, HDC has proven an ideal target to pharmacologically alter brain histamine levels. For example, administration of α-fluoromethylhistidine, which is an inhibitor of HDC, results in near complete depletion of brain histamine (Schneider et al. 2014; Watanabe and Yanai 2001).

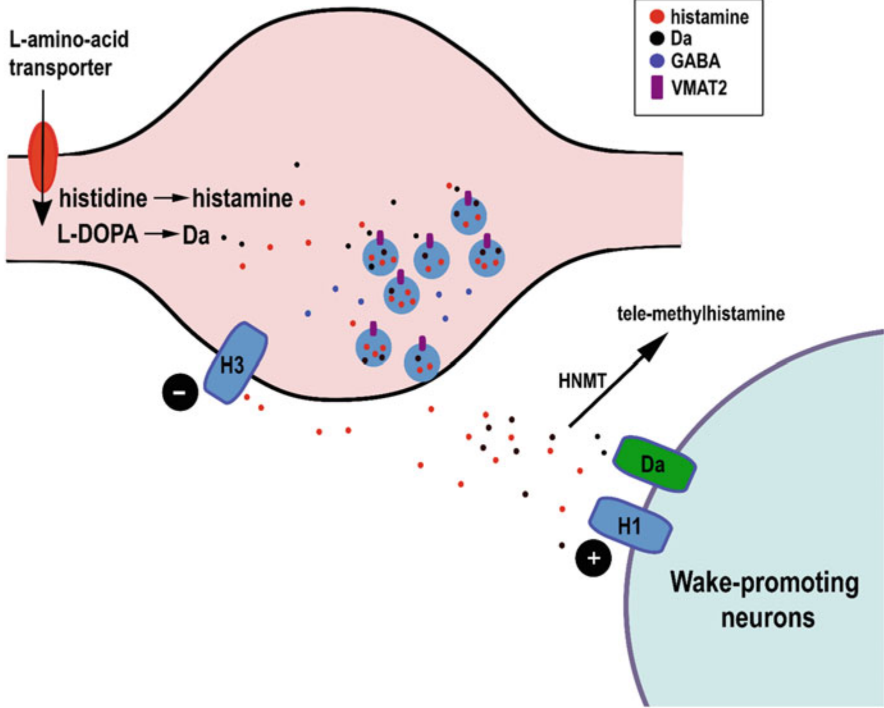

Fig. 1 Histamine synthesis, storage, release, and degradation. Histamine is synthesized from the essential amino acid L-histidine by the enzyme histidine decarboxylase. Histamine is then packaged into synaptic vesicles by the vesicular monoamine transporter (VMAT2). Once released into the extracellular space histamine binds to its receptors, which are located on both the pre- and post-synaptic membranes. Histamine is cleared from the extracellular space by methylation into inactive tele-methylhistamine by the enzyme histamine N-methyltransferase (HNMT). Histaminergic neurons might also use dopamine as neurotransmitter. TMN neurons can uptake L-DOPA through the L-type amino acid transporter, convert L-DOPA into dopamine and package dopamine (via VMAT2) along with histamine in synaptic vesicles for their co-release

Once histamine is synthesized it is packaged into synaptic vesicles by the vesicular monoamine transporter (VMAT2) (Puttonen et al. 2017) (Fig. 1). Electron microscopy studies have found HDC immunoreactivity and VMAT2-immunoreactive vesicles diffusely distributed throughout the perikarya, dendrites, and axons of histaminergic neurons suggesting that newly synthesized histamine could be taken into storage vesicles in all compartments of the neuron (Kukko-Lukjanov and Panula 2003). The functional significance of this vesicle distribution is still unclear, although one possibility is that histamine is also released non-synaptically from dendrites and somas. Dendritic and somatic release has been documented for other monoamines (Cheramy et al. 1981; Zaidi and Matthews 1997) but functional evidence for non-synaptic release of histamine remains lacking. Regardless, and like other monoamines, upon membrane depolarization, histamine is released in a Ca^{2+}-dependent manner from storage vesicles within varicosities,

which do not make close contact with postsynaptic sites (Haas and Panula 2003; Takagi et al. 1986). Once released into the extracellular space histamine binds to its receptors, which are located on both the pre- and post-synaptic membranes (Mochizuki et al. 1991).

Unlike other monoamine neurotransmitters, e.g., dopamine or serotonin, a high-affinity neuronal reuptake system for histamine does not exist and so once histamine is released it is cleared from the extracellular space by initial conversion (methylation) into inactive tele-methylhistamine by the enzyme histamine N-methyltransferase (HNMT) (Haas et al. 2008) (Fig. 1). Histamine can also be taken up by astrocytes and then inactivated by HNMT, which is found in the cytosol of astrocytes (Gasser et al. 2009; Panula and Nuutinen 2013; Yoshikawa et al. 2013). Predictably, pharmacological or genetic disruption of HNMT produces rapid increases in brain histamine levels (Naganuma et al. 2017; Yoshikawa et al. 2019). HNMT inhibitors that are currently commercially available still however lack specificity and the necessary blood–brain barrier permeability that would be required of a reliable therapeutic.

3 Other TMN Neurotransmitters

TMN histaminergic neurons are large cells (25–30 μM in diameter) (Panula et al. 1984; Watanabe et al. 1984) that contain a number of other putative neurotransmitters in addition to histamine, including: adenosine, thyrotropin releasing hormone (TRH), substance P, enkephalins, and galanin (Airaksinen et al. 1992; Köhler et al. 1985, 1986; Yamamoto et al. 1990). Most TMN neurons also express adenosine deaminase (ADA) (Senba et al. 1987; Staines et al. 1986). ADA is an enzyme that catalyzes the conversion of adenosine to inosine and, in fact, antibodies against ADA have been used to reliably label (histologically) TMN histamine neurons. Of interest, recent work has suggested that histaminergic neurons might also use dopamine as neurotransmitter: TMN neurons express the dopamine-producing enzyme, DOPA decarboxylase. It has thus been proposed that TMN neurons can uptake L-DOPA through the L-type amino acid transporter, convert L-DOPA into dopamine and package dopamine (via VMAT2) along with histamine in synaptic vesicles for their eventual co-release (Yanovsky et al. 2011) (Fig. 1).

Histamine neurons also express both isoforms of the GABA synthetic enzyme, glutamate decarboxylase (GAD65 and GAD67), suggesting the TMN histamine neurons may also use GABA as a co-transmitter (Airaksinen et al. 1992; Senba et al. 1985; Takeda et al. 1984). Consistent with the presence of GABA synthetic enzymes, TMN neurons also contain GABA (Airaksinen et al. 1992). GABA-immunoreactivity is specifically found as small granular deposits detected in all compartments of the TMN neuron including the soma, axon, and dendrites (Kukko-Lukjanov and Panula 2003). The ability of a neuron to release GABA, however, requires not only the GABA producing enzymes GAD65 and/or GAD67 but also a transporter to package GABA into the synaptic vesicles. The canonical vesicular

transporter for GABA is the vesicular GABA transporter (VGAT) (Tong et al. 2008; Wojcik et al. 2006), yet very few TMN histamine neurons appear to express the VGAT (Slc32a1) gene (Mickelsen et al. 2020; Venner et al. 2019), although this remains a controversial point among researchers. Two independent studies, for example, both using in situ hybridization, came to markedly different conclusions. Our group, for example, found that only ~7% of TMN histamine neurons express VGAT (Venner et al. 2019), whereas a recent paper from another lab reported 93% co-localization of VGAT and histamine in TMN neurons (Abdurakhmanova et al. 2020). The basis for these discrepant findings is unclear and future studies will be required to fully resolve this subcellular feature of TMN neurons. Meanwhile, and consistent with the former findings, limited expression of VGAT in TMN neurons was shown by a recent single-drop RNA sequence study that found that only a small subset of histamine TMN neurons expresses the VGAT gene. This particular subgroup was defined by the authors as a histamine-like subcluster as the neurons of this group expressed a number of canonical marker found within histamine neurons but all of these markers, including HDC itself, were expressed at low levels (Mickelsen et al. 2020). Whether these neurons expressing VGAT are, in fact, histamine neurons thus remains unclear and the questions of whether these neurons share the same projections and functions of the TMN histamine neurons likewise remain unanswered. One possibility is that these histamine-like neurons are potential histamine neurons that can express higher levels of histamine markers under specific circumstances. For example, it has been reported that the number of HDC-immunoreactive neurons is increased by 64–95% in the brains of people with narcolepsy type 1 (John et al. 2013; Valko et al. 2013) and this has been attributed to an increased expression of HDC in neurons that would have previously been undetectable by immunostaining for HDC (Scammell et al. 2019). Taken together, currently available data would support the contention that only a small percentage of TMN histamine neurons express VGAT.

An important question then, is: if the VGAT is only expressed in a small fraction of TMN histamine neurons, how would GABA be packaged into synaptic vesicles? One possibility is that TMN neurons may package and release GABA via VMAT2, as has been reported to occur in dopaminergic neurons of the ventral tegmental area (Tritsch et al. 2012, 2014). In these studies, the authors demonstrated that optogenetic activation of midbrain dopaminergic neuron evoked monosynaptic release of GABA in the striatum, and this release of GABA was blocked in animals treated with VMAT inhibitors. A similar mechanism has however yet to be demonstrated for TMN neurons. Also, the possibility that TMN neurons package GABA via VMAT2 is unlikely given that, in TMN neurons, GABA and histamine reside in separate vesicles and, moreover, that VMAT2 colocalizes with histamine but not GABA deposits (Kukko-Lukjanov and Panula 2003). Therefore, if only a small percentage of TMN neurons express VGAT, and vMAT2 is not located where GABA is detected, and uncertainty remains over whether GABA is even present in vesicles, it is premature to argue for a specific and/or definitive mechanism by which GABA is packaged in vesicles in these neurons (see below for in vivo evidence).

4 Histamine Receptors

There are four receptors for histamine and all four are metabotropic. The H1 and H2 receptors are expressed both in the brain and the periphery, whereas the H3 receptor is expressed near exclusively in the brain. Conversely, the fourth receptor, the H4, is expressed predominantly in the periphery (Haas and Panula 2003).

4.1 H1 Receptors

H1 receptors (H1Rs) are coupled to the Gq intracellular pathway. Studies using isotopic in situ labelling have demonstrated widespread distribution of the H1Rs in the central nervous system (Bouthenet et al. 1988; Chang et al. 1979; Martinez-Mir et al. 1990; Palacios et al. 1981). H1Rs are particular enriched in areas involved in arousal and they are accordingly, as discussed in more detailed later, the primary receptor target for sedating antihistamine drugs that can cross the blood–brain barrier (NB: most first-generation H1R “antagonists” possess high lipophilicity). The sedating effect of these antihistamine drugs is, in fact, absent in mice lacking H1Rs (Parmentier et al. 2016). H1Rs are specifically and highly expressed in the cortex, cholinergic cell groups of the mesopontine tegmentum and of the basal forebrain, locus coeruleus and raphe nuclei, hypothalamus and limbic system, including the septal nuclei, the amygdala and the hippocampus (Haas et al. 2008). Activation of the H1Rs is generally excitatory and results in membrane depolarization and an increase in firing frequency (Brown et al. 2001). Three different mechanisms however underlie H1R-mediated excitatory effects, and these include: blockade of a potassium leak conductance, which normally controls the cell resting membrane potential, (Berg and Bayliss 2007; Vu et al. 2015) the activation of a TTX-insensitive sodium current, or activation of the electrogenic Na^{+}/Ca^{2+} exchanger (Gorelova and Reiner 1996; Zhang et al. 2013). In addition, activation of H1Rs increases intracellular Ca^{2+} levels through a PLC mediated-release of calcium from intracellular stores (Mukai et al. 2020; Tabarean 2013). H1Rs are also expressed on presynaptic terminals where they are responsible for an increase in neurotransmitter releases (Brown et al. 2001). Although H1Rs are generally known for excitatory responses, they have also been shown to produce membrane hyperpolarization and depressions of neuronal firing. These inhibitory responses are usually indirect effects; for example, H1 mediated increases in intracellular calcium can activate a calcium-dependent potassium conductance that slows down neuronal firing (Brown et al. 2001) or activation of presynaptic H1Rs on GABAergic terminals can increase GABAergic transmission thus resulting in the inhibition of the postsynaptic neurons (Liu et al. 2010; Williams et al. 2014).

4.2 H2 Receptors

H2 receptors (H2Rs) are also excitatory receptors, although they couple to the Gs pathway and hence intracellular adenylyl cyclase/PKA (Haas and Panula 2003). Autoradiographic and in situ hybridization studies have found high levels of H2R expression in the basal ganglia, limbic system (including hippocampus and amygdala) and the cerebral cortex, whereas only low levels of H2R were detected in the cerebellum and hypothalamus (Jin and Panula 2005; Traiffort et al. 1995). In the cerebral cortex, H2Rs are mainly expressed in the superficial layers suggesting that they are most likely located on the dendrites of pyramidal cells. Dendritic expression of the H2Rs has also been suggested in the dentate gyrus (Brown et al. 2001). In cortical regions, H2Rs are involved in promoting cognitive functions and long-term potentiation (Dai et al. 2007; Nomura et al. 2019) whereas in other brain regions they affect pain perception and aggression (Hasanein 2011; Naganuma et al. 2017). Through H2 signaling, histamine blocks a Ca^{2+}-dependent K^{+} small conductance, which is responsible for long-lasting afterhyperpolarizations and firing accommodation (Haas and Konnerth 1983). Reducing this K^{+} conductance results in an increase in firing rate and/or the number of action potentials fired in response to stimuli without necessarily producing a membrane depolarization. Thus, in the presence of histamine, neurons might remain silent until a sensory stimulus arrives, which then results in a much enhanced and long-lasting response (Haas and Panula 2003). In other cases, however activation of H2Rs can result in membrane depolarization. This is usually due to a block of the voltage-gated K^{+} channels (Kv3) via the PKA pathway (Atzori et al. 2000) and/or by an increase in the hyperpolarization-activated cation current (Ih). The H2-mediated increase in Ih is attributed to a shift in activation toward more positive voltages and this effect is mediated by increases in intracellular cAMP (McCormick and Williamson 1991; Tabarean et al. 2012). In addition, presynaptic H2Rs potentiate the release of glutamate and GABA. For example, H2Rs have been shown to increase glutamatergic synaptic transmission in hippocampal principal neurons and striatal neurons (Ellender et al. 2011; Selbach et al. 1997), as well as GABA release in pyramidal neurons of the entorhinal cortex (via activation of cortical interneurons harboring the H2R) (Cilz and Lei 2017). H1Rs and H2Rs can also co-localize with concurrent activation resulting in a synergistic action as demonstrated in the hippocampus and in several aminergic cell groups (Brown et al. 2001).

4.3 H3 Receptors

H3 receptors (H3Rs) are inhibitory receptors that couple to the Gi/o intracellular pathway (Haas and Panula 2003). H3Rs are located on cell bodies, dendrites, and axons. In the TMN neurons H3 autoreceptors provide a negative feedback to restrict histamine synthesis and release (Arrang et al. 1983; Schlicker and Kathmann 2017).

H3Rs are also expressed by non-histaminergic neurons as heteroreceptors. These H3 heteroreceptors inhibit the release of several neurotransmitters including glutamate, acetylcholine, serotonin, norepinephrine, and dopamine (Brown and Haas 1999; Brown et al. 2001; Flik et al. 2015; Schlicker and Kathmann 2017; Schlicker et al. 1992). H3R expression is particularly enriched within the cerebral cortex (deep layers), hippocampus, striatum, thalamus, hypothalamus, and brainstem (Schlicker and Kathmann 2017; Yoshikawa et al. 2021). H3Rs can also be co-expressed with other histamine receptors. For example, basal forebrain cholinergic neurons express both H1 and H3 receptors and, accordingly, histamine has been found to both directly activate basal forebrain cholinergic neurons via H1Rs and inhibit cortical release of acetylcholine via H3Rs. These results suggest the possibility that, in basal forebrain cholinergic neurons, H1Rs and H3Rs are functionally segregated with the H1Rs expressed in the soma where they regulate neuronal firing and the H3Rs expressed in the synaptic terminals of the cortical projections where they inhibit the release of acetylcholine (Purón-Sierra and Miranda 2014). Similarly, H3R mRNA is abundantly expressed in monoamine neurons of the locus coeruleus and dorsal raphe, but these neurons also have low somatodendritic expression of H3R proteins and only a small fraction of locus coeruleus neurons responds to histamine via H3 signal. This suggests the possibility that the H3Rs are mainly expressed at the presynaptic terminals where they regulate the release of norepinephrine and serotonin (Korotkova et al. 2005; Pillot et al. 2002).

Activation of H3Rs produces two main effects: inhibition of high threshold Ca^{2+} currents and activation of the inward rectifying K^+ channels (Haas et al. 2008; Lin et al. 2011; Vázquez-Vázquez et al. 2020). Presynaptic inhibition of Ca^{2+} currents is likely the mechanism responsible for the H3R-mediated inhibition of synaptic transmission. The concomitant activation of the K^+ currents which can hyperpolarize the synaptic terminals might provide an additional synergistic effect. Finally, activation of K^+ currents is probably the main mechanism for the H3R-mediated inhibition of action potential firing, however it is also the case that concomitant inhibition of the Ca^{2+} currents may play a contributing role.

In summary, the H1 and H2 receptors primarily mediate excitatory responses, with their activation serving to increase neuronal firing and potentiates synaptic transmission. By contrast, H3Rs are inhibitory, and their activation produces autoinhibition of TMN neurons and inhibition of histamine release and of other neurotransmitters. Different histamine receptors can co-localize to the same membrane or they can be expressed in different cell compartments to exert differential control over neuronal firing and neurotransmitter release. In addition, both the H1 and the H3 receptors possess constitutive activity, which mean that they are in an activated state even in the absence of histamine (Gbahou et al. 2003; Morisset et al. 2000; Takahashi et al. 2003). This unique property of histamine receptors is actually exploited by drugs that are H1R and H3R antagonists which function to reduce the constitutive activity of H1 and H3 signaling, thereby acting as inverse agonists (see below on histamine drugs for treating sleep disorders).

5 Cell Diversity Within the Histamine Cell Group

Histamine neurons are involved in multiple physiological and neurobiological functions including the sleep-wake cycle, appetite, endocrine homeostasis, body temperature, pain perception, learning, memory, and emotion. It is, however, unclear whether these functions are controlled by different histamine neuronal subgroups. Originally it was thought that the histamine neurons comprised a single functional group (Wada et al. 1991b), but more recent work has indicated that histaminergic neurons are a more heterogeneous population organized into functionally distinct circuits, each with specific and differential projections and differential expressions of $GABA_A$ receptor subunits, peptides, and co-transmitters (Blandina et al. 2012). For example, different stress challenges activate selected populations of histaminergic neurons (Miklós and Kovács 2003) and histamine neurons have been shown to have differential co-expression of galanin, substance P, and met-enkephalin (Airaksinen et al. 1992; Köhler et al. 1986). In addition, histaminergic neurons display some electrophysiological heterogeneity, i.e., differences in firing. Whether or not however these firing rate differences reflect functional diversity has yet to be determined (Fujita et al. 2017). Going forward, studies on differential gene expression in TMN neurons could shed considerable light on this potential diversity. For example, transcriptomic analysis could help determine the extent to which histaminergic neurons consist of distinct functional subpopulations (Todd et al. 2020). As indicated above, results from a recent single-drop RNA sequence study have also found transcriptional heterogeneity among TMN neurons, and further parsed histamine neurons into four molecularly unique subclusters (Mickelsen et al. 2020). Specifically, a cluster of neurons in the ventral posterior hypothalamus was found to express canonical markers for histamine neurons, including: HDC, VMAT2, monoamine oxidase B (MAOB), orexin receptor type 2 (OxR2), and H3 receptors. These neurons also uniquely expressed very low levels of both VGAT and VGLUT2, although Gad1 was robustly expressed (Mickelsen et al. 2020).

As previously discussed, only a small subgroup of histamine neurons express VGAT and hence whether they are able to package and release GABA remains a matter of debate. There is however a relative dense group of VGAT (i.e. GABAergic) expressing neurons just medial to the histamine cell group (Venner et al. 2019). The role of these GABAergic neurons and how they are connected to the histamine group is unclear, but based upon their proximity to the histamine neurons it is possible that some of the lesion and tracing studies conducted in the past were sufficiently nonspecific, i.e., they did not selectively target the TMN HDC population, that they may have included, in part or completely, these adjacent GABAergic cell group(s). Hence, the possibility that these GABAergic neurons might have at least in part contributed to the findings of these prior studies cannot be excluded.

6 Afferent and Efferent Projections of the TMN Neurons

The activity of TMN histamine neurons is under considerable regulation by a wide range of presynaptic inputs, many of which are reciprocal in nature, i.e., the inputs arise from cell groups that themselves are postsynaptic targets of TMN histamine neurons. The TMN receives innervation from the preoptic area of the hypothalamus, septum, prefrontal cortex, subiculum, and dorsal tegmentum (Haas et al. 2008). Additional "afferent" input to TMN histamine neurons includes paracrine and humoral factors (Parmentier et al. 2009). In addition, significant inputs to TMN histamine neurons arise from many of the canonical arousal-related nuclei including the noradrenergic locus coeruleus, serotoninergic raphe, brainstem cholinergic nuclei, glutamatergic hypothalamic, and lateral hypothalamic hypocretin/orexin cells (Ericson et al. 1991). All of these inputs likely activate TMN histamine neurons as electrophysiological studies have shown that histamine neurons are excited by norepinephrine, serotonin, acetylcholine, and orexin. These neurotransmitters activate the TMN histamine neurons directly (Bayer et al. 2001; Eriksson et al. 2001a, b; Schone et al. 2012, 2014) and/or indirectly by disinhibition, i.e., by inhibiting GABAergic afferent inputs (Nakamura and Jang 2012; Stevens et al. 2004). Orexin neurons co-express and probably co-release the neuropeptide dynorphin (Chou et al. 2001; Muschamp et al. 2014), and in the TMN orexin and dynorphin have been shown to have a synergistic action. More specifically, orexin directly excites TMN histamine neurons by increasing the activity of the electrogenic Na^+/Ca^{2+} exchanger (Eriksson et al. 2001a) whereas dynorphin, which is an inhibitory signal, disinhibits TMN histamine by reducing the frequency of GABAergic synaptic events (Eriksson et al. 2004).

The TMN also receives a dense innervation from neurons of the hypothalamic preoptic area (Ericson et al. 1991; Steininger et al. 2001) including neurons of the ventrolateral preoptic nucleus (VLPO). The VLPO nucleus contains neurons that are active in sleep and activation of these neurons in vivo promotes sleep. These sleep-active and sleep-promoting VLPO neurons express the neuropeptide galanin (Kroeger et al. 2018; Sherin et al. 1996). A combination of retrograde and anterograde tracing studies and immunocytochemistry has also found that descending projection from the VLPO selectively targets the cell bodies and proximal dendrites of the histaminergic TMN neurons. Moreover, approximately 80% of VLPO neurons that were retrogradely labelled from the TMN were immunoreactive for galanin, indicating that the vast majority of VLPO neurons projecting to the TMN are, in fact, the sleep-promoting cell population (Sherin et al. 1998). And it is via these projections to the TMN, as well as to the locus coeruleus and dorsal raphe, that VLPO galanin neurons silence the monoaminergic arousal system to produce and maintain sleep.

Conversely, TMN histamine neurons project back to the VLPO and are thought to inhibit VLPO galanin neurons during wakefulness (Chou et al. 2002). This reciprocal inhibitory circuit between the VLPO and TMN is a common feature of wake and sleep circuits and its "design" is thought to ensure rapid and complete transitions

between states as well as to support the full expression of sleep and wake states, i.e., minimize the time spent in intermediary states (Saper et al. 2010).

With respect to their efferent projections, histamine neurons send diffuse projections throughout the brain with the densest innervation in the hypothalamus and moderately dense innervation of the hippocampus and most neocortical regions where they target the superficial layers. Two ascending and one descending histamine pathways have been described and many histamine neurons have been found to branch to more than one of these pathways. One ascending pathway travels ventrally to innervate the hypothalamus, diagonal band, septum, olfactory bulb, hippocampus, and cortex, whereas the other travels dorsally and runs along the third ventricle to provide innervation of the thalamus, basal ganglia, hippocampus, amygdala, and cortex. The descending path innervates the brain stem and spinal cord (Haas et al. 2008).

With high relevance to the putative role that the histaminergic system plays in behavioral state control, histamine neurons provide dense innervation of the medial preoptic region, VLPO, and the suprachiasmatic nuclei (Inagaki et al. 1988, 1990; Michelsen et al. 2005). At the level of the VLPO, histamine inhibits VLPO neurons indirectly by increasing a GABAergic input likely via H1R-mediated activation of local GABAergic interneurons within the VLPO (Liu et al. 2010; Williams et al. 2014). Inhibition of VLPO sleep-active neurons has been proposed to be a requirement for high level of vigilance. In addition, TMN neurons also innervate, and histamine dose-dependently activates, other wake-promoting nuclei such as the noradrenergic locus coeruleus, the serotonin dorsal raphe neurons, and the mesopontine cholinergic neurons, suggesting that histamine-induced arousal could also involve, in addition to inhibition of sleep-promoting neurons, activation of wake-promoting neurons (Haas et al. 2008; Korotkova et al. 2005; Lin et al. 1996; Monti 2010). Additionally, TMN neurons project to the suprachiasmatic neurons, the site of the master circadian clock, and a dense network of fibers passes through and innervates the supramammillary nucleus (SUM) which contains glutamatergic neurons that project to cortical areas (Haas et al. 2008). Acute activation of these SUM glutamatergic neurons has shown to produce long periods (several hours) of uninterrupted wakefulness (Pedersen et al. 2017). It is not known however how SUM glutamate neurons respond to histamine, although one possibility is that the histamine system drives vigilance and the maintenance of arousal in part by promoting SUM neuronal firing.

7 Histamine Levels During Sleep and Wake Cycle

Studies across species have consistently found that extracellular concentrations of histamine are higher during wakefulness than during NREM and REM sleep. Histamine releases in the basal forebrain and frontal cortex correlates with the percentage of time spent in wakefulness and with the level of alertness (Chu et al. 2004; Zant et al. 2012) and histamine release in the posterior hypothalamus

positively correlates with high EMG-activity and EEG activity in the high θ and γ ranges, supporting the concept that higher levels of histamine are required for (or otherwise support) attentive wakefulness (Rozov et al. 2014; Zant et al. 2012). Similar to histamine, its metabolite, tele-methylhistamine, follows the same patterns across behavioral states (Rozov et al. 2014). Extracellular levels of histamine measured during sleep deprivation are however not much higher than those measured during normal wakefulness, suggesting that histamine levels are not a reliable measurement of sleep pressure (Strecker et al. 2002). Accordingly, extracellular histamine increases immediately in the first hour of sleep deprivation and remains elevated without further increase for the entire duration of the sleep deprivation. Histamine levels do however rapidly decline during both normal sleep and recovery sleep after sleep deprivation (Strecker et al. 2002; Zant et al. 2012).

A review of the studies describing histamine levels across the 24-h cycles suggests that histamine production, and likely release, is under circadian regulation. Although the circadian rhythm of brain histamine levels has not been rigorously analyzed, in all reported cases central histamine levels are higher during the dark period compared to the light period (Leenaars et al. 2018) (NB: all of these studies were conducted in rats and mice which are nocturnal animals and are therefore more active during the dark period). Additional studies further support the view that the histamine system might be circadian regulated. For example, HDC mRNA levels change rhythmically over 24 h, and HDC protein levels peak during the dark period (Yu et al. 2014). Post-mortem analysis of brain tissue has revealed a similar diurnal rhythm in HDC mRNA in humans, with highest HDC mRNA levels during the day (Shan et al. 2012). Selective deletion of the circadian gene *Bmal1* from histamine neurons flattens the oscillations of HDC mRNA and HDC protein levels resulting in higher levels of histamine during the light or rest period, and this has been linked with sleep-wake fragmentation. In addition, circadian regulation of the histaminergic system might be regulated through the reciprocal connection with the suprachiasmatic nuclei (Abrahamson and Moore 2001; Krout et al. 2002). Increased levels of HDC protein during the dark period might ensure high histamine levels at the time when animals are more likely active.

Consistent with elevated histamine levels during wakefulness (or times of heightened alertness), TMN histamine neurons exhibit higher firing rates during wakefulness. Specifically, single unit recording studies in the TMN region in mice have found that these neurons discharge at a high rate during waking, at a lower rate during the drowsy state and in NREM sleep, and at the lowest rate during REM sleep (Takahashi et al. 2006). Based on the anatomical location and their broad action potentials, which is typical of aminergic neurons, these wake-active neurons are thought to be the histamine population, however direct confirmation of their histamine phenotype is still lacking. Additional analysis of the state-dependent activity of these putative TMN *histamine* neurons shows a pronounced delay in firing when the animals transition upon arousal regaining firing activity only after the onset of EEG desynchronization. In some cases, histamine neurons remain quiescent if the animals are not fully alert. Interestingly, putative histamine neurons did not respond to auditory stimulus unless the stimulus produced an alert state, suggesting that the

histamine system might not be involved in inducing wakefulness per se, but might be required for high level of vigilance and for cognitive processes (Takahashi et al. 2006). In addition, low histamine neuronal activity results in drowsiness and sustained low activity appears to be required for sleep. This interpretation of the electrophysiological data is supported by the results from lesion, inhibition, and knockout mouse studies as discussed in the next section (Scammell et al. 2019; Yoshikawa et al. 2021).

8 Histamine in Behavioral State Control

An arousal-promoting role for TMN histaminergic neurons, and histamine itself, has long been posited. As described in the foregoing, this hypothesis derives support from the fact that drugs targeting the central histaminergic system can modulate the level of arousal as well as the fact that TMN neurons fire fastest during waking and that CSF histamine levels are highest during waking. Additional support for a role of TMN histamine neurons in arousal comes from more recent studies showing that chemogenetic activation of TMN histamine neurons increases locomotor activity in an open field challenge (Yu et al. 2015). Results from chemogenetic inhibition or acute optogenetic inhibition of TMN histamine neurons have however produced inconsistent results. While some studies have found that inhibition of the TMN neurons induces slow-wave sleep and increases delta power (Fujita et al. 2017; Yu et al. 2019), others have not (Venner et al. 2019). These discordant findings could link to the fact that different HDC-Cre mouse lines were employed in these studies. Specifically, these genetically modified HDC-Cre mouse lines may have either under-expressed Cre or produce ectopic expression of Cre, both of which possibilities could have explanatory power for the difference in findings between studies. It is the case, however, that lesions of TMN cells produce limited alterations in sleep or wake in both rats and mice (Blanco-Centurion et al. 2007; Denoyer et al. 1991; Gerashchenko et al. 2004; Yu et al. 2019) although a compensatory response to the lesion cannot be ruled out. Consistent with the finding that lesions of the TMN cells do not alter sleep amounts, animals with TMN lesions show a response to stimulant drugs such as modafinil that is indistinguishable from animals without TMN lesions. Interesting, however, acute chemogenetic inhibition of TMN neurons does appear to attenuate the wake-promoting response to modafinil. This could suggest that part of modafinil's wake-promoting effects arise through the histaminergic system (Yu et al. 2019).

Similarly to the results of the lesion studies, HDC knockout mice exhibit only modest changes in baseline wakefulness (Anaclet et al. 2009; Parmentier et al. 2002), although these same mice show less wakefulness following a behavioral challenge, such as a cage change. HDC knockout mice also appear to be drowsier at the start of the active period ("lights off") compared with littermate controls. Selective deletion of the HDC gene in adult mice as opposed to a knockout in development does however produce an increase, albeit a modest one, in NREM sleep (Yamada et al. 2020).

Similarly, transgenic mice bearing a $GABA_A$ receptor loss-of-function mutation on HDC neurons, which results in increased HDC neuron excitability, exhibit higher arousal following a cage change but negligible changes in baseline sleep or wakefulness (Zecharia et al. 2012). As indicated above, there also remains considerable controversy as to whether or not TMN histamine neurons release, or co-release, GABA, and furthermore, whether or not such GABA release might contribute to sleep-wake regulation. For example, in one study, optogenetic stimulation of TMN terminals was reported to release GABA in the cortex (Yu et al. 2015), whereas another study reported an inability to elicit histamine terminals within the TMN and preoptic regions (Williams et al. 2014). Importantly, however, these studies stimulated different TMN terminal fields and used different HDC-Cre mouse lines, and as such it is possible that these studies may have stimulated two different subgroups of HDC-expressing neurons, one of which was able to release GABA and another that was not. Consistent however with the latter findings, a recent study found that selective genetic excision of GAD67 or VGAT from TMN histamine neurons was without effect on sleep or wakefulness (Venner et al. 2019). Taken together the available data suggest that TMN histamine neurons are required for vigilance maintenance under certain environmental and/or behavioral contexts but are neither necessary nor sufficient to promote EEG or behavioral wake at baseline.

9 Histamine Drugs for Treating Sleep Disorders

It was recognized early on that first-generation H1R antagonists (commonly referred to as "antihistamines"), which are highly lipophilic and therefore easily cross the blood brain barrier, produced, in addition to their anti-allergy effects, sedation. These H1R antagonists, which include over-the-counter drugs like diphenhydramine, chlorpheniramine, and doxylamine, are indeed commonly employed as sleep aids (Krystal et al. 2013). Of note, H1Rs are technically "inverse agonists" as they reduce the constitutive activity of H1Rs to produce their effects, including sedation. Newer, second generation H1R antagonists such as fexofenadine and loratadine are less lipophilic and have been found to be far less sedating (Simons 2004). In addition, some antidepressants and antipsychotics such as doxepin, amitriptyline, and olanzapine have H1R antagonist properties and have proven to be effective in treating insomnia (Scammell et al. 2019).

In contrast to H1 receptor antagonists, drugs that interfere with H3 signaling (e.g., ciproxifan, pitolisant) promote wakefulness. The arousal effects of these H3 antagonist – or inverse agonists – have been attributed to their ability to increase brain levels of histamine, although these drugs may also act on H3-expressing cholinergic and monoaminergic neurons (Ghamari et al. 2019; Schwartz 2011). Pitolisant, for example, is a H3-receptor inverse agonist that increases brain levels of histamine but also – by acting as inhibitory presynaptic heteroreceptors – the levels of other wake-promoting neurotransmitters (Ligneau et al. 2007; Schwartz 2011). In fact, pitolisant has been shown to enhance acetylcholine and monoamine

release within the cortex (Ligneau et al. 2007), which could contribute to its arousal-promoting properties. In both animal models of narcolepsy and in narcoleptic patients, pitolisant, which is generally well-tolerated, increased wakefulness, decreases NREM sleep, and reduced cataplexy rate by about 75% (Lin et al. 2008; Szakacs et al. 2017). On the basis of these and other findings, pitolisant has since become a drug of choice for treating excessive daytime sleepiness in narcolepsy. While most research on pitolisant (and other H3 inverse agonist) has focused on its application in treating symptoms of narcolepsy, pitolisant has also been shown to produce improvements in sleepiness in obstructive sleep apnea syndrome (Dauvilliers et al. 2020). Going forward, pitolisant and other drugs targeting H3Rs may be used clinically to manage not only the daytime sleepiness of narcolepsy and other hypersomnolence disorders, but also the sleepiness associated with other neurological and neurodegenerative disorders.

10 Conclusions

Results from studies over the last decades have indicated that the activity of histamine neurons correlates with wakefulness and in particularly with vigilance maintenance under conditions of imposed stress or novelty. And while much has been learned and revealed about the role of histamine in behavioral state regulation, important questions remain. For example, does the TMN histamine cell population comprise functionally distinct subgroups of neurons? What features of wakefulness are controlled by histamine? And what role(s) do the putative TMN co-transmitters play in regulating or modulating histamine signaling and hence arousal? Future studies, ranging from the synapse to whole brain, will be required to inform a more complete understanding of the role of the central histaminergic system in regulating behavioral state.

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