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

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Contents

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 chlorpheniramine 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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