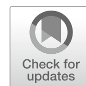
The Role of the Central Histaminergic System in Behavioral State Control



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Contents

1 The Anatomic Tuberomammillary Hypothalamus (TMN) 448
2 Histamine Synthesis, Storage, Release, Degradation, and Reuptake 448
3 Other TMN Neurotransmitters 450
4 Histamine Receptors 452
4.1 H1 Receptors 452
4.2 H2 Receptors 453
4.3 H3 Receptors 453
5 Cell Diversity Within the Histamine Cell Group 455
6 Afferent and Efferent Projections of the TMN Neurons 456
7 Histamine Levels During Sleep and Wake Cycle 457
8 Histamine in Behavioral State Control 459
9 Histamine Drugs for Treating Sleep Disorders 460
10 Conclusions 461
References 461

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).

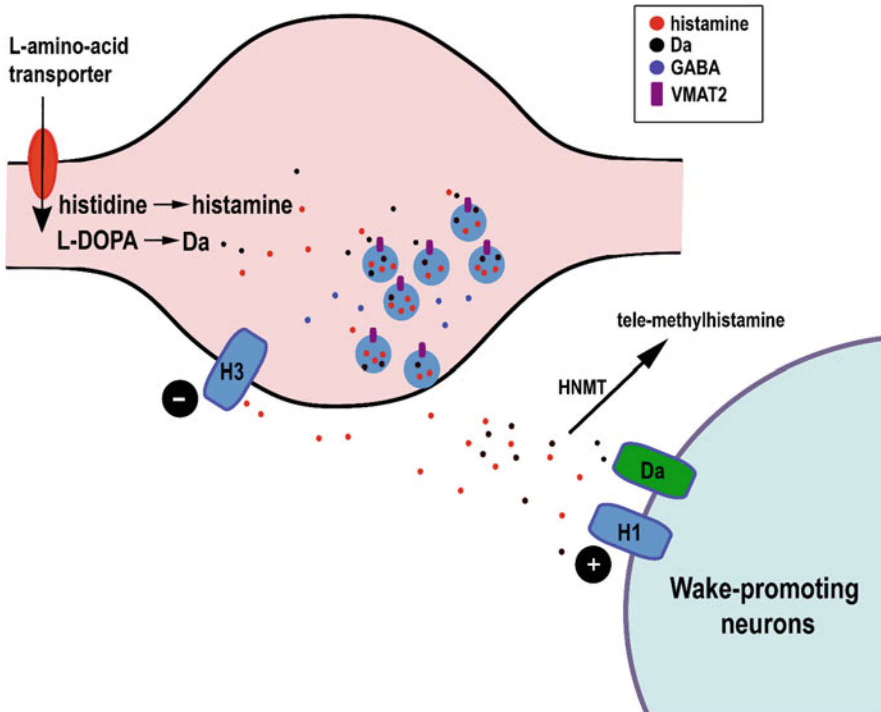

Fig. 1 Histamine synthesis, storage, release, and degradation. Histamine is synthesized from the essential amino acid L-histidine by the enzyme histidine decarboxylase. Histamine is then packaged into synaptic vesicles by the vesicular monoamine transporter (VMAT2). Once released into the extracellular 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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