Histamine: a key neuromodulator of memory consolidation and retrieval

Hiroshi Nomura[1*], Rintaro Shimizume[1,2], and Yuji Ikegaya[3]

Affiliations

[1]Department of Cognitive Function and Pathology, Institute of Brain Science, Nagoya City University Graduate School of Medical Sciences, Nagoya, 467-8601, Japan

[2]Department of Pharmacology, Graduate School of Pharmaceutical Sciences, Hokkaido University, Sapporo, 060-0812, Japan

[3]Laboratory of Chemical Pharmacology, Graduate School of Pharmaceutical Sciences, The University of Tokyo, Tokyo, 113-0033, Japan

*Correspondence to: hnomura@med.nagoya-cu.ac.jp

Abstract

In pharmacological studies conducted on animals over the last four decades, histamine was determined to be a strong modulator of learning and memory. Activation of histamine signaling enhances memory consolidation and retrieval. Even long after learning and forgetting, it can still restore the retrieval of forgotten memories. These findings based on animal studies led to human clinical trials with histamine H_3 receptor antagonists/inverse agonists, which revealed their positive effects on learning and memory. Therefore, histamine signaling is a promising therapeutic target for improving cognitive impairments in patients with various neuropsychiatric disorders, including Alzheimer's disease. While the memory-modulatory effects of histamine receptor agonists and antagonists have been confirmed by several research groups, the underlying mechanisms remain to be elucidated. This review summarizes how the activation and inhibition of histamine signaling influence memory processes, introduces candidate the cellular and circuit mechanisms, and discusses the relationship between the human histaminergic system and learning and memory.

Keywords: histamine, tuberomammillary nucleus, memory consolidation, memory retrieval, neuropsychiatric disorders

Overview

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

Histamine-producing neurons and histamine receptors in the brain

The histaminergic system in the brain is composed of approximately 64,000 histamine neurons in humans and 4,600 in rats, with cell bodies located in the tuberomammillary nucleus (TMN) in the hypothalamus and projecting to a wide range of regions in the brain (Ericson et al. 1987; Alraksinen et al. 1991). Histamine neurons are grouped in E1-

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

Four types of G protein-coupled histamine receptors (H_1R, H_2R, H_3R, and H_4R) have been identified. H_1Rs and H_2Rs exist in neurons and glial cells and are expressed postsynaptically in most brain regions, including areas involved in learning and memory, such as the cerebral cortex, hippocampus, and amygdala (Martinez-Mir et al. 1990). $G_{q/11}$ and phospholipase C are downstream of H_1R activation, which leads to Ca^{2+}-dependent events and the subsequent

excitation of postsynaptic cells. H_2Rs are coupled to G_s, which sequentially activates adenylyl cyclase and protein kinase A (PKA). Although most studies have not examined the contribution of neuronal and astrocytic histamine receptors separately, genetic studies using astrocyte- and neuron-specific conditional knockout mice suggest different roles of H_1R expressed on neurons and astrocytes in various brain functions, including learning and memory (Kárpáti et al. 2019). H_3Rs are present in neurons at both presynaptic and postsynaptic sites. H_3R activation promotes the activation of $G_{i/o}$, which inhibits adenylyl cyclase and subsequently downregulates PKA activation. In addition, histamine suppresses N- and P-type Ca^{2+} channels through H_3R activation (Takeshita et al. 1998). H_3Rs in the axons and somas of histamine neurons negatively regulate histamine release and synthesis (Arrang et al. 1983). H_3Rs are also found in nonhistamine neurons and regulate the release of other neurotransmitters, including γ-aminobutyric acid (GABA), glutamate, acetylcholine, and noradrenaline (Schlicker et al. 1994; Blandina et al. 1996b; Yamamoto et al. 1997). Although H_3Rs are known primarily as presynaptic receptors, they are also located postsynaptically. Postsynaptic H_3Rs have not been studied as extensively as presynaptic H_3Rs (Ellenbroek and Ghiabi 2014), and little is known about the contribution of postsynaptic H_3Rs to memory processing. H_4Rs are present in several brain regions, including the cerebral cortex, brainstem, thalamus, and amygdala (Strakhova et al. 2009), but the role of H_4Rs seems limited in learning and memory (Sanna et al. 2017).

Histamine and memory consolidation

The first paper examining the involvement of histamine in learning and memory was published by de Almeida and Izquierdo (de Almeida and Izquierdo 1986). They reported that a posttraining intracerebroventricular (i.c.v.) infusion

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

is blocked by the administration of an H_2R antagonist (Orsetti et al. 2001). However, local infusions of H_3R agonists and antagonists into the BLA induce opposite effects. A posttraining intra-BLA infusion of an H_3R antagonist decreases the conditioned fear response (Passani et al. 2001). In contrast, an intra-BLA injection of an H_3R agonist enhances the fear response (Cangioli et al. 2002). Acetylcholine modulation in the BLA might explain the different effects of systemic and intra-BLA administration of H_3R agonists and antagonists (Blandina et al. 2004). The muscarinic receptor activation in the amygdala is critical for consolidation of fear memory (Introini-Collison et al. 1996; Vazdarjanova and McGaugh 1999). The intra-BLA administration of H_3R agonists and antagonists enhance and reduce acetylcholine release in the BLA, respectively (Passani et al. 2001; Cangioli et al. 2002). Therefore, the histamine-acetylcholine interaction may regulate memory consolidation in the BLA.

H_2R-mediated phosphorylation of cAMP-responsive element-binding protein (CREB) is a possible mechanism by which histamine improves memory consolidation (Figure 1A). CREB is phosphorylated by several protein kinases, including PKA, and is a key transcription factor regulating the synthesis of proteins critical for memory consolidation (Bourtchuladze et al. 1994; Kida et al. 2002). H_2R is coupled to G_s, which activates adenylyl cyclase and PKA (Haas and Panula 2003). Therefore, H_2R activation is likely to modulate gene expression, which is critical for memory consolidation through the PKA-CREB pathway.

In addition, the histamine-induced modification of synaptic plasticity has been proposed to be a mechanism by which histamine improves memory consolidation (Figure 1A). Synaptic plasticity is possibly a cellular mechanism of learning and memory (Martin et al. 2000; Neves et al. 2008). Long-term potentiation (LTP) is defined as persistent increases in the synaptic efficacy of excitatory synaptic transmission and is a typical form of synaptic plasticity in

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

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

Histamine and memory retrieval

Memory retrieval is not only a reflection of memory traces in the brain but also a dynamic output process that is modulated by the internal states of subjects (Tarder-Stoll et al. 2020). Compared to memory encoding and consolidation, less is known about memory retrieval, despite the importance of its deficits in various neuropsychiatric disorders (Beatty et al. 1988; Westmacott et al. 2001; Meeter et al. 2006; Kopelman and Bright 2012; Thomas 2015). Histamine is a candidate key modulator of memory retrieval. Kamei and Tasaka revealed that a pretest i.c.v. infusion of histamine shortens the response latency in an active avoidance task in old rats in an H_1R-dependent manner (Kamei and Tasaka 1993). An i.c.v. administration of histamine and histidine facilitates the retrieval of short-term social memory (Prast et al. 1996). In a radial maze task, histamine (i.c.v.) and histidine (i.p.) administration ameliorated spatial memory deficits induced by MK-801 infusion, which was blocked by both H_1R and H_2R antagonists (Xu et al. 2005). These findings indicate that the exogenous application of histamine facilitates memory retrieval. In addition, the role of endogenous histamine in memory retrieval was examined. A pretest injection of H_1 receptor antagonists blocks the active avoidance response and contextual conditioned fear response (Nishiga et al. 2003; Nonaka et al. 2013). Depletion of histamine 1 day after training impairs the inhibitory avoidance response, which is rescued by a histamine infusion into the CA1 before the retention test (Fabbri et al. 2016). The effect of H_3R antagonists/inverse agonists is consistent with the facilitating effect of histamine on memory retrieval. Systemic administration of an H_3R antagonist prior to the memory test enhances the retrieval of social memory (Prast et al. 1996).

Forgotten memories persist latently in the brain because they are occasionally and spontaneously recollected. A few

animal studies have shown that long-term and/or highly invasive manipulation recovers retrograde amnesia. For example, chronic treatment with a histone deacetylase inhibitor and optogenetic activation of memory engram neurons restore forgotten fear memory (Fischer et al. 2007; Ryan et al. 2015). Treatment with H_3R antagonists/inverse agonists is a more clinically applicable method. A single administration of an H_3R antagonist/inverse agonist prevents natural forgetting in a novel object recognition task (Pascoli et al. 2009). Rats discriminate novel and familiar objects after the administration of the H_3R antagonist/inverse agonist in a memory test conducted 24 h following training, while control rats do not discriminate the two objects in the test. The improvement of memory retrieval requires the activation of both H_1R and H_2R. From a clinical perspective, an important goal is to determine whether H_3R antagonists/inverse agonists induce recovery long after learning and forgetting. We examined the effect of H_3R antagonists/inverse agonists (thioperamide and betahistine) on forgotten novel object recognition memories long after learning and forgetting to answer this question (Nomura et al. 2019). While control mice did not discriminate the novel and familiar objects 3 days after training, the mice receiving thioperamide discriminated the two objects 3 days, 1 week, and 1 month after training. Betahistine-treated mice also discriminated the two objects 1 week after the training. Based on these results, H_3R antagonists/inverse agonists recover the retrieval of forgotten memories long after learning. The recovery effect on memory retrieval depends on histamine release and H_2R activation in the perirhinal cortex (PRh) because an i.p. administration of thioperamide promoted histamine release in the PRh, the recovery effect was blocked by a local infusion of H_2R antagonist into the PRh, and an intra-PRh infusion of thioperamide mimicked the recovery effect. Therefore, we documented that H_3R antagonists/inverse agonists promote the retrieval of forgotten long-term memory through H_2R activation in the PRh (Nomura et al. 2019).

The enhanced retrieval may be due to histamine-induced excitatory effects (Figure 1B). H_1R activation exerts to an excitatory effect on neurons in most brain regions, including the hippocampus (Selbach et al. 1997; Manahan-Vaughan et al. 1998) and cerebral cortex (Reiner and Kamondi 1994). This excitatory effect involves a decrease in the leak K^+ current (Reiner and Kamondi 1994). H_2R is also involved in histamine-induced excitatory effects through several mechanisms. H_2R activation increases intracellular cAMP and activates PKA, which inhibits afterhyperpolarization by inhibiting Ca^{2+}-dependent K^+ channels, resulting in increased neuronal excitability. In addition, cAMP directly acts on the hyperpolarization-activated cation channel HCN2, leading to depolarization (Pedarzani and Storm 1995). Furthermore, H_2R activation suppresses the activity of inhibitory interneurons through $K_{v3.2}$-containing K^+ channels, and this effect also contributes to histamine-dependent modulation of neural network activity (Atzori et al. 2000). These excitatory effects of histamine may be related to its ability to promote memory retrieval. In fact, the depolarization of PRh neurons mimics the recovery of memory retrieval that is induced by an H_3R antagonist/inverse agonist injection (Nomura et al. 2019). When the excitability of PRh neurons is increased by a Designer Receptors Exclusively Activated by Designer Drug (DREADD) before the memory test, forgotten object memories are recovered by enhancing retrieval. Taken together, these findings suggest that the histamine-induced increase in neuronal excitability through H_1R and/or H_2R activation enhances memory retrieval.

How does the increased neuronal excitability facilitate memory retrieval? According to recent studies, memory retrieval is mediated by the selective reactivation of neuronal populations that were active during learning (Josselyn et al. 2015; Tonegawa et al. 2015). For example, a population of neurons in the BLA that is active during fear conditioning is reactivated during subsequent retrieval of fear memory (Reijmers et al. 2007; Nonaka et al. 2014;

Nakayama et al. 2014). Synaptic potentiation occurs specifically in the subpopulation of neurons active during fear conditioning (Nonaka et al. 2014). In addition, optogenetic activation of hippocampal dentate gyrus neurons that were active during fear conditioning triggers memory retrieval (Liu et al. 2012). Different memories appear to be stored in different subsets of neurons because the retrieval of different fear memories activates different subsets of amygdalar neurons (Nomura et al. 2012). These findings have prompted the hypothesis that the retrieval of individual memories requires specific reactivation of the responsible neurons. However, because histamine receptors are not exclusively expressed in neurons that were recruited into a memory trace, histamine may increase neuronal excitability throughout the neural circuit, including both neurons that were and were not recruited into the memory trace, similar to noise added to the neural circuits for memory retrieval. Here, stochastic resonance can explain how adding noise to the circuit enhances memory retrieval. Stochastic resonance is a phenomenon in which the addition of noise to a signal that is undetectable because it is smaller than a threshold causes the signal to exceed the threshold and become detectable. It has been used to explain various phenomena in biology and physics (Fauve and Heslot 1983; McDonnell and Ward 2011). The explanation of memory retrieval through stochastic resonance is provided below (Figure 2). When a subject re-encounters a stimulus that the subject memorized in the past, the memory of the stimulus is recalled correctly if neurons recruited into the memory trace are reactivated. However, as time passes after learning, when those neurons become less active and their activity is below the threshold for memory retrieval, the subject does not recall the memory. If histamine is present and increases neuronal excitability throughout the circuit, the activity of some of the neurons recruited into the memory trace will exceed the threshold. The activity of these neurons is presumed to allow the memory to be recalled. In fact, histamine has been shown to specifically

promote reactivation of neurons activated during learning (Nomura et al. 2019).

Moreover, gamma oscillations, which are rhythmic activities in local field potentials that span a range of frequencies between 30 and 120 Hz, might link histamine to memory retrieval. Slow gamma oscillations have been proposed to support memory retrieval since place cells in the hippocampus code familiar spatial trajectories during slow gamma oscillations (Zheng et al. 2016). Gamma oscillations are altered in patients with various neurological diseases, including Alzheimer's disease (AD), and in AD mouse models (Herrmann and Demiralp 2005; Van Deursen et al. 2008; Goutagny et al. 2013; Mably et al. 2017; Mondragón-Rodríguez et al. 2018). At a causal level, optogenetic gamma stimulation rescues memory retrieval impairments in an AD mouse model (Etter et al. 2019). The optogenetic stimulation of medial septal parvalbumin neurons at 40 Hz restores slow gamma oscillations in the hippocampus and rescues memory performance in the novel object place recognition task when it was performed during a memory test session. Based on these data, gamma oscillations are linked to memory retrieval. Histamine modulates gamma oscillations in the hippocampus and cortex. In hippocampal slices, histamine promotes gamma oscillations via H_1R activation in a KCNQ channel-dependent manner (Andersson et al. 2017). In a mouse model of Parkinson's disease based on 6-hydroxydopamine (6-OHDA), kainate-induced gamma oscillations are reduced in hippocampal slices. When 6-OHDA-treated mice are injected with H_3R antagonists for 3 days before slice preparation, the slice generates gamma oscillations comparable to sham mice (Masini et al. 2017). The effects of histamine on promoting gamma oscillations have also been confirmed *in vivo*. A local histamine infusion into the medial entorhinal cortex (MEC) increases gamma power in the MEC, which is blocked by H_1R and H_3R antagonists (Chen et al. 2018). Taken together, these findings suggest that histamine promotes memory retrieval possibly by increasing gamma oscillations.

Histamine and other memory processes

There are other processes that mediate memory storage and expression and are sensitive to drugs. In general, memory consolidation requires cellular and molecular changes that occur within several hours after learning (Hashikawa et al. 2011; Johansen et al. 2011). Blocking these changes leads to a memory deficit 24 h after learning. In addition to rapid changes, delayed molecular changes (e.g., c-Fos and Arc) occur 12-24 h after learning (Bekinschtein et al. 2007; Rossato et al. 2009; Nakayama et al. 2015) and retrieval (Nakayama et al. 2013; Nakayama et al. 2016). Blocking the delayed molecular changes prevents memory expression 7 days but not 2 days after learning, indicating that the maintenance of long-term memories requires delayed molecular changes following learning. Delayed Arc expression is suggested to induce the elimination of dendritic spines, leading to a refinement of functional memory circuits (Nakayama et al. 2015). Another memory stabilization process occurs after memory retrieval. Memory retrieval renders a consolidated memory labile again, and another round of consolidation and reconsolidation is required for its stabilization (Nader et al. 2000). Reconsolidation is sensitive to many types of drugs (Nader et al. 2000; Nomura and Matsuki 2008; Kindt et al. 2009), and blocking reconsolidation of fear memories has been proposed to be a medical treatment for posttraumatic stress disorder (PTSD). Although brief exposure to a conditioned stimulus (CS) induces reconsolidation in a classical conditioning paradigm, repeated or long-term exposure to CS extinguishes conditioned responses (Myers and Davis 2007). The extinction of conditioned responses is not permanent because CS reappears after the presentation of an unconditioned stimulus and is spontaneously recovered over time (Shen et al. 2013; Hitora-Imamura et al. 2015). Enhancing fear extinction and/or blocking fear reinstatement and spontaneous

recovery are important for treating PTSD. Long-term storage of memories over weeks, months, or years requires the reorganization of the brain network at the systems level (Frankland and Bontempi 2005; Klinzing et al. 2019). This long-term consolidation across brain areas is known as systems consolidation. Although the mechanisms of a variety of memory processes partially overlap with those of early consolidation, different mechanisms have also been proposed at the levels of molecules, cells, and circuits (Alberini 2005; Myers and Davis 2007; Nakayama et al. 2015; Tonegawa et al. 2018). Therefore, the effect of histamine on each memory process should be examined separately to elucidate the whole picture of the effects of histamine on learning and memory. The involvement of some neuromodulators in these memory processes has been studied over the past 20 years. Dopamine D1R is involved in delayed steps 12 hours after learning, contributing to memory persistence (Rossato et al. 2009). D1R is also critical for fear reinstatement, as blocking prefrontal D1R prevents synaptic depression, changes in amygdala activity, and the reappearance of conditioned fear induced by a reminder shock (Hitora-Imamura et al. 2015). In contrast, a very limited number of studies have analyzed the effects of histamine on memory processes other than initial learning and retrieval. For example, an intra-CA1 infusion of histamine facilitates the consolidation of fear extinction memory through H_2R-dependent activation of ERK signaling (Bonini et al. 2011). H_3R antagonists reverse the deficit in reconsolidation induced by NMDAR antagonists, although H_3R antagonists alone do not influence memory reconsolidation (Charlier and Tirelli 2011; Brabant et al. 2013). Further studies are needed to understand the overall role of histamine in various memory processes.

Effects of the genetic manipulation of histamine signaling on learning and memory

Among studies using genetically modified mice, some reports support the hypothesis that histamine promotes learning and memory, but the opposite results have also been reported. Chronic brain histamine depletion in adulthood via a local infusion of an adeno-associated virus expressing Cre recombinase into the TMN of Hdc flox mice impairs aversive memory (Yamada et al. 2020). Both H_1R- and H_2R-deficient mice show impaired spatial memory in the Barnes maze and impaired object memory in the novel object recognition test (Dai et al. 2007; Zlomuzica et al. 2009; Ambrée et al. 2014). However, both H_1R- and H_2R-deficient mice show greater conditioned fear responses than wild-type mice in the fear conditioning test (Dai et al. 2007). HDC-deficient mice exhibit impaired object memory but enhanced conditioned fear responses in the fear conditioning test (Dere et al. 2003; Liu et al. 2007). In a study using male HDC-deficient mice, spatial memory in the water maze task was shown to be enhanced (Dere et al. 2003), but another study using female mice showed a deficit of spatial memory in HDC-deficient mice (Acevedo et al. 2006). H_3R-deficient mice show enhanced spatial memory in the Barnes maze but comparable object recognition and location memories in the novel location and object recognition tasks compared to wild-type controls (Rizk et al. 2004). The contradictory findings may be due to the long-term manipulation of gene expression in the mutant mice. Conventional genetically modified mice may not be appropriate to analyze the role of histamine signaling in learning and memory because histamine signaling is modified outside of the time of learning and in various brain areas. Future studies using spatial- and/or temporal-specific genetic manipulation of histamine signaling are needed to improve our understanding of the role of histamine in specific memory processes.

Activity of histamine neurons *in vitro* and *in vivo*

The activity of histamine neurons during memory processing must be elucidated to understand the contributions of histamine to learning and memory. Histamine neurons show a slow regular firing pattern *in vitro* and *in vivo* (Reiner and McGeer 1987; Haas and Reiner 1988). Their action potentials are broad with slow rise and decay times, followed by a large afterhyperpolarization (Stevens et al. 2001). Recently, the development of genetically modified mice in which histamine neurons are labeled with a fluorescent protein has enabled the performance of electrophysiological recordings specifically from histamine neurons (Fujita et al. 2017; Michael et al. 2020). These studies showed that the electrophysiological properties of genetically identified histamine neurons are broadly consistent with classical observations. These properties are similar across subregions of the TMN and between male and female mice (Michael et al. 2020). In addition, unsupervised hierarchical cluster analysis revealed that histamine neurons are categorized into 2 subclasses, in which histamine type 1 neurons exhibit lower input resistance values, lower membrane time constants, greater afterhyperpolarization (AHP) amplitudes, shorter action potential half-widths, faster rise and decay times, and higher maximum firing rates than type 2 neurons (Fujita et al. 2017).

The activity of histamine neurons *in vivo* is dynamically modulated by the subject's internal state. Microdialysis studies have shown that extracellular histamine concentrations in the hypothalamus and cortex increase during wakefulness (Strecker et al. 2002; Chu et al. 2004). Electrophysiological analyses revealed that histamine neurons are active during wakefulness, but not drowsiness and NREM and REM sleep (Vanni-Mercier et al. 2003). This histamine activity has been proposed to play an important role in the maintenance of wakefulness. A motivational state may be another key modulator of the activity of histamine neurons. The presentation of inaccessible food to a fasted rat, but not a fed rat, increases c-Fos expression in histamine neurons and histamine release in the hypothalamus

(Valdés et al. 2005; Valdés et al. 2010). The deprivation of anticipated food under scheduled feeding also induces c-Fos expression in histamine neurons (Umehara et al. 2010; Umehara et al. 2011). Therefore, histamine neurons are active during the appetitive phase of feeding. Furthermore, histamine neurons appear responsive to other motivational states. Exposure of male rats to proestrus female rats increases c-Fos expression in the TMN of male rats (Contreras et al. 2016). In contrast, exposure to diestrus female rats has no effect on c-Fos expression. Although water deprivation has no effect on c-Fos expression in the TMN, the presentation of an empty water bottle to thirsty rats increases c-Fos expression in the TMN (Contreras et al. 2016). Taken together, these findings indicate an increase in the activity of histamine neurons when subjects are awake and motivated. The dynamics of arousal and motivation during and after memory tasks might influence memory processing through histamine signaling. Future studies using activity recordings from genetically identified histamine neurons (e.g., calcium imaging, unit recordings from opto-tagged cells (Williams et al. 2014)) will elucidate the activity dynamics of histamine neurons and their effects on learning and memory.

Human histaminergic system and memory

Based on the findings from the animal studies described above, studies have also assessed whether H_3R antagonists/inverse agonists improve memories in humans (Sadek et al. 2016; Provensi et al. 2020). Because pretest administration of betahistine (H_3R antagonist and weak H_1R agonist) improves the retrieval of 1-week-old forgotten object memory in mice, we conducted a randomized double-blind, placebo-controlled crossover trial to determine whether pretest treatment with betahistine improves object recognition memory 1 week after learning in humans

(Nomura et al. 2019). During the learning session, 38 healthy participants studied serial images of 128 objects. Seven and 9 days after learning, we administered 108 mg of betahistine or placebo orally 30 min before the test session started. The participants were asked whether they had seen the target images during the learning phase. Betahistine treatment increased the overall correct ratio. More specifically, betahistine improved the correct rate to a greater extent in subjects with poorer performance after the placebo treatment. On the other hand, a study with healthy participants showed that betahistine (48 mg) had no effect on performance in working memory and paired associates learning tasks (van Ruitenbeek and Mehta 2013). The effects of H_3R antagonists/inverse agonists may depend on the dose, task difficulty, and/or memory type.

Several lines of evidence support the hypothesis that the histaminergic system is altered in several neuropsychiatric disorders, suggesting a possible role of the histaminergic system in cognitive impairments in these disorders (Shan et al. 2017). A positron emission tomography study using a radioligand for H_1R revealed that the binding potential of H_1R is reduced in the frontal and temporal areas of patients with AD (Higuchi et al. 2000). Receptor binding correlated with the severity of AD. The binding of H_2R is not altered in the prefrontal cortex of patients with AD (Perry et al. 1998). The number of HDC-positive neurons in the TMN is reduced in the brains of individuals with AD (Oh et al. 2019), although HDC mRNA expression in the TMN is not altered in patients with AD (Shan et al. 2012). While some studies reported decreased histamine levels in the hippocampus, frontal cortex, and temporal cortex of postmortem brain tissues from patients with AD (Mazurkiewicz-Kwilecki and Nsonwah 1989; Panula et al. 1997), others reported increased histamine levels in the frontal cortex, basal ganglia, and hippocampus (Cacabelos et al. 1989). A study using postmortem brain samples from patients with AD showed that H_3R binding in the frontal cortex

correlates with dementia severity, while H_3R binding is not different between the brains of individuals with AD and age-matched controls (Medhurst et al. 2009). In patients with nonsyndromic autosomal recessive intellectual disability, two homozygous HMT mutations (p.Gly60Asp and p.Leu208Pro) have been identified (Heidari et al. 2015). The p.Gly60Asp mutation disrupts the enzymatic activity of HMT, and p.Leu208Pro leads to the instability of HMT. However, HNMT-deficient mice show no deficit in the passive avoidance test (Naganuma et al. 2017).

Clinical trials are currently underway to test whether H_3R antagonists/inverse agonists improve cognitive impairments in patients with AD. A randomized, double-blind, placebo-controlled study with 8 patients with mild to moderate AD showed that treatments with GSK239512, an H_3R antagonist, for 4 weeks exert positive effects on memory (J. Nathan et al. 2013). In addition, a study with 99 placebo-treated subjects and 97 GSK239512-treated subjects revealed that GSK239512 treatments for 16 weeks improved episodic memory, although the treatments had no significant effect on other cognitive domains (Grove et al. 2014). Further studies with larger populations are needed to test whether H_3R antagonists/inverse agonists improve learning and memory in patients with AD.

Conclusions and perspectives

Behavioral pharmacological studies have provided a large amount of evidence supporting the hypothesis that histamine improves memory consolidation and retrieval. Although we introduced candidates for the underlying mechanisms in this review, most of them have not yet been tested *in vivo*. De novo gene expression is essential for memory consolidation. The mechanism by which histamine modulates gene expression following learning and how the modulation of gene expression regulates the cellular machinery responsible for memory consolidation remain

elusive. Although we have provided evidence that histamine augments the reactivation of neurons that were active during learning in slices(Nomura et al. 2019), the mechanism by which histamine modulates neuronal activity *in vivo* remains to be elucidated. Recently, imaging of activity across large populations of neurons during naturalistic behavior, including learning and memory, has been performed in vivo (Resendez et al. 2016). Optogenetics and DREADDs enable the manipulation of neuronal activities in a cell type-specific manner. Further studies using these imaging and manipulation techniques will elucidate the mechanisms by which histamine improves memory consolidation and retrieval. Few studies have examined the effects of histamine on other memory processes, such as memory maintenance, memory reconsolidation, extinction memory, reinstatement, and systems consolidation. An understanding of these effects will require separate analyses of memory processes, including temporally and spatially restricted genetic manipulation. Because clinical trials of H_3R antagonists/inverse agonists with a small number of participants showed positive effects on memory, histamine likely improves learning and memory in humans. Clinical trials with larger populations are expected to test whether histamine is a novel target for improving cognitive impairments in patients with neuropsychiatric disorders.

Acknowledgments

This work was partly supported by grants from JSPS KAKENHI (No. 20H03551 to HN and No. 20K21557 to HN) and MEXT KAKENHI (No. 20H05045 to HN and No. 21H00296 to HN).

Figures

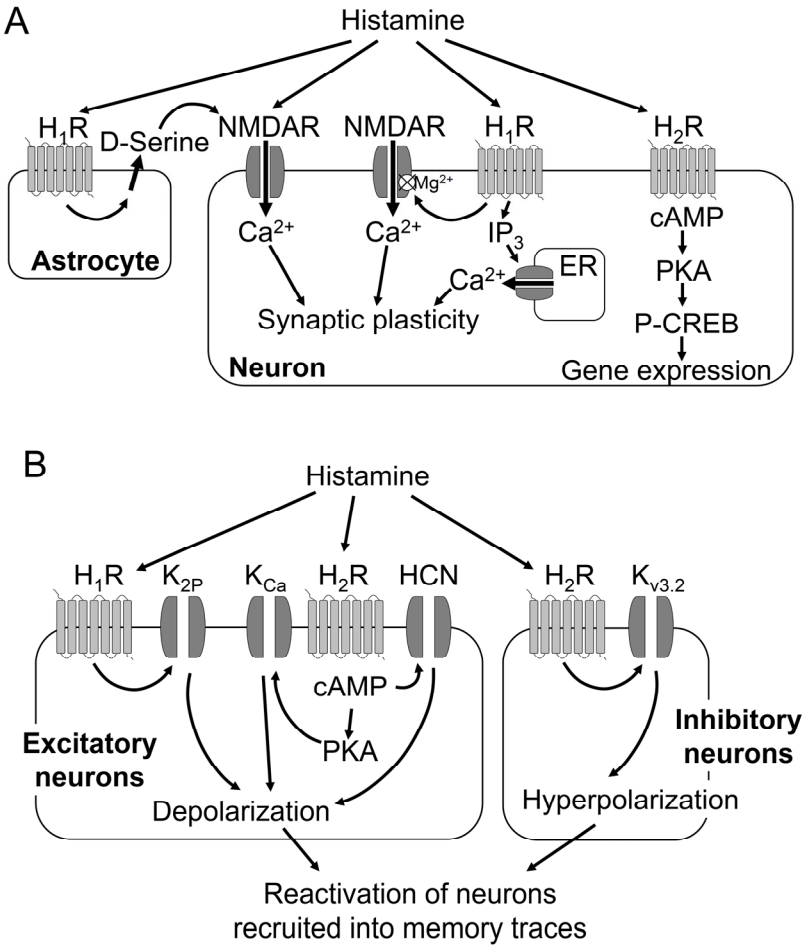

Figure 1. Possible mechanisms by which histamine enhances memory consolidation and retrieval. (A) H_2R activation leads to the phosphorylation of CREB, which is a critical transcription factor for memory consolidation. Histamine increases synaptic plasticity possibly by enhancing NMDA function and/or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

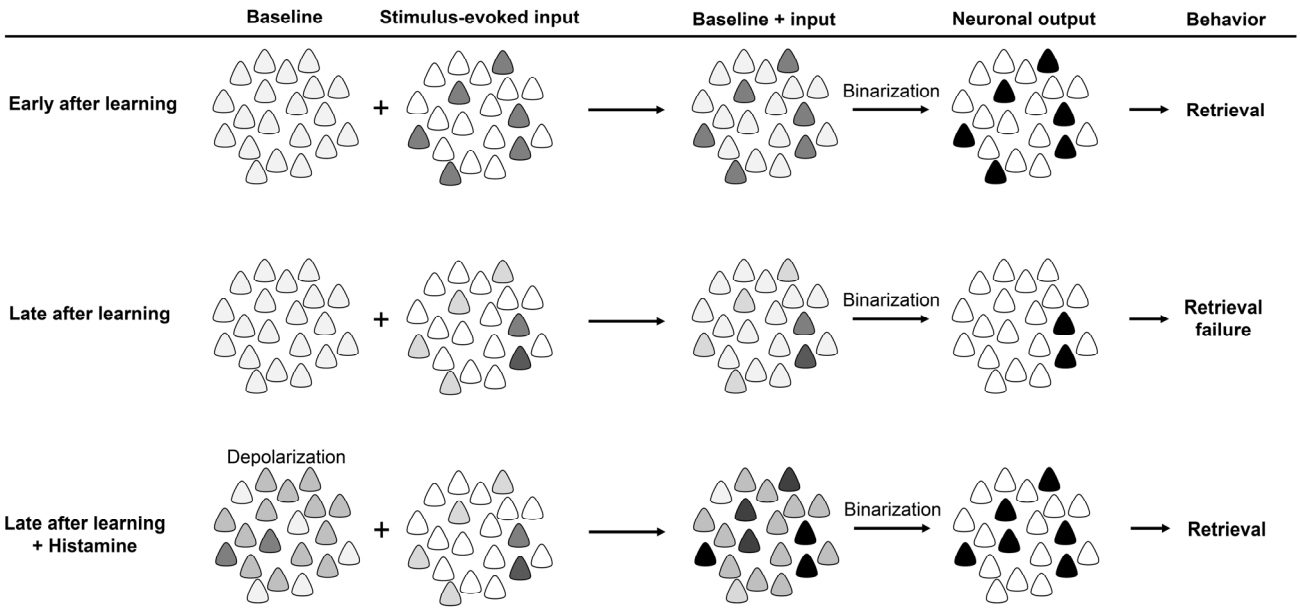

Figure 2. A stochastic resonance model explaining how histamine enhances memory retrieval. Early after learning, when a subject re-encounters a stimulus that he/she memorized in the past, the stimulus-evoked input is sufficiently large to activate neurons recruited into a memory trace (memory neurons), which leads to memory retrieval. However, as time passes after learning, the stimulus-evoked input is smaller than the threshold and the memory neurons are not activated, which results in retrieval failure. When histamine is present and increases neuronal excitability throughout the neural circuit, the activity of some memory neurons exceeds the threshold, even if the stimulus-evoked input is small. The activity of these neurons induces memory retrieval.

References

Acevedo SF, Pfankuch T, Ohtsu H, Raber J (2006) Anxiety and cognition in female histidine decarboxylase knockout (Hdc -/-) mice. Behav Brain Res 168(1):92–99. https://doi.org/10.1016/j.bbr.2005.10.016

Alberini CM (2005) Mechanisms of memory stabilization: are consolidation and reconsolidation similar or distinct processes? Trends Neurosci 28(1):51–6. https://doi.org/10.1016/j.tins.2004.11.001

Alraksinen MS, Paetau A, Palja¨rvi L, Reinikainen K, Rlekkinen P, Suomalainen R, Panula P (1991) Histamine neurons in human hypothalamus: Anatomy in normal and alzheimer diseased brains. Neuroscience 44(2):465–481. https://doi.org/10.1016/0306-4522(91)90070-5

Ambrée O, Buschert J, Zhang W, Arolt V, Dere E, Zlomuzica A (2014) Impaired spatial learning and reduced adult hippocampal neurogenesis in histamine H1-receptor knockout mice. Eur Neuropsychopharmacol 24(8):1394–1404. https://doi.org/10.1016/j.euroneuro.2014.04.006

Andersson R, Galter D, Papadia D, Fisahn A (2017) Histamine induces KCNQ channel-dependent gamma oscillations in rat hippocampus via activation of the H1 receptor. Neuropharmacology 118:13–25. https://doi.org/10.1016/j.neuropharm.2017.03.003

Arrang JM, Garbarg M, Schwartz JC (1983) Auto-inhibition of brain histamine release mediated by a novel class (H3) of histamine receptor. Nature 302(5911):832–7

Atzori M, Lau D, Tansey EP, Chow A, Ozaita A, Rudy B, McBain CJ (2000) H2 histamine receptor-phosphorylation of Kv3.2 modulates interneuron fast spiking. Nat Neurosci 3(8):791–798. https://doi.org/10.1038/77693

Beatty WW, Salmon DP, Butters N, Heindel WC, Granholm EL (1988) Retrograde amnesia in patients with Alzheimer's

disease or Huntington's disease. Neurobiol Aging 9(C):181–186. https://doi.org/10.1016/S0197-4580(88)80048-4

Bekinschtein P, Cammarota M, Katche C, Slipczuk L, Rossato JI, Goldin A, Izquierdo I, Medina JH (2007) BDNF is essential to promote persistence of long-term memory storage. :0–5

Bekkers JM (1993) Enhancement by histamine of NMDA-mediated synaptic transmission in the hippocampus. Science 261(5117):104–106. https://doi.org/10.1126/science.8391168

Benetti F, Guerino Furini CR, De Carvalho Myskiw J, Provensi G, Passani MB, Baldi E, Bucherelli C, Munari L, Izquierdo I, Blandina P (2015) Histamine in the basolateral amygdala promotes inhibitory avoidance learning independently of hippocampus. Proc Natl Acad Sci U S A 112(19):E2536–E2542. https://doi.org/10.1073/pnas.1506109112

Benetti F, Izquierdo I (2013) Histamine infused into basolateral amygdala enhances memory consolidation of inhibitory avoidance. Int J Neuropsychopharmacol 16(7):1539–45. https://doi.org/10.1017/S1461145712001514

Best J, Nijhout HF, Samaranayake S, Hashemi P, Reed M (2017) A mathematical model for histamine synthesis, release, and control in varicosities. Theor Biol Med Model 14(1). https://doi.org/10.1186/s12976-017-0070-9

Blandina P, Efoudebe M, Cenni G, Mannaioni P, Passani MB (2004) Acetylcholine, Histamine, and Cognition: Two Sides of the Same Coin. Learn. Mem. 11:1–8

Blandina P, Giorgetti M, Bartolini L, Cecchi M, Timmerman H, Leurs R, Pepeu G, Giovannini MG (1996a) Inhibition of cortical acetylcholine release and cognitive performance by histamine H3 receptor activation in rats. Br J Pharmacol 119(8):1656–1664. https://doi.org/10.1111/j.1476-5381.1996.tb16086.x

Blandina P, Giorgetti M, Cecchi M, Leurs R, Timmerman H, Giovannini MG (1996b) Histamine H3 receptor inhibition

of K(+)-evoked release of acetylcholine from rat cortex in vivo. Inflamm Res 45 Suppl 1:S54-5

Blandina P, Munari L, Provensi G, Passani MB (2012) Histamine neurons in the tuberomamillary nucleus: A whole center or distinct subpopulations? Front. Syst. Neurosci. 6

Bliss TVP, Collingridge GL (1993) A synaptic model of memory: Long-term potentiation in the hippocampus. Nature 361:31–39

Bonini JS, Da Silva WC, Da Silveira CKB, Köhler CA, Izquierdo I, Cammarota M (2011) Histamine facilitates consolidation of fear extinction. Int J Neuropsychopharmacol 14(9):1209–17. https://doi.org/10.1017/S1461145710001501

Bourtchuladze R, Frenguelli B, Blendy J, Cioffi D, Schutz G, Silva a J (1994) Deficient long-term memory in mice with a targeted mutation of the cAMP-responsive element-binding protein. Cell 79(1):59–68

Brabant C, Charlier Y, Tirelli E (2013) The histamine H3-receptor inverse agonist Pitolisant improves fear memory in mice. Behav Brain Res 243(1):199–204. https://doi.org/10.1016/j.bbr.2012.12.063

Brown RE, Fedorov NB, Haas HI, Reyman KG (1995) Histaminergic modulation of synaptic plasticity in area CA1 of rat hippocampal slices. Neuropharmacology 34(2):181–190. https://doi.org/10.1016/0028-3908(94)00138-I

Burban A, Faucard R, Armand V, Bayard C, Vorobjev V, Arrang JM (2010) Histamine potentiates N-methyl-D-aspartate receptors by interacting with an allosteric site distinct from the polyamine binding site. J Pharmacol Exp Ther 332(3):912–921. https://doi.org/10.1124/jpet.109.158543

Cacabelos R, Yamatodani A, Niigawa H, Hariguchi S, Tada K, Nishimura T, Wada H, Brandeis L, Pearson J (1989) Brain histamine in Alzheimer's disease. Methods Find Exp Clin Pharmacol 11(5):353–360

Cangioli I, Baldi E, Mannaioni PF, Bucherelli C, Blandina P, Passani MB (2002) Activation of histaminergic H3 receptors in the rat basolateral amygdala improves expression of fear memory and enhances acetylcholine release. In: European Journal of Neuroscience. Eur J Neurosci, pp 521–528

Charlier Y, Tirelli E (2011) Differential effects of histamine H 3 receptor inverse agonist thioperamide, given alone or in combination with the N-methyl-d-aspartate receptor antagonist dizocilpine, on reconsolidation and consolidation of a contextual fear memory in mice. Neuroscience 193:132–142. https://doi.org/10.1016/j.neuroscience.2011.07.034

Chen Q, Luo F, Yue F, Xia J, Xiao Q, Liao X, Jiang J, Zhang J, Hu B, Gao D, He C, Hu Z (2018) Histamine Enhances Theta-Coupled Spiking and Gamma Oscillations in the Medial Entorhinal Cortex Consistent With Successful Spatial Recognition. Cereb Cortex 28:2439–2457. https://doi.org/10.1093/cercor/bhx145

Chu M, Huang ZL, Qu WM, Eguchi N, Yao MH, Urade Y (2004) Extracellular histamine level in the frontal cortex is positively correlated with the amount of wakefulness in rats. Neurosci Res 49(4):417–420. https://doi.org/10.1016/j.neures.2004.05.001

Contreras M, Riveros ME, Quispe M, Sanchez C, Perdomo G, Torrealba F, Valdes JL (2016) The Histaminergic Tuberomamillary Nucleus Is Involved in Appetite for Sex, Water and Amphetamine. PLoS One 11(2). https://doi.org/10.1371/journal.pone.0148484

da Silva WC, Bonini JS, Bevilaqua LRM, Izquierdo I, Cammarota M (2006) Histamine enhances inhibitory avoidance memory consolidation through a H2 receptor-dependent mechanism. Neurobiol Learn Mem 86(1):100–6. https://doi.org/10.1016/j.nlm.2006.01.001

da Silveira CKB, Furini CRG, Benetti F, Monteiro SDC, Izquierdo I (2013) The role of histamine receptors in the

consolidation of object recognition memory. Neurobiol Learn Mem 103:64–71. https://doi.org/10.1016/j.nlm.2013.04.001

Dai H, Kaneko K, Kato H, Fujii S, Jing Y, Xu A, Sakurai E, Kato M, Okamura N, Kuramasu A, Yanai K (2007) Selective cognitive dysfunction in mice lacking histamine H1 and H2 receptors. Neurosci Res 57(2):306–13. https://doi.org/10.1016/j.neures.2006.10.020

de Almeida MA, Izquierdo I (1986) Memory facilitation by histamine. Arch Int Pharmacodyn Ther 283(2):193–8

Dere E, De Souza-Silva MA, Topic B, Spieler RE, Haas HL, Huston JP (2003) Histidine-decarboxylase knockout mice show deficient nonreinforced episodic object memory, improved negatively reinforced water-maze performance, and increased neo- and ventro-striatal dopamine turnover. Learn Mem 10(6):510–9. https://doi.org/10.1101/lm.67603

Ellenbroek BA, Ghiabi B (2014) The other side of the histamine H3 receptor. Trends Neurosci 37(4):191–199. https://doi.org/10.1016/j.tins.2014.02.007

Ericson H, Watanabe T, Köhler C (1987) Morphological analysis of the tuberomammmillary nucleus in the rat brain: Delineation of subgroups with antibody again L-histidine decarboxylase as a marker. J Comp Neurol 263(1):1–24. https://doi.org/10.1002/cne.902630102

Esbenshade TA, Browman KE, Bitner RS, Strakhova M, Cowart MD, Brioni JD (2008) The histamine H_3 receptor: an attractive target for the treatment of cognitive disorders. Br J Pharmacol 154(6):1166–1181. https://doi.org/10.1038/bjp.2008.147

Etter G, van der Veldt S, Manseau F, Zarrinkoub I, Trillaud-Doppia E, Williams S (2019) Optogenetic gamma

stimulation rescues memory impairments in an Alzheimer's disease mouse model. Nat Commun 10(1). https://doi.org/10.1038/s41467-019-13260-9

Fabbri R, Furini CRG, Passani MB, Provensi G, Baldi E, Bucherelli C, Izquierdo I, De Myskiw JC, Blandina P (2016) Memory retrieval of inhibitory avoidance requires histamine H¥1¥ receptor activation in the hippocampus. Proc Natl Acad Sci U S A 113(19):E2714–E2720. https://doi.org/10.1073/pnas.1604841113

Fauve S, Heslot F (1983) Stochastic resonance in a bistable system. Phys Lett A 97(1–2):5–7. https://doi.org/10.1016/0375-9601(83)90086-5

Fischer A, Sananbenesi F, Wang X, Dobbin M, Tsai L-H (2007) Recovery of learning and memory is associated with chromatin remodelling. Nature 447(7141):178–82. https://doi.org/10.1038/nature05772

Frankland PW, Bontempi B (2005) The organization of recent and remote memories. Nat Rev Neurosci 6(2):119–30. https://doi.org/10.1038/nrn1607

Fujita A, Bonnavion P, Wilson MH, Mickelsen LE, Bloit J, de Lecea L, Jackson AC (2017) Hypothalamic tuberomammillary nucleus neurons: electrophysiological diversity and essential role in arousal stability. J Neurosci 37(39):0580–17. https://doi.org/10.1523/JNEUROSCI.0580-17.2017

Giannoni P, Passani MB, Nosi D, Chazot PL, Shenton FC, Medhurst AD, Munari L, Blandina P (2009) Heterogeneity of histaminergic neurons in the tuberomammillary nucleus of the rat. Eur J Neurosci 29(12):2363–2374. https://doi.org/10.1111/j.1460-9568.2009.06765.x

Goutagny R, Gu N, Cavanagh C, Jackson J, Chabot JG, Quirion R, Krantic S, Williams S (2013) Alterations in hippocampal network oscillations and theta-gamma coupling arise before Aβ overproduction in a mouse model of

Alzheimer's disease. Eur J Neurosci 37(12):1896–1902. https://doi.org/10.1111/ejn.12233

Grove RA, Harrington CM, Mahler A, Beresford I, Maruff P, Lowy MT, Nicholls AP, Boardley RL, Berges AC, Nathan PJ, Horrigan JP (2014) A randomized, double-blind, placebo-controlled, 16-week study of the H3 receptor antagonist, GSK239512 as a monotherapy in subjects with mild-to-moderate Alzheimer's disease. Curr Alzheimer Res 11(1):47–58

Haas H, Panula P (2003) The role of histamine and the tuberomamillary nucleus in the nervous system. Nat Rev Neurosci 4(2):121–130. https://doi.org/10.1038/nrn1034

Haas HL, Reiner PB (1988) Membrane properties of histaminergic tuberomammillary neurones of the rat hypothalamus in vitro. J Physiol 399(1):633–646. https://doi.org/10.1113/jphysiol.1988.sp017100

Haas HL, Sergeeva OA, Selbach O (2008) Histamine in the nervous system. Physiol Rev 88(3):1183–241. https://doi.org/10.1152/physrev.00043.2007

Hashikawa K, Matsuki N, Nomura H (2011) Preferential Arc transcription at rest in the active ensemble during associative learning. Neurobiol Learn Mem 95(4):498–504. https://doi.org/10.1016/j.nlm.2011.02.013

Heidari A, Tongsook C, Najafipour R, Musante L, Vasli N, Garshasbi M, Hu H, Mittal K, McNaughton AJM, Sritharan K, Hudson M, Stehr H, Talebi S, Moradi M, Darvish H, Rafiq MA, Mozhdehipanah H, Rashidinejad A, Samiei S, Ghadami M, Windpassinger C, Gillessen-Kaesbach G, Tzschach A, Ahmed I, Mikhailov A, James Stavropoulos D, Carter MT, Keshavarz S, Ayub M, Najmabadi H, Liu X, Ropers HH, Macheroux P, Vincent JB (2015) Mutations in the histamine N-methyltransferase gene, HNMT, are associated with nonsyndromic autosomal recessive intellectual disability. Hum Mol Genet 24(20):5697–5710. https://doi.org/10.1093/hmg/ddv286

Herrmann CS, Demiralp T (2005) Human EEG gamma oscillations in neuropsychiatric disorders. Clin. Neurophysiol. 116:2719–2733

Higuchi M, Yanai K, Okamura N, Meguro K, Arai H, Itoh M, Iwata R, Ido T, Watanabe T, Sasaki H (2000) Histamine H1 receptors in patients with Alzheimer's disease assessed by positron emission tomography. Neuroscience 99(4):721–729. https://doi.org/10.1016/S0306-4522(00)00230-X

Hitora-Imamura N, Miura Y, Teshirogi C, Ikegaya Y, Matsuki N, Nomura H (2015) Prefrontal dopamine regulates fear reinstatement through the downregulation of extinction circuits. Elife 4. https://doi.org/10.7554/eLife.08274

Introini-Collison IB, Dalmaz C, McGaugh JL (1996) Amygdala β-noradrenergic influences on memory storage involve cholinergic activation. Neurobiol Learn Mem 65(1):57–64. https://doi.org/10.1006/nlme.1996.0006

J. Nathan P, Boardley R, Scott N, Berges A, Maruff P, Sivananthan T, Upton N, T. Lowy M, J. Nestor P, Lai R (2013) The Safety, Tolerability, Pharmacokinetics and Cognitive Effects of GSK239512, a Selective Histamine H_3 Receptor Antagonist in Patients with Mild to Moderate Alzheimer's Disease: A Preliminary Investigation. Curr Alzheimer Res 10(3):240–251. https://doi.org/10.2174/1567205011310030003

Johansen JP, Cain CK, Ostroff LE, LeDoux JE (2011) Molecular mechanisms of fear learning and memory. Cell 147(3):509–24. https://doi.org/10.1016/j.cell.2011.10.009

Josselyn SA, Köhler S, Frankland PW (2015) Finding the engram. Nat Rev Neurosci 16(9):521–534. https://doi.org/10.1038/nrn4000

Kamei C, Tasaka K (1993) Effect of Histamine on Memory Retrieval in Old Rats. Biol Pharm Bull 16(2):128–132. https://doi.org/10.1248/bpb.16.128

Kárpáti A, Yoshikawa T, Naganuma F, Matsuzawa T, Kitano H, Yamada Y, Yokoyama M, Futatsugi A, Mikoshiba K, Yanai K (2019) Histamine H1 receptor on astrocytes and neurons controls distinct aspects of mouse behaviour. Sci Rep 9(1). https://doi.org/10.1038/s41598-019-52623-6

Katoh Y, Niimi M, Yamamoto Y, Kawamura T, Morimoto-Ishizuka T, Sawada M, Takemori H, Yamatodani A (2001) Histamine production by cultured microglial cells of the mouse. Neurosci Lett 305(3):181–184. https://doi.org/10.1016/S0304-3940(01)01835-3

Kida S, Josselyn S a, Peña de Ortiz S, Kogan JH, Chevere I, Masushige S, Silva AJ (2002) CREB required for the stability of new and reactivated fear memories. Nat Neurosci 5(4):348–55. https://doi.org/10.1038/nn819

Kindt M, Soeter M, Vervliet B (2009) Beyond extinction: erasing human fear responses and preventing the return of fear. Nat Neurosci 12(3):256–8. https://doi.org/10.1038/nn.2271

Kitamura T, Inokuchi K (2014) Role of adult neurogenesis in hippocampal-cortical memory consolidation. Mol. Brain 7

Klinzing JG, Niethard N, Born J (2019) Mechanisms of systems memory consolidation during sleep. Nat Neurosci :1–13. https://doi.org/10.1038/s41593-019-0467-3

Köhler CA, da Silva WC, Benetti F, Bonini JS (2011) Histaminergic mechanisms for modulation of memory systems. Neural Plast 2011:328602. https://doi.org/10.1155/2011/328602

Kopelman MD, Bright P (2012) On remembering and forgetting our autobiographical pasts: Retrograde amnesia and Andrew Mayes's contribution to neuropsychological method. Neuropsychologia 50(13):2961–2972. https://doi.org/10.1016/j.neuropsychologia.2012.07.028

Kuo MC, Dringenberg HC (2008) Histamine facilitates in vivo thalamocortical long-term potentiation in the mature

visual cortex of anesthetized rats. Eur J Neurosci 27(7):1731–1738. https://doi.org/10.1111/j.1460-9568.2008.06164.x

Lenz KM, Pickett LA, Wright CL, Davis KT, Joshi A, McCarthy MM (2018) Mast cells in the developing brain determine adult sexual behavior. J Neurosci 38(37):8044–8059. https://doi.org/10.1523/JNEUROSCI.1176-18.2018

Liao R, Chen Y, Cheng L, Fan L, Chen H, Wan Y, You Y, Zheng Y, Jiang L, Chen Z, Zhang X, Hu W (2019) Histamine H1 Receptors in Neural Stem Cells Are Required for the Promotion of Neurogenesis Conferred by H3 Receptor Antagonism following Traumatic Brain Injury. Stem Cell Reports 12(3):532–544. https://doi.org/10.1016/j.stemcr.2019.01.004

Liu L, Zhang S, Zhu YY, Fu Q, Zhu YY, Gong Y, Ohtsu H, Luo J, Wei E, Chen Z (2007) Improved learning and memory of contextual fear conditioning and hippocampal CA1 long-term potentiation in histidine decarboxylase knock-out mice. Hippocampus (8):634–641

Liu X, Ramirez S, Pang PT, Puryear CB, Govindarajan A, Deisseroth K, Tonegawa S (2012) Optogenetic stimulation of a hippocampal engram activates fear memory recall. Nature 484(7394):381–5. https://doi.org/10.1038/nature11028

Mably AJ, Gereke BJ, Jones DT, Colgin LL (2017) Impairments in spatial representations and rhythmic coordination of place cells in the 3xTg mouse model of Alzheimer's disease. Hippocampus 27(4):378–392. https://doi.org/10.1002/hipo.22697

Manahan-Vaughan D, Reymann KG, Brown RE (1998) In vivo electrophysiological investigations into the role of histamine in the dentate gyrus of the rat. Neuroscience 84(3):783–790. https://doi.org/10.1016/S0306-

4522(97)00540-X

Martin SJ, Grimwood PD, Morris RGM (2000) Synaptic plasticity and memory: An evaluation of the hypothesis. Annu. Rev. Neurosci. 23:649–711

Martinez-Mir MI, Pollard H, Moreau J, Arrang JM, Ruat M, Traiffort E, Schwartz JC, Palacios JM (1990) Three histamine receptors (H1, H2 and H3) visualized in the brain of human and non-human primates. Brain Res 526(2):322–7

Masini D, Lopes-Aguiar C, Bonito-Oliva A, Papadia D, Andersson R, Fisahn A, Fisone G (2017) The histamine H3 receptor antagonist thioperamide rescues circadian rhythm and memory function in experimental parkinsonism. Transl Psychiatry 7(4):e1088-9. https://doi.org/10.1038/tp.2017.58

Masuoka T, Ikeda R, Konishi S (2019) Persistent activation of histamine H 1 receptors in the hippocampal CA1 region enhances NMDA receptor-mediated synaptic excitation and long-term potentiation in astrocyte- and D-serine-dependent manner. Neuropharmacology 151:64–73. https://doi.org/10.1016/j.neuropharm.2019.03.036

Mazurkiewicz-Kwilecki IM, Nsonwah S (1989) Changes in the regional brain histamine and histidine levels in postmortem brains of Alzheimer patients. Can J Physiol Pharmacol 67(1):75–78. https://doi.org/10.1139/y89-013

McDonnell MD, Ward LM (2011) The benefits of noise in neural systems: bridging theory and experiment. Nat Rev Neurosci 12(7):415–426. https://doi.org/10.1038/nrn3061

Medhurst AD, Roberts JC, Lee J, Chen CPLH, Brown SH, Roman S, Lai MKP (2009) Characterization of histamine H 3 receptors in Alzheimer's Disease brain and amyloid over-expressing TASTPM mice. Br J Pharmacol 157(1):130–138. https://doi.org/10.1111/j.1476-5381.2008.00075.x

Meeter M, Eijsackers E V., Mulder JL (2006) Retrograde amnesia for autobiographical memories and public events in mild and moderate Alzheimer's disease. J. Clin. Exp. Neuropsychol. 28:914–927

Michael NJ, Zigman JM, Williams KW, Elmquist JK (2020) Electrophysiological Properties of Genetically Identified Histaminergic Neurons. Neuroscience 444:183–195. https://doi.org/10.1016/j.neuroscience.2020.06.031

Ming GL, Song H (2005) Adult neurogenesis in the mammalian central nervous system. Annu. Rev. Neurosci. 28:223–250

Molina-Hernández A, Velasco I (2008) Histamine induces neural stem cell proliferation and neuronal differentiation by activation of distinct histamine receptors. J Neurochem 106(2):706–717. https://doi.org/10.1111/j.1471-4159.2008.05424.x

Mondragón-Rodríguez S, Gu N, Manseau F, Williams S (2018) Alzheimer's transgenic model is characterized by very early brain network alterations and β-CTF fragment accumulation: Reversal by β-secretase inhibition. Front Cell Neurosci 12. https://doi.org/10.3389/fncel.2018.00121

Moriwaki C, Chiba S, Wei H, Aosa T, Kitamura H, Ina K, Shibata H, Fujikura Y (2015) Distribution of histaminergic neuronal cluster in the rat and mouse hypothalamus. J Chem Neuroanat 68:1–13. https://doi.org/10.1016/j.jchemneu.2015.07.001

Myers KM, Davis M (2007) Mechanisms of fear extinction. Mol Psychiatry 12(2):120–50. https://doi.org/10.1038/sj.mp.4001939

Nader K, Schafe GE, Le Doux JE (2000) Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. Nature 406(6797):722–6. https://doi.org/10.1038/35021052

Naganuma F, Nakamura T, Yoshikawa T, Iida T, Miura Y, Kárpáti A, Matsuzawa T, Yanai A, Mogi A, Mochizuki T, Okamura N, Yanai K (2017) Histamine N-methyltransferase regulates aggression and the sleep-wake cycle. Sci Rep 7(1). https://doi.org/10.1038/s41598-017-16019-8

Nakayama D, Baraki Z, Onoue K, Ikegaya Y, Matsuki N, Nomura H (2014) Frontal Association Cortex Is Engaged in Stimulus Integration during Associative Learning. Curr Biol 25(1):117–123. https://doi.org/10.1016/j.cub.2014.10.078

Nakayama D, Hashikawa-Yamasaki Y, Ikegaya Y, Matsuki N, Nomura H, Nomura H (2016) Late Arc/Arg3.1 expression in the basolateral amygdala is essential for persistence of newly-acquired and reactivated contextual fear memories. Sci Rep 6(1):21007. https://doi.org/10.1038/srep21007

Nakayama D, Iwata H, Teshirogi C, Ikegaya Y, Matsuki N, Nomura H (2015) Long-delayed expression of the immediate early gene Arc/Arg3.1 refines neuronal circuits to perpetuate fear memory. J Neurosci 35(2):819–830. https://doi.org/10.1523/JNEUROSCI.2525-14.2015

Nakayama D, Yamasaki Y, Matsuki N, Nomura H (2013) Post-retrieval late process contributes to persistence of reactivated fear memory. Learn Mem 20(6):307–10. https://doi.org/10.1101/lm.029660.112

Nautiyal KM, McKellar H, Silverman AJ, Silver R (2009) Mast cells are necessary for the hypothermic response to LPS-induced sepsis. Am J Physiol - Regul Integr Comp Physiol 296(3). https://doi.org/10.1152/ajpregu.90888.2008

Neves G, Cooke SF, Bliss TVP (2008) Synaptic plasticity, memory and the hippocampus: A neural network approach to causality. Nat. Rev. Neurosci. 9:65–75

Nishiga M, Fujii Y, Konishi M, Hossen MA (2003) Effects of second-generation histamine H1 receptor antagonists on

the active avoidance response in rats. Clin Exp Pharmacol Physiol 30(1–2):60–3

Nomura H, Matsuki N (2008) Ethanol enhances reactivated fear memories. Neuropsychopharmacology 33(12):2912–2921. https://doi.org/10.1038/npp.2008.13

Nomura H, Mizuta H, Norimoto H, Masuda F, Miura Y, Kubo A, Kojima H, Ashizuka A, Matsukawa N, Baraki Z, Hitora-Imamura N, Nakayama D, Ishikawa T, Okada M, Orita K, Saito R, Yamauchi N, Sano Y, Kusuhara H, Minami M, Takahashi H, Ikegaya Y (2019) Central Histamine Boosts Perirhinal Cortex Activity and Restores Forgotten Object Memories. Biol Psychiatry 86(3):230–239. https://doi.org/10.1016/j.biopsych.2018.11.009

Nomura H, Nonaka A, Imamura N, Hashikawa K, Matsuki N (2012) Memory coding in plastic neuronal subpopulations within the amygdala. Neuroimage 60(1):153–61. https://doi.org/10.1016/j.neuroimage.2011.12.022

Nonaka A, Masuda F, Nomura H, Matsuki N (2013) Impairment of fear memory consolidation and expression by antihistamines. Brain Res 1493:19–26. https://doi.org/10.1016/j.brainres.2012.11.030

Nonaka A, Toyoda T, Miura Y, Hitora-Imamura N, Naka M, Eguchi M, Yamaguchi S, Ikegaya Y, Matsuki N, Nomura H (2014) Synaptic Plasticity Associated with a Memory Engram in the Basolateral Amygdala. J Neurosci 34(28):9305–9309. https://doi.org/10.1523/JNEUROSCI.4233-13.2014

Oh J, Eser RA, Ehrenberg AJ, Morales D, Petersen C, Kudlacek J, Dunlop SR, Theofilas P, Resende EDPF, Cosme C, Alho EJL, Spina S, Walsh CM, Miller BL, Seeley WW, Bittencourt JC, Neylan TC, Heinsen H, Grinberg LT (2019) Profound degeneration of wake-promoting neurons in Alzheimer's disease. Alzheimer's Dement 15(10):1253–1263. https://doi.org/10.1016/j.jalz.2019.06.3916

Orsetti M, Ghi P, Carlo G Di (2001) Histamine H3-receptor antagonism improves memory retention and reverses the

cognitive deficit induced by scopolamine in a two-trial place recognition task. In: Behavioural Brain Research. Elsevier, pp 235–242

Panula P, Nuutinen S (2013) The histaminergic network in the brain: basic organization and role in disease. Nat Rev Neurosci 14(7):472–87. https://doi.org/10.1038/nrn3526

Panula P, Rinne J, Kuokkanen K, Eriksson KS, Sallmen T, Kalimo H, Relja M (1997) Neuronal histamine deficit in Alzheimer's disease. Neuroscience 82(4):993–997. https://doi.org/10.1016/S0306-4522(97)00353-9

Pascoli V, Boer-Saccomani C, Hermant J-F (2009) H3 receptor antagonists reverse delay-dependent deficits in novel object discrimination by enhancing retrieval. Psychopharmacology (Berl) 202(1–3):141–52. https://doi.org/10.1007/s00213-008-1171-2

Passani MB, Cangioli I, Baldi E, Bucherelli C, Mannaioni PF, Blandina P (2001) Histamine H3 receptor-mediated impairment of contextual fear conditioning and in-vivo inhibition of cholinergic transmission in the rat basolateral amygdala. Eur J Neurosci 14(9):1522–1532. https://doi.org/10.1046/j.0953-816X.2001.01780.x

Payne GW, Neuman RS (1997) Effects of hypomagnesia on histamine H1 receptor-mediated facilitation of NMDA responses. Br J Pharmacol 121(2):199–204. https://doi.org/10.1038/sj.bjp.0701123

Pedarzani P, Storm JF (1995) Protein kinase A-independent modulation of ion channels in the brain by cyclic AMP. Proc Natl Acad Sci U S A 92(25):11716–20. https://doi.org/10.1073/pnas.92.25.11716

Perry E, Court J, Goodchild R, Griffiths M, Jaros E, Johnson M, Lloyd S, Piggott M, Spurden D, Ballard C, McKeith I, Perry R (1998) Clinical neurochemistry: Developments in dementia research based on brain bank material. J Neural Transm 105(8–9):915–933. https://doi.org/10.1007/s007020050102

Prast H, Argyriou A, Philippu A (1996) Histaminergic neurons facilitate social memory in rats

Provensi G, Costa A, Izquierdo I, Blandina P, Passani MB (2020) Brain histamine modulates recognition memory: possible implications in major cognitive disorders. Br. J. Pharmacol. 177:539–556

Reijmers LG, Perkins BL, Matsuo N, Mayford M (2007) Localization of a stable neural correlate of associative memory. Science 317(5842):1230–3. https://doi.org/10.1126/science.1143839

Reiner PB, Kamondi A (1994) Mechanisms of antihistamine-induced sedation in the human brain: H1 receptor activation reduces a background leakage potassium current. Neuroscience 59(3):579–588. https://doi.org/10.1016/0306-4522(94)90178-3

Reiner PB, McGeer EG (1987) Electrophysiological properties of cortically projecting histamine neurons of the rat hypothalamus. Neurosci Lett 73(1):43–47. https://doi.org/10.1016/0304-3940(87)90028-0

Resendez SL, Jennings JH, Ung RL, Namboodiri VMK, Zhou ZC, Otis JM, Nomura H, McHenry JA, Kosyk O, Stuber GD (2016) Visualization of cortical, subcortical and deep brain neural circuit dynamics during naturalistic mammalian behavior with head-mounted microscopes and chronically implanted lenses. Nat Protoc 11(3):566–597. https://doi.org/10.1038/nprot.2016.021

Rizk A, Curley J, Robertson J, Raber J (2004) Anxiety and cognition in histamine H3 receptor-/- mice. Eur J Neurosci 19(7):1992–1996. https://doi.org/10.1111/j.1460-9568.2004.03251.x

Rodríguez-Martínez G, Velasco I, García-López G, Solís KH, Flores-Herrera H, Díaz NF, Molina-Hernández A (2012) Histamine is required during neural stem cell proliferation to increase neuron differentiation. Neuroscience 216:10–17. https://doi.org/10.1016/j.neuroscience.2012.04.049

Rossato JI, Bevilaqua LRM, Izquierdo I, Medina JH, Cammarota M (2009) Dopamine controls persistence of long-term memory storage. Science 325(5943):1017–20. https://doi.org/10.1126/science.1172545

Ryan TJ, Roy DS, Pignatelli M, Arons A, Tonegawa S (2015) Memory. Engram cells retain memory under retrograde amnesia. Science 348(6238):1007–13. https://doi.org/10.1126/science.aaa5542

Sadek B, Saad A, Sadeq A, Jalal F, Stark H (2016) Histamine H3 receptor as a potential target for cognitive symptoms in neuropsychiatric diseases. Behav. Brain Res. 312:415–430

Sakimura K, Kutsuwada T, Ito I, Manabe T, Takayama C, Kushiya E, Yagi T, Shinichi A, Inoue Y, Sugiyama H, Mishina M (1995) Reduced hippocampal LTP and spatial learning in mice lacking NMDA receptor ε1 subunit. Nature 373:151–155

Sanna MD, Ghelardini C, Thurmond RL, Masini E, Galeotti N (2017) Behavioural phenotype of histamine H4 receptor knockout mice: Focus on central neuronal functions. Neuropharmacology 114:48–57. https://doi.org/10.1016/j.neuropharm.2016.11.023

Schlicker E, Kathmann M, Detzner M, Exner HJ, Göthert M (1994) H3 receptor-mediated inhibition of noradrenaline release: an investigation into the involvement of Ca2+ and K+ ions, G protein and adenylate cyclase. Naunyn Schmiedebergs Arch Pharmacol 350(1):34–41

Schwartz J-C (2011) The histamine H3 receptor: from discovery to clinical trials with pitolisant. Br J Pharmacol 163(4):713–21. https://doi.org/10.1111/j.1476-5381.2011.01286.x

Selbach O, Brown RE, Haas HL (1997) Long-term increase of hippocampal excitability by histamine and cyclic AMP. Neuropharmacology 36(11–12):1539–1548. https://doi.org/10.1016/S0028-3908(97)00144-5

Sergeeva OA, Eriksson KS, Sharonova IN, Vorobjev VS, Haas HL (2002) GABAA receptor heterogeneity in histaminergic neurons. Eur J Neurosci 16(8):1472–1482. https://doi.org/10.1046/j.1460-9568.2002.02221.x

Shan L, Bao AM, Swaab DF (2017) Changes in histidine decarboxylase, histamine n-methyltransferase and histamine receptors in neuropsychiatric disorders. In: Handbook of Experimental Pharmacology. Springer New York LLC, pp 1–18

Shan L, Bossers K, Unmehopa U, Bao AM, Swaab DF (2012) Alterations in the histaminergic system in Alzheimer's disease: A postmortem study. Neurobiol Aging 33(11):2585–2598. https://doi.org/10.1016/j.neurobiolaging.2011.12.026

Shen H, Igarashi H, Imamura N, Matsuki N, Nomura H (2013) N-methyl-D-aspartate receptors and protein synthesis are necessary for reinstatement of conditioned fear. Neuroreport 24(14):763–767. https://doi.org/10.1097/WNR.0b013e328363b36c

Stevens DR, Eriksson KS, Brown RE, Haas HL (2001) The mechanism of spontaneous firing in histamine neurons. In: Behavioural Brain Research. Behav Brain Res, pp 105–112

Strakhova MI, Nikkel AL, Manelli AM, Hsieh GC, Esbenshade TA, Brioni JD, Bitner RS (2009) Localization of histamine H4 receptors in the central nervous system of human and rat. Brain Res 1250:41–48. https://doi.org/10.1016/j.brainres.2008.11.018

Strecker RE, Nalwalk J, Dauphin LJ, Thakkar MM, Chen Y, Ramesh V, Hough LB, McCarley RW (2002) Extracellular histamine levels in the feline preoptic/anterior hypothalamic area during natural sleep-wakefulness and prolonged wakefulness: An in vivo microdialysis study. Neuroscience 113(3):663–670. https://doi.org/10.1016/S0306-

4522(02)00158-6

Takeshita Y, Watanabe T, Sakata T, Munakata M, Ishibashi H, Akaike N (1998) Histamine modulates high-voltage-activated calcium channels in neurons dissociated from the rat tuberomammillary nucleus. Neuroscience 87(4):797–805. https://doi.org/10.1016/S0306-4522(98)00152-3

Tarder-Stoll H, Jayakumar M, Dimsdale-Zucker HR, Günseli E, Aly M (2020) Dynamic internal states shape memory retrieval. Neuropsychologia 138. https://doi.org/10.1016/j.neuropsychologia.2019.107328

Thomas SA (2015) Neuromodulatory signaling in hippocampus-dependent memory retrieval. Hippocampus 25(4):415–431. https://doi.org/10.1002/hipo.22394

Tonegawa S, Morrissey MD, Kitamura T (2018) The role of engram cells in the systems consolidation of memory. Nat Rev Neurosci 19(8):485–498. https://doi.org/10.1038/s41583-018-0031-2

Tonegawa S, Pignatelli M, Roy DS, Ryan TJ (2015) Memory engram storage and retrieval. Curr Opin Neurobiol 35:101–109. https://doi.org/10.1016/J.CONB.2015.07.009

Umehara H, Mizuguchi H, Fukui H (2012) Identification of a histaminergic circuit in the caudal hypothalamus: An evidence for functional heterogeneity of histaminergic neurons. In: Neurochemistry International. Neurochem Int, pp 942–947

Umehara H, Mizuguchi H, Mizukawa N, Matsumoto M, Takeda N, Senba E, Fukui H (2010) Innervation of histamine neurons in the caudal part of the arcuate nucleus of hypothalamus and their activation in response to food deprivation under scheduled feeding. Methods Find Exp Clin Pharmacol 32(10):733–736. https://doi.org/10.1358/mf.2010.32.10.1545781

Umehara H, Mizuguchi H, Mizukawa N, Matsumoto M, Takeda N, Senba E, Fukui H (2011) Deprivation of anticipated food under scheduled feeding induces c-Fos expression in the caudal part of the arcuate nucleus of hypothalamus through histamine H1 receptors in rats: Potential involvement of E3 subgroup of histaminergic neurons in tuberomammillary nucleus. Brain Res 1387:61–70. https://doi.org/10.1016/j.brainres.2011.02.018

Valdés JL, Farías P, Ocampo-Garcés A, Cortés N, Serón-Ferré M, Torrealba F (2005) Arousal and differential Fos expression in histaminergic neurons of the ascending arousal system during a feeding-related motivated behaviour. Eur J Neurosci 21(7):1931–1942. https://doi.org/10.1111/j.1460-9568.2005.04013.x

Valdés JL, Sánchez C, Riveros ME, Blandina P, Contreras M, Farías P, Torrealba F (2010) The histaminergic tuberomammillary nucleus is critical for motivated arousal. Eur J Neurosci 31(11):2073–2085. https://doi.org/10.1111/j.1460-9568.2010.07241.x

Van Deursen JA, Vuurman EFPM, Verhey FRJ, Van Kranen-Mastenbroek VHJM, Riedel WJ (2008) Increased EEG gamma band activity in Alzheimer's disease and mild cognitive impairment. J Neural Transm 115(9):1301–1311. https://doi.org/10.1007/s00702-008-0083-y

van Ruitenbeek P, Mehta MA (2013) Potential enhancing effects of histamine H_1 agonism/H_3 antagonism on working memory assessed by performance and bold response in healthy volunteers. Br J Pharmacol 170(1):144–155. https://doi.org/10.1111/bph.12184

Vanni-Mercier G, Gigout S, Debilly G, Lin JS (2003) Waking selective neurons in the posterior hypothalamus and their response to histamine H3-receptor ligands: An electrophysiological study in freely moving cats. Behav Brain Res 144(1–2):227–241. https://doi.org/10.1016/S0166-4328(03)00091-3

Vazdarjanova a, McGaugh JL (1999) Basolateral amygdala is involved in modulating consolidation of memory for classical fear conditioning. J Neurosci 19(15):6615–22

Vorobjev VS, Sharonova IN, Haas HL, Sergeeva OA (2003) Expression and function of P2X purinoceptors in rat histaminergic neurons. Br J Pharmacol 138(5):1013–1019. https://doi.org/10.1038/sj.bjp.0705144

Vorobjev VS, Sharonova IN, Walsh IB, Haas HL (1993) Histamine potentiates N-methyl-d-aspartate responses in acutely isolated hippocampal neurons. Neuron 11(5):837–844. https://doi.org/10.1016/0896-6273(93)90113-6

Wada H, Inagaki N, Yamatodani A, Watanabe T (1991) Is the histaminergic neuron system a regulatory center for whole-brain activity? Trends Neurosci 14(9):415–8

Wasielewska JM, Grönnert L, Rund N, Donix L, Rust R, Sykes AM, Hoppe A, Roers A, Kempermann G, Walker TL (2017) Mast cells increase adult neural precursor proliferation and differentiation but this potential is not realized in vivo under physiological conditions. Sci Rep 7(1):1–13. https://doi.org/10.1038/s41598-017-18184-2

Westmacott R, Leach L, Freedman M, Moscovitch M (2001) Different patterns of autobiographical memory loss in semantic dementia and medial temporal lobe amnesia: A challenge to consolidation theory. Neurocase 7(1):37–55. https://doi.org/10.1093/neucas/7.1.37

Williams RH, Chee MJS, Kroeger D, Ferrari LL, Maratos-Flier E, Scammell TE, Arrigoni E (2014) Optogenetic-mediated release of histamine reveals distal and autoregulatory mechanisms for controlling arousal. J Neurosci 34(17):6023–9. https://doi.org/10.1523/JNEUROSCI.4838-13.2014

Xu LS, Yang LX, Hu WW, Yu X, Ma L, Liu LY, Wei EQ, Chen Z (2005) Histamine ameliorates spatial memory deficits induced by MK-801 infusion into ventral hippocampus as evaluated by radial maze task in rats. Acta Pharmacol

Sin 26(12):1448–1453. https://doi.org/10.1111/j.1745-7254.2005.00229.x

Yamada Y, Yoshikawa T, Naganuma F, Kikkawa T, Osumi N, Yanai K (2020) Chronic brain histamine depletion in adult mice induced depression-like behaviours and impaired sleep-wake cycle. Neuropharmacology 175. https://doi.org/10.1016/j.neuropharm.2020.108179

Yamakami J, Sakurai E, Kuramasu A, Sakurai E, Yanai K, Watanabe T, Tanaka Y (2000) L-Histidine decarboxylase protein and activity in rat brain microvascular endothelial cells. Inflamm Res 49(5):231–235. https://doi.org/10.1007/s000110050584

Yamamoto Y, Mochizuki T, Okakura-Mochizuki K, Uno A, Yamatodani A (1997) Thioperamide, a histamine H3 receptor antagonist, increases GABA release from the rat hypothalamus. Methods Find Exp Clin Pharmacol 19(5):289–98

Zhao C, Deng W, Gage FH (2008) Mechanisms and Functional Implications of Adult Neurogenesis. Cell 132:645–660

Zheng C, Bieri KW, Hsiao YT, Colgin LL (2016) Spatial Sequence Coding Differs during Slow and Fast Gamma Rhythms in the Hippocampus. Neuron 89(2):398–408. https://doi.org/10.1016/j.neuron.2015.12.005

Zlomuzica A, Dere D, Binder S, De Souza Silva MA, Huston JP, Dere E (2016) Neuronal histamine and cognitive symptoms in Alzheimer's disease. Neuropharmacology 106:135–145

Zlomuzica A, Ruocco LA, Sadile AG, Huston JP, Dere E (2009) Histamine H 1 receptor knockout mice exhibit impaired spatial memory in the eight-arm radial maze. Br J Pharmacol 157(1):86–91. https://doi.org/10.1111/j.1476-5381.2009.00225.x