**Chapter 14**

**Modulation of Memory Consolidation, Retrieval and Extinction by Brain Histamine**

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**Abstract**

The brain histaminergic system, whose cell bodies are in the tuberomammilary nucleus, regulates various memory types. The best studied is inhibitory avoidance, which depends on histamine H2 receptors in hippocampus and basolateral amygdala, contextual fear conditioning, which depends on histamine H3 receptors in hippocampus, and the extinction of these two tasks which relies on histamine H2 receptors in ventromedial prefrontal cortex, hippocampus and the basolateral amygdala. In addition, histamine can promote fear extinction through H1 receptors and inhibit it through H2 receptors, both in hippocampus.

**Keywords**

Memory consolidation; Memory retrieval; H1 receptors; H2 receptors; Hippocampus; Basolateral amygdala.

**The multiple consolidation of memoryModulation memory (1): different parallel brain systems are in charge of memory consolidation (2).**

For at least a century, perhaps even from before Pavlov (3) proposed that “temporary connections” are “closed” at specific sites “in the cerebral cortex”, it was more or less taken for granted that different memories are made and stored at restricted sites in the brain. One memory, one site. This may have resulted from the remnants of Franz Joseph Gall’s old phrenology, in which head bumps predicted character and brain function, or those of its also infelicitous successor, the “new neuropharmacological phrenology” (a name coined in irony by Steve (4), which caught neuroscientists at the time when modern work on brain neurotransmitters was just beginning and led many to believe that each of the molecules, no matter where it was released, specialized in some function (acetylcholine in memory; dopamine in pleasure, norepinephrine in excitement). A giant leaps backward from Paul Ehrlich’s concept of receptors. Still today, some science writers adhere to those strange ideas.

Growing evidence began to accumulate showing that many areas of the brain were involved in memory, and questions were raised as to where and how they are involved. It took the power of modern biochemistry and pharmacology (1,2,5–10) and more recently and more spectacularly that of the optogenetic revolution (11–15) to accept the now older but finally undisputable fact that memories are made and modulated in several brain regions concomitantly and often simultaneously by different sets of neurons (see (16–21). The making of memories and their modulation in many parts of the brain became a major research field, and the variety of modulatory systems guaranteed the diversity of the different memory engrams formed.

Over 30 years ago, Jorge Brioni called attention to “the multiple consolidation of memory” in an article commenting on the widely disseminated role of γ-aminobutyric acid (GABA) in memories formed in many places of the brain (1). Our own group reported at the same time that the microinfusion of norepinephrine, timolol, glutamate, oxotremorine, scopolamine, picrotoxin, and muscimol or several combinations thereof affected the memory consolidation of inhibitory avoidance (IA) similarly when infused immediately posttraining into the CA1 region of the hippocampus, the basolateral amygdala (BLA), or the medial septum (2). Likewise, glutamate receptor antagonists also affected IA memory consolidation similarly when microinfused into hippocampus CA1, BLA (22), or medial septum/diagonal band nucleus (23).

Clearly, both the data from Brioni (1) and our own set of data (2,22,23) in the early 1990s could be taken as reasonable suggestions that memories were made and modulated at several brain sites simultaneously or in close succession and that there is in fact parallel memory processing in several such places at the time of consolidation. But as will be seen, belief in parallel memory processing had to await the new methods of optogenetics to become accepted by one-memory/one-site diehards (see (24). Very interestingly, as has been recently shown (25) and will be discussed in the last section of this chapter, in the case of histamine, **the same** neural pathway mediates both the enhancement and the inhibition of retrieval, the difference being only at the level of the receptor in the last neuron of the pathway: H1 for enhancing and H2 for inhibition. The switch that selects between the two must be located in the tuberomammillary nucleus itself.

Obviously, the larger the number of available concurrent or consecutive sites of consolidation, the bigger the chances for neurotransmitter systems with multiple projections to modulate memory (1), and the histaminergic system is clearly highly promiscuous as to the brain sites it innervates (16,26–29) (30). It is certainly safer to store information in more than one place of the brain in order to circumvent failures or injuries in one or in a few of them, exactly for the same reasons that it is safer to store important files in more than one electronic device. Parallel processing implies great advantages for the survival of important brain functions, such as memory. If one neuron or one subsystem fails, another one can pick up the flag and go; witness to this are the millions of mostly asymptomatic people and animals that daily survive strokes.

Then, as a consequence of this greatly renewed way of thinking, the “new neuropharmacologic phrenology” envisioned by Zornetzer (4) experienced a rebirth that began to make sense. Different traces of different duration and modulated by a diversity of systems clearly led to more interesting, colorful, and complex views of the organization of memory than the much more rigid idea of single punctual storage sites. For example, the neurons that have been best studied so far as memory makers are probably the pyramidal cells of the hippocampus (e.g., (31–34). They are innervated by a large number of modulatory fibers: noradrenergic, cholinergic, serotoninergic, histaminergic, and various peptide-releasing fibers, as can be seen in any of the major recent reviews available on its function (35–38); in addition, these cells rely on modulation by neurotrophic factors (35) and neurogenesis (39) among other factors. How far we have come now from the days of one memory, one site.

# **14.1. Histamine and Memory: The Early Work**

All the neurons that produce and contain histamine are restricted to one single nucleus (the tuberomammillary nucleus (40) , with quite scattered projections reaching many areas of the brain, including some well known to be involved in memory consolidation processes (28,29). So it was only a question of time that, as had been the case with other major neurotransmitters (acetylcholine, serotonin, and the catecholamines), a role for brain histamine in memory modulation would be investigated.

The first to study this were de Almeida and Izquierdo (41), who showed that the immediate posttraining intracerebroventricular (i.c.v.) infusion of histamine facilitated memory of the IA in rats. In a subsequent experiment, 48/80, a well-known polymer then popularly produced by the condensation of *N*-methyl-*p*-methoxyphenethylamine with formaldehyde that releases histamine from mast cells, had no effect on memory when given i.c.v., which pointed to a role for neuronal and not mast cell histamine in memory modulation (42). At that time, the presence of histamine in the brain (43), as well as that of histidine decarboxylase was determined (44) and that of mast cells containing histamine in brain (45) had already been well ascertained (43). Brain neurons (45) and fibers (40) containing histamine were being discovered. The tuberomammillary nucleus was soon found to be involved in many aspects of brain function, including prominently regulating the waking state (46–50) and food intake (51), both of which can be affected by stress (51). Stress, in turn, as is known, strongly affects memory, an interaction that involves endocannabinoids (24,52–56).

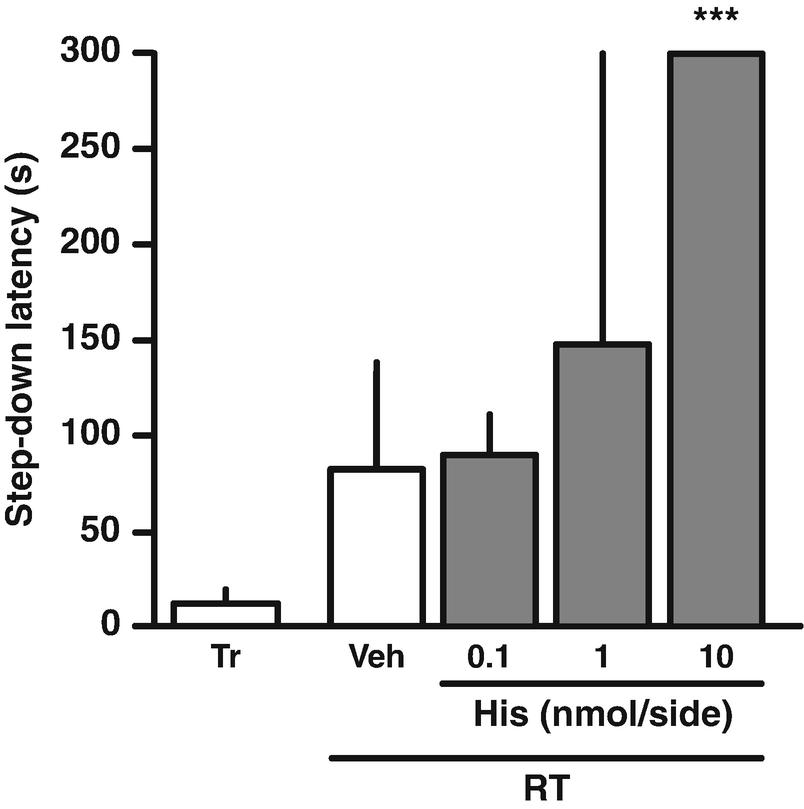
Back in 1986, the effects of histamine were immediately correlated with the well-known depressant action and sleepiness induced by the popular over-the-counter “antihistamine” compounds available at that time, most of which acted on peripheral receptors of the H1 type. Its putative relation to memory processing, particularly fear-related memories, was suggested later in part by the parallel description of connections to the tuberomammillary nucleus from the septum/diagonal band nucleus (57), a nucleus that has a strong connection to the hippocampus (58) and through it plays a major role in fear motivated and many other types of learning (2,23).

Histamine was soon discovered to have also other receptors: H2, H3, and H4. The histaminergic system in the brain was in the process of becoming known, so soon this system and its H1, H2, and H3 receptor subtypes began to be intensely studied as memory modulators, as they are now (16,28,37,59). Much of these works are carried out using fear conditioning models and localized infusion of histamine or its mimetic and antagonists into brain areas known to regulate memory consolidation and by enhancing the action of endogenous histamine. The results are coincident in that histamine, acting on different receptors depending both on the brain site into which it is infused and on the task studied, enhances different forms of fear conditioning and fear extinction.

The tuberomammillary nucleus is composed of different subpopulations of histaminergic cells which innervate multiple brain areas each with different histamine receptor types (28,29). This suggests that histaminergic neurons are “heterogeneous, organized into functionally distinct circuits, impinging on different brain regions, and displaying selective control mechanisms. This could imply independent functions of subsets of histamine neurons according to their respective origin and terminal projections,” to put it in the authors’ own words.

Many effects of histamine on memory have been attributed to H1, H2, or H1 plus H2 receptors (41,60–64) but as will be seen below, clearly other effects in areas critical for memory formation are mediated by H3 receptors (26).

Histamine given into several brain regions modulates memory consolidation of various learning tasks, including mainly fear-motivated tasks. As mentioned, the first report of memory modulation by histamine was an enhancement of the consolidation of the IA with posttraining i.c.v. administration (41). In that paper, histamine was effective at low doses (1 or 10 ng/rat) and was blocked by the H1 receptor antagonist, promethazine, and by the H2 antagonist, cimetidine, given together, but not by either drug alone. Since then, the effects on memory of histamine, histamine releasers, enhancers, and antagonists given into various structures of the brain were studied in different forms of memory. Some reports have concluded that histamine facilitates consolidation and others that depresses it by actions on different receptors in different brain sites (26,40,60–62,65–69). It appears that at some receptors and in some brain areas, histamine enhances memory consolidation of certain tasks, and at other receptors and in other areas or tasks, it may have different effects. For example, memory facilitation of IA has been described on one hand with histamine given into i.c.v. (41) or into BLA (30,59) (Fig. [14.1](#Fig1)) and on the other with pharmacological inhibition of the tuberomammillary nucleus (70).



**Fig. 14.1** Infusion of histamine into the basolateral nuclear complex of the amygdala (BLA) enhances aversive memory. Rats with infusion cannulas implanted in the BLA were trained (Tr) in inhibitory avoidance and immediately after that received infusions of vehicle (Veh) or histamine (His). Retention was evaluated 24 h after (RT). (Figure modified from (30); histamine infused into basolateral amygdala enhances memory consolidation of inhibitory avoidance. International Journal of Neuropsychopharmacology, 16:1539–1545)

Here we will concentrate on mainstream studies on histamine modulation of well-known tasks, whose mechanisms have been well studied and on which there is wide agreement (24,54,56): contextual fear conditioning (CFC) and extinction (27,64,71,72), IA (7,8,16,73), social and object recognition (74–80).

# **14.2. Effects of Histaminergic Modulation of Inhibitory avoidance (IA)**

IA has an edge of advantage over the other tasks: it is, by far, the behavioral model in which the molecular mechanisms of consolidation have been best and most extensively studied (7,8,16,73,81,82). Especially concerning the memory facilitation by histamine. Its effect depends on the phosphorylation of the constitutive transcription factor c-AMP response element-binding protein (CREB) both in the hippocampus and in the BLA (5,6,16), and on the activation of the extracellularly regulated kinase system (ERK) coupled with cholinergic stimulation (67).

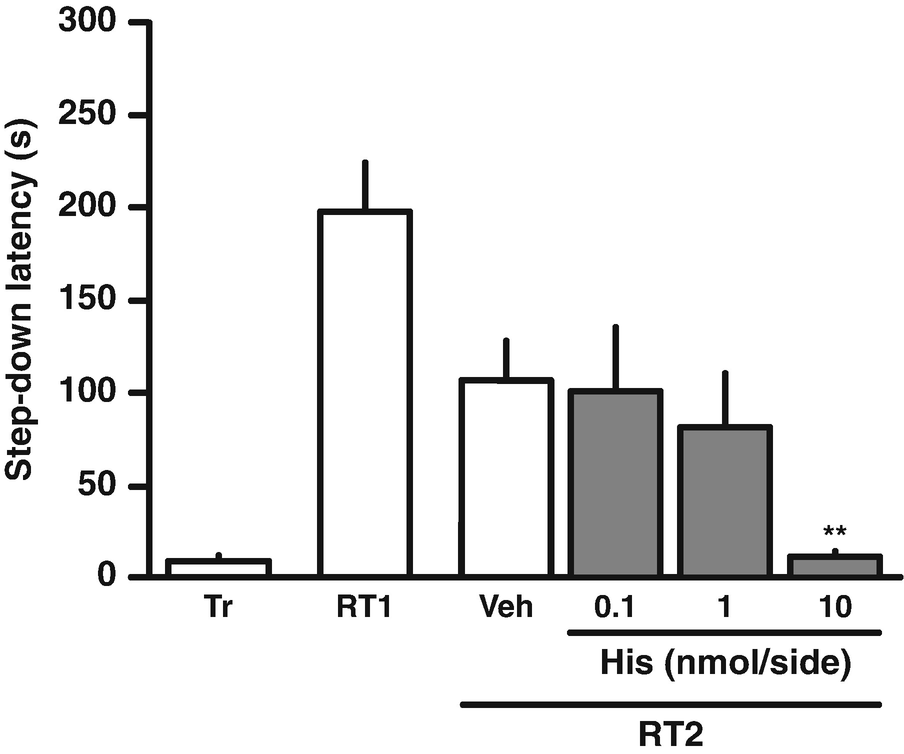
The effect of the histamine *N*-methyltransferase inhibitor, SKF9188 that prolongs the half-life of histamine action (30,64), and of a variety of histamine H1 and H2 receptor antagonists in BLA and hippocampus have been well studied, and the results are very consistent.

Endogenous histamine production can be blocked by α-fluoro-methylhistidine, a suicide inhibitor of histidine decarboxylase infused into the brain ventricles, which reaches the tuberomammillary nucleus and suppresses histamine production in the projections of that nucleus (16,26,27). By this procedure, a full blockade of brain histamine-mediated transmission can be obtained (29). This inhibits the consolidation of, for example, IA, which is known to be sustained by both the BLA and the hippocampus (see (7,8,83–86). The deleterious effect of α-fluoro-methylhistidine on IA consolidation can be overcome by the infusion of histamine into either BLA or hippocampus; i.e., histamine can act on one of these structures while the other one is depleted and impaired. This observation suggests parallel processing of the modulation of memory consolidation by BLA and hippocampus (see (2,16,22,87). Therefore, histamine modulation of IA consolidation occurs independently in BLA and in hippocampus (59), which strongly suggests that in physiological conditions, it should be rather synchronous in both (8). This adds to the literature on an independent modulation of fear memory consolidation by these two brain structures (85,86,88).

The modulatory effect of histamine fibers on IA consolidation is exerted both at the BLA and at the CA1. Interestingly, when one of these two histaminergic connection sites fails, the other one takes over (16).

Experiments with dimaprit, ranitidine, and thioperamide have shown that H1, H2, and H3 histamine receptors in BLA, hippocampus and ventromedial prefrontal cortex (vmPFC), facilitate memory consolidation of IA and CFC, and their specific antagonists have an opposite effect in the consolidation of different tasks (26,30,64). The cognitive deficit in a Morris water maze, in an object recognition task (77) and in IA learning (59,89,90) visible in adult life of rats submitted to brief daily maternal deprivation during the first 10 days of life, is in part due to a histamine deficit, and it can be corrected by histamine given into the BLA or by the histamine *N*-methyltransferase inhibitor and histamine enhancer, SKF91488 (30). This deficit can also be reversed by physical exercise (89,90) or by pro-cholinergic drugs, such as galantamine and donepezil (91), so it is possible that this cognitive deficit is due to a failure of various transmitter systems. Interestingly, the H3 receptor antagonist, thioperamide, has been reported to enhance consolidation in some tasks or brain regions (92–94), and also to antagonize the enhancing action of histamine in others. H3 receptors act through fostering the release both of acetylcholine and of histamine itself from axon terminals (27,95).

Histamine is a major modulator of fear extinction (Fig. [14.2](#Fig2)). The histamine *N*-methyltransferase inhibitor SKF9188 enhances, and the H2 histamine receptor antagonist ranitidine inhibits extinction of both CFC and IA learning regardless of whether they were administered into the vmPFC, the dorsal hippocampus, or the BLA, which are the three main regions for consolidation of the extinction of both tasks. Only the indirect stimulant of the NMDA receptor, d-serine, has such a generalized effect on extinction among many drugs tested, including noradrenergic and dopaminergic agonists and antagonists (64); see also (62).



**Fig. 14.2** Histamine into the CA1 facilitates the extinction of inhibitory avoidance memory. Rats with infusion cannulas implanted in the CA1 region of hippocampus were trained (Tr) in inhibitory avoidance and 24 h later submitted to a non-reinforced test session (RT1). Immediately thereafter, animals received infusions of vehicle (Veh) or histamine (His). Retention was evaluated 24 h after RT1 (RT2). (Figure modified from (62); histamine facilitates consolidation of fear extinction. International Journal of Neuropsychopharmacology, 14:1209–1217)

# **14.3. Brain Histamine and the Consolidation of Contextual Fear Conditioning (CFC)**

There have been several important hints in the literature on a role of histaminergic processes in the consolidation of CFC in the hippocampus. These hints point each in a different direction, so the picture so far is not very clear.

Liu et al. (96) reported improved learning and memory of CFC and hippocampal CA1 long-term potentiation (LTP) in histidine decarboxylase knockout mice. Brabant et al. (97) described a clear enhancing effect of the H3 inverse agonist, pitolisant, on CFC when given systemically to female mice. Pitolisant, 1-{3-[3-(4-Chlorophenyl)propoxy]propyl}piperidine hydrochloride), is the first H3 receptor inverse agonist that has been tested in human trials and is well tolerated.

The most complex but perhaps more definite or definable evidence for a role of histamine H3 receptors points in a different direction from those of the two previously cited data. Benetti et al. (27) infused histaminergic receptor ligands into the nucleus basalis magnocellularis (NBM) of rats right after CFC and observed increased CFC freezing behavior 72 h after training, which ensures that the infused material did not influence acquisition or retrieval but just consolidation. They found that posttraining blockade of H3 receptors with the antagonist/inverse agonist thioperamide or activation of those receptors with immepip in the NBM potentiates or decreases, respectively, freezing response at retrieval. Thioperamide-induced memory enhancement seemed to depend on H2 but not H1 receptor activation, as the H2 receptor antagonist zolantidine blocked the effect of thioperamide, whereas the H1 receptor antagonist pyrilamine was ineffective. The H2 agonist amphetamine improved fear memory expression independently of the H3 agonist effect. Their findings indicate that activation of postsynaptic H2 receptors within the NBM by endogenous histamine is responsible for the potentiated expression of fear responses.

Recently it was demonstrated that the fat-sensing lipid mediator oleoylethanolamide (OEA) indirectly activates histaminergic neurons to exert its hypophagic effects. However, it remained unclear whether histaminergic neurotransmission is also necessary for the modulation of emotional memory induced by OEA in a CFC paradigm. Thus it was verified that posttraining administration of OEA enhanced freezing time during the retention test in the CFC task. This effect was blocked by both i.c.v. infusions of alpha-fluoromethylhistidine and intra-amygdala infusions of either H1 or H2 receptor antagonists, pyrilamine or zolantidine, respectively, suggesting that activation of the histaminergic system in the amygdala plays a role in the memory-enhancing effects of OEA (98).

# **14.4. Histamine Modulation of IA and CFC Fear Extinction**

Until 2012 there had been a relative neglect of the modulatory mechanisms of fear extinction, despite the fact that it is involved in the delicate and often fragile treatment of the post-traumatic stress disorder (PTSD) by the so-called exposure therapy (99). We launched a short but effective program to study the influence of well-known neuromodulatory substances (norepinephrine acting via β receptors, dopamine acting via D1/D5 receptors, histamine, and d-serine) infused into the three main sites of regulation of the memory consolidation of both CFC and IA extinction: the CA1 region of the hippocampus, the BLA, and the ventromedial prefrontal cortex (72). We came out with two very solid modulators: d-serine, which acts at an allosteric site within glutamate *N*-methyl-aspartate (NMDA) receptors and would have been a prime suspect anyway, and histamine acting on H2 ranitidine-sensitive receptors (64), which may offer a translational possibility worthy of further study. Both d-serine and histamine enhanced extinction of the two fear tasks in all the three brain sites studied, and their effects were antagonized, respectively, by AP5 and by ranitidine (56,64).

Another study investigated the participation of hippocampal H2-histaminergic, β-adrenergic and 5-HT1A-serotonergic receptors in the enhancement of extinction memory caused by novelty, demonstrating that a β-adrenergic inhibitor and a 5-HT1A-serotonergic receptors agonist were able to block the enhancing effect of the exposure to the novelty. The β-adrenergic inhibitor, but not the other drugs, was also capable of blocking the consolidation of extinction memory. However, regarding H2-histaminergic receptors, the retrieval of CFC, but not the extinction learning or extinction consolidation, was impaired by both the H2-histaminergic receptor agonist (dimaprit) and antagonist (ranitidine) (100).

# **14.5. Histamine Modulation of Social and Object Recognition**

Ennaceur and Delacour (77) introduced the so-called object recognition task as a very welcome non-aversive learning procedure in which rodents express their preference for the remaining close to and investigating a novel object rather than a previously known object. Part of the considerable interest aroused by this task is that recognition memory fails quite specifically early in Alzheimer’s disease (101).

The neural basis for object recognition involves the hippocampus (101), the entorhinal (102), and to a great extent the perirhinal cortex (74,75). It relies on CA1 LTP (103).

Brain histamine has a very ample and diversified modulatory influence on object recognition memory. When infused in the CA1 region immediately, 30, 120, or 360 min posttraining, the H1 receptor antagonist pyrilamine, the H2 receptor antagonist ranitidine, and the H3 receptor agonist imetit blocked the long-term memory retention in a time-dependent manner (30–120 min) without affecting general exploratory behavior, anxiety state, or hippocampal function (104). Our data indicate that histaminergic system modulates consolidation of object recognition memory through H1, H2, and H3 receptors.

Additionally, the administration of the non-imidazole H3 antagonist ABT-239 to wild-type mice before the training and retention test improved memory in the object recognition paradigm. However, the efficacy of ABT-239 on recognition memory was not observed in animals whose brain histamine had been depleted through the i.c.v. infusion of histidine decarboxylase irreversible inhibitor, α-fluoromethylhistidine, suggesting that endogenous histamine is crucial for the effects of H3 receptor ligands on memory (105).

Social recognition memory is crucial for social interaction, adaptive social behavior, reproduction, and survival (80,106,107). In rodents, this memory is assessed through their natural tendency to investigate unfamiliar conspecifics more persistently than familiar ones, in what has become known as the social-discrimination paradigm (79,80,108–110).

The investigation of histamine receptors on social recognition memory demonstrated that intra-CA1 or intra-BLA infusions of an H2 histamine receptor antagonist (Ranitidine) and agonist (Dimaprit), administered immediately after learning of a social discrimination task, are involved in the consolidation of social recognition memory in both the CA1 and BLA regions (78). However, H2 receptors in the insular cortex do not seem to participate in the consolidation of social recognition memory (111).

Rani and collaborators demonstrated that disrupting or enhancing histaminergic neurotransmission differentially affects short (STM) and long-term (LTM) social recognition memory. Histamine-deprived animals, either chronically (*Hdc−/−* mice lacking the histamine-synthesizing enzyme histidine decarboxylase) or acutely (mice treated with the histidine decarboxylase irreversible inhibitor α-fluoromethylhistidine, administered i.c.v.) exhibited impaired LTM social recognition without effect on STM. Additionally, the reduction of histamine release, induced by H3 receptor activation with VUF16839 impaired both STM and LTM social recognition, as well as the consolidation and retrieval of social recognition LTM, indicating that reduction of histaminergic neurotransmission impaired long-term recognition memory. However, increasing brain histamine availability with ciproxifan, an H3 receptor antagonist/inverse agonist, produced a procognitive effect that was absent in both *Hdc−/−* and α-fluoromethylhistidine-treated mice (112).

# **14.6. Histamine and Memory: The Histamine Retrieval Switch**

Fabbri, Furini, and coworkers showed that the retrieval of inhibitory avoidance was prevented by previous depletion of brain histamine by α-fluoro-methylhistidine, and it was reinstated by the microinfusion of histamine into the CA1 region of the hippocampus but not into the BLA or the vmPFC in the histamine-depleted animals; this effect of histamine was antagonized by the H1 receptor antagonist, pyrilamine (25). This finding was in contrast to the previously shown inhibitory effect of histamine on retrieval mediated by H2 receptors in CA1, BLA, and vmPFC described above (64), an effect indeed that underlies the influence of histamine in the three structures on normal extinction of both contextual fear conditioning and inhibitory avoidance (see (25,64).

The fact that histamine can support retrieval by an action in CA1 mediated by H1 receptors and inhibit retrieval by an action on CA1, the BLA, and the vmPFC mediated by H1 receptors clearly points to a **histamine switch** located at the tuberomammillary nucleus by which this structure must decide whether to activate the neurons that innervate CA1 H1 receptors and thereby stimulate retrieval or those that innervate CA1, BLA, and vmPFC H2 receptors and thereby inhibit extinction. It is not yet known whether this **histamine switch** presumably in the tuberomammillary nucleus acts only on the retrieval of fear-motivated memories or in that of other memories as well. This point deserves further investigation.

Meanwhile, evidence points to the necessary location of this **switch** that controls the decision of whether the animal should perform or inhibit retrieval in the tuberomammillary nucleus. The existence of cell subpopulations in that nucleus has been convincingly argued for by Blandina et al. (28): there are no other histaminergic nuclei except that one, there are no intermediate stations between the tuberomammillary nucleus and the structures it projects to, and the decision of whether that nucleus will send this or the other contingent of neurons to release histamine on H1 or H2 receptors here or there must be taken ahead of the structures that contain those receptors (in this case, CA1, basolateral amygdala and vmPFC).

# **14.7. To Summarize**

Recent evidence indicates a major role of the brain histaminergic system, whose cell bodies are in the tuberomammillary nucleus, in the regulation of various different types of memory. The best studied of these are IA, which depends on histamine H2 receptors in the hippocampus and in the BLA; CFC, where regulation depends on histamine H3 receptors in the hippocampus; and the extinction of IA and CFC, whose consolidation relies on histamine H2 receptors in the ventromedial prefrontal cortex, in the CA1 region of the hippocampus, and in the BLA. Furthermore, histamine receptors also play a significant role in object and social recognition memory, influencing how these memories are stored and retrieved. In all cases, histamine regulation should be viewed as integrated into modulatory networks related to pathways involving other neurotransmitters.

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