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Review

# The role of histamine on cognition

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ABSTRACT

Histamine was intensively studied at the beginning of the 20th century because of its important role in allergic and inflammation processes. In those days it was very difficult that researchers could envisage another impacting function for the imidazolamine in the living systems. Once the imidazolamine was found located in neuron compartment in the brain, increasing evidence supported many regulatory functions including its possible role in memory and learning. The specific participation of histamine in cognitive functions followed a slow and unclear pathway because the many different experimental learning models, pharmacologic approaches, systemic and localized applications of the histamine active compounds into the brain used by researchers showed facilitating or inhibitory effects on learning, generating an active issue that has extended up to present time. In this review, all these aspects are analyzed and discussed considering the many intracellular different mechanisms discovered for histamine, the specific histamine receptors and the compartmentalizing proprieties of the brain that might explain the apparent inconsistent effects of the imidazolamine in learning. In addition, a hypothetical physiologic role for histamine in memory is proposed under the standard theories of learning in experimental animals and humans.



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## 1. Introduction

The biological role for histamine has experienced a long and increasing recognition, since the molecule was originally isolated from the mould ergot in 1910 by Sir Henry Dale and his colleagues at the Wellcome Laboratories. In spite that at the beginning, histamine called the attention of many researchers for its relation to allergic reactions and inflammation, and later near the end of the 20th century for its possible role in the central nervous system, still traditional pharmacologists refer to histamine as an "autacoids", natural molecules in search of a biological function [12]. It was difficult to be accepted by them that the imidazolamine could have a physiological role in the brain. Description that histamine was contained into neuron compartments, and that there was only one site in the central nervous system where histamine is synthesized, was strong evidence establishing the biological role of histamine in the

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brain [51,63,58]. Histamine-producing neurons are located at the posterior hypothalamus in the tuberomammillary nucleus of the brain [17].

## 2. The tuberomammillary nucleus as a general integrating neural center

Histaminergic neuron cells are about 30 μm in diameter and appear organized into three main cell clusters in the hypothalamic tuberomammillary nucleus [28,51,63]. Each of these cell clusters is composed of a rather small number of cells; about 600 neurons for the medial tuberomammillary subgroup; 1500 neurons for the ventral tuberomammillary subgroup, and about 100 cells for the diffuse tuberomammillary subgroup [17]. At first sight the relative modest number of neurons for each of the tuberomammillary regions appears contrasting to the many physiological functions attributed to histamine in the brain [17,54,35]. However, a simple mathematical analysis can show that the amount of histaminergic neurons might be enough to fulfill many of the biological functions where histamine participates. Lets assume that any of the neurons in the tuberomammillary nucleus can exist in only two states: conducting an electric signal at a frequency $f_1$ or at a frequency $f_2$ where $f_2 \neq f_1$, and each frequency controls one function. This assumption is based on what it is known about the electric proprieties of the tuberomammillary neuron which appears to be of the type *pacemaker* [35]. Thus, when one neuron is active there will be only two functions ("$f_1$", one signal, and "$f_2$", other signal). If two neurons act in combination in order to form an elemental two-cells net, four functions could be codified. Three neurons at the same time could codify eight functions, and if 300 neurons are taken into combination, about $2 \times 10^{90}$ different functions could be performed. This is simply because the combined activation of neurons acting in "$f_1$–$f_2$" fashion follows an exponential function of the type $Y = 2^X$, where $Y$ = number of functions (or commands) and $X$ = number of neurons involved.

In spite of the existence of the three main histaminergic neuronal regions in the tuberomammillary nucleus suggesting specific functional specialization, it is thought that because of projection patterns of fibers to different parts of the brain are similar and considerably overlap, all regions can function as a unity [62]. Nevertheless, from a functional point of view, discrete modulating neuron units controlling different functions are predictable, and the histaminergic clusters of the tuberomammillary nucleus should not be homogeneous. Hypothalamic histaminergic neurons send axons practically the entire brain, including the spinal cord [51,63]. This innervation occurs by two ascending and one descending pathways [50], thus many important brain structures such as the septum, olfactory bulb, thalamus, hippocampus, amygdala, forebrain structures, brain stem and spinal cord are innervated [17]. It is possible to visualize that the hypothalamic tuberomammillary nucleus might represent a complex multicompartment neural unit modulating general coping behaviour, since the physiological actions of histamine involve arousal, homeostatic mechanisms, cognition, motivation, pain perception and stress which sustain this behavioural mechanisms [54,17,15,57,39].

## 3. Histamine receptors

Now it is clear that the histamine effects on biological systems are mediated by the specific activation of four receptor types; $H_1$-, $H_2$-, $H_3$- and $H_4$-receptors [17,35,52]. The molecular activation of the membrane receptors produces various biological responses because receptors are coupled to several G-protein mediators such as $G_{q/11}$, $G_s$ and $G_{i/o}$ which are linked to several intermediate complex effector systems such as phospholipase C, phospholipase A, and adenylyl cyclase [35,17]. The various cascade intermediate molecules which are activated by the intermediate complex effectors give an amazing spectrum of responses which can activate or inhibit the neuron's functions [60,64,36,17]. Perhaps, this is one of the reasons why many times it has been reported opposing actions for histamine in some brain functions. The pharmacology and molecular proprieties for the different histamine receptors have been reviewed in extensive details by other authors [35,17,52].

## 4. Histamine and learning

The first evidence that histamine might be involved in the complex processes of learning and memory came from the basic experiments performed by de Almeida and Izquierdo [21,22], whom in a step-down inhibitory avoidance task model found that the combination of cimetidine and promethazine blocked the facilitation of the step-down inhibitory avoidance behaviour induced by the intracerebroventricular injection of histamine. In spite that the intracerebroventricular route of administration for the imidazolamine and its antagonists represents a very wide spectrum for possible histamine targets in the brain, and the side effects at central level of cimetidine and promethazine, including sedation, incoordination, blurred vision, anticholinergic actions, and confusional effects can distort the putative brain action of histamine, this evidence suggested that during learning histamine has a facilitatory action on consolidation of the task. Since it was necessary the injection of both $H_1$- and $H_2$-histamine receptor antagonists in order to block the assumed histamine effect on memory, it was apparent that both histamine receptors were mediating the consolidation of the task [21]. Nevertheless, this conclusion was based on the prolonged time the animals stand in the step-down during testing. Recently, it was found that the imidazolamine locally applied into the baso-lateral amygdala and the nucleus accumbens decreased exploration and increased emotionality in a conflictive environment (Alvarez and Banzan, unpublished results, Fig. 1). Thus, the prolonged permanency in the platform of the step-down inhibitory avoidance task may not necessarily be related to an increased efficiency of memory but to an increased resistance to step-down due to an increased emotionality. Nevertheless, the role of histamine on learning gained additional support because of evidence of some other authors working with a variant of the step-down avoidance response model [42,44]. In this model the task consisted to avoid an electric shock delivered to the feet of the animals in a dark room after an sliding door was opened, guiding the rat to a safe lighten room. The oral administration of classical $H_1$-histamine receptors inhibited the active avoidance response by prolonging the latency to escape of animals [42], and similar results were found when the histamine receptors antagonists were administered by intracerebroventricular route [44]. In addition, the administration of α-fluoromethylhistidine, an inhibitor of the histamine synthesis enzyme, either by systemic or intracerebroventricular injection prolonged the response latency of the active avoidance response in rats [43]. Unfortunately, α-fluoromethylhistidine is a compound that binds irreversibly to the histamine synthesis enzyme, and the only possible site where this inhibitor can act is at the level of the posterior hypothalamus, the only brain region where neurons can synthesize histamine. Thus, the reduction of histamine brain levels affects many important neural histamine centers controlling several homeostatic functions that can interfere indirectly with the learning process, weakening the idea about a direct histamine action on cognitive functions. In spite of this, the role of histamine on learning gained additional support with the description that histamine locally applied into the ventral hippocampus of rats was able to interfere the evocation of an active avoidance response to an ultrasonic tone [1]. In this model, the task consisted

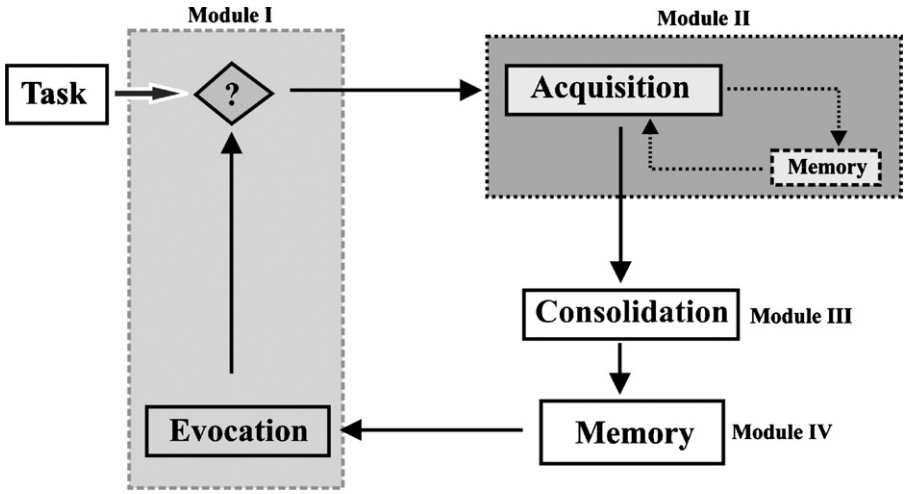


**Fig. 1.** Simplified diagram of the "Learning Loop" [10] assumed to be located in the learning neural circuits in the brain and constituting the basic common mechanism responsible to generate a memory. The unit is organized into three main processes: (1) acquisition, (2) consolidation and (3) evocation, which the experimental evidence supports as independent mechanisms. Each process is represented as occurring in modules. Modules are not required to exist in the same physical location. Process of learning is visualized as input information in a set of contextual cues identified as a "task". A comparison is performed between the incoming information and the recalled or evocated information at module I. If the incoming information does not coincide with, or there is not an equal image from the memory store, data from the task follow the next step, acquisition (module II). Acquisition generates an unstable memory trace that it will be stored as memory if the consolidation process is performed fully (module III). Once consolidation is finished, original data are stored in a memory register (module IV). The whole process is repeated when new or "unknown" information addresses module I, otherwise memory is recalled [10].

to avoid an electric shock applied to the feet of the animals in a "punishing" compartment by passing through a swinging door to a safe compartment, during 30 s duration of an ultrasonic tone. During acquisition of the task, rats were progressively decreasing the latency to escape (30 s initially to about 7 s at the end), and gaining a learning efficiency from 0% up to 80%. Since rats were implanted with microinjection cannulae into the ventral hippocampus, histamine administration was locally applied; avoiding redistribution to other brain areas. Thus, any disturbance to the evocation of the avoiding response had to be interpreted as a consequence of a localized treatment [1]. Histamine in these conditions was found to inhibit the evocation response [1]. Administration of ranitidine, an $H_2$-histamine receptor antagonist concomitantly with histamine was not able to suppress the inhibitory effect of histamine on the retrieval of the avoiding response. However, the administration of pyrilamine, an $H_1$-histamine receptor antagonist with histamine, blocked the inhibitory action of histamine on the avoiding response [3], suggesting that in evocation processes, the main histamine receptor involved was an $H_1$-histamine receptor. It is interesting to note that not taking into account the final effect of histamine on learning (facilitation or inhibition), this evidence support the notion previously reported by Kamei et al. [42,44] that an $H_1$-histamine receptor is participating in the evocation phase of the learning loop of a task (see Fig. 2). The question if histamine is also involved in the other phases of the learning loop [10] was analyzed by Alvarez and Banzan [4,5] where histamine and histamine receptor antagonists were microinjected into the ventral hippocampus during the acquisition of an avoiding response to the ultrasonic tone in their two-compartment cage model. Histamine treatment blocked the decreasing tendency of latency and reduced significantly the learning efficiency of the acquisition of the avoiding response [4,6]. Interestingly, the concomitant administration of histamine and ranitidine to the animals in these conditions was completely effective to block the latency response to avoid the electric shock and their learning efficiency [4,6]. Meanwhile, the co-administration of pyrilamine and histamine affected slightly the latency to escape and had a minor interference to the learning efficiency of the avoiding response [6]. These data suggested opposing effects for the stimulation of the histamine receptors, where the activation of hippocampal $H_1$-histamine receptors inhibits acquisition, and activation of $H_2$-histamine receptors facilitates the acquisition of the avoiding response. This evidence supported the facilitatory action of histamine on learning described previously by other authors [21,22,42,44].

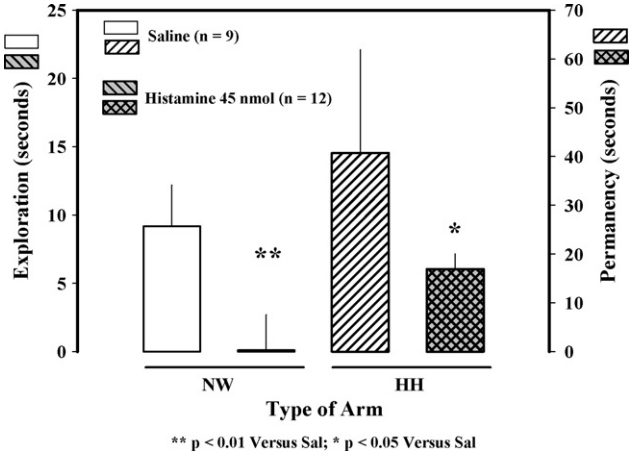


**Fig. 2.** Exploration and emotionality status of male adult rats implanted with microinjection cannulae into the baso-lateral amygdala and nucleus accumbens exposed during 5 min to a novel conflictive environment. An unknown environment is denominated "conflictive" when the animal attracted for the novelty evaluates the choice to explore because of fear or potential risk of the place [6]. The elevated asymmetric plus maze, formed by four arms at 90° to each other, fulfills this requirement. Arm with no walls (NW) and the arm with high walls (HH) represent the extreme values of very high emotionality (most fear-inducing) and very low emotionality (no fear-inducing) features of the arms. Time of exploration (left panel in the figure), and time of permanency which is approximately inverse related to emotionality (right panel of the figure) in animals treated with histamine show that the imidazolamine inhibits the motivated exploration due to an increase in the emotionality (Alvarez and Banzan, unpublished results). $^{**}p < 0.01$ versus Sal; $^{*}p < 0.05$ versus Sal.

$H_3$-histamine receptors were reported also to modulate the histamine effects on learning of an active avoidance response in a T-maze in mice [33]. $H_2$- and $H_3$-agonists and antagonist were microinjected into the septal complex of animals after training of the task, evaluating the role of the imidazolamine in the consolidation phase of the learning loop [10]. Unfortunately, 500 μl of volume injection was used to administer drugs into the septum of

mice, a very high liquid volume that has a large diffusion radius, compromising other nearby brain structures such as the caudate nucleus and the lateral ventricles. Thus, in spite those microinjections were performed into the septal region it is not possible to define that this is the precise location for the histamine related effects described in this study. It is interesting to note that the final effects of histamine on learning might not necessarily involve a direct action of histaminergic neurons on neural circuits controlling memory processes. *In situ* measurements of extracellular levels of acetylcholine by *in vivo* microdialysis and HPLC electrochemical detection, showed a dose-dependent increase of about 570% of baseline levels in frontal cortex, and about 600% in hippocampus after intraperitoneally administration of the $H_1$-histamine receptor antagonist chlorpheniramine [26]. Once again, the participation of the $H_1$-histamine receptor in neural circuits appeared as an important molecular agent controlling the complex brain processes of learning. Histamine and its histamine receptors were clearly established as involved in memory and learning after increasing new evidence accumulated in the last 10 years. Chemical or electrolytic lesions of the $E_2$ neuronal region of the tuberomammillary nucleus of the posterior hypothalamus of the rat, part of the histamine source in the brain, clearly affected a number of different tasks, such as habituation, inhibitory avoidance, discrimination and spatial learning [30]. In addition, consolidation processes of an inhibitory avoidance task were also significantly improved after transitory inactivation of the same $E_2$ histamine subregion of the posterior hypothalamus by lidocaine [31]. Numerous experimental models, pointing to acquisition, consolidation or evocation of many different tasks have contributed definitively to support on a firm ground the role of histamine on the physiological mechanisms of memory in rats and other animal species [18,61,30,8,6,56,9,24].

## 5. Histamine effects on learning: facilitatory or inhibitory actions?

After the proposal about the histamine participation on learning, opposing actions on these processes have been claimed for this imidazolamine [21,22,42,44,1,3,4,6,55,32,40,30,20,45]. Perhaps, it is necessary to point out that histamine by itself does have not intrinsic inhibitory or facilitatory actions. The final histamine effects on biological systems are a function of its specific receptor activation, which is very different according to its particular biophase in the various brain circuits. This is not surprising because of the second messenger cascade triggered by the histamine receptor activation may follow diverging pathways ending in paradoxical opposing biological actions [17,35]. For example, activation of $H_1$-histamine receptor by histamine is followed by excitation of the $G_{q/11}$ protein complex leading to formation of the second messenger Inositol-1,4,5-triphosphate, releasing $Ca^{2+}$ from internal stores and activating membrane $Na^+$–$Ca^{2+}$-exchanger which in the supraoptic neurons provokes depolarization [35,60]. Meanwhile, the same activation path opens the small conductance $K^+$ channels, resulting in hyperpolarization and inhibition of the pyramidal cells in the hippocampus [59]. It is interesting to point out that histamine in cultured dorsal ganglions neurons of the mouse inhibits the neuron axonal transport in anterograde and retrograde directions, and this effect appears to be mediated by $H_1$- and $H_3$-histamine receptors activation [11].

Discrepancies about the cellular actions of histamine on learning processes can be understood in part if the following points are considered.

### 5.1. Neural models

Even if it is to be accepted that the only cellular effect of histamine is a facilitatory action, classical network physiology can offer many examples whereby a *final* facilitatory or inhibitory biological effect is possible (Fig. 3).

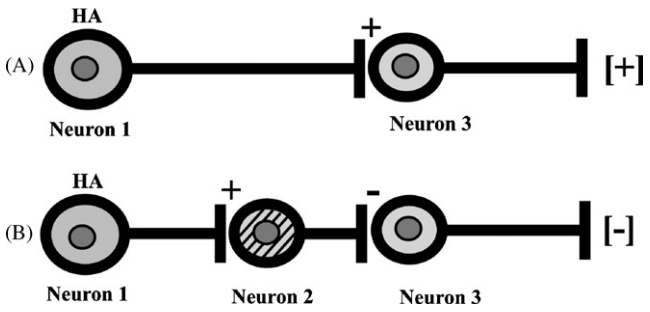


**Fig. 3.** Possible situations whereby histamine assuming to have only a facilitatory action on effector neurons, can produce an inhibitory effect. Classical neuronal network physiology can explain opposed final effects for a neuron with excitatory actions. (A) The most simple and direct situation. The histaminergic neuron excites another excitatory neuron. (B) The histaminergic excitatory neuron excites an inhibitory interneuron, which inhibits the effector neuron, giving an inhibition of the controlled function. In a similar way, if the histamine neuron is inhibitory, other possibilities can explain the same effects. HA, histamine.

### 5.2. Experimental models

Conclusions about the histamine effects on learning have been based on a variety of experimental models where specific paths were selectively chosen from the learning loop [10]. It is apparent that each of these processes has different intrinsic mechanisms. Thus, receptor activation might lead to a different expected result. For example, in the learning of an active avoidance response to an ultrasonic tone in a two-compartment cage during acquisition, the stimulation with histamine of the hippocampal $H_1$-histamine receptor while the $H_2$-receptor is blocked, leads to complete inhibition of learning [6]. Meanwhile, stimulation with histamine of the $H_2$-receptor while the $H_1$-histamine receptor is blocked, a nearly normal acquisition curve of the response was observed [6]. Thus, both histamine receptors appeared to be important to modulate learning of the task. However, with the same model but working on the *evocation* or *recall* of the avoiding response (after consolidation), the stimulation of the $H_2$-receptor with histamine, with the $H_1$-receptor blocked, no inhibitory effect of histamine was observed. Meanwhile, stimulation of the $H_1$-receptor with histamine, while the $H_2$-receptor is blocked, the inhibitory action of histamine on recall of the avoiding response was present [6]. In this case, only the $H_2$-histamine receptor appeared to have a modulatory role on learning. Consequently, different actions can be ascribed to histamine receptors, depending on what path is affected in the learning loop [10].

### 5.3. Doses and routes of administration

In the abundant studies that have been published, authors have used various routes of administration and doses of histamine or its antagonists in their experimental models [21,22,42,1,55,32,56,8]. Systemic or intracerebroventricular administration is difficult to evaluate regarding the specific influence of the imidazolamine on learning because of the presence of multiple active receptor sites affecting many fundamental physiological processes that indirectly can affect learning and memory. Ranges of doses also present some problematic perspectives, and very low doses [21,22] or higher doses of histamine active molecules [1,3,4] have been used to affect memory processes. Some researchers have pointed out that the use of very high concentrations of agonists or antagonists exceeding the determined apparent dissociation constant for histamine receptors, as measured *in vitro* systems [34] cannot appropriately describe the

physiological actions for histamine. Being true that *in vivo* studies researchers have used many times histamine active compounds in apparent concentrations above the dissociation constant for histamine receptors, some caution must be taken to infer that in these conditions *artificial* concentrations are present at the receptor sites. It is known that in the brain there exists an exquisite cellular compartmentalization that makes the *in situ* concentrations likely to be very much higher than it is supposed to. The synaptic cleft of histamine synapses is very narrow, containing in a very small volume high concentration of histamine molecules after release of the neurotransmitter from the synaptic vesicles. Production of histamine molecules in the tuberomammillary neurons by the same reason appears incredibly higher. For example, it has been measured that the content of histamine in the whole brain is about 223 pmol/g of tissue. However, in the hypothalamus there exists about 1280 pmol/g of tissue, i.e. about six times that of the *whole* brain [38]. This can only be explained because of neural compartmentalization and the existence of only one region responsible to synthesize histamine [17,35,14,53]. Thus, the use of nmol ranges of histamine or histamine active molecules into the brain does not necessarily mean *excessive* amounts of compounds affecting determined physiological functions.

### 5.4. Interacting actions of histamine

Although in the earlier studies about histamine effects on learning, there was the idea that the imidazolamine might be acting directly on the respective neural circuits controlling memory; evidence has been accumulated that histamine interacts with some other neurotransmitters. As previously mentioned, blocking of $H_1$-histamine receptors produces increases in extracellular acetylcholine in rat frontal cortex and hippocampus [26], suggesting that histamine could be expressing its molecular effects by activation of acetylcholine receptors [15]. By manipulation of the presynaptic $H_3$-histamine receptors with $H_3$-histamine agonists in the baso-lateral amygdala of rats, an augmented spontaneous release of acetylcholine was observed [19]. Rats receiving this treatment showed "stronger" memory for the context of foot shock association in a contextual conditioned freezing test, supporting the inhibitory actions described for histamine [19]. Using other experimental approaches, such as the classic step-through passive avoidance response [27]; the histidine decarboxylase-KO mice model [23]; the simultaneous *in vivo* localized chemical stimulation of the ventral hippocampus and baso-lateral amygdala with glutamic acid and histamine [7], or glutamic acid antagonists [67]; the brain slices preparations for electrophysiological recordings, and *in vivo* septo-hippocampal cholinergic neurons identification [66], clearly have shown a relationship of histamine with acetylcholine, glutamic acid and serotonin neurotransmitters.

### 5.5. Complex mechanisms of action for histaminergic and histamine sensitive neurons

In addition to the factors previously mentioned about histamine receptor activation and the final behavioural effects, histamine neurons have been revealed as very complex functional units. Histaminergic neurons also store other neuroactive substances and related metabolic enzymes involving GABA, glutamate decarboxylase, adenosine deaminase, substance P, and galanin with some species-specific properties [54], suggesting putative interactions during neuron activation in spite that it is not known if these compounds are released from the histaminergic terminals during neuron activation. Thus, virtually nothing is known about its internal neuron mechanisms leading to some final neuronal response. An interesting feature to be considered to understand the regulatory mechanisms of the histaminergic neurons is the differential innervation of the histaminergic fibers to specific brain regions known to be involved in learning [2]. Histamine sensitive sites controlling learning of a conditioned avoidance response appeared to be more concentrated in the ventral posterior hippocampus than in the dorsal anterior hippocampus [2]. This evidence is suggesting that whatever the functional role histamine is performing into the hippocampal neuron circuit apparently is restricted to a much localized neuronal region. It is uncertain if this regional specialization is a particular characteristic of the hippocampal structure, or is a common feature for the rest of the histaminergic sites present in other brain structures.

Consideration that in the brain, input signals from the environment are reaching many neural structures at the same time, gives the perspective that processing of the input information in parallel might represent an additional complexity in neural regulation. This situation was examined for the baso-lateral amygdala and the ventral hippocampus regarding the histamine sensitive sites in relation to an avoidance conditioned response to an ultrasonic tone in rats [8]. Ipsilateral chemical stimulation with histamine of the hippocampus or the amygdala were more efficient to inhibit the acquisition of the avoidance response than the simultaneous stimulation of both brain structures [8]. This evidence is showing that the regulatory mechanisms of the histamine neural circuits on cognitive processes are more subtle and possibly constituting a dynamic connecting neural network with many substructures. Finally, it has been found that some other brain zones such as the nucleus basalis magnocellularis region also is involved in learning [56,68], presenting the interesting perspective that the "histamine neural network" responsible for the modulation of learning could be more wider that it was suspected.

In synthesis, the facilitatory or the inhibitory actions for the histamine receptors can be explained in terms of the complexity of neural projections, regionalized histamine sites in brain structures, many interacting actions with some other neurotransmitters, different synaptic networks and differential actions of receptors. It is quite possible that both biological effects for histamine can be operating in the brain.

## 6. The probable physiologic role of histamine on cognitive processes

Cognitive mechanisms, exemplified by learning have received much attention from researchers mainly in all those processes related to acquiring information leading to a stable memory in the brain [13]. However, equally important is forgetting which can be described as a mechanism that opposes the recall or the evocation of memory [16]. In spite that forgetting sometimes has been considered as a failure to encode or maintain information [65,49], it is difficult to think that determined data that fail to consolidate, therefore are not stored, can be later be "forgotten". Interpreting forgetting in terms of the "learning loop", leads to the option that it is an *active* mechanism that opposes the normal recall of the stored information. This is so because according to this model, it is possible to forget *only* that information that once was learned and conserved as memory. Process of forgetting appears as complex as other processes in learning, and in spite of some debate, forgetting not only can occur in spontaneous situations but also it is possible to "induce" it in a very similar way such as the recall of some memory [41,65]. Noradrenergic influence has been reported to modulate the process in humans using adrenoceptor antagonists and selective nor epinephrine reuptake-inhibitors [41], and in other experimental paradigms, specific activation of the medial frontal gyrus, middle temporal gyrus, parahippocampal gyrus, and cingulate gyrus as determined by event-related functional magnetic resonance imaging, was found to be involved to "intentional" for-

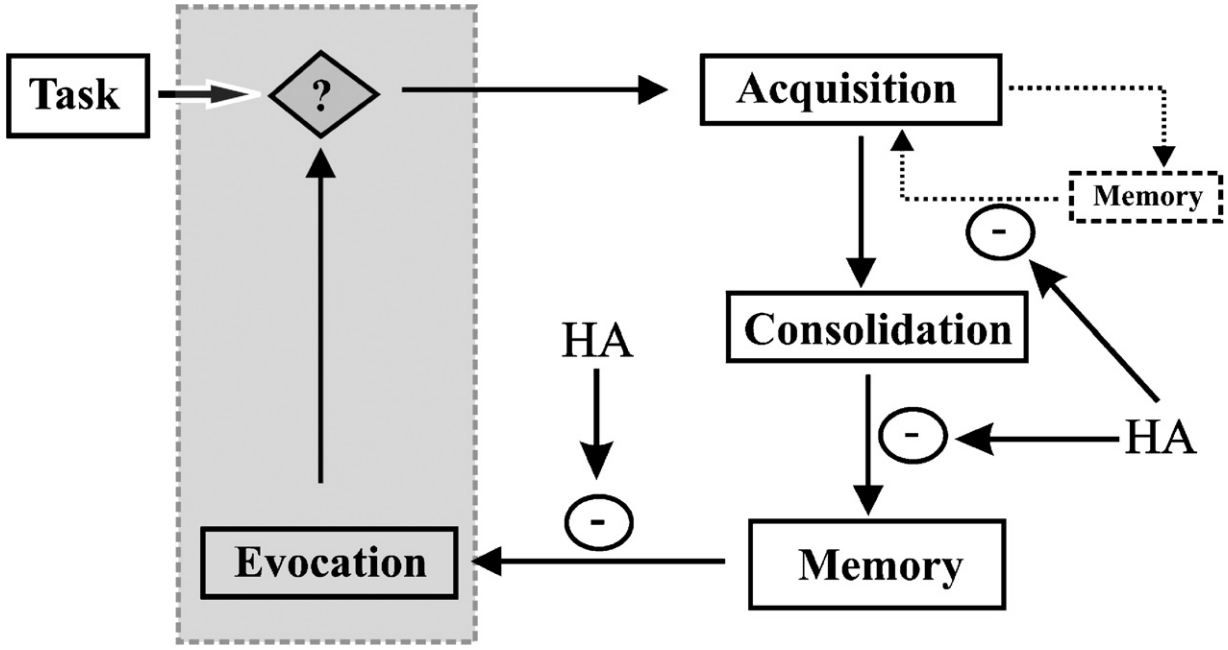


**Fig. 4.** Hypothetical role of histamine as a modulating neurotransmitter to the learning process. In this description, it is assumed that the main role of histamine is inhibitory. By inhibiting the evocation of a stored memory, histamine can facilitate forgetting. By the same action at acquisition it can interfere with learning. Apparently, histamine also is participating in the consolidation process, which as well gives an identical negative effect on learning.

getting [65]. Considering the memory-related actions described for histamine it is tempting to speculate that the histaminergic system could be participating in the mechanisms of forgetting as it is outlined schematically in Fig. 4. In monkeys and humans the distribution of the histamine $H_2$ receptor mRNA as measured by *in situ* hybridization histochemistry showed the highest density of the $H_2$ receptor mRNA in the external layers of the cerebral cortex, caudate, and putamen nuclei; while moderate amounts were found in the hippocampal formation [37]. Part of these brain structures have been found to be involved in cognitive processes, and this evidence suggests that the imidazolamine might have a potential role in human learning similar to that it was described in experimental animals. On line with the previous arguments, the observations that in some human neurological and neuropsychiatric diseases, the specific histamine $H_2$-antagonist famotidine was efficient in the treatment of Parkinson disease [48], and in other degenerative neuronal disorders such as the Huntington chorea [46], and also to alleviate some schizophrenic symptoms [25], alterations of $H_2$-histamine receptors were found, giving additional support to a participation of histamine in cognitive processes, since it is known that these brain disorders are linked to severe cognitive dysfunctions. Interestingly, some roles of $H_3$-histamine receptors in these brain dysfunctions also have been described [29]. Independently of the particular cases of the neuropsychiatric degenerative diseases affecting the cognitive abilities of humans, the most natural process which is also frequently accompanied with cognitive disorders is aging. Regarding this point, Mazurkiewicz-Kwilecki and Nsonwah have reported that the levels of histamine in the brain increase with age [47]. In conclusion, histamine as a neuromodulating neurotransmitter appears to fulfill the requirements to participate in the processes of learning by the specific activation of $H_1$-, $H_2$- and $H_3$-receptors, which in the present model of the learning loop might be controlling the mechanisms of forgetting.

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