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# REVIEW ARTICLE

# Brain histamine modulates recognition memory: possible implications in major cognitive disorders

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Several behavioural tests have been developed to study and measure emotionally charged or emotionally neutral memories and how these may be affected by pharmacological, dietary or environmental manipulations. In this review, we describe the experimental paradigms used in preclinical studies to unravel the brain circuits involved in the recognition and memorization of environmentally salient stimuli devoid of strong emotional value. In particular, we focus on the modulatory role of the brain histaminergic system in the elaboration of recognition memory that is based on the judgement of the prior occurrence of an event, and it is believed to be a critical component of human declarative memory. The review also addresses questions that may help improve the treatment of impaired declarative memory described in several affective and neuropsychiatric disorders such as ADHD, Alzheimer's disease and major neurocognitive disorder.

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## Abbreviations

ADHD, attention deficit hyperactivity syndrome; GSK-3β, glycogen synthase kinase-3β; APP, amyloid precursor protein gene; DBB, dried bonito broth; FSL, Flinders Sensitive Line; HDC-KO, histidine decarboxylase knockout; nAChR, nicotinic ACh receptor; TMN, tuberomamillary nucleus; VGAT, vesicular GABA transporter; VLPO, ventrolateral preoptic nucleus



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## Introduction

Despite the early diffidence in accepting the existence of a brain histaminergic system, its cardinal role in regulating several aspects of behaviour and arousal are now well established. The investigation of the histaminergic neuronal system lagged behind the exploration of other aminergic neurotransmitter systems, as the methods available were useful for characterizing brain catecholaminergic and serotonergic neurons, but were not suitable for visualizing **histamine** due to a strong interference by the ubiquitous **spermidine** (Hakanson *et al.*, 1972). Thus, while disturbances of dopaminergic, noradrenergic and serotonergic systems were soon hypothesized to be implicated in affective states, the failure to demonstrate histamine localization in the brain greatly limited the understanding and acceptance of this neuronal system (Haas *et al.*, 2008). However, in the early 1980s, two major discoveries convinced the scientific community of the existence of a central histaminergic system: the pharmacological identification of $H_3$ autoreceptors (Arrang *et al.*, 1983) and the direct evidence of histaminergic neurons after the development of antibodies against histamine (Panula *et al.*, 1984) and **histidine decarboxylase** (Watanabe *et al.*, 1984). The brain histaminergic system is well conserved throughout many species, from zebrafish (Sundvik and Panula, 2012) to humans (Panula *et al.*, 1990), and in all species studied so far, histaminergic projections cover all encephalic areas although with different densities in different brain regions (Inagaki *et al.*, 1988a; Panula *et al.*, 1989).

Histamine is implicated in arousal, awakening and maintenance of wakefulness and has a pivotal role in the maintenance of high vigilance that is required for cognitive processes (Thakkar, 2011). Not surprisingly, current research is providing evidence that malfunctioning of the histaminergic system is associated with neuropathological disorders (reviewed in Shan *et al.*, 2017). For instance, deficits in the histaminergic system are associated with neuropsychiatric disorders such as Gilles de la Tourette's syndrome (Ercan-Sencicek *et al.*, 2010; Karagiannidis *et al.*, 2013). As proof of concept, the group of Pittenger found that histidine decarboxylase knockout (HDC-KO) mice exhibit stereotypic locomotor behaviours that replicate the core phenomenology of Tourette's syndrome (Rapanelli *et al.*, 2017). Although many questions remain about the involvement of this histaminergic system in autism spectrum disorder, recent studies have suggested a potential involvement of histamine in this pathology (Fernandez *et al.*, 2012; Wright *et al.*, 2017).

Four **histamine receptors** have been cloned ($H_1$–$H_4$), and the $H_{1-3}$ receptors have been unequivocally found in distinctive patterns in the brain. The role of the **$H_4$ receptor** in cognitive processes is still a matter of debate. The $H_3$ receptor has been the focus of much research in the last 20 years as preclinical studies have demonstrated procognitive and awakening properties of $H_3$ antagonists (reviewed in Passani and Blandina, 2011; Schlicker and Kathmann, 2017).

In this review, we summarize the main findings describing the role of the brain histaminergic system and its receptors in recognition memory. Experimental paradigms that are used in preclinical studies to unravel the brain circuits involved in the animal equivalent of declarative memory in humans will be covered in this review, as well as the few reported cases of brain histamine involvement in human studies.

## The brain histaminergic system

We will briefly summarize the fundamental characteristics of the brain histaminergic system. For more detailed information, we refer the readers to other extensive reviews (Haas *et al.*, 2008; Panula and Nuutinen, 2013; Schlicker and Kathmann, 2017).

In vertebrates, the source of brain histamine in physiological conditions is mainly attributed to neurones residing in the tuberomamillary nuclei (TMN) in the posterior hypothalamus and different species differ in their number of histaminergic neurons and density of innervation (Ekstrom *et al.*, 1995; Eriksson *et al.*, 1998; Panula *et al.*, 1984; Takeda *et al.*, 1984). In rodents, a detailed mapping of TMN provided a subdivision of histaminergic neurons in distinct subpopulations. In the rat brain, histaminergic neuronal somata are grouped within the TMN in five clusters, E1–E5, each of which sends overlapping projections throughout the neuroaxis (Moriwaki *et al.*, 2015). A similar pattern of distribution has been reported in the brains of other mammals and non-mammalian vertebrates (Sundvik and Panula, 2012; Wada *et al.*, 1991).

Mast cells are another source of histamine in the brain of some species. For instance, in birds, immature mast cells infiltrate the CNS and undergo *in situ* differentiation within the neuropile (Zhuang *et al.*, 1999), and massive mast cell migrations into the brain have been associated with courting behaviour in doves (Silverman *et al.*, 1994). Also, brain mast cells and histamine release have been implicated in the modulation of anxiety-like behaviour and learning (Nautiyal *et al.*, 2008). Other possible sources of histamine in the brain may include microglia and microvascular endothelial cells (Katoh *et al.*, 2001; Yamakami *et al.*, 2000).

The main terminal areas of the histaminergic projections from the TMN are different in different species, but they cover essentially the whole CNS (Inagaki *et al.*, 1988b; Panula *et al.*, 1989). Retrograde tracing studies have shown that histaminergic neurons are a relatively uniform cell group, as they do not segregate according to projection areas (Inagaki *et al.*, 1990; Köhler *et al.*, 1985). However, functional differences exist among TMN neurones, suggesting that they do not belong to a homogeneous population but are organized in distinct functional subpopulations (Blandina *et al.*, 2012). Both neuroanatomical and functional observations in our and others' laboratories point to this conclusion. By using the double-probe microdialysis technique, we discriminated groups of histaminergic neurons impinging on different brain regions (Giannoni *et al.*, 2009); furthermore, immunohistochemical staining with anti-$H_3$ receptor antibodies demonstrated that histaminergic neuronal populations differ significantly in the expression level of this receptor (Blandina *et al.*, 2012). Recent chemo- and optogenetic studies have demonstrated the existence of separable behavioural effects as a consequence of TMN excitation of specific brain circuits (Fujita *et al.*, 2017; Rapanelli *et al.*, 2017). However, despite the accepted notion that histaminergic neurons may be functionally heterogeneous, the identification of specific

subpopulations of histaminergic neurons that modulate the different phases of memorization has been elusive.

### *Histamine receptors*

The basic homeostatic and higher functions, including cognition, regulated by brain histamine are due to the action of at least three metabotropic receptors: **$H_1$**, **$H_2$** and $H_3$ receptors, which are expressed at different densities in different brain areas. The $H_4$ receptor has been detected in the brain, but its function is not quite clear yet (Schneider and Seifert, 2016). All metabotropic histamine receptors ($H_{1–4}$) belong to the rhodopsin-like family of GPCRs. The action of $H_{1–2}$ receptors is usually excitatory (Panula *et al*., 2015). $H_1$ receptors are found at particularly high density in brain regions concerned with arousal and nutritional state control. Brain-penetrating antihistamines as well as antidepressant and antipsychotics that activate the $H_1$ receptor cause sedative and metabolic side effects (Provensi *et al*., 2016a). $H_2$ agonists potentiate hippocampal synaptic transmission and increase the firing of many types of neurons (Selbach *et al*., 1997). $H_3$ receptors are both presynaptic autoreceptors that inhibit histamine synthesis and release from histaminergic neurons, and heteroreceptors mediating the release of other neurotransmitters (Panula *et al*., 2015). Therefore, by blocking $H_3$ receptors, histamine release as well as the release of other neurotransmitters is augmented in brain regions crucial for maintenance of alertness and storage of information (Brown *et al*., 2001).

### *Histamine functions in the CNS*

Histamine exerts several functions in the brain, and only some aspects that are relevant to cognition are briefly reviewed here. Histamine is the major wake-promoting neuromodulator in the CNS and histaminergic neurons with their extensive networks sustain wake and arousal by modulating and interacting with different brain circuitries (Thakkar, 2011). The hypothesis that histaminergic neurons are involved in brain arousal is supported by several studies. Earlier works showed that $H_1$ receptor-KO mice have an impaired sleep–wake cycle, and in these animals, the wake-promoting effect of $H_3$ antagonists is abolished (Huang *et al*., 2006; Lin *et al*., 2002). Furthermore, c-Fos activation was observed in the TMN during waking (Lin *et al*., 2000; Nelson *et al*., 2002, 2003; Scammell *et al*., 2000; Sherin *et al*., 1998). More recently, lesion studies demonstrated that inactivation of the TMN with the GABA agonist **muscimol** induces long-lasting, non-rapid eye movement sleep (Xie *et al*., 2017), and optogenetic activation of a subpopulation of TMN neurons induces wakefulness (Fujita *et al*., 2017). Histamine maintains wakefulness through direct projections of the TMN to the thalamus and the cortex and indirectly through activation of other, cholinergic (Khateb *et al*., 1990, 1995; Xu *et al*., 2004) and aminergic (Brown *et al*., 2001; Korotkova *et al*., 2002, 2005) ascending arousal systems. The activity of TMN neurons varies according to the state of wakefulness: it is low during quiet waking, moderate during active waking and highest during attentive waking (Takahashi *et al*., 2006). The transition between wakefulness and sleep and *vice versa* requires the regulation of antagonism between sleep-promoting neurons in the ventrolateral preoptic nucleus (VLPO) that provide **GABA**- and galanin-mediated inhibition of histaminergic neurons, and brainstem cholinergic and monoaminergic neurons (reviewed in Benarroch, 2010). Furthermore, histaminergic and orexinergic neurons cooperate in the hypothalamic control of the sleep–wake states exerting a distinct but complementary and synergistic control of wakefulness (Anaclet *et al*., 2009). Release of histamine from TMN neurons can disinhibit histaminergic neurons and suppress the activity of sleep-active VLPO neurons to promote histaminergic neuronal firing and arousal (Williams *et al*., 2014). Cortical histamine release is also stimulated by an appetitive state most likely related to increased behavioural activation during active food searching (Riveros *et al*., 2015; Valdés *et al*., 2010). Histaminergic neurons express the **glutamic acid decarboxylase** (GAD) enzymes, GABA (Airaksinen *et al*., 1992; Kukko-Lukjanov and Panula, 2003; Takeda *et al*., 1984; Trottier *et al*., 2002) and the **vesicular GABA transporter** (VGAT/VIAAT) (Yu *et al*., 2015). Recently, it was demonstrated that histamine and GABA co-transmission in the neocortex and striatum are necessary for appropriate wakefulness. By ablating the VGAT gene on murine histaminergic neurons, Yu and colleagues observed an increase in general activity and sustained wakefulness. The intriguing proposal of the authors states that wake-active TMN neurons 'generate a paracrine GABAergic signal that serves to provide a brake on over-activation, but could also increase the precision of neocortical processing' (Yu *et al*., 2015). However, this is not a general feature of histaminergic neurons; in fact, TMN neurons are heterogeneous in this respect as well, as not all of them co-transmit GABA. Optogenetic stimulation of histaminergic neuron projections to the hypothalamic preoptic nucleus produces only histamine release which in turn stimulates local GABAergic neurons to induce a net inhibitory effect (Williams *et al*., 2014). In addition to GABA, a subpopulation of histaminergic neurons co-expresses **thyrotropin releasing hormone** (TRH) and **galanin** (Airaksinen *et al*., 1992; Chotard *et al*., 2002), but the physiological relevance is not clear. Other functions of histamine may affect learning and memory processes such as thermoregulation, energy expenditure and feeding (reviewed in Tabarean, 2016 and Provensi *et al*., 2016a). A novel role of histamine was described in the cerebellar nuclei, where histamine selectively depolarizes output projections and improves cerebellar nuclei-mediated motor balance and coordination (Zhang *et al*., 2016) that may contribute to the exploratory locomotor activity induced by activation of $H_2$ receptors (Mohsen *et al*., 2014).

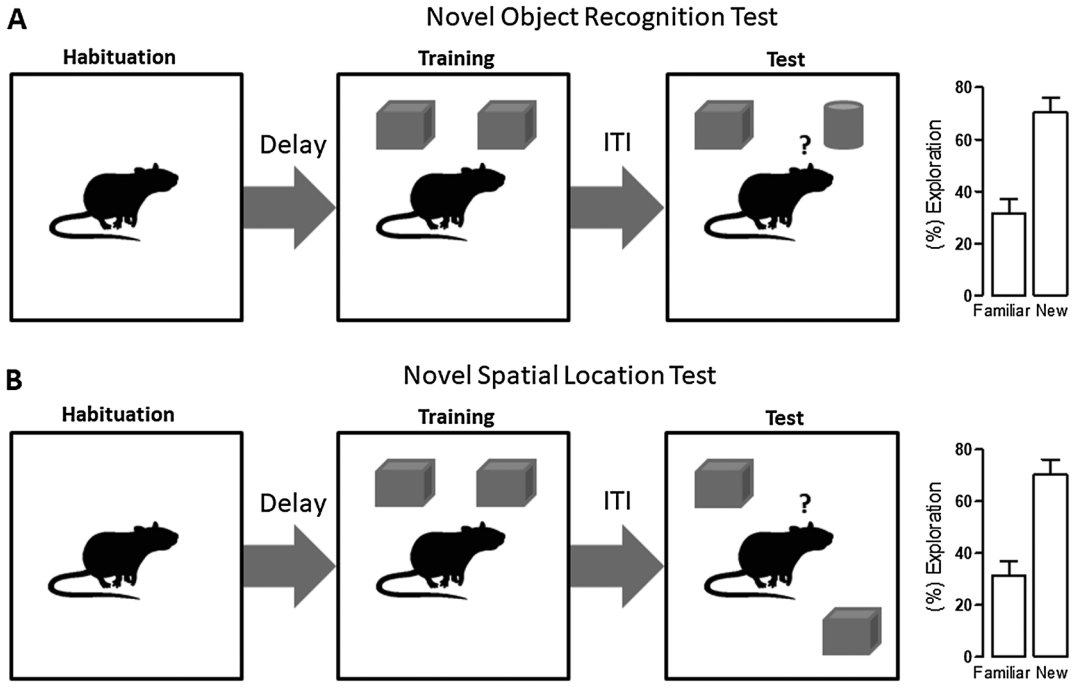
## Different types of memory and memory modulation by histamine

The term memory covers three important aspects of information processing: encoding, storage (consolidation) and recall or retrieval. *Encoding* is the acquisition of an engram, or specific information, and, therefore, entails learning. During *consolidation*, the engram is stored for variable periods of time as short-term or long-term memories; the former may last hours or days, the latter may last forever. *Retrieval* is the process of accessing the engram. In animal studies, retrieval is the only measurable behavioural

expression of an acquired and stored memory. During retrieval, the engram may become labile and can be reconsolidated (Josselyn *et al.*, 2015). As time passes, even the most consolidated memories may disappear, a process called forgetting (Davis and Zhong, 2017). All these related but dissociable events involve the elaboration of disparate learning situations requiring different degrees of activation in distinct brain region at different times (Passani *et al.*, 2007). It is not surprising that such important and dynamic processes are modulated by several neurotransmitter systems including histamine and by disparate brain circuitries that become active at different time points during the many phases of memorization.

Emotionally charged events are often remembered more accurately and more vividly than events devoid of an emotional component. Furthermore, emotionally neutral situations usually lead to the creation of shorter lasting memories of the event (Reisberg and Heuer, 2005). Several behavioural tests have been developed to study and measure emotionally charged or emotionally neutral memories and how these may be affected by pharmacological, dietary or environmental manipulations. Emotionally charged memories will be dealt with in another chapter of this issue. *Recognition* memory is based on the judgement of the prior occurrence of an event, and it is believed to be a critical component of human declarative memory, a kind of memory we use to answer questions like 'where?', 'who?' and 'when?' (Winters *et al.*, 2008). Although highly conserved among species, the expression of declarative memories varies greatly among different species (Paul *et al.*, 2009). Declarative memory in humans, for example, is formulated through language and other explicit representations. Animals, on the other hand, cannot represent such knowledge verbally or symbolically, and different tests have been used as models of episodic memory tasks in rodents (reviewed in Fouquet *et al.*, 2010). The most used tasks are the object recognition task and variations thereof (Ennaceur and Delacour, 1988; Leger *et al.*, 2013). The comparability of these *episodic memory* tests in animals with human episodic memory tests is limited; however, it appears that similar brain regions do support this type of memory both in humans and animals (Allen and Fortin, 2013). Therefore, such preclinical tests are still widely used to address questions that may help improve the treatment of impaired declarative memory described in several affective and neuropsychiatric disorders such as attention-deficit hyperactivity syndrome (ADHD), Alzheimer's disease and major neurocognitive disorders.

The novel object recognition (Figure 1A) and the novel spatial location tests (Figure 1B) rely on the motivational strength of novelty, as they are based on the natural tendency of rodents to search and explore novel objects or the new location where an object has been displaced. These procedures have become popular methods for studying emotionally neutral memories as they do not require punishments, food or water restriction, and several behavioural endpoints can be rapidly obtained, including general activity, reactivity to novelty, and learning (Blaser and Heyser, 2015). Experimental animals usually remember objects previously encountered in an open arena and their location and spend more time exploring new objects or their new location. Usually, this type of memory is labile and does not last for more than 6–12 h. However, long habituation sessions before the training may produce a longer lasting memory for the novel object that persists days after the test (da Silveira *et al.*, 2013).




## Figure 1

Schematic representation of the novel object recognition and novel spatial location paradigm.

Another paradigm is based on *social recognition*, a fundamental behaviour to form and consolidate social groups; hence, it is important for reproduction, species survival and the establishment of dominance hierarchies. In addition to these forms of long-term social recognition, rodents are also known to form transient, short-term memories of recently encountered individuals (Thor and Holloway, 1982; Winslow and Insel, 2004). In rodents, social recognition memory is tested by using their instinctive tendency to investigate unfamiliar conspecifics with respect to familiar ones (van der Kooij and Sandi, 2012). Social recognition relies largely on odour recognition whereas other sensory inputs are considered much less important (Wacker and Ludwig, 2012). In the most used experimental design, the habituation/dishabituation paradigm (Figure 2A), an adult rodent is exposed to an unfamiliar, juvenile subject. The two animals engage in a series of social investigative behaviours to become acquainted with each other. During the subsequent encounter, the retention trial, the juvenile subject is 'recognized' and will be investigated for a shorter period of time. This decrease in social investigation upon repeated encounters can be interpreted as an index for social recognition. Usually, this is a form of short-term memory with a limited duration (30 min to 2 h) in individually housed mice and rats (Burman and Mendl, 2000; Lemaire, 2003; Okuyama *et al.*, 2016). Another version of the social recognition paradigm is the *social discrimination* test (Figure 2B; Engelmann *et al.*, 1995) that shares the initial phase with the habituation/dishabituation paradigm. However, during the retention test, the familiar juvenile and a novel conspecific are simultaneously presented to the adult animal, and the time it spends exploring each conspecific is recorded. Again, if the animal recognizes the familiar juvenile, it will spend more time exploring the novel one.

## *Histamine and social recognition memory*

As previously mentioned, social memory refers to the ability to remember the identity of a conspecific, which is fundamental to the building of social relationships and survival. Neurotransmitters such as **noradrenaline**, **dopamine** and **acetylcholine** (Griffin and Taylor, 1995; Di Cara *et al.*, 2007; Deiana *et al.*, 2011) and hormones such as **oxytocin** (Raam *et al.*, 2017; Lin *et al.*, 2018) have been suggested to play key roles in social discrimination and memory. Early work by Philippu and colleagues showed that histamine is also involved in this type of memory, as an increased histamine concentration in the brain improved short-term recognition memory, whereas depletion of neuronal histamine had an amnesic effect (Prast *et al.*, 1996). Social recognition is disrupted by ageing as well; adult rats recognize a juvenile for long periods of time, whereas aged rats hardly retain the information for longer than 30 min (Markham and Juraska, 2007). The $H_3$ antagonist **ABT-239** that does not significantly improve social memory in adult rats improved recall in aged rats to the extent that their performance was comparable to that of adult rats, without altering exploratory behaviour (Fox *et al.*, 2005). Other recently synthesized $H_3$ antagonists were also found to enhance short-term memory in the rat social recognition memory model (Hudkins *et al.*, 2014). Using a protocol entailing re-exposure of the adult rat to the same juvenile 90 min after the first encounter, Kraus and colleagues suggested that histaminergic neurotransmission within the nucleus accumbens facilitated short-term social memory without influencing cholinergic and glutamatergic transmission (Kraus *et al.*, 2013). Of note, one of the components of the storage site of social memory appears to be the ventral hippocampus and its projections to the nucleus accumbens shell (Okuyama *et al.*, 2016). Another study used the social discrimination protocol (see above) to show

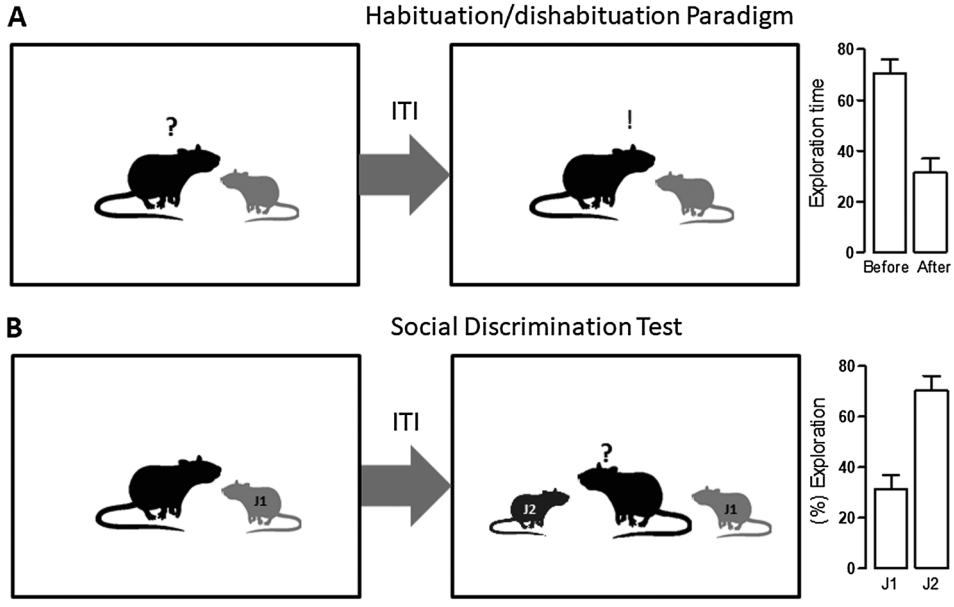



**Figure 2**
Schematic representation of two paradigms used to evaluate social recognition.

that recognition consolidation is mediated by $H_2$ receptors in both the amygdala and dorsal hippocampus, as rats injected with the $H_2$ antagonist **ranitidine** spent a similar length of time exploring the novel and familiar juveniles, and the $H_2$ agonist **dimaprit** reversed this effect (Garrido Zinn *et al*., 2016). Nevertheless, $H_2$ receptor activation in the infralimbic cortex does not appear to participate in the consolidation of social recognition memory (Cavalcante *et al*., 2017). Kraus and colleagues had previously reported that an infusion of **famotidine**, another $H_2$ antagonist, did not affect the **thioperamide**-induced facilitatory effect on recognition memory (Kraus *et al*., 2013). These apparently contrasting results could be related to differences in the injection site. Famotidine was administered into the brain ventricular system, whereas ranitidine was given directly into the BLA or CA1 at very similar dosages; thus, it is conceivable that the final concentration of famotidine within these specific structures was not sufficient to prevent thioperamide's effects.

## *The histaminergic system and object recognition memory: pharmacological studies in rodents*

Early work by the group of Blandina *et al*. (1996) described the effects of systemic administration of the $H_3$ agonists **imetit** and **R-α-methylhistamine** prior to the acquisition session in the object discrimination test. As expected for a short inter-trial interval (60 min), control rats remembered the previous encounter with the familiar object and spent significantly more time exploring the novel one. However, the memory of $H_3$ agonist-treated rats was impaired as they showed no significant differences in the time spent exploring either object (Blandina *et al*., 1996). Furthermore, **scopolamine**-induced memory impairment was prevented by pretreatment with the $H_3$ antagonists thioperamide or **clobenpropit** (Giovannini *et al*., 1999). These results suggest a localization of $H_3$ receptors on presynaptic histaminergic terminals, where their activation reduces histamine synthesis and release.

Using a slightly different procedure, Ghi *et al*. (1999) explored sexual differences in the object recognition task with different inter-trial intervals and the promnesic effects of $H_3$ receptor antagonism. They found that female rats preserved their memory for the novel object for longer periods of time with respect to males. In this context, the $H_3$ antagonist thioperamide preserved the ability to discriminate the familiar and novel objects when administered 40 min before the retention test, hence suggesting that histaminergic modulation of recognition memory facilitates memory retrieval (Ghi *et al*., 1999). Nowadays, most experimental observations agree that $H_3$ antagonists prolong recognition memory and prevent anterograde or retrograde, pharmacologically-induced memory impairment. Bongers *et al*. (2004), however, observed that systemic treatment with the $H_3$ antagonists thioperamide and clobenpropit caused memory impairments (Bongers *et al*., 2004). The discrepancy may be explained by the fact that the study was performed in mice rather than rats, with long habituation and acquisition sessions and using high doses of $H_3$ antagonists that are known to produce an inverted U-shaped dose–response curve in the object recognition test (Pascoli *et al*., 2009).

An open issue regarding the efficacy of $H_3$ antagonists on recognition memory is the specific memory phase affected by these compounds. Some studies report the effects of pharmacological treatments administered before acquisition or retention sessions or both, others before habituation. Two studies specifically investigated the effects of drug treatments given at different time-points during the object recognition paradigm. In one study, memory facilitation occurred when the $H_3$ antagonist **ciproxifan** was given before the retention session, whereas administration before or immediately after training was ineffective (Pascoli *et al*., 2009). The other study reported that the same compound prevented time-induced memory impairment when administered shortly after training as well as before retention sessions, but not when given 1 h before acquisition (Trofimiuk and Braszko, 2014). These results are in agreement with the majority of studies indicating that $H_3$ receptor blockade facilitates retrieval; in other words, it facilitates the expression of the memory. However, there is experimental evidence that acute $H_3$ antagonist injection before acquisition has a beneficial effect on recognition memory, but this was mostly using experimental designs that entail short inter-trial intervals (5–180 min). Considering the high occupancy of brain $H_3$ receptors that is rapidly achieved after systemic administration and their low elimination rate (Le *et al*., 2008; Sakurai *et al*., 1994), it is conceivable that when using short inter-trial intervals, the drugs may affect all phases of the mnemonic process.

Recent evidence of the relevance of histamine neurotransmission in object recognition was provided by Sadek's group who showed that acute systemic post-training administration of a newly synthesized $H_3$ antagonist ameliorated the performance of rats with cognitive impairments induced by **dizocilpine** (MK-801; Alachkar *et al*., 2017). The same group also demonstrated the efficacy of another $H_3$ antagonist, which counteracted the MK-801-induced mnemonic deficit when injected shortly before the retrieval session (Eissa *et al*., 2018). The authors suggested that the postsynaptic receptor that mediates the promnesic effect is the $H_2$ receptor without providing information of what brain structure is primarily responsible for the effect.

As mentioned above, $H_3$ receptor antagonists increase histamine release as well as the release of other neurotransmitters in brain regions crucial for the maintenance of alertness and storage of information. In keeping with this hypothesis, we demonstrated that administration of the non-imidazole $H_3$ antagonist, ABT-239, to wild-type mice before training *and* retention test improved memory in the object recognition paradigm; the efficacy of ABT-239 on memory was not observed in the brain of histamine-depleted mice, suggesting that endogenous histamine is crucial for the mnemonic effects of $H_3$R ligands (Provensi *et al*., 2016b).

The results summarized so far support the concept that memory improvement generated by $H_3$R antagonists is caused by increased endogenous histaminergic tone and subsequent activation of post-synaptic histaminergic receptors. Indeed, several studies point towards this conclusion as, for instance, intra-hippocampal infusion of the $H_1$R antagonist **pyrilamine** 30–120 min after training impaired recognition memory, whereas no effects on retention were observed when the drug was infused immediately or 360 min after acquisition (da Silveira *et al*., 2013). Similar findings were observed

when the $H_2R$ antagonist ranitidine or the $H_3R$ agonist imetit were directly delivered into the CA1 region of the hippocampus (da Silveira *et al*., 2013).

Nozawa and colleagues in Japan performed a very curious study. They investigated the effects of oral administration of dried bonito broth (DBB) to rodents in several learning paradigms, including the object recognition. DBB is a hot-water extract of dried bonito (skipjack tuna) muscle, which is ubiquitous in the Japanese diet, enhancing the taste and flavour of dishes that presents high levels of the histamine precursor, **histidine** (Fuke and Konosu, 1991). Oral administration of 1.6 $g \cdot kg^{-1}$ of DBB to mice significantly increased not only plasma histidine levels but also histamine levels in the hypothalamus. This diet prevented time-induced natural forgetting to the same extent as thioperamide and L-histidine acute injections (Nozawa *et al*., 2014). These results suggest that histamine participates in the DBB-induced procognitive effects and contributes to understanding previously reported mood improvement (Nozawa *et al*., 2008) and better performance in calculation tasks observed in humans (Kuroda *et al*., 2007).

## *The histaminergic system and object recognition memory: studies in genetically modified mice*

Results obtained with genetically modified mice lacking components of the histaminergic system have significantly increased our understanding of the histaminergic system. Comprehensive overviews of the behavioural phenotypes of these mice can be found in Schneider *et al*. (2014a,b). In line with the findings observed using classical pharmacological approaches, the results obtained using knockout models depend on the task and the type of memory being evaluated. Regarding specifically the novel object recognition, it was reported that the performance of histamine-deficient mice, both males (Acevedo *et al*., 2006a) and females (Acevedo *et al*., 2006b), did not differ significantly from age-matched wild-type mice. In contrast, Dere and co-workers described a poorer performance for HDC-KO male mice in a non-reinforced object exploration task (Dere *et al*., 2003). These discrepancies could be ascribed to considerable differences in the tasks used: in the first studies, a classical, one-trial novel object recognition is used; the latter paper describes a very complex protocol in which the mice were presented to four objects and were demanded to discriminate among the objects based on the temporal sequence of presentation. In this case, memory retention was evaluated by the number of contacts with each object: wild-type mice explored for a longer time, whereas HDC-KO were unable to differentiate the objects' order (Dere *et al*., 2003). It is important to note that the sum of contacts observed in HDC-KO animals was lower than those of wild types, which may have contributed to the results observed.

Several reports suggest that $H_1R$ as well as $H_2R$ deficiency impairs learning and memory, including object recognition (Dai *et al*., 2007). Mice lacking the $H_1R$ display also episodic-like memory impairments as evaluated in a complex spatial and temporal object recollection task (Dere *et al*., 2008). More recently, the same group observed that wild-type mice preferentially explore the objects based on the temporal order of presentation, but $H_1R$-KO are completely unable to maintain temporal or order information (Zlomuzica *et al*., 2013). Interestingly, these animals did not develop a conditioned place-preference induced by novel objects, even though they still explored novel objects, suggesting that although motivation to explore novel objects was unchanged, their reinforcing value was probably diminished (Zlomuzica *et al*., 2008). Mice lacking $H_2R$ function exhibit selective cognitive deficits along with an impairment of hippocampal LTP (Dai *et al*., 2007).

Although pharmacological studies have shown consistently that $H_3R$ modulation results in alterations of the mnemonic processes (either improvement or impairment depending on the test), $H_3R$ deficiency does not cause significant impairments in several memory tasks (Toyota *et al*., 2002) including the object recognition (Rizk *et al*., 2004). Recent findings indicate that also the ablation of $H_4R$ did not result in significant alterations of recognition memory (Sanna *et al*., 2017).

## *The histaminergic system and recognition memory: novel object versus novel location recognition memory*

Despite several studies reporting the participation of the central histaminergic system in the modulation of spatial memories, studies using the spatial version of the object recognition task are scarce. As previously mentioned, the novel object location test relies on a rodent's innate preference for novelty. The major difference between the two versions of the test occurs on the day of testing: in the object recognition test, one of the familiar objects presented during the acquisition session is replaced with a new one in the same location, while in the novel object location version, one of the familiar objects is moved to a new position in the arena. Therefore, animals that remember the original training experience will preferentially explore the object in the new location relative to the non-displaced object (Weible *et al*., 2009; Vogel-Ciernia and Wood, 2014). Acevedo and co-workers demonstrated sex- and age-dependent alterations in cognitive performance in HDC-KO mice. Female histamine-deficient mice did not differ from wild-type controls in the novel location recognition task throughout lifespan (Acevedo *et al*., 2006b). On the other hand, while male HDC-KO mice showed impaired novel location recognition in adulthood, middle-aged animals did not differ from age-matched controls in this test (Acevedo *et al*., 2006a). These results underscore the influence of gender and age in behaviour experiments. The spatial impairment observed in young male HDC-KO mice is in agreement with results showing spatial memory facilitation following histamine central administration (Chen *et al*., 2001; Huang *et al*., 2003) but is more difficult to reconcile with the better performance of young HDC-KO than age-matched controls in the hidden platform session using the Morris water maze (Dere *et al*., 2003). However, it is important to note that these two tests are based on a different number of training and testing trials and involve different motivational factors; thus, histamine-deficient mice could either remember the location of the hidden platform better or might be more motivated to find it (Acevedo *et al*., 2006a). Novel spatial location memory was also unaffected in $H_1R$-KO mice (Zlomuzica *et al*., 2008). To the best of our knowledge, there are no reports describing

the consequences of $H_2R$, $H_3R$ and $H_4R$ silencing using the new object location memory test.

## *Histamine and stress: effects on recognition memory*

Memory processes can be profoundly affected by stress, although the impact of diverse stressful stimuli on cognitive functions is not the same: while moderate stress can facilitate learning, excessive stress (acute or chronic) leads to impairments of memory function (Sandi and Pinelo-Nava, 2007). Trofimiuk and Braszko (2014) observed that daily restrained rats for 21 days were unable to differentiate the novel from the familiar objects when the retention session was performed 24 h after the acquisition. Acute ciproxifan treatment counteracted the deleterious effects of chronic restrain stress on long-term recognition memory (Trofimiuk and Braszko 2014). Prolonged exposure to stress evokes profound structural, physiological and molecular changes in brain areas related to cognition and emotions and increases the risks of developing neuropsychiatric disorders, such as depression (Schneiderman *et al.*, 2005; McEwen and Gianaros, 2010). The Flinders Sensitive Line (FSL) is a suitable rat model to study emotional and cognitive deficits of depression-like symptoms because this inbred rat model shows impaired emotional and recognition memory (Eriksson *et al.*, 2012; Gomez-Galan *et al.*, 2013; Overstreet and Wegener, 2013). The behavioural repertoire of FSL rats acutely treated with the $H_3R$ antagonist clobenpropit or saline was compared with that of Sprague–Dawley (SD) rats treated with saline. During the test session, performed 24 h after training, SD rats preferentially explored the novel objects, whereas saline-treated FSL rats showed no object preference. Treatment of FSL rats with clobenpropit increased the recognition index to the same level observed in SD rats, indicating that the drug treatment restored recognition memory (Femenia *et al.*, 2015).

Perinatal asphyxia is a severe condition associated with obstetric complications during labour and delivery with high mortality. It may affect virtually any organ, but hypoxic–ischaemic encephalopathy is the most studied clinical condition as it is burdened with the most severe sequelae (Antonucci *et al.*, 2014). Animal studies confirmed that perinatal asphyxia results in cognitive impairments in adulthood in several models (Boksa *et al.*, 1995; Simola *et al.*, 2008) and, among others, alteration of neurotransmitters in the hypothalamus (Kohlhauser *et al.*, 1999). Flores-Balter and co-workers evaluated neurochemical and behavioural consequences of perinatal asphyxia in adulthood with particular attention to the histaminergic system. Interestingly, asphyxia-exposed rats exhibited an impaired performance in the object recognition test, which was correlated with a decreased number of ventral TMN neurons and marked reduction of histidine decarboxylase expression in the hypothalamus. Acute treatment with the $H_3R$ antagonist thioperamide dose-dependently reverted perinatal asphyxia-induced recognition memory impairment in adulthood (Flores-Balter *et al.*, 2016).

Some evidence suggests that prenatally or immediately postnatal exposure to **methamphetamine**, a highly addictive amphetamine-like psychomotor stimulant widely used worldwide (Courtney and Ray, 2014), may result in long-term hippocampus-dependent spatial learning and memory deficits in rodents (Williams *et al.*, 2003a,b). As histamine mediates some effects of methamphetamine when given acutely in adulthood (Kubota *et al.*, 2002; Dai *et al.*, 2004; Kitanaka *et al.*, 2007), Raber's group examined whether histamine could also contribute to the long-term cognitive deficits observed in early-life methamphetamine-exposed mice. Mice received the treatments from post-natal days 11 to 20 and were tested at 3 months of age using a complex novel location and novel object recognition test. When a known object was moved to a novel location, control animals (saline treated males and females) recognized the novel spatial arrangement of familiar objects. Methamphetamine- and thioperamide-treated females showed impairments in novel location recognition. In contrast to females, no cognitive deficits were observed in males, suggesting that females might be more susceptible. Finally, co-administration of the $H_3R$ agonist **immepip** prevented methamphetamine-induced spatial recognition deficit in females (Acevedo *et al.*, 2007, 2008; Acevedo and Raber, 2011). Accordingly, the same group demonstrated that methamphetamine administration to neonatal mice increased brain histamine levels and activated the hypothalamic–pituitary–adrenal axis; both effects were more pronounced in female than male mice (Acevedo *et al.*, 2008). Moreover, the same treatment reduced levels of the dendritic marker microtubule-associated protein 2 in the CA3 region of the hippocampus and the enthorhinal cortex. Such reduction was not observed in mice receiving immepip along with methamphetamine, and the animals did not show cognitive impairments, suggesting that these brain areas are particularly important for the long-term effects of methamphetamine on cognitive function (Acevedo *et al.*, 2008). These data support a role for histamine in the effects of methamphetamine on the developing brain.

## *Efficacy of histamine ligands in animal models of cognitive disorders*

The preclinical results showing procognitive effects of $H_3R$ antagonists raised great expectations on the translational values of these compounds, given the encouraging results obtained in preclinical models of cognitive disorders. As an example, the administration of SAR110894, a potent $H_3R$ antagonist, 1 h before the acquisition session significantly attenuated impaired short-term episodic memory performance in the object recognition task of rodents that received i.c.v. injection of the Aβ23-35 amino acid sequence of the **amyloid peptide** (Chen *et al.*, 1996; Olariu *et al.*, 2001; Griebel *et al.*, 2012). Long-term treatment with the same $H_3R$ antagonist inhibited τ pathology and prevented cognitive deficits in a τ transgenic mouse model (THY-Tau22) by reducing τ hyperphosphorylation in the hippocampus, decreasing the formation of neurofibrillary tangles in the cortex, hippocampus and amygdala and macrophage inflammatory protein 1-α mRNA expression. SAR110894 also prevented episodic memory deficits, and this effect persisted after treatment washout (Delay-Goyet *et al.*, 2016). Similar procognitive effects were observed when the $H_3R$ antagonist ciproxifan was administered to mice that express a mutant form of the human

amyloid precursor protein gene ($APP_{Tg2576}$) associated with familiar early-onset Alzheimer's disease. Treatment with ciproxifan 30 min before the retention session of the object recognition test prevented the discrimination deficits observed in 12- to 14-month-old $APP_{Tg2576}$ animals (Bardgett *et al.*, 2011). Using the same animal model, Bitner and coworkers demonstrated that the treatment with another $H_3R$ antagonist, ABT-239, normalized the hyperactivation of hippocampal glycogen synthase kinase-3β (**GSK-3β**) and prevented τ hyperphosporlylation. However, they found that **donepezil**, an **AChE** inhibitor, was unable to modify GSK-3β phosphorylation. Interestingly, ABT-239-stimulated GSK-3β phosphorylation in the hippocampus was blunted in **α7 nicotinic ACh receptor** (nAChR)-KO mice (Bitner *et al.*, 2011). We recently confirmed and expanded these observations: ABT-239 and donepezil, given as systemic treatments, augment GSK-3β phosphorylation in cortical and hippocampal homogenates of wild-type but not of acutely or chronically histamine-depleted mice. Furthermore, administration of the **PI3K** inhibitor **LY 294002**, which blocks GSK-3β phosphorylation, prevented ABT-239-induced procognitive effects as measured in the object recognition test of wild-type mice (Provensi *et al.*, 2016b). Taken together, these results point to the requirement of an intact histaminergic system for both donepezil and ABT-239 to exert their procognitive effects, whereas increased ACh release and subsequent α7 nAChR activation seems not to play a major role.

More recently, the efficacy of the $H_3$ antagonist thioperamide was tested in an experimental model of Parkinsonism (Bonito-Oliva *et al.*, 2014a). This model produces a partial depletion of dopamine without affecting horizontal motor activity, mimicking a relatively early stage of Parkinson's disease (Bonito-Oliva *et al.*, 2014b). Mice with a partial lesion of the midbrain dopaminergic system fail to recognize a novel object when tested 24 h after the acquisition phase (Bonito-Oliva *et al.*, 2014b; Masini *et al.*, 2017). This deficit was abolished by systemic treatment with thioperamide 20 min before both the acquisition and test phases (Masini *et al.*, 2017).

Animal social behaviour is often used as a measure to study disorders characterized by alterations in sociability, such as the autism spectrum disorder. Considering this fact, the efficacy of the $H_3$ antagonist ciproxifan was tested in the animal model of autism induced by prenatal exposure to **valproic acid** (Baronio *et al.*, 2015). This animal model is based on the evidence that treatment with valproic acid during pregnancy is associated with an increased incidence of autism spectrum disorder in children (Bromley *et al.*, 2013). Moreover, *in utero* exposure of rodents to valproic acid results in neuroanatomical, behavioural and biochemical features replicating some characteristics observed in autistic patients, such as reduced sociability and social novel preference as measured in the three chamber test (Schneider and Przewlocki, 2005). This test is a commonly used method to measure social approach behaviour in mice (Figure 3). The apparatus consists of a three-chamber arena: one of which contains a stimulus mouse positioned in a wire mesh container, while in the opposite chamber, a similar container holds an inanimate object. After adaptation to the arena, the animal is placed into the middle chamber and left free to explore the apparatus. The tendency to approach or avoid the compartment with the stimulus mouse provides a measure of sociability. In a second session, the object is replaced by a novel unfamiliar mouse, and the time spent in exploring the known and the novel animals is used to calculate the social novelty index (Yang *et al.*, 2011). Using this approach, it was observed that ciproxifan treatment normalized sociability, but not social novelty impairments displayed by animals who had been exposed to valproic acid *in utero*. Interestingly, the treatment with the $H_3$ antagonist also attenuated the repetitive behaviour detected in mice exposed to valproic acid, as assessed in the marble burying test (Baronio *et al.*, 2015).

The zebrafish is rapidly becoming a new popular model organism in neuroscience research, due to some similarities with both humans and rodents regarding anatomy, neurotransmitter systems and pharmacology (Kalueff *et al.*, 2014). Zebrafish are highly social and prefer to swim in groups for different reasons, such as mating, foraging or avoiding predators. The behavioural and neurochemical alterations of both larval and adult zebrafish exposed to valproic acid during neural tube formation was recently reported (Baronio *et al.*, 2018). It was found that larvae exposed to valproic acid showed a significant reduction in the number of histaminergic neurons, histamine content as well as HDC, $H_1$, $H_2$ and $H_3$ receptor mRNA expression along with decreased motor activity and an abnormal flash-dark response. These altered responses to sudden darkness are probably related to reduced histaminergic transmission, since this is a phenotype characteristic of larvae lacking the ability to synthesize histamine (Sundvik and Panula, 2012). No difference in the basal locomotor activity was found between control and valproic acid-exposed adult zebrafish. However, valproic-treated zebra fish showed impaired sociability, as they spent less time swimming in the zone closest to the compartment with the

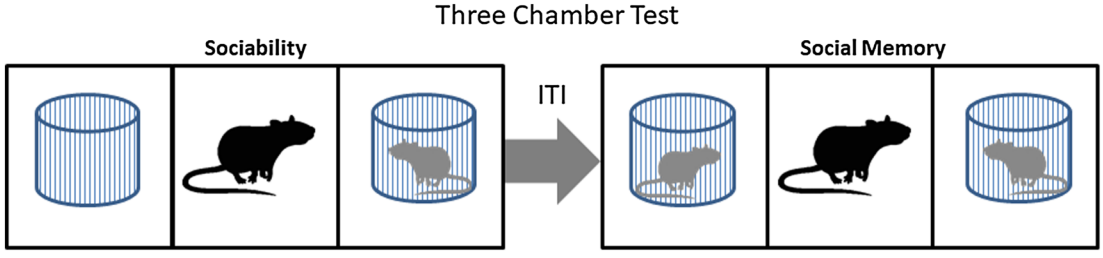



**Figure 3**
Schematic representation of the three-chamber test used to evaluate sociability and social memory.

stimulus fish. Regarding the histaminergic system, the reduced mRNA expression of HDC and $H_3$ receptors persisted in adult zebrafish exposed to valproic acid, although normal levels of brain histamine were found (Baronio *et al.*, 2018). These findings support the hypothesis that at least some of the main clinical alterations present in autism spectrum disorder could be attenuated by $H_3$ antagonists even in a late developmental stage (Baronio *et al.*, 2015).

## *Clinical studies*

Evidence of the involvement of the central histaminergic system in memory and cognition mainly derive from preclinical animal models. However, over the last decade, evidence has accumulated showing that histamine may play an important role in humans as well, and therefore, the histaminergic system has been considered a possible target for pharmacological interventions to ameliorate cognitive deficits in clinical disorders.

In the late 1980, antihistamines were already widely used for the treatment of allergic diseases, but their sedative properties were a major concern. Car and work accidents as well as a decline in productivity and learning efficiency was observed in patients taking antihistamine drugs. Therefore, the introduction of a second-generation antihistamines was a major advance in the field. These compounds were argued to have a better safety profile since they were minimally or non-sedating because of their limited penetration of the blood–brain barrier (Hu *et al.*, 2015). At that time, clinical research was focused on the comparison of first- and second-generation antihistamines regarding their potential side effects with particular attention to psychomotor, sedative and cognitive domains. For instance, Meador *et al.* (1989) measured the P3-evoked potential in a placebo-controlled, double-blind, randomized trial in healthy adult subjects. The P3 is a cognitively evoked electroencephalographic response that is an objective and sensitive measure of sustained attention and cerebral processing speed. This measure is modified by drugs and disease states, for example, scopolamine slows cognitive processing speed and prolongs P3 latency (Potter *et al.*, 2000). A grater latency was observed in **chlorpheniramine**-treated subjects compared to **terfenadine** or placebo groups, suggesting that second-generation antihistamines may be particularly advantageous in patients who require alertness and intact cognitive abilities (Meador *et al.*, 1989).

Following this initial study, many others have attempted to investigate the effects of several $H_1$ receptor antihistamines on cognition. The vast majority failed to detect significant memory alterations at therapeutically used doses, with mild effects on memory performance observed only at high doses (Kerr *et al.*, 1994; Vuurman *et al.*, 1994; Patat *et al.*, 1995; Hindmarch and Shamsi, 2001; Tagawa *et al.*, 2002; Theunissen *et al.*, 2004; van Ruitenbeek *et al.*, 2010a; Taubel *et al.*, 2016). One of the possible explanations of these dose-related effects was that, at higher doses, impaired psychomotor performance and increased sedation may have affected cognitive performance. To address this question, van Ruitenbeek and co-workers performed a study to clarify the effects of the $H_1$ antagonist **dexchlorpheniramine** on sedation and memory performance. Memory tasks and cortical activity were measured between 1.5 and 2.5 h after drug administration (i.e. during the peak of psychomotor impairment) and compared to those of placebo and **lorazepam**, a benzodiazepine known for its sedative and amnesic properties. They found that $H_1$ receptor blockade induced clear sedative effects without affecting memory performance. In contrast, lorazepam affected both working memory and sedation (Van Ruitenbeek *et al.*, 2010b). Therefore, it can be concluded that sedation is not necessarily associated with impaired memory and that the memory impairment observed with potentially sedative drugs could be related to effects on neuronal networks independent of those that affect arousal (Turner *et al.*, 2006).

In the clinical evaluation of the potential cognitive-enhancing properties of $H_3$ antagonists, Cho *et al.* (2011) performed a randomized, double-blind, placebo-controlled study in healthy subjects. The results obtained show that a single-dose treatment with the $H_3$ antagonist MK-3134 ameliorates the decline in cognitive functions induced by scopolamine, particularly attention, psychomotor and executive function to a similar extent as that observed in the group receiving donepezil, a standard AChE inhibitor (Cho *et al.*, 2011).

The results of both preclinical and *post-mortem* studies indicate the possible therapeutic use of $H_3$ antagonists in patients with major cognitive impairments such as Alzheimer's disease or dementia with Lewy bodies (Sadek *et al.*, 2016; Lethbridge and Chazot, 2016). However, the clinical trials failed to demonstrate unequivocal cognitive improvements. In a randomized, double-blind, placebo-controlled study with a small group of patients ($n = 8$) with mild-to-moderate Alzheimer's disease, it was found that treatment with GSK239512 for 4 weeks, using a titration regimen in order to find the optimal dose for individual patients, resulted in positive effects on attention and memory (Nathan *et al.*, 2013). In a subsequent study using a larger population (99 placebo and 97 treated subjects), it was observed that the treatment with the same drug for 16 weeks improved episodic memory, but not other cognitive domains such as executive functions and working memory (Grove *et al.*, 2014). In both studies, the $H_3$ antagonist had an acceptable safety and tolerability profile. Although promising, these results need to be replicated in larger scale Phase III clinical trials to confirm the efficacy of GSK239512 treatment in Alzheimer's disease patients.

The safety profile of another $H_3$ antagonist, **ABT-288**, was assessed in healthy young adults and elderly volunteers. The drug's pharmacokinetics were comparable between the two populations studied. Moreover, single as well as multiple doses up to 3 mg were generally safe and well tolerated, and the most frequently reported adverse events were hot flushes, headaches, abnormal dreams, insomnia, nausea and dizziness (Othman *et al.*, 2013). Therefore, ABT-288 was advanced to Phase II evaluation in Alzheimer's patients. The proof-of-concept, randomized, placebo-controlled study was designed to evaluate the efficacy and safety of the two doses of ABT-288 (1 and 3 mg) and compared with that of donepezil (10 mg) in the symptomatic treatment of subjects with mild-to-moderate Alzheimer's disease. However, after 12 weeks, the study was prematurely terminated because neither dose of ABT-288 demonstrated a procognitive effect with respect to placebo, whereas donepezil showed a significant improvement in the primary endpoint. The positive

results obtained with the active comparator donepezil suggest that the lack of efficacy of the $H_3$ antagonist treatment was not related to the design and conduct of the trial (Haig *et al.*, 2014). Similar results were obtained in a previous pilot randomized study in which mild-to-moderate Alzheimer's disease patients received placebo or the $H_3$ antagonist/inverse agonist **MK-0249** for 4 weeks. Although the treatment was generally well tolerated, no differences in cognitive function were observed between MK-0249 and placebo-treated patients (Egan *et al.*, 2012).

Currently, a Phase II clinical study is assessing SAR110894, an $H_3$ receptor antagonist with excellent drug-like properties, on the cognitive performance of patients with mild-to-moderate Alzheimer's disease in comparison to placebo (Griebel *et al.*, 2012). The clinical outcomes have not been disclosed yet (clinicaltrials.gov Identifier: NCT01266525).

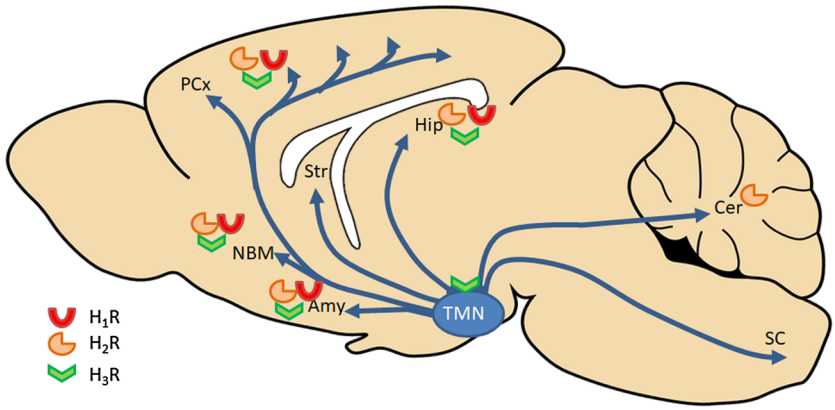
## *Concluding remarks*

The actual state of the art indicates that histamine, acting in different brain sites, has an important role as a regulator of memory consolidation/retrieval in various learning paradigms. The role of histamine receptors in recognition memory has been extensively studied using both specific ligands and also transgenic animals. The data collected in our review strongly suggest a role for hippocampal $H_1$, $H_2$ and $H_3$ receptors in object recognition and $H_2$ receptors within the hippocampus and amygdala in social recognition (Figure 4).

Due to its actions as an auto/heteroreceptor, regulating not only histamine synthesis but also the release of other important neurotransmitters critically involved in cognition, the $H_3$ receptor has received great attention by the scientific community as a good target for the development of new centrally acting drugs, and many academic groups as well as pharmaceutical companies have synthesized numerous selective and potent $H_3$ receptor ligands. However, despite their excellent 'drug-like' profile, particularly in cognition and attention models (Sadek *et al.*, 2016), which suggests that $H_3$ antagonists could be effective therapeutic compounds, clinical studies have proved that they lack efficacy or have only minor beneficial effects on cognitive performance in Alzheimer's disease patients (Zlomuzica *et al.*, 2016). Although these initial failures have markedly dampened the enthusiasm, it is important to note that recently, **pitolisant**, the first $H_3$ receptor antagonist tested in humans (Schwartz, 2011), received market approval from the European Medicines Agency for the treatment of narcolepsy, and this could open up the opportunity for also accessing its efficacy for other disorders in off-label clinical trials.

In summary, more than 30 years have passed since the role of histamine in the regulation of memory consolidation was firstly proposed by De Almeida and Izquierdo in 1986, and since then, many advances have been made, and today, there is compelling evidence that alterations in the central histaminergic system are associated with the cognitive impairments observed in several neurodegenerative disorders. The discrepancies between preclinical data and the results of clinical trials has initiated several questions that need to be addressed in future studies using cutting-edge technologies.

The data discussed in this review are broadly consistent with the hypothesis that diverse functional roles are served by different subpopulations of histaminergic neurons, implying that histaminergic neurons are presumably organized into distinct circuits responding to selective inputs, and engaged according to their projections to the brain region required for a specific behavioural outcome (Figure 4). In addition to this spatial compartmentalization, that is, number and type of cells participating in a functional pathway, we recently provided experimental evidence of differences




## Figure 4

Schematic representation of the brain histaminergic projections involved in cognition. Histamine-producing cell bodies are restricted to the TMN and histaminergic fibres project to various brain regions including the prefrontal cortex, nucleus basalis magnocellularis (NBM), the striatum (Str), the amygdala (Amy), the hippocampus (Hip), the cerebellum (Cer) and spinal cord (SC). Histamine effects in the brain are mediated by four receptors ($H_1$ to $H_4$ R) with different distribution across the brain. In recognition memory, the role of specific receptor activation in discrete brain regions was just marginally studied as most studies were performed using systemically injected compounds (see text). Only two studies analysed the effects of local drug infusions: $H_1$ and $H_2$ antagonists, as well as an $H_3$ agonist directly infused into the hippocampal CA1 region blocked long-term consolidation of object recognition memory (da Silveira *et al.*, 2013). An $H_2$ antagonist delivered into hippocampal CA1 or basolateral amygdala impaired social recognition memory (Garrido Zinn *et al.*, 2016).

in the kinetics of neuronal activation, that is, a temporal regulation of histaminergic activity in different brain regions (Benetti *et al.*, 2015; Fabbri *et al.*, 2016). Therefore, translational histamine research should start afresh given the availability of HDC-Cre mice that will allow the use of cutting-edge technologies such as optogenetic or chemogenetic approaches. This will afford a better understanding of the temporal and anatomical modulation by histaminergic neurons. These approaches hopefully will clarify the inconsistent actions of histamine receptors, due presumably to the discrepant actions of histamine receptors in different brain regions and cellular types. Furthermore, histamine receptors are expressed on glial cells (reviewed in Hu and Chen, 2017), and their potential role in learning and memory is as yet unexplored.

### *Nomenclature of targets and ligands*

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Harding *et al.*, 2018), and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18 (Alexander *et al.*, 2017a,b).

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## Conflict of interest

The authors declare no conflicts of interest.

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