British Journal of Pharmacology (2009), 157, 86–91

0007-1188/09
www.brjpharmacol.org

RESEARCH PAPER

Histamine H_1 receptor knockout mice exhibit impaired spatial memory in the eight-arm radial maze

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Background and purpose: In the mammalian brain, histaminergic neurotransmission is mediated by the postsynaptic histamine H_1 and H_2 receptors and the presynaptic H_3 autoreceptor, which also acts as a heteroreceptor. The H_1 receptor has been implicated in spatial learning and memory formation. However, pharmacological and lesion studies have revealed conflicting results. To examine the involvement of histamine H_1 receptor in spatial reference and working memory formation, H_1 receptor knockout mice (KO) were tested in the eight-arm radial maze. Previously, we found that the H_1 receptor-KO mice showed reduced emotionality when confronted with spatial novelty. As it is known that emotions can have an impact on spatial learning and memory performance, we also evaluated H_1 receptor-KO mice in terms of emotional behaviour in the light–dark box.
Experimental approach: Mice lacking the H_1 receptor and wild-type mice (WT) were tested for spatial reference and working memory in an eight-arm radial maze with three arms baited and one trial per day. Emotional behaviour was measured using the light–dark test.
Key results: The H_1 receptor-KO mice showed impaired spatial reference and working memory in the radial maze task. No significant differences between H_1 receptor-KO and WT mice were observed in the light–dark test.
Conclusions and implications: The spatial memory deficits of the H_1 receptor-KO mice might be due to the reported changes in cholinergic neurochemical parameters in the frontal cortex and the CA1 subregion of the hippocampus, to impaired synaptic plasticity in the hippocampus, and/or to a dysfunctional brain reward/reinforcement system.
British Journal of Pharmacology (2009) **157**, 86–91; doi:10.1111/j.1476-5381.2009.00225.x

Keywords: hippocampus; tuberomammillary nucleus; working memory; reference memory; anxiety; Morris water maze; acetylcholine

Abbreviations: ACh, acetylcholine; KO, knockout

Introduction

The tuberomammillary nucleus in the posterior part of the hypothalamus contains the histaminergic neurons which innervate wide parts of the brain including the hippocampal formation. Histamine regulates a broad range of physiological functions, including the sleep–wake cycle, energy and endocrine homeostasis, emotionality and memory processes.

The H_1 receptor has been proposed to have a role in spatial learning and memory processes; however, the results are controversial. While pharmacological blockade of the H_1 receptor improves spatial learning in the Morris water maze (Hasenöhrl *et al.*, 1999), it, conversely, impairs spatial learning in the 8-arm radial maze (Masuoka and Kamei, 2007; Masuoka *et al.*, 2008). The ameliorating effects of histamine on spatial memory impairments induced by NMDA-receptor blockade are abolished after concomitant H_1 receptor blockade (Huang *et al.*, 2003; Xu *et al.*, 2005). In contrast, both the pharmacological blockade of the histamine synthesizing enzyme histidine-decarboxylase in rats and its genetic inactivation in the mouse improve spatial memory (Sakai *et al.*, 1998; Dere *et al.*, 2003). The H_1 receptor-knockout (KO) mice showed impaired spatial memory performance in the Barnes maze (Dai *et al.*, 2007) and spatial novelty-induced alternation performance in the Y-maze (Zlomuzica *et al.*, 2008). However, performance in an object-place recognition task was

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Received 3 November 2008; revised 16 December 2008; accepted 29 December 2008

normal in the H_1 receptor-KO mice (Zlomuzica *et al.*, 2008). These and the above findings leave open the question of whether H_1 receptor activation has a beneficial or detrimental effect on spatial learning and memory. Therefore, we investigated spatial reference and working memory functions in H_1 receptor-KO mice.

Behavioural phenotypes of transgenic mice in the domain of spatial learning and memory can be confounded by concomitant emotional phenotypes (Dere *et al.*, 2001). H_1 receptor-KO mice showed reduced emotional arousal when confronted with spatial novelty together with neurochemical differences in the amygdala (Zlomuzica *et al.*, 2008). Lesions to parts of the nucleus tuberomammilaris (Frisch *et al.*, 1998) as well as H_1 receptor blockade induced anxiolytic effects (Hasenöhrl *et al.*, 1999; Ito, 2000; Malmberg-Aiello *et al.*, 2002), while stimulation of H_1 receptors induced anxiogenic effects (Malmberg-Aiello *et al.*, 2002). It is possible that an emotional phenotype of the H_1 receptor-KO mice could interplay with their spatial memory performance in the radial-maze task. Therefore, we also assessed emotional behaviour of H_1 receptor-KO mice in the light–dark box.

Methods

Animals

The experiments were performed under German legislation on animal experimentation (German Animal Welfare Act, TSchG) and were approved by the North Rhine Westphalia State Authority. Nineteen male offspring from breeding of adult homozygous H_1 receptor-KO mice (Zlomuzica *et al.*, 2008), backcrossed for at least nine generations onto a C57BL/6J background, and 20 age-matched wild-type C57BL/6J (WT) controls were used in this study. Of these animals 10 H_1 receptor-KO and 10 WT mice were tested in the eight-arm radial maze task. Another batch of experimentally naïve nine H_1 receptor-KO and 10 WT mice were tested in the light–dark test. The animals were housed in individual cages with a 12 h light–dark cycle (lights on from 07 h 00 min to 19 h 00 min) and were maintained under temperature- and humidity-controlled conditions. Experiments were carried out during the light cycle, between 09 h 00 min and 16 h 00 min.

Spatial memory in the radial arm maze

Apparatus. The radial maze was made of gray polyvinylchloride and consisted of eight arms (length: 32 cm, width: 8 cm, height: 19 cm) extending radially from an octagonal central area (20 cm across). Remote-controlled sliding doors allowed entry into each of the arms and were manipulated by an experimenter who sat behind a panel observing and recording the animal's behaviour. At the end of each arm, there was a well (0.5 cm deep) in which reward (water) was placed. The entire apparatus was elevated 50 cm above the floor and surrounded by extra-maze cues such as posters, objects and ceiling textures, which probably served for spatial orientation. To exclude the possibility that the animal's performance is guided by olfactory cues, several cups filled with fresh water were placed on different positions in the area adjacent to the radial arm maze. The positions of the cups were rearranged over all days of the experimentation. After each trial, the maze was cleaned with water containing 50 % ethanol.

Behavioural testing. Beginning on the day prior to the adaptation phase, the animals were maintained on a water deprivation schedule, which only allowed access to water for 5 h·day^{-1} in their home cages. Food (Ssniff Spezialdiaeten, Soest, Germany) was freely available during the time of experiments.

Adaptation phase. The mice were adapted to the radial maze once per day for 2 days prior to the acquisition phase. During the adaptation phase, water (0.1 mL) served as reward and was inserted in the wells of three chosen arms. Each mouse was placed in the central area of the radial arm maze with all arm entries closed. After 10 s, the doors of the three baited arms were opened and the animals were allowed to explore the baited arms for 10 min while the remaining arms were kept closed.

Learning phase. After the adaptation phase, the mice were trained for 14 consecutive days with one trial per day. Each mouse was placed in the centre of the maze with all arm entries closed. After 10 s, the doors were opened and the mouse was permitted to enter any of the eight arms. Only three of the eight arms contained water. The rationale for using three instead of four baited arms was to increase the sensitivity of the task in measuring reference memory errors by decreasing the probability to exert a correct choice by chance. The three arms containing water were randomly determined for each mouse and have been retained unchanged over the 14 acquisition days. Arms containing water during the adaptation phase were not reused during the acquisition phase. An arm entry was scored when the mouse had all four paws within an arm. A trial was terminated after either all the bait was consumed or after 10 min had elapsed, whatever occurred first. During the learning phase, an experimenter who was blind to the genotype of the animals scored: (i) reference memory errors: entries into arm which was never baited; and (ii) working memory errors: re-entries into an arm already visited on the ongoing trial.

Anxiety-like behaviour

Light–dark box. This task utilizes the congenital tendency of nocturnal rodents to escape from brightly lit arrears into darker ones. The light–dark box consisted of two compartments: a dark compartment (24 cm width × 33 cm length × 30 cm height) and a white one, with identical measurements, that was illuminated by a 60 W lamp providing 400 Lux in the central part of the white compartment. The illumination in the dark compartment was ca 15 Lux. The whole apparatus was open at the top and was made of Plexiglas. A small Plexiglas opening (10 cm width × 10 cm height) separated the dark box from the light box and allowed the animal to switch between the compartments. New batches of experimentally naïve H_1 receptor-KO ($n = 9$) and WT ($n = 10$) mice were used for this test. The mouse was placed in the light compartment and the latency to escape to the dark compartment (s) was measured. The time spent in the light and dark compartments

(s) was measured for 5 min. An entry into a compartment was scored after the mouse entered the compartment with all four paws. Twenty-four hours after the first exposure to the light–dark box, emotional behaviour was reassessed during a second trial, which was identical to the first.

Statistical analysis. The radial maze data are expressed as mean error number ± s.e.m. Statistical significance was assessed using analysis of variance (ANOVA) with repeated measures. Student's *t*-tests were used to assess between-group differences for single trials. Light–dark test data are expressed as the mean (±s.e.m.) time spent (s) in the two chambers and the latency to enter the dark chamber (s) on the first and second trial. Kolmogorow–Smirnow tests indicated that the light–dark data were not normal distributed and were therefore analysed by distribution-free, non-parametric statistics. Within-group differences were analysed by means of Wilcoxon tests, between-group differences were analysed by means of Mann–Whitney *U*-tests. The *P*-values given are two-tailed and were considered significant when $P < 0.05$.

Results

Radial arm maze

The number of reference memory errors observed during acquisition trials for both genotypes, the H_1 receptor-KO and WT mice, are depicted in Figure 1. Analysis of variance revealed main effects of trial on the number of reference memory errors [$F(13, 234) = 4.733$; $P < 0.001$], suggesting that both groups improved their performance across the acquisition trials. There was a main effect of genotype [$F(1, 18) = 17.278$; $P = 0.001$] and a significant genotype × trial interaction [$F(13, 234) = 1.795$; $P = 0.045$]. Post-hoc *t*-tests for single trials revealed that H_1 receptor-KO mice showed significantly higher number of reference memory errors on trials 2, 5, 8, 11 and 14 (all *P*s < 0.05). As the number of reference memory errors was comparable between the groups on the beginning of the acquisition phase, the reference memory impairment of the H_1 receptor-KO mice is unlikely to be due to non-cognitive effects of H_1 receptor-deficiency.

Working memory (Figure 1B) was also impaired in the H_1 receptor-KO mice [main effect of genotype, $F(1, 18) = 15.316$; $P = 0.001$; repeated measures ANOVA] as compared with the WT mice. Although both groups showed a progressive decrease in the number of re-entries into already visited arms across the days of acquisition [main effect of trial, $F(13, 234) = 3.598$; $P < 0.001$], the H_1 receptor-KO mice made significantly more working memory errors on trials 5, 11 and 14 (all *P*s < 0.05, Student's *t*-tests). However, there was no genotype × trial interaction [$F(13, 234) = 1.387$; $P = 0.166$] in the number of working memory errors.

Light–dark test

The data obtained in the light–dark test on trials 1 and 2 are summarized in Table 1. Both genotypes spent significantly more time in the dark compartment as compared with the light one on day 1 as well as on day 2 (*P*s < 0.05; Wilcoxon-test). Thus, in both the H_1 receptor-KO and WT mice the light compartment induced fear and avoidance behaviour. However, on both trials there were no significant effects of genotype either in the time spent in the black compartment, in the light compartment or in the latency to escape to the dark compartment (all *P*s > 0.05; Mann–Whitney *U*-test). These results indicate that the H_1 receptor-KO mice did not show increased/or decreased emotionality in terms of brightly lit spaces. The time needed to escape from the light compartment, that is, escape latency, significantly decreased from day 1 to day 2 in the WT ($P = 0.032$; Wilcoxon test), but not in the H_1 receptor-KO mice ($P > 0.05$). These results suggest that the fear of brightly lit areas is not altered in the H_1 receptor-KO mice.

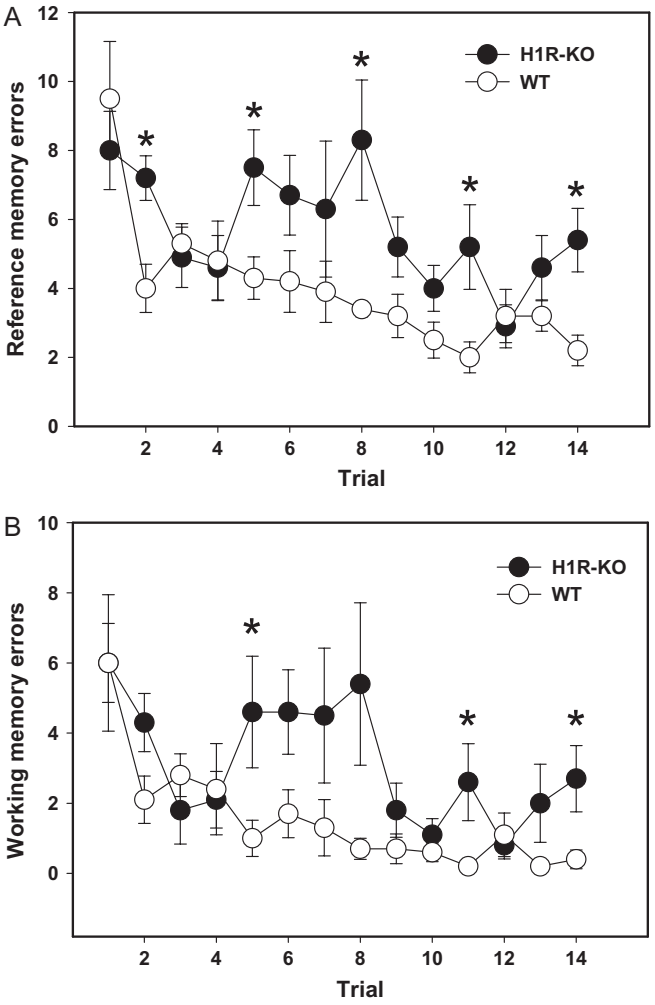

Figure 1 Histamine H_1 receptor (H1R) knockout in the mice leads to impairments in spatial reference (A) and working memory (B). H_1 receptor-KO mice (H1R-KO) ($n = 10$) and WT controls ($n = 10$) were subjected to an eight-arm radial maze with three arms baited over 14 trials. Data are expressed as mean ± s.e.m. The symbol asterisk (*) represents statistical difference between H_1 receptor-KO and WT mice on the indicated trials: $P < 0.05$. KO, knockout; WT, wild–type.

Discussion

To date, several pharmacological studies have been performed to determine whether H_1 receptor blockade would have a

Table 1 Emotional behaviour in H1R-KO mice

	Latency to enter the dark chamber		*Time spent in the dark chamber*		*Time spent in the light chamber*	
	Day 1	*Day 2*	*Day 1*	*Day 2*	*Day 1*	*Day 2*
H1R-KO	10.1 ± 1.8	11.3 ± 3.7	206.3 ± 12.4	221.6 ± 11.3	93.7 ± 12.4**	78.4 ± 11.3**
WT	23.6 ± 7.4	8.5 ± 1.5*	194.9 ± 10.1	194.2 ± 12.1	105.1 ± 10.1**	105.8 ± 12.1**

Anxiety-related behaviour in the light–dark test is not significantly different between H1R-KO and WT mice. Mean (±s.e.m.) time spent (s) in the two chambers and the latency to enter the dark chamber (s) for H1R-KO ($n = 9$) and WT ($n = 10$) mice. Within-group comparisons: *day 1 versus day 2, $P < 0.05$, **time spent in the light versus the dark chamber, $P < 0.05$, by Wilcoxon tests.
H1R, Histamine H_1 receptor; KO, knockout; WT, wild-type.

beneficial or detrimental effect on spatial learning and memory performance (Hasenöhrl *et al.*, 1999; Chen *et al.*, 2001; Taga *et al.*, 2001; Huang *et al.*, 2003; Xu *et al.*, 2005; Masuoka and Kamei, 2007; Masuoka *et al.*, 2008). In the present study we aimed to examine the role of H_1 receptors in spatial learning and memory by using H_1 receptor-KO mice. The H_1 receptor-KO mice were subjected to a radial maze protocol that allows the measurement of spatial reference memory [the ability to memorize and retrieve information, which remains constant throughout the days of acquisition (Eichenbaum, 2001)]. The H_1 receptor-KO mice showed significantly more reference and working memory errors compared with the WT, suggesting that they are either impaired in the encoding or acquisition of place-reward associations. Their ability to rehearse or retain place-reward information even within a trial seems to be very limited. This finding is in line with previous observations of impaired spontaneous alternation (Zlomuzica *et al.*, 2008) and Barnes maze performance (Dai *et al.*, 2007) in the H_1 receptor-KO mice and with pharmacological studies showing that H_1 receptor antagonists can cause spatial reference and working memory deficits in the radial arm maze (Chen *et al.*, 2001; Taga *et al.*, 2001; Huang *et al.*, 2003; Masuoka and Kamei, 2007; Masuoka *et al.*, 2008).

Performance in the radial maze task has been proposed to depend critically on the integrity of the hippocampus and the frontal cortex. Hippocampal lesions (Rossi-Arnaud *et al.*, 1991; Ammassari-Teule and De Marsanich, 1996) and lesions to the prefrontal cortex (Joel *et al.*, 1997) disrupted performance in the standard radial arm maze task in rats and mice. Previous studies also revealed impairments after lesions to the cholinergic nucleus basalis (Murray and Fibiger, 1985; Dornan *et al.*, 1997). Histamine and its precursor histidine have been shown to reverse the spatial memory performance deficits in the radial arm maze induced by scopolamine (Chen and Kamei, 2000), suggesting that both histamine and acetylcholine (ACh) neurotransmission in the hippocampus and possibly the frontal cortex are important for spatial memory formation. We previously showed that the H_1 receptor-KO mice had significantly lower levels of acetylcholine-esterase activity in the dentate gyrus and CA1 subregions of the hippocampus but higher ACh concentrations in the frontal cortex as compared with the WT mice (Dere *et al.*, 2008; Zlomuzica *et al.*, 2008). Furthermore, H_1 receptor-KO mice showed a reduced induction of synaptic long-term potentiation in the CA1 region of the hippocampus (Dai *et al.*, 2007). It is noteworthy that hippocampal synaptic plasticity in the CA1 area can be modulated by, both, histamine H_1 receptors and cholinoceptors (Selbach *et al.*, 1997; Ovsepian *et al.*, 2004). Changes in long-term potentiation induced at hippocampal CA1 synapses have been related to spatial learning impairments in the radial arm maze (Altinbilek and Manahan-Vaughan, 2007). Therefore, it is possible that the changes in the cholinergic system in the frontal cortex and the CA1 area of the hippocampus are related to the concomitant deficits in hippocampal long-term potentiation and spatial memory in H_1 receptor-KO mice.

It has been proposed that histamine might act via different mechanisms on memory processes, for example, by the modulation of the hippocampal synaptic plasticity (Haas and Panula, 2003; Vorobjev *et al.*, 1993) or through an indirect effect on memory transcription via modulation of the brain's reinforcement system (Huston *et al.*, 1997). The H_1 receptor-KO mice showed impaired novel-object induced conditioned place-preference performance (Zlomuzica *et al.*, 2008). Therefore, it is also possible that the H_1 receptor-KO mice are unable to form lasting place-reward associations because of a dysfunctional brain reward system (Huston and Oitzl, 1989; Huston *et al.*, 1997).

Emotional factors are likely to interplay with memory performance of mice in spatial learning and memory tasks. For example, enhanced cholinergic transmission in the vmPFC induces anxiety in challenging environments and enhances spontaneous spatial working memory performance (Wall *et al.*, 2001; Wall and Messier, 2002). Interestingly, the H_1 receptor-KO mice showed impaired spontaneous alternation performance and increased levels of ACh in the frontal cortex (Zlomuzica *et al.*, 2008). While H_1 receptor-KO mice showed intact object-place memory at short retention interval of 15 min (Zlomuzica *et al.*, 2008), they showed impaired object-place memory after a longer retention interval of 50 min in an episodic-like object memory task (Dere *et al.*, 2008).

Pharmacological blockade of the H_1 receptor induces anxiolytic effects (Hasenöhrl *et al.*, 1999; Ito, 2000; Malmberg-Aiello *et al.*, 2002). In contrast (Yanai *et al.*, 1998) reported no emotional phenotype for the H_1 receptor-KO mice in the elevated plus-maze test. Although H_1 receptor-KO mice show decreased novelty-induced emotional responses in the open field (Zlomuzica *et al.*, 2008), they show no significant changes in emotional behaviour in the light–dark test, corroborating the findings by Yanai *et al.* (1998).

In conclusion, it seems that genetic inactivation of the H_1 receptor in the mouse leads to spatial working and reference

memory impairments, while having no significant effect on emotional behaviour in the light–dark test. It is possible that the spatial learning impairments of the H_1 receptor-KO mice are related to either changes in cholinergic neurochemical parameters in the frontal cortex and the CA1 subregion of the hippocampus, impaired synaptic plasticity in the hippocampus and/or a dysfunctional brain reward/reinforcement system.

Acknowledgement

This work was supported by the Deutsche Forschungsgemeinschaft (DFG) with grant DE1149/2-1 to ED and JPH.

Conflict of interest

The authors state no conflict of interest.

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