Available online at www.sciencedirect.com
SCIENCE DIRECT®
European Journal of Pharmacology 465 (2003) 91–96
www.elsevier.com/locate/ejphar

# Effects of histamine and cholinergic systems on memory retention of passive avoidance learning in rats

Maryam Eidi[a], Mohammad-Reza Zarrindast[b,*], Akram Eidi[a], Shahrbanoo Oryan[a], Kazem Parivar[a]

[a] Department of Biology, Sciences and Research Campus, Azad University, Tehran, Iran
[b] Department of Pharmacology, School of Medicine, Tehran University of Medical Sciences, P.O. Box 13145-784, Tehran, Iran

Received 18 December 2002; received in revised form 6 February 2003; accepted 7 February 2003

**Abstract**

In the present study, the effects of the histamine and cholinergic systems on memory retention in adult male rats were investigated. Post-training intracerebroventricular injections were carried out in all the experiments. Cholinoceptor agonist, acetylcholine (1–10 μg/rat) or nicotine (1–10 μg/rat), increased, while a cholinoceptor antagonist, scopolamine (5–20 μg/rat), decreased memory retention. The response to acetylcholine was attenuated by scopolamine. Administration of histamine (5–20 μg/rat) reduced, but the histamine $H_1$ receptor antagonist, pyrilamine (10–50 μg/rat), and the histamine $H_2$ receptor antagonist, cimetidine (1–50 μg/rat), increased memory retention in rats. The histamine receptor antagonists attenuated the response to histamine. Histamine reduced the acetylcholine- or nicotine-induced enhancement. The histamine receptor antagonists enhanced the nicotine- or acetylcholine-induced response. Histamine potentiated the inhibitory effect induced by scopolamine. It is concluded that histaminergic and cholinergic systems have opposing effects on memory retention. Also, the histaminergic system elicits an interaction with the cholinergic system in memory retention.


*Keywords:* Memory retention; Passive avoidance; Cholinoceptor drug; Histaminergic agent; (Rat)

## 1. Introduction

Evidence that accumulated within the last few years has established that histamine plays an important role as a central neurotransmitter in the brain (Haas et al., 1991; Schwarts et al., 1991; Onodera et al., 1994). Neuronal histamine is concentrated in the tuberomammillary nucleus of the posterior hypothalamus, with efferent varicose fibers in almost all parts of the brain (Panula et al., 1984; Watanabe et al., 1984). The actions of histamine appear to be mediated by three different types of receptors, which differ in pharmacology, localization and intracellular response that they mediate (Leurs et al., 1995). Histamine receptors include postsynaptic histamine $H_1$ and $H_2$ receptors and presynaptic histamine $H_3$ receptors which control the release of neuronal histamine (Prell and Green, 1986; Schwarts et al., 1986; Arrang et al., 1985) and many other neurotransmitters such as noradrenaline, dopamine, serotonin and acetylcholine as auto- and heteroreceptors, respectively (Endou et al., 2001; Pollard et al., 1993; Schlicker et al., 1994). A number of studies have indicated that the histaminergic system is involved in many physiological functions or responses such as stress (Bugajski and Gadek, 1983; Ghi et al., 1995), feeding, drinking, aggression and sexual behaviors (Itowi et al., 1988; Lecklin et al., 1994; Tuomisto et al., 1994). Also, there is evidence revealing that neuronal histamine plays an important role in learning and memory behaviors (Kamei and Tasaka, 1991; Flood et al., 1998).

Many clinical (Beatty et al., 1986; Eagger et al., 1991; Jones et al., 1992) and experimental (Dunnett et al., 1985) studies have also shown that the cholinergic system plays an important role in learning, memory and attention. Since cholinergic dysfunctions might interact well with those of other neurotransmitter systems to cause additive or even synergistic effects on cognition, the role of interactions between acetylcholine and other neurotransmitters affecting cognition is of considerable interest. In behavioral experiments, histaminergic modulation of cholinergic activity is

* Corresponding author. Tel.: +98-21-6112801; fax: +98-21-6402569.
*E-mail address:* zarinmr@ams.ac.ir (M.-R. Zarrindast).

0014-2999/03/$ - see front matter © 2003 Elsevier Science B.V. All rights reserved.
doi:10.1016/S0014-2999(03)01440-7

suggested by results of experiments showing that several histamine receptor ligands can antagonize spatial learning deficits caused by scopolamine (Smith et al., 1994; Miyazaki et al., 1995a). Furthermore, performance in several learning tasks, thought to depend on cholinergic transmission (Haroutunian et al., 1985; Fontana et al., 1994; Quirion et al., 1995), is enhanced by lesions of tuberomammillary nucleus of the hypothalamus that produce a striking loss of histamine markers in the tuberomammillary nucleus (Huston et al., 1997; Frisch et al., 1998). The aim of this study was to define the interaction of cholinergic and postsynaptic histamine systems in memory retention in rats.

## 2. Materials and methods

### 2.1. Animals

Male Wistar rats weighing 200–250 g were used in these experiments. The animals were housed 5 per cage at room temperature (22–24 °C) and a 12/12-h light–dark cycle, with light beginning at 7 a.m. and food and water ad libitum. Each animal was used once only. Eight animals were used in each experiment.

### 2.2. Cannula guide implantation

The animals were anesthetized with ketamine hydrochloride (100 mg/kg) and xylizine (rompun; 5 mg/kg). A permanent stainless-steel guide cannula (21 gauge, 0.8 mm in diameter) was implanted stereotaxically within the right lateral ventricle (David Koft Instruments, USA). The tip of the cannula was aimed at the following coordinates: 0.8 mm posterior to the bregma, 1.6 mm lateral to the midline and 3.4 mm below the top of the skull (Paxinos and Watson, 1986). The cannula was fixed to the skull using one screw and dental acrylic. A stylet was inserted into the cannula to keep it patent prior to injections. The animals were allowed a 1-week recovery period before initiation of behavioral experiments.

### 2.3. Intracerebroventricular (i.c.v.) injections

The rats were gently restrained by hand, the stylet was withdrawn from the guide cannula and a 27-gauge injection needle (0.5 mm beyond the tip of the implanted guide cannula) was inserted. The injection needle was attached to a polyethylene tube fitted to a 5-μl Hamilton syringe. The injection solutions were administered in a total volume of 2 μl. The injection needle was retained in the guide cannula for an additional 30 s after the injection to facilitate diffusion of the drugs.

### 2.4. Passive avoidance apparatus

The passive avoidance apparatus consisted of a light compartment (white opaque resin, 20 × 20 × 30 cm) and a dark compartment (black opaque resin, 20 × 20 × 30 cm) separated by a guillotine door (7 × 9 cm). The floor of the dark compartment was made of stainless steel (2.5 mm in diameter) separated by a distance of 1 cm. Intermittent electric shocks (50 Hz, 1.5 s, 2 mA intensity) were delivered to the grid floor of the dark compartment by an insulated stimulator.

### 2.5. Training

The rats were allowed to habituate to the experimental room for 1 h prior to testing. All training and testing sessions were done between 0800 and 1400 h. All experimental groups were first habituated to the apparatus. Each animal was gently placed in the light compartment for 5 s, after which the guillotine door was lifted and the latency with which the animal crossed to the dark (shock) compartment was timed. Animals that waited more than 100 s to cross to the other side were eliminated from the experiment. Once the animal crossed with all four paws to the next compartment, the door was closed and the rat was taken from the dark compartment into the home cage. The habituation trial was repeated after 30 min and was followed after the same interval by the acquisition trial during which the guillotine door was closed and a foot shock (50 Hz, 2 mA and 1.5 s) was delivered immediately after the rat had entered the dark compartment. After 20 s, the rat was removed from the apparatus and placed temporarily into the home cage. Two minutes later, the rat was retested in the same way as before; if the rat did not enter the dark compartment during 120 s, successful acquisition of passive avoidance response was recorded. Otherwise, when the rat entered the dark compartment a second time, the door was closed and the rat received the same shock as above. After retesting, if the rat reached acquisition of passive avoidance successfully, it was removed from the apparatus and injected via the guide cannula.

### 2.6. Retention test

Twenty-four hours after training, a retention test was performed to determine long-term memory. Each animal was placed in the light compartment for 5 s, the door was opened, and the step-through latency was measured for entering into the dark compartment. The test session ended when the animal entered the dark compartment or remained in the light compartment for 300 s (criterion for retention). During these sessions, no electric shock was applied.

### 2.7. Drugs

The drugs included histamine dihydrochloride (Merck, Germany), pyrilamine maleate, the histamine $H_1$ receptor antagonist (Sigma, Poole, UK), cimetidine, the histamine $H_2$ receptor antagonist (Richter, Hungary), acetylcholine dihy-

drochloride, the cholinoceptor agonist (Sigma, USA), nicotine bitartrate, the nicotinic receptor agonist (BDH, Poole, UK) and scopolamine *N*-butylbromide, the muscarinic receptor antagonist (Boehringer Ingelheim, Germany). All the drugs were dissolved in saline. The drugs were used (i.c.v.) in a volume of 2 μl/rat immediately after the training session.

### 2.8. Data analysis

Overall treatment effects in behavioral experiments were evaluated using a repeated-measures two-way analysis of variance (ANOVA). The criterion for statistical significance was $P < 0.05$.

### 2.9. Histology

At the end of the experiment, all rats were given 2 μl of methylene blue in a lateral ventricle, and then were anaesthetized with a high dose of ether and perfused transcardically with a phosphate-buffered saline solution (pH 7.4) and then formaldehyde (10%). All rats were decapitated and the brains were removed and placed in formaldehyde (4%). After 3 days, the brains were sliced into 60-μm-thin slices. Data from rats with incorrect placement were excluded from the analysis.

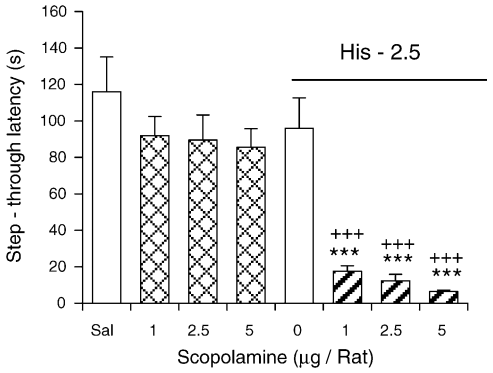


Fig. 2. The effect of scopolamine in the presence or absence of histamine on memory retention in rats. The animals were injected (i.c.v.) either with saline (Sal, 2 μl/rat) or different doses of scopolamine (1, 2.5 and 5 μg/rat) immediately after the training session. Histamine (His, 2.5 μg/rat) was administered 5 min after scopolamine administration and step-through latencies were tested 24 h after drug injections. Each point is the mean ± S.E.M. for eight rats. ***$P < 0.001$, different from saline control group. $^{+++}P < 0.001$, different from histamine control group.

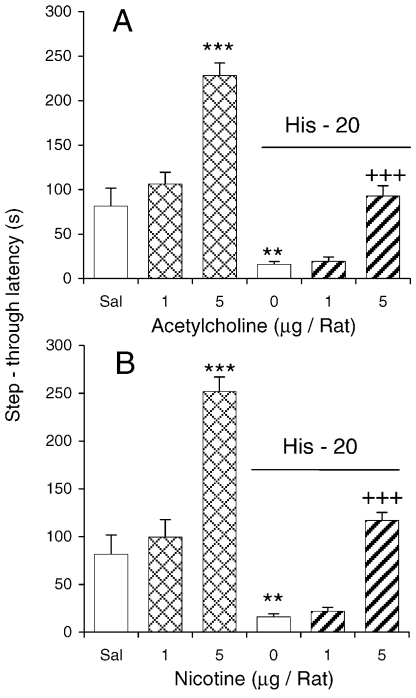


Fig. 1. The effect of acetylcholine (A) or nicotine (B) in the presence or absence of histamine on memory retention. The animals were injected (i.c.v.) either with saline (Sal, 2 μl/rat) or different doses of acetylcholine (1 and 5 μg/rat) or nicotine (1 and 5 μg/rat) immediately after the training session. Histamine (His, 20 μg/rat) was administered 5 min after acetylcholine or nicotine injections and step-through latencies were tested 24 h after drug injections. Each point is the mean ± S.E.M. for eight rats. **$P < 0.01$, ***$P < 0.001$, different from saline control group. $^{+++}P < 0.001$, different from histamine control group.

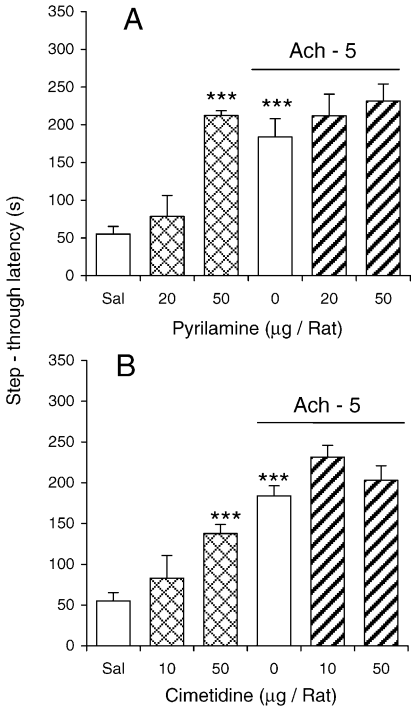


Fig. 3. The effect of pyrilamine (A) or cimetidine (B) in the presence or absence of acetylcholine on memory retention. The animals were injected (i.c.v.) either with saline (Sal, 2 μl/rat) or different doses of pyrilamine (20 and 50 μg/rat) or cimetidine (10 and 50 μg/rat) immediately after the training sessions. Acetylcholine (Ach, 5 μg/rat) was administered 5 min after pyrilamine or cimetidine administration and step-through latencies were tested 24 h after acetylcholine injection. Each point is the mean ± S.E.M. for eight rats. ***$P < 0.001$, different from saline control group.

## 3. Results

Fig. 1 shows the effect of acetylcholine or nicotine on the histamine-induced response. Two-way ANOVA indicated that histamine (20 μg/rat) interacts with acetylcholine (1 and 5 μg/rat) [histamine, $F(1,42)=92.6$, $P<0.0001$; acetylcholine, $F(2,42)=49.5$, $P<0.0001$; histamine × acetylcholine, $F(2,42)=4.3$, $P<0.05$] and nicotine (1 and 5 μg/rat) [histamine, $F(1,42)=76.0$, $P<0.0001$; nicotine, $F(2,42)=66.4$, $P<0.0001$; histamine × nicotine, $F(2,42)=4.0$, $P<0.05$]. Further analysis showed that post-training injections of histamine attenuated, while acetylcholine or nicotine potentiated memory retention. Histamine reduced acetylcholine- or nicotine-induced enhancements.

Fig. 2 shows the effect of scopolamine alone or in combination with histamine on memory retention. Two-way ANOVA indicated that the lower doses of scopolamine (1, 2.5 and 5 μg/rat) interacted with histamine (2.5 μg/rat) on memory retention. Histamine potentiated the inhibitory effect induced by scopolamine [scopolamine, $F(3,56)=11.6$, $P<0.0001$; histamine, $F(1,56)=58.6$, $P<0.0001$; scopolamine × histamine, $F(3,56)=3.0$, $P<0.05$]. Further analysis showed that post-training injections of histamine or scopolamine decreased memory retention, and lower doses of the two drugs, which did not elicit any response by themselves, showed inhibition of memory retention.

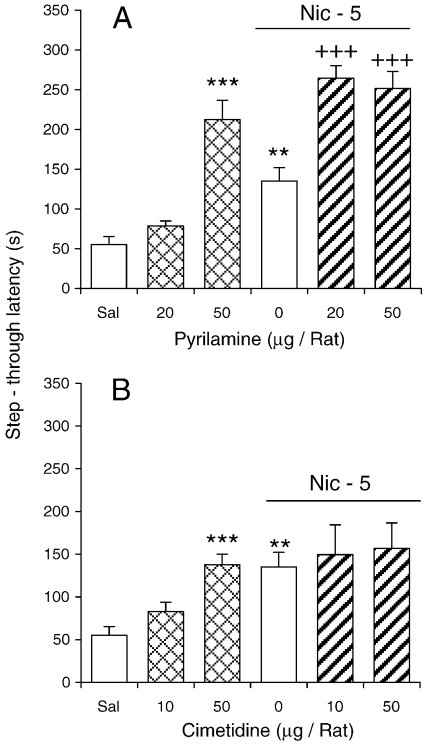


Fig. 4. The effect of pyrilamine (A) or cimetidine (B) in the presence or absence of nicotine on memory retention. The animals were injected (i.c.v.) either with saline (Sal, 2 μl/rat) or different doses of pyrilamine (20 and 50 μg/rat) or cimetidine (10 and 50 μg/rat) immediately after the training session. Nicotine (Nic, 5 μg/rat) was administered 5 min after pyrilamine or cimetidine administration and step-through latencies were tested 24 h after drug injection. Each point is the mean ± S.E.M. for eight rats. $^{**}P<0.01$, $^{***}P<0.001$, different from saline control group. $^{+++}P<0.001$, different from nicotine control group.

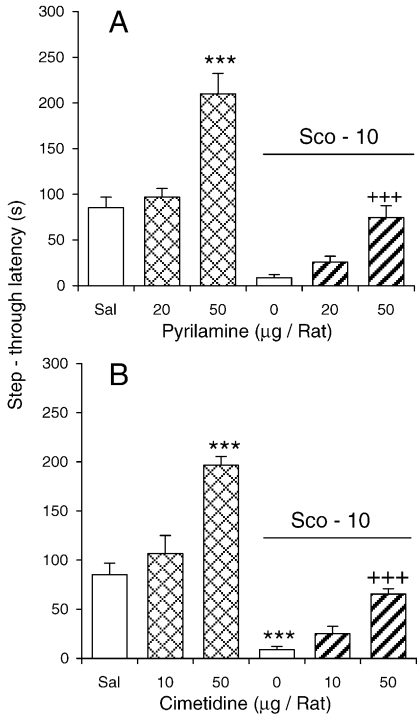


Fig. 5. The effect of pyrilamine (A) or cimetidine (B) in the presence or absence of scopolamine on memory retention. The animals were injected (i.c.v.) either with saline (Sal, 2 μl/rat) or different doses of pyrilamine (20 and 50 μg/rat) or cimetidine (10 and 50 μg/rat) immediately after the training session. Scopolamine (Sco, 10 μg/rat) was administered 5 min after pyrilamine or cimetidine injections and step-through latencies were tested 24 h after scopolamine injection. Each point is the mean ± S.E.M. for eight rats. $^{***}P<0.001$, different from saline control group. $^{+++}P<0.001$, different from scopolamine control group.

Fig. 3 shows the effect of acetylcholine on the histamine receptor antagonist-induced responses. Two-way ANOVA indicated a significant difference between the response to acetylcholine (5 μg/rat) alone or in combination with pyrilamine (20 and 50 μg/rat) [acetylcholine, $F(1,42)=27.8$, $P<0.0001$; pyrilamine, $F(2,42)=12.0$, $P<0.0001$; acetylcholine × pyrilamine, $F(2,42)=4.4$, $P<0.05$] or cimetidine (10 and 50 μg/rat) [acetylcholine, $F(1,42)=69.6$, $P<0.0001$; cimetidine, $F(2,42)=5.0$, $P<0.05$; acetylcholine × cimetidine, $F(2,42)=3.4$, $P<0.05$]. However, further analysis showed that acetylcholine potentiated pyrilamine- or cimetidine-induced responses at some doses.

Fig. 4 shows the effect of nicotine alone or in combination with histamine receptor antagonists on memory retention. Two-way ANOVA indicated that nicotine (5 μg/rat) interacted with pyrilamine (20 and 50 μg/rat) [nicotine, $F(1,42)=54.2$, $P<0.0001$; pyrilamine, $F(2,42)=32.8$, $P<0.0001$; nicotine × pyrilamine, $F(2,42)=10.0$, $P<0.001$]. However, further analysis showed that pyrilamine increased

the nicotine-induced enhancement. Two-way ANOVA showed that the response to nicotine (5 μg/rat) did not alter the cimetidine-induced effect (10 and 50 μg/rat) [nicotine, $F(1,42)=9.9$, $P<0.01$; cimetidine, $F(2,42)=3.0$, $P>0.05$; nicotine × cimetidine, $F(2,42)=1.1$, $P>0.05$].

Fig. 5 shows the effect of scopolamine on histamine receptor antagonist-induced responses. Two-way ANOVA indicated that scopolamine (10 μg/rat) interacts with pyrilamine (20 and 50 μg/rat) [scopolamine, $F(1,42)=84.6$, $P<0.0001$; pyrilamine, $F(2,42)=33.4$, $P<0.0001$; scopolamine × pyrilamine, $F(2,42)=4.0$, $P<0.05$] or cimetidine (10 and 50 μg/rat) [scopolamine, $F(1,42)=129.3$, $P<0.0001$; cimetidine, $F(2,42)=36.0$, $P<0.0001$; scopolamine × cimetidine, $F(2,42)=4.2$, $P<0.05$]. Analysis showed that scopolamine attenuated the histamine receptor antagonist-induced enhancements.

## 4. Discussion

There has been considerable interest in the involvement of central neurotransmitters in the symptomatology of Alzheimer's disease. Identification of one neurotransmitter system being of primary importance in the disease may be impossible. Catecholamine, cholinergic, peptidergic and hormonal systems have been the focus of great attention in learning and memory studies (Squire and Davis, 1981; Gold and Zornetzer, 1983).

In the present study, i.c.v. injections of acetylcholine or nicotine potentiated memory retention, while the muscarinic receptor antagonist, scopolamine, attenuated the response. The effects of the cholinergic agonists were reduced by scopolamine. The present data are in agreement with those from other investigations (Beatty et al., 1986; Jones et al., 1992; Givens and Olton, 1990; Jerusalinsky et al., 1997).

The data indicated that post-training administration of different doses of histamine attenuated memory retention. The data are in agreement with the results of others (Kamei and Tasaka, 1991; Flood et al., 1998). Consistently, depletion of histamine by the administration of α-fluoromethylhistidine, a selective inhibitor of the histamine-synthesizing enzyme (Watanabe et al., 1990), caused an attenuation of active avoidance acquisition (Kamei et al., 1993). However, experimental evidence indicated that central histamine might have a role in cognitive function as this amine has been shown to enhance memory (recall) in both a passive (DeAlmeida and Izquierdo, 1986) and active avoidance task (Kamei et al., 1993; Miyazaki et al., 1995b). Our data showed that the histamine $H_1$ receptor antagonist, pyrilamine, or the histamine $H_2$ receptor antagonist, cimetidine, increased memory retention. Both antagonists attenuated the histamine-induced memory impairment, which has also been shown previously (Tasaka et al., 1985). It has been shown that the histamine $H_1$ receptor antagonist increases acetylcholine levels in the hippocampus and neocortex by an unknown mechanism (Dringenberg et al., 1998). Furthermore, histamine $H_2$ receptors seem also to be involved in the modulation of acetylcholine release (Prast et al., 1999). In addition, histamine release in target regions is under the control of inhibitory muscarinic $M_1$ receptors (Prast et al., 1994). The outflow of neurotransmitter is enhanced by the histamine $H_2$ receptor antagonists, famotidine and ranitidine (Philippu and Prast, 2001). Therefore, the antagonists may elicit their effects through this mechanism. These results show that the inactivation of histamine $H_1$ receptors by histamine receptor antagonists increases memory retention. The same hypothesis has been presented previously (Frisch et al., 1998). However, there are contradictory reports indicating that histamine $H_1$ receptor activation may increase memory recall in both passive (DeAlmeida and Izquierdo, 1986), active avoidance tasks (Kamei and Tasaka, 1991) and working memory (Nakazato et al., 2000), whereas activation of the histamine $H_2$ receptor was ineffective (Kamei and Tasaka, 1991).

Our data indicate that the memory improvement induced by acetylcholine or nicotine can be impaired by histamine. The present data show that scopolamine, the muscarinic receptor antagonist, potentiates the histamine-induced decrease of memory retention, while the histamine receptor antagonists, pyrilamine and cimetidine, increased the acetylcholine- or nicotine-induced enhancement, but attenuated the inhibitory response induced by scopolamine. Thus, histaminergic system may interact with the cholinergic system on memory retention. In support of our findings, it has been shown that stimulation of muscarinic receptors by muscarinic agonists decreases the release of histamine in rat brain (Gulat-Murray et al., 1989), and that histamine modulates the activity of cultures of cholinergic cells via histamine $H_1$ and $H_2$ receptors (Khateb et al., 1995).

## Acknowledgements

We thank Dr. Touraj Nayer Nouri for his assistance in preparing the manuscript.

## References

Arrang, J.M., Garbarg, M., Schwartz, J.C., 1985. Autoregulation of histamine release in brain by presynaptic $H_3$ receptors. Neuroscience 15, 553–562.

Beatty, W.W., Butters, N., Janowsky, D., 1986. Memory failure after scopolamine treatment: implications for cholinergic hypothesis of dementia. Behav. Neural Biol. 45, 196–211.

Bugajski, J., Gadek, A., 1983. Central $H_1$- and $H_2$-histamine receptor stimulation of pituitary–adrenocortical response under stress in rats. Neuroendocrinology 36, 424–430.

DeAlmeida, M.A.M., Izquierdo, I., 1986. Memory facilitation by histamine. Arch. Int. Pharmacodyn. Ther. 283, 193–198.

Dringenberg, H.C., DeSouza-Silva, M.A., Ro_müller, J., Huston, J.P., Schwarting, K.W., 1998. Histamine $H_1$ receptor antagonists produce increase in extracellular acetylcholine in rat frontal cortex hippocampus. J. Neurochem. 70, 1750–1758.

Dunnett, S.B., Toniolo, G., Fine, A., Ryan, C.N., Björklund, A., Iversen, S.D., 1985. Transplantation of embryonic ventral forebrain neurons to the nucleus basalis magnocellularis: II. Sensorimotor and learning impairments. Neuroscience 16, 787–797.

Eagger, S.A., Levy, R., Sahakian, B.J., 1991. Tacrine in Alzheimer's disease. Lancet 337, 989–992.

Endou, M., Kazuhiko, Y., Sakurai, E., Fukudo, S., Hongo, M., Watanabe, T., 2001. Food-deprived activity stress decreased the activity of the histaminergic neuron system in rats. Brain Res. 981, 32–41.

Flood, J.F., Uezu, K., Morley, J.E., 1998. Effect of histamine $H_2$ and $H_3$ receptor modulation in the septum on post-training memory processing. Psychopharmacology 140, 279–284.

Fontana, D.J., Inouye, G.T., Johnson, R.M., 1994. Linopirdine (DuP 996) improves performance in several tests of learning and memory by modulation of cholinergic neurotransmission. Pharmacol. Biochem. Behav. 49, 1075–1082.

Frisch, C., Hasenhrl, R.U., Haas, H.L., Weiler, H.T., Steinbusch, H.W.M., Huston, J.P., 1998. Facilitation of learning after lesions of the tuberomammillary nucleus region in adult and aged rats. Exp. Brain Res. 118, 447–456.

Ghi, P., Ferretti, C., Blengio, M., Partaleone, P., 1995. Stress-induced changes in histaminergic system: effects of diazepam and amitriptyline. Pharmacol. Biochem. Behav. 51, 65–68.

Givens, B.S., Olton, D.S., 1990. Cholinergic and GABAergic modulation of medial septal area: effect on working memory. Behav. Neurosci. 104, 849–855.

Gold, P.E., Zornetzer, S.F., 1983. The mnemon and its juices: neuromodulation of memory processes. Behav. Neural Biol. 38, 151–189.

Gulat-Murray, C., Lafitte, A., Arrang, J.M., Schwartz, J.C., 1989. Regulation of histamine release and synthesis in the brain by muscarinic receptors. J. Neurochem. 52, 248–254.

Haas, H.L., Reiner, P.B., Greene, R.W., 1991. Histaminergic and histaminoceptive neurons: electrophysiological studies in vertebrates. In: Wanatabe, T., Wada, H. (Eds.), Histaminergic Neurons; Morphology and Function. CRC Press, Boca Raton, pp. 195–208.

Haroutunian, V., Barnes, E., Davis, K.L., 1985. Cholinergic modulation of memory in rats. Psychopharmacology (Berl.) 87, 266–271.

Huston, J.P., Wagner, U., Hasenhrl, R.U., 1997. The tuberomammillary nucleus projections in the control of learning, memory and reinforcement process: evidence for an inhibitory role. Behav. Brain Res. 83, 97–105.

Itowi, N., Nagai, K., Nakagawa, H., Watanabe, T., Wada, H., 1988. Changes in the feeding behavior of rats elicited by histamine infusion. Physiol. Behav. 44, 221–226.

Jerusalinsky, D., Kornisiuk, E., Izquierdo, I., 1997. Cholinergic neurotransmission and synaptic plasticity concerning memory processing. Neurochem. Res. 22, 507–515.

Jones, G.M.M., Sahakian, B.J., Levy, R., Warburton, D.M., Gray, J.A., 1992. Effects of acute subcutaneous nicotine on attention, information processing and short-term memory in Alzheimer's disease. Psychopharmacology 108, 485–494.

Kamei, C., Tasaka, K., 1991. Participation of histamine in the step-through active avoidance response and its inhibition by $H_1$-blockers. Jpn. J. Pharmacol. 57, 473–482.

Kamei, C., Okumura, Y., Tasaka, K., 1993. Influence of histamine depletion on learning and memory recollection in rats. Psychopharmacology 111, 376–382.

Khateb, A., Fort, P., Pegna, A., Jones, B.E., Mühlethaler, M., 1995. Cholinergic nucleus basalis neurons are excited by histamine in vitro. Neuroscience 69, 495–506.

Lecklin, A., Järvikylä, M., Tuomisto, L., 1994. The effect of metoprine on glucoprivic feeding induced by 2-deoxy-D-glucose. Pharmacol. Biochem. Behav. 49, 853–857.

Leurs, R., Smit, M.J., Timmerman, H., 1995. Molecular pharmacological aspects of histamine receptors. Pharmacol. Ther. 66, 413–463.

Miyazaki, S., Imaizumi, M., Onodera, K., 1995a. Effects of thioperamide, a histamine $H_3$-receptor antagonist, on a scopolamine-induced learning deficit using an elevated plus-maze test in mice. Life Sci. 57, 2137–2144.

Miyazaki, S., Imaizumi, M., Onodera, K., 1995b. Ameliorating effects of histidine on learning deficits in an elevated plus-maze test in mice and the contribution cholinergic neuronal systems. Methods Find. Exp. Clin. Pharmacol., Suppl. C, 57–63.

Nakazato, E., Yamamoto, T., Ohno, M., Watanabe, S., 2000. Cholinergic and glutamaergic activation reverses working memory failure by hippocampal histamine $H_1$ receptor blockade in rats. Life Sci. 67, 1139–1147.

Onodera, K., Yamatodani, A., Watanabe, T., Wada, H., 1994. Neuropharmacology of the histaminergic neuron system in the brain and its relationship with behavioral disorders. Prog. Neurobiol. 42, 685–702.

Panula, P., Yang, H.Y., Costa, E., 1984. Histamine-containing neurons in the rat hypothalamus. Proc. Natl. Acad. Sci. U. S. A. 81, 2572–2576.

Paxinos, G., Watson, C., 1986. The Rat Brain in Stereotaxic Coordinates. Press, Sydney.

Philippu, A., Prast, H., 2001. Importance of histamine in modulatory processes, locomotion and memory. Behav. Brain Res. 124, 151–159.

Pollard, H., Moreau, J., Arrang, J.M., Schwartz, J.C., 1993. A detailed autoradiographic mapping of histamine $H_3$ receptors in rat brain areas. Neuroscience 52, 169–189.

Prast, H., Fischer, H.P., Prast, M., Philippu, A., 1994. In vivo modulation of histamine release by autoreceptors and muscarinic acetylcholine receptors in the rat anterior hypothalamus. Naunyn-Schmiedeberg's Arch. Pharmacol. 350, 599–604.

Prast, H., Tran, M.H., Lamberti, C., Fischer, H., Kraus, M., Grass, K., Philippu, A., 1999. Histaminergic neurons modulate acetylcholine release in the ventral striatum: role of $H_1$ and $H_2$ receptors. Naunyn-Schmiedeberg's Arch. Pharmacol. 360, 552–557.

Prell, C.D., Green, J.P., 1986. Histamine as a neuroregulator. Annu. Rev. Neurosci. 9, 209–254.

Quirion, R., Wilson, A., Rowe, W., Aubert, I., Richard, J., Doods, H., Parent, A., White, N., Meaney, M.J., 1995. Facilitation of acetylcholine release and cognitive performance by an m2-muscarinic receptor antagonist in aged memory-impaired rats. J. Neurosci. 15, 1455–1462.

Schlicker, E., Malinowska, B., Kathman, M., Gothert, M., 1994. Modulation of neurotransmitter release via histamine $H_3$ heteroreceptors. Fundam. Clin. Pharmacol. 8, 128–137.

Schwarts, J.C., Arrang, J.M., Garbarg, M., 1986. Three classes of histamine receptor in brain. Trends Pharmacol. Sci. 7, 24–28.

Schwarts, J.C., Arrang, J.M., Garbarg, M., Pollard, H., Ruat, M., 1991. Histaminergic transmission in the mammalian brain. Physiol. Rev. 71, 1–51.

Smith, C.P.S., Hunter, A.J., Bennet, G.W., 1994. Effects of (*R*)-alpha-methylhistamine and scopolamine on spatial learning in the rat assessed using a water maze. Psychopharmacology (Berl.) 114, 651–656.

Squire, L.R., Davis, H.P., 1981. The pharmacology of memory: a neurobiological perspective. Annu. Rev. Pharmacol. Toxicol. 21, 323–356.

Tasaka, K., Kamei, C., Akahori, H., Kitazumi, K., 1985. The effects of histamine and some compounds on conditioned avoidance response in rats. Life Sci. 37, 2005–2015.

Tuomisto, L., Yamatodani, A., Jolkkonen, J., Sainio, E.L., Airaksinen, M., 1994. Inhibition of brain histamine synthesis increases food intake and attenuates vasopressin response to salt loading in rats. Methods Find. Exp. Clin. Pharmacol. 16, 355–359.

Watanabe, T., Taguchi, Y., Shiosaka, S., Tanaka, J., Kubota, H., Terano, Y., Tohyama, M., Wada, H., 1984. Distribution of histaminergic neuron system in the central nervous system of rats; a fluorescent immunohistochemical analysis with histidine decarboxylase as a marker. Brain Res. 295, 13–25.

Watanabe, T., Yamatodani, A., Maeyama, K., Wada, H., 1990. Pharmacology of α-fluoromethylhistidine, a specific inhibitor of histidine decarboxylase. Trends Pharmacol. Sci. 11, 363–366.