H1 but not H2 histamine antagonist receptors mediate anxiety-related behaviors and emotional memory deficit in mice subjected to elevated plus-maze testing

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Abstract

This study investigated the role of H1 and H2 receptors in anxiety and the retrieval of emotional memory using a Trial 1/Trial 2 (T1/T2) protocol in an elevated plus-maze (EPM). Tests were performed on 2 consecutive days, designated T1 and T2. Before T1, the mice received intraperitoneal injections of saline (SAL), 20 mg/kg zolantidine (ZOL, an H2 receptor antagonist), or 8.0 or 16 mg/kg chlorpheniramine (CPA, an H1 receptor antagonist). After 40 min, they were subjected to the EPM test. In T2 (24 h later), each group was subdivided into two additional groups, and the animals from each group were re-injected with SAL or one of the drugs. In T1, the Student t-test showed no difference between the SAL and ZOL or 8 mg/kg CPA groups with respect to the percentages of open arm entries (%OAE) and open arm time (%OAT). However, administration of CPA at the highest dose of 16 mg/kg decreased %OAE and %OAT, but not locomotor activity, indicating anxiogenic-like behavior. Emotional memory, as revealed by a reduction in open arm exploration between the two trials, was observed in all experimental groups, indicating that ZOL and 8 mg/kg CPA did not affect emotional memory, whereas CPA at the highest dose affected acquisition and consolidation, but not retrieval of memory. Taken together, these results suggest that H1 receptor, but not H2, is implicated in anxiety-like behavior and in emotional memory acquisition and consolidation deficits in mice subjected to EPM testing.

Key words: Chlorpheniramine; Zolantidine; Anxiety; Memory; Elevated plus-maze

Introduction

Histamine is a neurotransmitter present in both the peripheral and central nervous systems that is involved in the modulation of anxiety-related behavior in animals. Furthermore, it has been implicated in cognitive functions, including learning and memory (1,2). The functions of histamine are mediated through different receptor subtypes: H1, H2, H3, and H4 (3,4).

It has been suggested that the histaminergic system may exert tonic modulatory control over emotional behavior (5). In addition, some evidence supports the concept that histaminergic neurons influence anxiety-related behavior via H1 and H2 receptor activation (6,7). For example, administration of the H1 receptor antagonist pyrilamine or H2 receptor antagonist ranitidine in the dorsal hippocampus was found to induce anxiogenic-like behavior in mice in a hole-board test (7). Furthermore, evidence has demonstrated that histamine can facilitate long-term potentiation by activating histamine receptor subtypes (H1 and H2) and consequently modulates synaptic plasticity (2,8). It is accepted that synaptic plasticity is the cellular basis of emotional memory because long-term potentiation is correlated with memory trace formation (2). Studies have
also investigated the effects of $H_1$ and $H_2$ histaminergic receptor activation on emotional memory in animals (9,10) and humans (11).

The elevated plus-maze (EPM) is a widely used test for animal anxiety (12,13) and according to Galvis-Alonso et al. (14), animals acquire information about safe and dangerous areas of the maze during EPM testing. Repeated testing provides a measure of the acquisition and retention of memories because experience-dependent behavioral changes can be observed. Our laboratory has performed studies on the histaminergic system addressing anxiety and emotional memory in mice using a Trial 1/Trial 2 (T1/T2) protocol in an EPM (15,16). Although these studies have indicated that histamine $H_1$ receptors could have a modulatory effect on memory processes, few studies have investigated the effects of histamine mediated by $H_2$ receptors on emotional behavior using repeated testing in an EPM.

Therefore, the objective of the present study was to investigate the effects of a systemically administered selective histamine $H_2$ receptor antagonist, zolantidine (ZOL) and a histamine $H_1$ receptor antagonist, chlorpheniramine (CPA), on the modulation of anxiety-related behaviors and the retrieval and acquisition of emotional memory in mice re-exposed to EPM testing.

Subjects and Methods

Subjects

The experimental subjects were adult male Swiss albino mice supplied by the Animal Facility of Universidade Federal de Sáo Carlos, Sáo Carlos, SP, Brazil, weighing 30-35 g at testing. The mice were housed in groups of 10 per cage (41 x 34 x 16 cm) and maintained under a 12-h light cycle (light on at 7:00 am) in a controlled environment with a temperature of 23 ± 1°C and a relative humidity of 50 ± 5%. The experimental subjects were adult male Swiss albino mice supplied by the Animal Facility of Universidade Federal de Sáo Carlos, Sáo Carlos, SP, Brazil, weighing 30-35 g at testing. The mice were housed in groups of 10 per cage (41 x 34 x 16 cm) and maintained under a 12-h light cycle (light on at 7:00 am) in a controlled environment with a temperature of 23 ± 1°C and a relative humidity of 50 ± 5%. The experimental subjects were adult male Swiss albino mice supplied by the Animal Facility of Universidade Federal de Sáo Carlos, Sáo Carlos, SP, Brazil, weighing 30-35 g at testing. The mice were housed in groups of 10 per cage (41 x 34 x 16 cm) and maintained under a 12-h light cycle (light on at 7:00 am) in a controlled environment with a temperature of 23 ± 1°C and a relative humidity of 50 ± 5%. The experimental subjects were adult male Swiss albino mice supplied by the Animal Facility of Universidade Federal de Sáo Carlos, Sáo Carlos, SP, Brazil, weighing 30-35 g at testing. The mice were housed in groups of 10 per cage (41 x 34 x 16 cm) and maintained under a 12-h light cycle (light on at 7:00 am) in a controlled environment with a temperature of 23 ± 1°C and a relative humidity of 50 ± 5%. The experimental subjects were adult male Swiss albino mice supplied by the Animal Facility of Universidade Federal de Sáo Carlos, Sáo Carlos, SP, Brazil, weighing 30-35 g at testing. The mice were housed in groups of 10 per cage (41 x 34 x 16 cm) and maintained under a 12-h light cycle (light on at 7:00 am) in a controlled environment with a temperature of 23 ± 1°C and a relative humidity of 50 ± 5%.

Drugs

Zolantidine (an $H_2$ receptor antagonist; Sigma, USA) and chlorpheniramine maleate salt (an $H_1$ receptor antagonist; Sigma) were dissolved in sterile 0.9% saline. The drugs were injected intraperitoneally ($ip$) at a volume of 2 mL/kg body weight, and the final dose was 20 mg/kg ZOL and 8.0 or 16 mg/kg CPA. The applied doses were based on previous studies (6,15,17) and on pilot work performed in our laboratory.

Saline (SAL) was used as control. Both drugs (ZOL and CPA), and SAL were placed in coded Eppendorf tubes under refrigeration. This coding was unknown to the experimenter at the time of the behavioral analysis testing.

Apparatus

The apparatus used for EPM testing was similar to those previously developed and validated for rats (12) and for mice (13). It was constructed from wood, and its enclosed arms had transparent glass walls. The maze consisted of four arms: two open (30 x 5 x 0.25 cm) and two enclosed arms (30 x 15 x 5 cm) extending from a common central platform (5 x 5 cm) and was elevated to a height of 38.5 cm from the floor. All tests were conducted under moderate illumination (77 lx, measured on the central platform of the EPM) during the light phase of the diurnal cycle.

Experimental procedure

On the day of the experiment, to facilitate adaptation, animals were transported to a dimly lit room and left undisturbed for at least 1 h before testing to facilitate adaptation. The experiments were performed on two consecutive days, designated T1 and T2. In T1, the mice received an ip injection of SAL, ZOL, and 8 or 16 mg/kg CPA. For each drug tested there was a corresponding control group in T1, resulting in the following paired groups: SAL (n = 20) and ZOL (n = 21), SAL (n = 20) and 8 mg/kg CPA (n = 20), and SAL (n = 20) and 16 mg/kg CPA (n = 22). Forty minutes after the injections (6,18), the mice were exposed to the EPM (T1). In T2 (24 h later), each group was subdivided into two new groups, and the animals from each group were re-injected with SAL or one of the drugs prior to conducting T2. For each drug administered, the animals were randomly assigned to four groups based on the drug treatment: 20 mg/kg ZOL: SAL-SAL (n = 11), SAL-ZOL (n = 9), ZOL-SAL (n = 10), ZOL-ZOL (n = 11); 8 mg/kg CPA: SAL-SAL (n = 13), SAL-CPA (n = 10), CPA-SAL (n = 8), CPA-CPA (n = 9), and 16 mg/kg CPA: SAL-SAL (n = 12), SAL-CPA (n = 10), CPA-SAL (n = 10), CPA-CPA (n = 10).

Each testing session began by placing the subject on the central platform of the maze facing an open arm. The subject was allowed 5 min of free exploration. Between animals, the maze was thoroughly cleaned with 20% alcohol and dry cloths. All sessions were video recorded using a camera positioned above and at a 50° angle with respect to the maze to permit the discrimination and documentation of all behaviors. The video signal was also relayed to a monitor for real-time observation in another room.

Behavioral analysis

Videotapes were scored by a highly trained observer using the ethological analysis software package X-Plot-Rat developed at Laboratório de Comportamento Exploratório, USP, Ribeirão Preto (19). The conventional measures recorded were the frequency of closed arm entries (arm entry = all four paws into an arm), percentage of open arm entries [%OAE = (open / total) x 100] and percentage of time spent (%OAT) in open arms.
Table 1. Effects of systemic treatment with zolantidine (ZOL) or chlorpheniramine (CPA) prior to Trial 1 on behavioral measures in mice exposed to elevated plus-maze testing.

| Behaviors | SAL (n = 20) | ZOL (n = 21) | SAL (n = 20) | CPA (8 mg/kg) (n = 20) |
|-----------|-------------|-------------|-------------|----------------------|
| %OAE      | 28.72 ± 4.60| 31.82 ± 3.53| 27.76 ± 2.68| 22.40 ± 3.17        |
| %OAT      | 11.76 ± 2.72| 12.39 ± 2.64| 12.93 ± 1.74| 11.12 ± 2.94        |

Data are reported as means ± SE for Trial 1. The mice received, ip, 20 mg/kg ZOL, 8 mg/kg CPA or saline (SAL). %OAE = percentage of open arm entries; %OAT = percentage of time spent in open arms. There were no significant differences between groups (Student t-test).

Table 2. Effects of systemic treatment with zolantidine (ZOL) or chlorpheniramine (CPA) prior to Trial 1 on behavioral measures in mice exposed to elevated plus-maze testing.

| Behavior | SAL (n = 20) | ZOL (n = 21) | SAL (n = 20) | CPA (8 mg/kg) (n = 20) | SAL (n = 20) | CPA (16 mg/kg) (n = 22) |
|----------|-------------|-------------|-------------|----------------------|-------------|------------------------|
| EAE      | 9.36 ± 0.97 | 9.82 ± 0.25 | 11.77 ± 0.61| 14.22 ± 0.94         | 12.17 ± 10.7| 14.08 ± 1.0             |

Data are reported as means ± SE for Trial 1. The mice received, ip, 20 mg/kg ZOL, 8 or 16 mg/kg CPA or saline (SAL). EAE = enclosed arm entries. There were no significant differences between groups (Student t-test).
Student t-test detected no differences between the SAL and CPA groups for EAE (t(20) = 1.30, P > 0.05) in T1 (Table 2), indicating that the highest dose of CPA did not affect locomotor activity.

Table 3 presents a comparison between T1 and T2, and repeated measures ANOVA revealed a significant effect of the trials on %OAE (F(1,41) = 21.91, P < 0.05) and %OAT (F(1,41) = 32.53, P < 0.05). The post hoc test indicated a reduction in both variables for the SAL-SAL and SAL-CPA groups, but not for the CPA-SAL and CPA-CPA groups in T2 (ANOVA, P > 0.05).

Discussion

The main results of this study show that systemic administration of 8 mg/kg CPA and 20 mg/kg ZOL did not affect behavioral measures of anxiety. Treatment with CPA at the highest dose induced anxiety-related behavior in mice subjected to the EPM. Importantly, no significant changes were observed in the number of EAE in T1, a parameter considered to be a valid measure of locomotor activity in EPM tests (20).

Our results show that the injection of ZOL or 8 mg/kg CPA ip prior to T1 did not affect anxiety because no significant difference in open arm activity (%OAE and %OAT) was observed between the SAL and ZOL or CPA groups during T1. Our results are consistent with previous studies conducted in our laboratory, which have demonstrated that ip injection of 8 mg/kg CPA and intra-amygdala infusions of CPA (0.016 and 0.052 nmol/0.1 μL) do not alter anxiety levels in mice exposed to the EPM (15,16).

In another study, treatment with 20 mg/kg ip ZOL, an H₂ receptor antagonist, also did not affect anxiety in mice subjected to the EPM (6). In the present study, administration of CPA at the highest dose (16 mg/kg) decreased %OAT and %OAE, which are parameters associated with anxiety-related behavior, without locomotor impairment in the EPM, indicating an anxiogenic response, which is in agreement with the data obtained in previous studies (6,21). It has been proposed that histamine modulates the release of acetylcholine via stimulation of H₁ receptors. For example, superfusion with an H₁ receptor antagonist was found to decrease the release of acetylcholine in the rat ventral striatum (22). Since acetylcholine may modulate anxiety-related behaviors (23), one may expect that this response of the highest doses of antagonist CPA is mediated through changes in acetylcholine levels, but this hypothesis has not yet been tested. In contrast, other studies have reported an anxiolytic response mediated by H₁ receptors in rats and mice (24,25). The reported discrepancies could be related to experimental differences among the many factors that appear to influence the aversion to open arms, such as the time of day at which testing occurs (26) and the levels of illumination in the testing room (27).

We detected a notable decrease in open arm activity (%OAE and %OAT) in the animals treated with ZOL and CPA at a dose of 8 mg/kg during T2. Our results indicate that learning occurred in these groups during T1 and that emotional memory was evoked in T2, which corroborates...
the findings of previous studies performed in our laboratory indicating that CPA does not affect emotional memory in mice (15,16). Behavioral studies have indicated that $H_1$ and $H_2$ receptors enhance the processes of learning and memory in rats (24,28). Another study has suggested that neither $H_1$ nor $H_2$ receptors alter lithium state-dependent retrieval of memory in mice when administered as pre-test treatment (29). In our study, the animals that received CPA at the highest dose did not show altered activity in the open arms upon a second exposure to the EPM, indicating an emotional memory acquisition and consolidation deficits. These results could primarily be explained by the anxiety responses observed in the group that received 16 mg/kg CPA prior to the first exposure to the EPM, impairing the normal acquisition of configural and contextual characteristics of the maze and inducing the performance impairment observed in the T2 session. However, the anxiety-related behaviors induced by this drug in the EPM are associated with a normal and adaptive anxiety range and it is unlikely that the memory impairment is due to this anxiety. A recent study investigating the relationship between anxiety and cognitive functions found no short-memory or long-memory impairment in mouse strains that display adaptive anxiety (30). Our results agree with other studies showing that administration of CPA impairs learning and memory processes (31,32). A recent study conducted in our laboratory demonstrated that infusion of CPA (0.16 nmol/0.1 μL) in the amygdala induces emotional memory impairment per se at the highest dose tested (16). Furthermore, behavioral evidence has indicated that the regulatory mechanisms of histamine neural circuits affecting learning and memory are possibly related to their dynamic neural network connections with many structures (33), suggesting tonic modulatory control of this neurotransmitter.

The widespread extension of histaminergic neurons suggests that this system might influence different brain regions; one such area, the locus coeruleus, modulates the attentional state and presents a tight neuromodulatory interaction with the amygdala (34), which play an important regulatory role in the acquisition of emotionally based learning and memory (35). An in vitro study conducted by Korotkova et al. (36) demonstrated that histamine excites noradrenergic neurons in the rat locus coeruleus via $H_1$ receptors. We suggest that ip injection of CPA, an $H_1$ histaminergic antagonist, at the highest dose tested, decreased adrenergic neuron activation in this structure, which impaired emotional memory retrieval in mice during a second exposure to the EPM. Our results suggest that the emotional memory impairment induced by chlorpheniramine in rodents is under the tonic modulatory control of histamine.

We conclude that anxiety-like behavior and emotional memory acquisition and consolidation deficits are mediated by $H_1$ but not $H_2$ receptors in mice re-exposed to EPM testing.

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References

1. Brown RE, Stevens DR, Haas HL. The physiology of brain histamine. Prog Neurobiol 2001; 63: 637-672, doi: 10.1016/S0301-0082(00)00039-3.

2. Haas HL, Sergeeva OA, Selbach O. Histamine in the nervous system. Physiol Rev 2008; 88: 1183-1241, doi: 10.1152/physrev.00043.2007.
3. Leurs R, Smith MJ, Timmerman H. Molecular pharmacological aspects of histamine receptors. *Pharmacol Ther* 1995; 66: 413-463, doi: 10.1016/0163-7258(95)00006-3.

4. Strakhova MI, Nikkel AL, Manelli AM, Hsieh GC, Esbenshade TA, Brion JD, et al. Localization of histamine h4 receptors in the central nervous system of human and rat. *Brain Res* 2009; 1250: 41-48, doi: 10.1016/j.brainres.2008.11.018.

5. Santos NR, Huston JP, Brando MO. Escape behavior under tonic inhibitory control of histamine h(2)-receptor mediated mechanisms in the midbrain tectum. *Behav Brain Res* 2001; 124: 167-175, doi: 10.1016/S0166-4328(01)00228-5.

6. Kumar KV, Krishna DR, Palit G. Histaminergic H1 receptors mediate l-histidine-induced anxiety in elevated plus-maze test in mice. *Behav Pharmacol* 2007; 18: 213-217, doi: 10.1097/FBP.0b013e328157f450.

7. Zarrindast MR, Nasehi M, Piri M, Bina P. Anxiety-like behavior induced by histaminergic agents can be prevented by cannabinydroic WIN55,212-2 injected into the dorsal hippocampus in mice. *Pharmacol Biochem Behav* 2010; 94: 387-396, doi: 10.1016/j.pbb.2009.09.021.

8. Luo T. Endogenous histamine facilitates long-term potentiation in the hippocampus during walking. *J Neurosci* 2010; 30: 7845-7852, doi: 10.1523/JNEUROSCI.1127-10.2010.

9. Zarrindast MR, Parsaei L, Ahmadi S. Redacted administration of histamine improves memory retrieval of inhibitory avoidance by lithium in mice. *Pharmacology 2008*; 81: 187-194, doi: 10.1159/000111767.

10. Zlomuzica A, Viggiano D, De Souza Silva MA, Ishizuka T, Gironi Carnevale UA, Rucco LA, et al. The histamine H1-receptor mediates the motivational effects of novelty. *Eur J Neurosci* 2008; 27: 1461-1474, doi: 10.1111/j.1460-9568.2008.06115.x.

11. Kay GG, Harris AG. Loratadine: a non-sedating antihistamine. Review of its effects on cognition, psychomotor performance, mood and sedation. *Clin Exp Allergy* 1999; 29 (Suppl 3): 147-150, doi: 10.1046/j.1365-2222.1999.029063147.x.

12. Lister RG. The use of a plus-maze to measure anxiety in the mouse. *Psychopharmacology 1987*; 92: 180-185.

13. Pellow S, Chopin P, File SE, Briley M. Validation of open-closed arm entries in an elevated plus-maze as a measure of anxiety in the rat. *J Neurosci Methods* 1985; 14: 149-167, doi: 10.1016/0165-0270(85)90031-7.

14. Galvis-Alonso OY, Garcia AM, Orejarena MJ, Lamprea MR, Botelho S, Conde CA, et al. A combined study of behavior and Fos expression in limbic structures after re-testing Wistar rats in the elevated plus-maze. *Brain Res Bull* 2010; 81: 595-599, doi: 10.1016/j.brainresbull.2010.01.007.

15. Gianlorenzo AC, Canto-de-Souza A, Mattioli R. l-histidine induces state-dependent memory deficit in mice mediated by H(1) receptor. *Prog Neuropsychopharmacol Biol Psychiatry* 2011; 35: 91-95, doi: 10.1016/j.pnpbp.2010.09.006.

16. Serafim KR, Gianlorenzo AC, Daher FP, Mattioli R. H(1)-histamine receptors in the amygdala are involved in emotional memory but do not mediate anxiety-related behaviors in mice submitted to EPM testing. *Brain Res Bull* 2012; 89: 1-7, doi: 10.1016/j.brainresbull.2012.06.009.

17. Cofel LP, Mattioli R. Involvement of histamine receptors in the acquisition of inhibitory avoidance in *Carassius auratus*. *Prog Neuropsychopharmacol Biol Psychiatry* 2006; 30: 1246-1250, doi: 10.1016/j.pnpbp.2006.03.017.

18. Serafim KR, Kishi M, Canto-de-Souza A, Mattioli R. L-histidine provokes a state-dependent memory retrieval deficit in mice re-exposed to the elevated plus-maze. *Braz J Med Biol Res* 2010; 43: 100-106, doi: 10.1590/S0100-879X2009007500025.

19. Garcia AM, Cardenas FP, Morato S. Effect of different illumination levels on rat behavior in the elevated plus-maze. *Physiol Behav* 2005; 85: 265-270, doi: 10.1016/j.physbeh.2005.04.007.

20. Cruz AP, Frei F, Graeff FG. Ethopharmacological analysis of rat behavior on the elevated plus-maze. *Pharmacol Biochem Behav* 1994; 49: 171-176, doi: 10.1016/0091-3997(94)90472-3.

21. Zarrindast MR, Moghadam AH, Rostami P, Roohbakhsh A. The effects of histaminergic agents in the central amygdala of rats in the elevated plus-maze test of anxiety. *Behav Pharmacol* 2005; 16: 643-649, doi: 10.1097/00008877-200512000-00007.

22. Prast H, Tran MH, Lamberti C, Fischer H, Kraus M, Grass K, et al. Histaminergic neurons modulate acetylcholine release in the ventral striatum: role of H1 and H2 histamine receptors. *Neuropsychobiology 1999*; 360: 552-557, doi: 10.1007/s000109900098.

23. Degroot A, Treit D. Dorsal and ventral hippocampal cholinergic systems modulate anxiety in the plus-maze and shock-probe tests. *Brain Res 2002*; 949: 60-70, doi: 10.1016/S0006-8993(02)02965-7.

24. Privou C, Knoche A, Hasenohrl RU, Huston JP. The H1- and H2-histamine blockers chlorpheniramine and ranitidine applied to the nucleus basalis magnocellularis region modulate anxiety and reinforcement related processes. *Neuropsychopharmacology 1998*; 37: 1019-1032, doi: 10.1016/S0893-133X(99)00087-2.

25. Miyata S, Hirano S, Ohawa M, Kamei J. Chlorpheniramine exerts anxiolytic-like effects and activates prefrontal 5-HT systems in mice. *Psychopharmacology 2011*; 213: 441-452, doi: 10.1007/s00213-010-1695-0.

26. Griebel G, Moreau JL, Jenk F, Martin JR, Misslin R. Some critical determinants of the behaviour of rats in the elevated plus-maze. *Behav Processes 1993*; 29: 37-48, doi: 10.1016/0376-6357(93)90026-N.

27. Garcia AM, Cardenas FP, Morato S. The effects of pentylenetetrazol, chlordiazepoxide and caffeine in rats tested in the elevated plus-maze depend on the experimental illumination. *Behav Brain Res 2011*; 217: 171-177, doi: 10.1016/j.bbr.2010.09.032.

28. Da Silva WC, Bonini JS, Bevilacqua LR, Izquierdo I, Cammarota M. Histamine enhances inhibitory avoidance memory consolidation through a H2 receptor-dependent mechanism. *Neurobiol Learn Mem 2006*; 86: 100-106, doi: 10.1016/j.nlm.2006.01.001.

29. Zarrindast MR, Fazli-Tabar M, Khalilzadeh A, Farahanianfar M, Yahyavi SH. Cross state-dependent retrieval between histamine and lithium. *Physiol Behav 2005*; 86: 154-163, doi: 10.1016/j.physbeh.2005.07.005.

30. Salomons AR, Armst SS, Ohl F. Impact of anxiety profiles on cognitive performance in BALB/c and 129P2 mice. *Cogn Affect Behav Neurosci*. www.springer.com. Accessed September 18, 2012.
31. Masuoka T, Mikami A, Kamei C. Ameliorative effect of a hippocampal metabotropic glutamate-receptor agonist on histamine H1 receptor antagonist-induced memory deficit in rats. *J Pharmacol Sci* 2010; 113: 41-47, doi: 10.1254/jphs.10022FP.

32. Zarrindast MR, Ahmadi R, Oryan S, Parivar K, Haeri-Rohani A. Effects of alpha-adrenoceptor agonists and antagonists on histamine-induced impairment of memory retention of passive avoidance learning in rats. *Eur J Pharmacol* 2002; 454: 193-198, doi: 10.1016/S0014-2999(02)02497-4.

33. Alvarez EO. The role of histamine on cognition. *Behav Brain Res* 2009; 199: 183-189, doi: 10.1016/j.bbr.2008.12.010.

34. McGaugh JL. The amygdala modulates the consolidation of memories of emotionally arousing experiences. *Annu Rev Neurosci* 2004; 27: 1-28, doi: 10.1146/annurev.neuro.27.070203.144157.

35. Ribeiro AM, Barbosa FF, Mungha H, Costa MS, Cavalcante JS, Silva RH. Basolateral amygdala inactivation impairs learned (but not innate) fear response in rats. *Neurobiol Learn Mem* 2011; 95: 433-440, doi: 10.1016/j.nlm.2011.02.004.

36. Korotkova TM, Sergeeva OA, Ponomarenko AA, Haas HL. Histamine excites noradrenergic neurons in locus coeruleus in rats. *Neuropharmacology* 2005; 49: 129-134, doi: 10.1016/j.neuropharm.2005.03.001.