DOI: 10.5567/pharmacologia.2015.258.263

Comparative Study of Learning and Memory Effects of Antihistamines Applied by Different Routes in Rats

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ABSTRACT

Background and Objective: H1 receptor blockers, also called antihistamines inhibit the histamine receptors and terminate the effect of the released histamine. They are divided into three generations, according to the time of their synthesis, properties and side effects for therapeutic purposes. The objective of this research was to investigate the effects of antihistamines chlorpheniramine (1st generation), Loratadine (2nd generation) and Levocetirizine (3rd generation) applied i.p. and i.c.v. on learning and memory in male Wistar rats. **Materials and Methods:** A passive avoidance task (step through) was used as a test for learning and memory. **Results:** Chlorpheniramine (1st generation) applied i.p., at doses of 10 and 20 mg kg^{-1} impaired learning and memory processes expressed by the shortened latency time on the retention tests (3 and 24 h after training) and by the decreased percentage of rats that have reached the learning criterion while Loratadine (2nd generation) and Levocetirizine (3rd generation) at doses of 10 and 20 mg kg^{-1} did not affect significantly the performance of rats. The i.c.v. infusion of Chlorpheniramine, Loratadine and Levocetirizine at doses of 10 and 20 μg significantly impaired learning and memory. Comparing the effects of antihistamines after i.p and i.c.v. administration on the step through active avoidance response, it was found that Chlorpheniramine (1st generation) caused a potent inhibition of the avoidance response after its i.p and i.c.v. administration while Loratadine (2nd generation) and Levocetirizine (3rd generation) impaired learning and memory only after i.c.v. application. **Conclusion:** These findings suggest that the impaired learning and memory effect of antihistamines might be connected with inhibition of brain H1 receptors.

Key words: H1-antagonists, chlorpheniramine, loratadine, levocetirizine, learning, memory

Pharmacologia 6 (6): 258-263, 2015

INTRODUCTION

Histamine [2-(4-imidazole)-ethylamine] is an endogenous short acting biogenic amine formed by decarboxylation of the amino acid L-histidine in a reaction catalysed by the enzyme histidine decarboxylase[1]. It possesses a wide spectrum of activities, including its function in neurotransmission[2]. As a neurotransmitter, histamine is involved in the regulation of sleep and wakefulness, water intake, motor activity, nociception, learning and memory and energy and endocrine homeostasis[3,4,5]. It also modulates the release of several neurotransmitters through presynaptic receptors located on histaminergic and non-histaminergic neurons of the central and peripheral nervous system.

Histamine exerts its effects through four distinct subtypes of G-protein-coupled receptors, designated H1, H2, H3 and H4 that are differentially expressed in various cell types. H1 and H2 receptors are widely distributed, H3 receptors are mainly presynaptic and H4 receptors are mainly haematopoietic[6].

Histamine H1 receptor antagonists as known as antihistamines, are widely used drugs to treat allergy symptoms by blocking the peripheral histamine H1 receptor. The antihistamines (H1 receptor blockers) are divided into three generations, according to the time of their synthesis, properties and side effects for therapeutic

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purposes[7]. The H1-receptor antagonists or H1 antihistamines include the older-type, sedating, multipotent blockers or the so-called first-generation H1 antihistamines, including chlorpheniramine, dexchlorpheniramine, promethazine and cyclizine and the newer non-sedating, selective H1-receptor blockers or the so-called second-generation H1 antihistamines and more recent improvements, generally in the form of active metabolites, so-called third-generation antihistamines[7].

It is well known that the first-generation antihistamines are hydrophilic molecules that can easily go across the blood brain barrier and affect the Central Nervous System (CNS)[8]. Some literatures have reported that the disturbance of central histaminergic receptors by the first-generation antihistamines may underlie their neuronal toxic effects on the neuronal system[9,10]. The drugs belonging to the second and third generation have a very limited ability to do so or none at all. These antihistamines differ from first-generation ones because of their elevated specificity and affinity for peripheral H1 receptors and because of their lower penetration of the CNS, having fewer sedative effects as a result[7].

Most currently known antihistamines have been reclassified as inverse agonists and the term histamine antagonists is only reserved for those compounds that function as true antagonists. H1-antihistamines are not receptor antagonists but are inverse agonists in that they produce the opposite effect on the receptor to histamine[11].

Antihistamines have been shown to impair learning and memory[12,13]. For example, diphenhydramine, promethazine, chlorpheniramine and triprolidine have been reported to impair spatial memory in rats, with alteration of the theta rhythm[14]. It was found that diphenhydramine-first generation antihistamine which easily crosses the blood-brain barrier[15] impaired the consolidation and expression of conditioned fear, whereas the second generation anti-histamines levocetirizine[16] and olopatadine[17] which have poor brain penetration[18,19] had no effect on fear, memory consolidation and expression[20].

The aim of the present study was to compare the effects of antihistamines (first, second and third generation) administered intraperitoneally (i.p.) and intracerebroventriculary (i.c.v.) on learning and memory using passive avoidance test in rats.

MATERIALS AND METHODS

Animals: The experiments were carried out on male Wistar 3-months aged rats (200-220 g at the beginning of the experiments). The animals were maintained in a constant temperature environment (22±2°C) on a 12 h light/dark cycle. The behavior experiments were carried out between 10:00 am and 1:00 pm. The experiments were performed according to the "Rules for care and experiments on laboratory animals" of the Ethics Committee of the Institute of Neurobiology, Bulgarian Academy of Sciences.

Stereotaxic implantation and drug injection into ventriculus ventrolateralis dextra: After anaesthesia (Calypsol 50 mg kg^{-1} i.p.), the rats were placed in a stereotaxic apparatus (Stoelting, USA) and guide cannulae were implanted into ventriculus ventrolateralis dextra (p = 0.9 mm; L = 1.6 mm; h = -3.0 mm) according to the coordinates of the stereotaxic atlas of Pellegrino and Cushman[21]. After surgery, the animals were allowed for seven days to recover before the behavioral test. During the recovery period, the rats were handled daily.

Following the termination of the experiments and immediately prior to sacrificing the rats were injected with 1 mL of 2% fast green dye through the injection cannula for verification and their brains were examined macroscopically after sectioning.

Drugs: The following drugs were used: Chlorpheniramine (Sigma)-CLPH (1st generation), Loratadine (Sigma)-CLAR (2nd generation) and Levocetirizine (Sigma)-KSYS (3rd generation).

One-way passive avoidance test (step through): In the passive avoidance task, the rat must learn to remain in a brightly lit compartment and not enter the preferred dark compartment to avoid a mild foot shock. One training trial and two retention tests were conducted according to the method of Buresovaand Bures[22]. The training trial was started by placing the rat in the light compartment. Once the rat had entered the dark compartment, the guillotine door was closed and an electrical shock (0.3-0.35 mA for 3 sec) was delivered to the animal through the grid floor. Each rat underwent one trial. Retention tests (no shocks) were performed 3 and 24 h after the acquisition trial. At that time, the animals were returned to the light compartment and step-through latency was estimated by measuring the length of time (latent time) for the rat to move to the dark compartment. A maximum latency of 180 sec was used as a criterion for learning.

The step through passive avoidance task was performed on 140 rats divided in two main groups: A)

Treated i.p. 70 rats divided in 7 groups of 10 animals each. The tested drugs were applied in two doses: 10 and 20 mg i.p., in a volume 0.5 mL/100 g b.wt. Training started 60 min after i.p., administrations; B) Treated i.c.v. 70 rats divided in 7 groups of 10 animals each. The drugs were applied in two doses: 10 and 20 µg. The drugs were dissolved *ex tempore* in saline and 1 µL of drug solution (pH 7.4) was infused i.c.v. 30 min before the behavior test.

Statistical analysis: One-way ANOVA was used to process the data obtained for the latent time. ANOVA data were further analyzed by post hoc t-test. Analysis of the data for the learning criteria was performed using χ^2 test. GraphPad Prism statistical software was used.

RESULTS

Effects of antihistamines applied i.p. at a dose of 10 mg kg^{-1}: One way ANOVA of the effects of antihistamines applied i.p., on the latent time demonstrated a significant effect for factor "drug" on the 3rd h ($F_{1, 39}$ = 3,680; p≤0.05) and 24th h ($F_{1, 39}$ = 3,773; p≤0.05). Post-hoc comparisons showed that Chlorpheniramine (CLPH) significantly decreased the latent time at 3rd h (t = 2.03; p≤0.03) and at 24th h (t = 2.40; p≤0.02) and decreased the percentage of animals, that reached the learning criteria on the 3rd h (30%- χ^2 = 1,818, p = NS) and 24th h (20%- χ^2 = 5,051, p≤0.02)in the retention test as compared to the control group, treated with saline (60 and 70%, respectively) as shown in Fig. 1(a, b). The i.p., injections of Loratadine(CLAR) and Levocetirizine (KSYS) did not affect significantly the tested parameters in the rats as compared to the respective saline-treated controls.

Effects of antihistamines applied i.p., at a dose of 20 mg kg^{-1}: ANOVA of the effects of CLPH, CLAR and KSYS on the latent time showed a significant effect for factor "drug" on the 3rd h ($F_{1,39}$ = 4.802; p≤0.006) and 24th h ($F_{1,39}$ = 5,946; p≤0.002).

CLPH injected i.p., at a dose of 20 mg kg^{-1} shorten the latent time in the retention test on the 3rd h (t = 3.99; p≤0.001) and on the 24th h (t = 4.56; p≤0.001) and decreased the percentage of the rats reaching the learning criteria on the 3rd h (10%-χ^2 = 5,495, p≤0.02) and on the 24th h (0%-χ^2 = 10,769, p≤0.001) as compared to the respective saline-treated rats(60 and 70%, respectively) (Fig. 1a, b). The effect of CLAR (20 mg kg^{-1}) and KSYS (20 mg kg^{-1}) did not differ significantly from the control group (Fig. 1a, b).

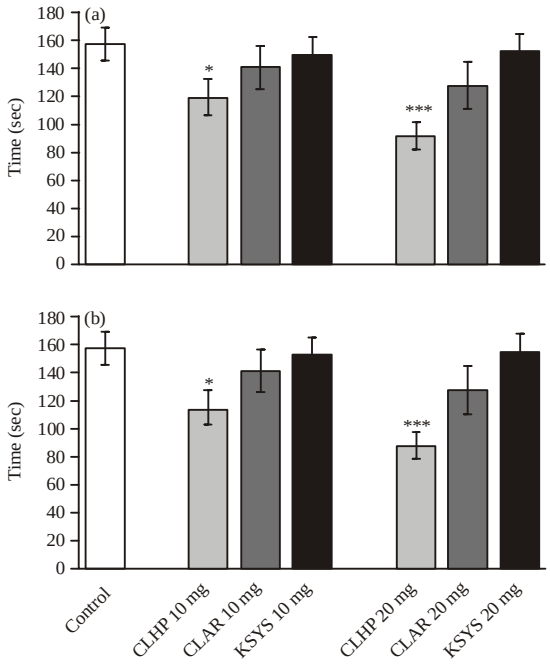

Fig. 1(a-b): Effects of Chlorpheniramine (CLPH), Loratadine (CLAR) and Levocetirizine (KSYS) injected i.p. at doses of 10 and 20 mg kg^{-1} on the latent time on the (a) 3rd h and (b) 24th h (step through test) n = 10. *p≤0.05, ***p≤0.001, asterisks depict-drug vs. saline-treated controls. Means±SEM are presented

Effects of antihistamines applied i.c.v. at a dose of 10 µg: ANOVA of the effects of anti-histamines infused i.c.v. on the latent time demonstrated a significant effect for factor "drug" on the 3rd h ($F_{1, 39}$ = 4,180; p≤0.02) and 24th h ($F_{1, 39}$ = 6,755; p≤0.001).

Post-hoc t-test comparisons demonstrated that CLPH, CLAR and KSYS infused i.c.v. at doses of 10 µg significantly decreased the latent time at 3rd h (t = 2.51, p≤0.03; t = 2.12, p≤0.02; t = 1.71, p≤0.05, respectively) and at 24th h (t = 3.57, p≤0.001; t = 4.38, p≤0.001; t = 2.56, p≤0.01, respectively) thus decreasing the percentage of the rats that reached the learning criteria on the 3rd h (30%-χ^2 = 1,818, p = NS; 30%-χ^2 = 1,818, p = NS; 40%-χ^2 = 0,808, p = NS, respectively) and on the 24th h (10%-χ^2 = 5,495, p≤0.02; 10%-χ^2 = 5,495, p≤0.02; 20%-χ^2 = 7,500; p≤0.01, respectively) as compared to the controls (60 and 70%, respectively) (Fig. 2a, b).

Effects of antihistamines applied i.c.v. at a dose of 20 µg: ANOVA of the effects of antihistamines infused

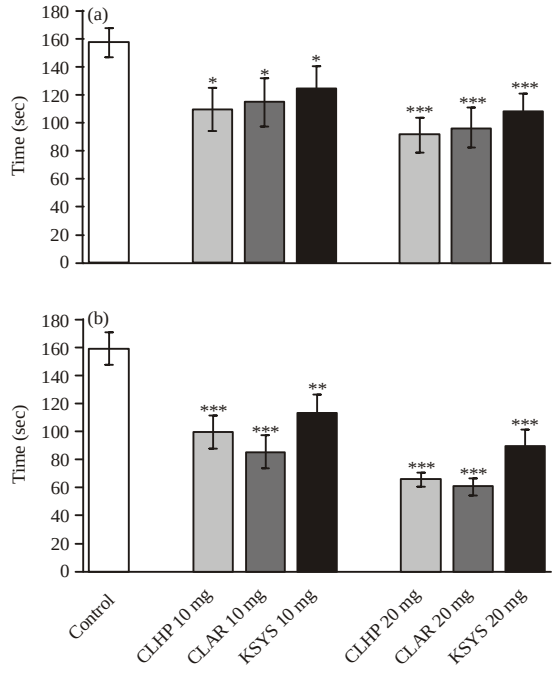

Fig. 2(a-b): Effects of Chlorpheniramine (CLPH), Loratadine (CLAR) and Levocetirizine (KSYS) injected i.c.v. at doses of 10 and 20 μg on the latent time on the (a) 3rd h and (b) 24th h (step through test) n = 10. *p≤0.05, ***p≤0.001, asterisks depict-drug vs. saline-treated controls. Means ± SEM are presented

i.c.v. on the latent time demonstrated a significant effect for factor "drug" on the 3rd h ($F_{1, 39}$ = 5,384; p≤0.01) and 24th h ($F_{1, 39}$ = 24,308; p≤0.001).

I.C.V. infusions of CLPH, CLAR and KSYS at doses of 20 μg showed a significant decrease of the latent time in the retention tests: On 3rd h after training (t = 3.99, p≤0.001; t = 3.36, p≤0.002; t = 2.92, p≤0.005, respectively) and on 24th h after training (t = 7.29, p≤0.001; t = 7.48, p≤0.001; t = 4.12, p≤0.001, respectively) as compared to the saline-treated controls (60 and 70%, respectively). CLPH, CLAR and KSYS significantly decreased the percentage of the rats that reached the learning criteria on the 3rd h (10%-χ^2 = 5,495, p≤0.02; 20%-χ^2 = 3,853, p≤0.05; 20%-χ^2 = 3,853, p≤0.05, respectively) and on the 24th h (0%-χ^2 = 8,571, p≤0.001; 0%-χ^2 = 8,571, p≤0.001; 10%-χ^2 = 5,495, p≤0.01, respectively) compared to the saline-treated rats (60 and 70%, respectively) (Fig. 2a, b).

DISCUSSION

In recent years, the effects of antihistamines in cognitive function has been investigated intensively. Most studies performed in animals show that a decrease in histamine neurotransmission results in impaired performance. However, some studies have shown stimulating effects of decreased histamine neurotransmission, induced by the administration of H1-antagonists[23,24].

In the present study, the effects on learning and memory of three generations of antihistamines Chlorpheniramine, Loratadine and Levocetirizine applied in different way in rats have been studied. These results demonstrated that Chlorpheniramine (1st generation) applied i.p., at doses of 10 and 20 mg kg^{-1} impaired learning and memory. The effect was expressed as a decrease of the latent time on 3rd and 24th h of the retention test and a decrease of the rats that reached the learning criteria. The i.p. administration of Loratadine (2nd generation) and Levocetirizine (3rd generation) at doses of 10 and 20 mg kg^{-1} did not affect significantly the performance of rats in the step through task. No correlation between lower and higher dose of any antihistamine drugs was found.

Some results correlate with the findings of the earlier research study as reviewed herein. It has been reviewed in experimental as well as in clinical studies[25]. The first generation antihistamines are associated with CNS side effects like sedation and the secondary effects like psychomotor impairment. Although second and third generation H1 antihistamines claim to be "non-sedating", some agents still cause CNS side effects, though findings are conflicting with one and another[26]. The effects of antihistamines on CNS are determined by their capability to cross blood brain barrier and capacity to bind with H1 receptor. Capability of drugs to cross blood brain barrier depends on the lipophilic nature of drug entity and its affinity towards P glycoprotein[27].

First generation antihistamines penetrates blood brain barrier readily due to their lipophilicity/solubility ratios, relatively low molecular weight and for some, lack of recognition by the P-glycoprotein reflux pump expressed on the luminal surfaces of endothelial cells in the cerebral vasculature[28].

Second and third generation drugs are highly specific for histamine receptors. They penetrate poorly into the CNS due to their lipophilic nature, relatively high molecular weight or recognition by the P glycoprotein reflux pump expressed on the luminal surfaces of endothelial cells in the cerebral vasculature[28].

Therefore, the administration of antihistamines in the ventricular system is a more convenient way to study their role in the CNS than peripheral administration, since some ligands might be more prone to cross the blood-brain barrier and there is less potential for peripheral side effects.

To assess the involvement of H1 receptors in learning and memory processes, the antihistamines (1st, 2nd and 3rd generation) have been applied by i.c.v. route. The results showed that i.c.v. infusion of Chlorpheniramine, Loratadine and Levocetirizine at doses of 10 and 20 µg significantly impaired learning and memory in step through test. As compared the effects of anti-histamines after i.p. and i.c.v. administration on the step through active avoidance response, it has been found that Chlorpheniramine (1st generation) caused a potent inhibition of the avoidance response after its i.p. and i.c.v. administration while Loratadine (2nd generation) and Levocetirizine (3rd generation) impaired learning and memory only in i.c.v. application. It has been supposed that this discrepancy of the effects of antihistamines from different generations might be due to the difference in administration routes. This suggests that Chlorpheniramine (1st generation) easily cross the blood-brain barrier, while Loratadine (2nd generation) and Levocetirizine(3rdgeneration) did not penetrate into the CNS. From these findings, it can be assumed that the inhibitory effect of antihistamines on the avoidance response may be exerted through the H1-receptor. Thus, this impairment learning and memory effect of the antihistamines could be associated with inhibitions of H1 receptors. The involvement of the histaminergic system and especially role of the brain H1 receptors in learning and memory has been generally associated with contradictory data[29]. For example, histamine was reported to improve inhibitory and active avoidance conditioning[30], whereas administration of H1-antagonists disrupted learning in an active avoidance task[31, 32, 33, 34].

CONCLUSION

This study provides information on cognitive effects of antihistamines from three generation (chlorpheniramine, loratadine and levocetirizine) applied in different routes in rats. These findings suggest that antihistamines-Chlorpheniramine (1st generation), Loratadine (2nd generation) and Levocetirizine (3rd generation) infused i.c.v. exert impairing learning and memory effect. The impaired learning and memory effect of antihistamines might be connected with inhibition of brain H1 receptors mediating these processes or interactions of H1 blockers with brain neurotransmitters (GABA, glutamate, dopamine, acetylcholine).

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