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Research Report

Histaminergic receptors of medial septum and conditioned place preference: D1 dopamine receptor mechanism

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ABSTRACT

In the present study, the effects of intra-medial septum injections of histamine and/or the histamine H_1 or H_2 receptor antagonists on the acquisition of conditioned place preference (CPP) in male Wistar rats have been investigated. Our data showed that the conditioning treatments with intra-medial septum injection of different doses of histamine (0.5–15 μg/rat) induced a significant CPP for the drug-associated place. Using a 3-day schedule of conditioning, it was found that the histamine H_1 receptor antagonist, pyrilamine (10 and 15 μg/rat, intra-medial septum) also induced a significant place preference. In addition, pyrilamine inhibited the histamine (7.5 μg/rat)-induced place preference. Intra-medial septum administration of the histamine H_2 receptor antagonist, ranitidine (5–15 μg/rat) alone or in combination with histamine did not produce a significant place preference or place aversion. On the other hand, intra-medial septum administration of the dopamine D_1 receptor antagonist, SCH 233390 (0.5, 0.75 and 1 μg/rat) inhibited the histamine (7.5 μg/rat) or pyrilamine (15 μg/rat)-induced place preference in a dose-dependent manner, but no effect was observed for the dopamine D_2 receptor antagonist, sulpiride on the histamine or pyrilamine response. The administration of histamine (2.5–15 μg/rat) or pyrilamine (10 and 15 μg/rat) during acquisition increased locomotor activity of the animals on the testing days. The results suggest that histaminergic receptors of the medial septum may be involved in CPP and thus it is postulated that dopamine D_1 receptors may play an important role in this effect.

1. Introduction

A number of pharmacological studies have shown that histaminergic neuronal system is involved in the control of learning and memory (Alvarez and Ruarte, 2002; Giovannini et al., 1999, 2003), reinforcement processes (Cohn et al., 1973; Hasenohrl et al., 2001; Mattioli et al., 1996) and motivated behaviors (Kraly et al., 1995; Tuomisto and Tuomisto, 1980).

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Histamine (HA) is a biogenic amine which is synthesized from L-histidine by histidine decarboxylase in a small number of neurons located in tuberomammillary nucleus of the hypothalamus (Panula et al., 1989; Unterwald et al., 1984). These neurons project efferent varicose fibers to all areas of the central neurons system (Inagaki et al., 1990; Onodera et al., 1994). Histamine interacts with specific receptors; postsynaptic H_1 and H_2 receptors, and a presynaptic autoreceptors, an H_3 receptor which regulates HA synthesis and release (Hill et al., 1997).

The conditioned place preference (CPP) is well known as an adequate model for studying the rewarding effects of drugs and reward-related learning (McBride et al., 1999; Tzschentke, 1998). There now is a general consensus that psychostimulants and opioids can induce reward, reinforcement and addictive behaviors through activity in the mesolimbic dopaminergic system (McBride et al., 1999; Olmstead and Franklin, 1997a; Tzschentke, 1998). Some studies suggested that reinforcing or rewarding effects also occur with peptides such as substance P (Boix et al., 1995) or common antihistamines (Cohn et al., 1973; Unterwald et al., 1984; Wauquier and Niemegeers, 1981). It has also been reported that the injection of the H_1 receptor antagonist, chlorpheniramine into the nucleus basalis magnocellularis induced CPP in rats (Privou et al., 1998). Histamine is also involved in learning and memory (Alvarez and Ruarte, 2002; Giovannini et al., 2003), but there are many contradictory results about the actual role of this modulatory neurotransmitter during acquisition and storage of information. It has been reported that histamine facilitated (Kamei et al., 1993a) and suppressed active avoidance conditioning (Alvarez and Banzan, 1996). In addition, the administration of the H_1 receptor antagonist impaired radial maze task (Taga et al., 2001) and improved water maze (Hasenohrl et al., 1999). The cause of these discrepancies is not clear; however, it might be associated with two different mechanisms. One mechanism might act directly on the brain's memory substrate via the modulation of hippocampal synaptic plasticity (Haas and Panula, 2003), whereas the other might have an indirect effect on memory inscription via modulation of the brain's reinforcement system (Huston et al., 1997).

The medial septum which strongly modulates hippocampal activity (Hasselmo, 1995) participates in learning and memory processes (Numan; Rokers et al., 2002). Some studies indicated that the pharmacological disruption of the medial septum impairs conditioning in rabbits (Asaka et al., 2000; Solomon et al., 1983). In addition to participating in learning and memory processes, the septal area, which is regarded as part of the reward circuit, may also contribute to the addictive properties of opioids (Alreja et al., 2000). Furthermore, CPP is a learning paradigm requiring the formation of associations between reward and particular locations (Calcagnetti and Schechter, 1991; Hoffman, 1989; Tzschentke, 1998). Histaminergic system is involved in the modulation of reward and also learning processes (Eidi et al., 2003; Kamei and Tasaka, 1993; Zarrindast et al., 2002), and state-dependent learning (Zarrindast et al., 2005). We therefore hypothesized that intra-medial septum injection of histaminergic agents can induce a CPP. If our hypothesis was correct, we intended to examine the possible role of dopamine receptor subtypes in this effect.

2. Results

2.1. *Effect of histamine on the acquisition of CPP*

Fig. 1A shows the effects of intra-medial septum injection of histamine on the acquisition of CPP. The conditioning treatments with histamine induced a CPP for the drug-associated place. One-way ANOVA revealed that histamine caused a significant and dose-related preference [$F(6,49)=40.9$, $P<0.0001$]. Fig. 1B illustrates the effect of intra-medial septum injection of histamine on the locomotor activity in the testing phase. One-way ANOVA indicated that histamine (2.5, 5, 7.5, 10 and 15 μg/rat) increased the locomotor activity [$F(6,49)=9.2$, $P<0.001$].

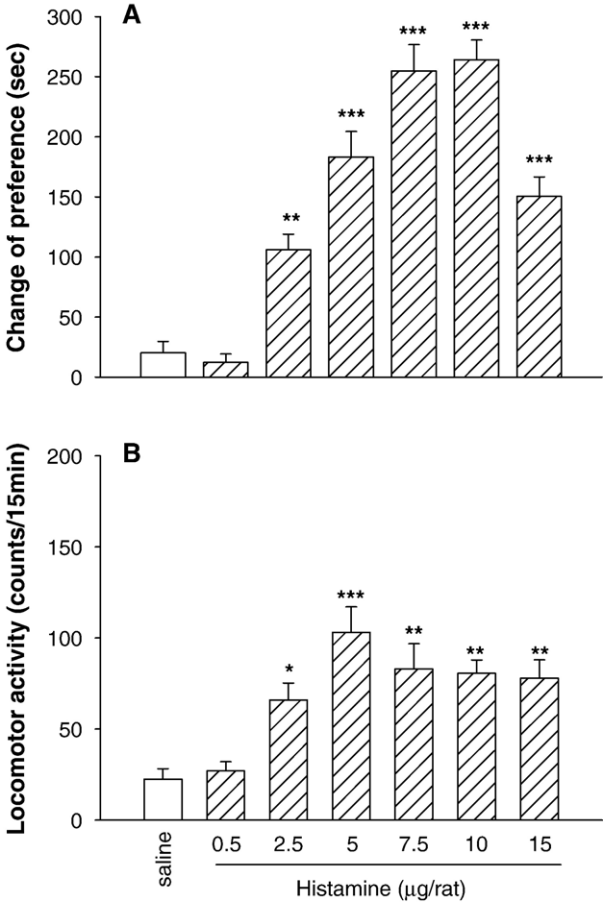

Fig. 1 – Place preference produced by histamine. Different doses of histamine (0.5, 2.5, 5, 7.5, 10, 15 μg/rat) and saline (1 μl/rat) were injected into the medial septum in a 3-day schedule of conditioning. On the test day, the animals were observed for a 15-min period. The change of preference was assessed as the difference between the time spent on the day of testing and the time spent on the day of the preconditioning session. Data are expressed as mean ± SEM of 8 animals per group. *$P<0.05$, **$P<0.01$, ***$P<0.001$ different from the saline control group.

2.2. *Effect of pyrilamine with or without histamine on the acquisition of CPP*

Fig. 2A shows the effects of intra-medial septum injection of pyrilamine in the absence or presence of histamine on the acquisition of CPP. Two-way ANOVA indicates an interaction between histamine and pyrilamine in the acquisition of place preference [within-group comparison: treatment effect: $F(1,56)=410.2$, $P<0.001$, dose effect: $(3,56)=11.6$, $P<0.001$, treatment × dose interaction: $F(3,56)=56.8$, $P<0.001$]. Further analysis revealed that the higher dose of histamine (7.5 μg/rat) or pyrilamine (10 and 15 μg/rat, Intra-medial septum) induced a significant place preference. Moreover, pyrilamine inhibited the histamine (7.5 mg/kg)-induced place preference.

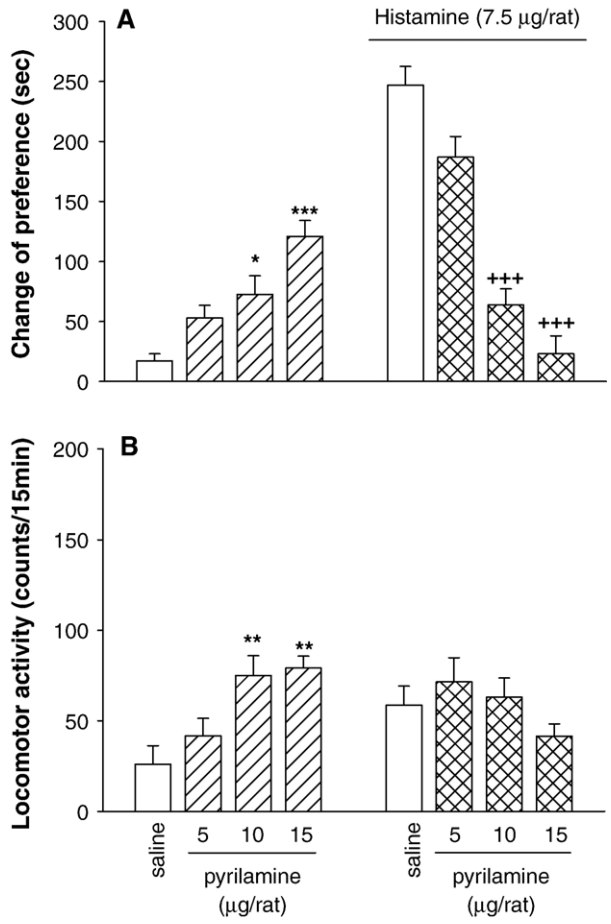

Fig. 2 – The effects of intra-medial septum injection of pyrilamine, either alone or in combination with histamine, on the acquisition of a conditioned place preference. The animals received pyrilamine (5, 10 and 15 μg/rat) or saline (1 μl/rat) with or without histamine (7.5 μg/rat), in a 3-day schedule of conditioning. On the test day, the animals were observed for a 15-min period. The change of preference was assessed as the difference between the time spent on the day of testing and the time spent on the day of the preconditioning session. Data are expressed as mean ± SEM of 8 animals per group. $^{*}P<0.05$, $^{***}P<0.001$ different from the saline control group; $^{+++}P<0.001$ different from the saline/histamine control group.

Fig. 2B illustrates the effect of the drugs on the locomotor activity in the testing phase. Two-way ANOVA indicated a significant effect for treatment × dose interaction $[F(3,56)=5.7$, $P<0.01]$, but no effect was observed for dose $[F(3,56)=2.4$, $P>0.05]$ and treatment $[F(1,56)=0.2$, $P>0.05]$, on the locomotor activity, by the drugs. Analysis indicates that pyrilamine (5, 10 and 15 μg/rat, Intra-medial septum) alone increased the locomotor activity, but in combination with histamine (7.5 μg/rat, Intra-medial septum) had no effect on the locomotor activity.

2.3. *Effect of ranitidine with or without histamine on the acquisition of CPP*

Fig. 3A shows the effects of intra-medial septum injection of ranitidine in the absence or presence of histamine on the acquisition of CPP. One-way ANOVA indicated that intra-medial septum injection of ranitidine alone did not induce a significant CPP $[F(3,28)=0.07, P>0.05]$. In addition, the injection of different doses of ranitidine (5, 10 and 15 μg/rat) into the medial septum cannot also affect the histamine (7.5 μg/rat)-induced place preference. Fig. 3B illustrates the effect of intra-medial septum injection of ranitidine in the absence or presence of histamine on the locomotor activity in the testing phase. One-way ANOVA indicated that ranitidine alone $[F(3,28)=0.2$, $P>0.05]$ or in combination with histamine $[F(3,28)=0.1$, $P>0.05]$ did not change on locomotor activity.

2.4. *Effects of SCH 23390 on the histamine- or pyrilamine-induced place preference*

Fig. 4A shows the effects of intra-medial septum injection of SCH 23390 on the histamine- or pyrilamine-induced place preference. One-way ANOVA revealed that the administration of SCH 233390 (0.5, 0.75 and 1 μg/rat, intra-medial septum) inhibited the histamine (7.5 μg/rat, intra-medial septum) $[F(3,28)=97.5$, $P<0.001]$ or pyrilamine-(15 μg/rat, intra-medial septum)$[F(3,28)=13.9$, $P<0.001]$ induced place preference in a dose-dependent manner. Moreover, intra-medial septum injection of SCH 23390 did not induce any response by itself [one-way ANOVA; $F(3,28)=2.9$, $P>0.05]$. Fig. 4B also illustrates the effect of intra-medial septum injection of SCH 23390 in the presence or absence of histamine or pyrilamine on the locomotor activity in the testing phase. One-way ANOVA indicated that co-administration of SCH 23390 with saline $[F(3,28)=2.1$, $P>0.05]$, histamine $[F(3,28)=0.7$, $P>0.05]$ or pyrilamine $[F(3,28)=0.6$, $P>0.05]$ did not alter the locomotor activity.

2.5. *Effects of sulpiride on histamine- or pyrilamine-induced place preference*

Fig. 5A shows the effects of intra-medial septum injection of sulpiride on the histamine- or pyrilamine-induced place preference. One-way ANOVA revealed that the administration of sulpiride (0.2, 1 and 5 μg/rat, intra-medial septum) did not alter the histamine- (7.5 μg/rat) $[F(3,28)=1.2$, $P>0.05]$ or pyrilamine- (15 μg/rat) $[F(3,28)=1.5$, $P>0.05]$ induced place preference. Fig. 4B also illustrates the effect of co-administration of sulpiride with histamine or pyrilamine on the

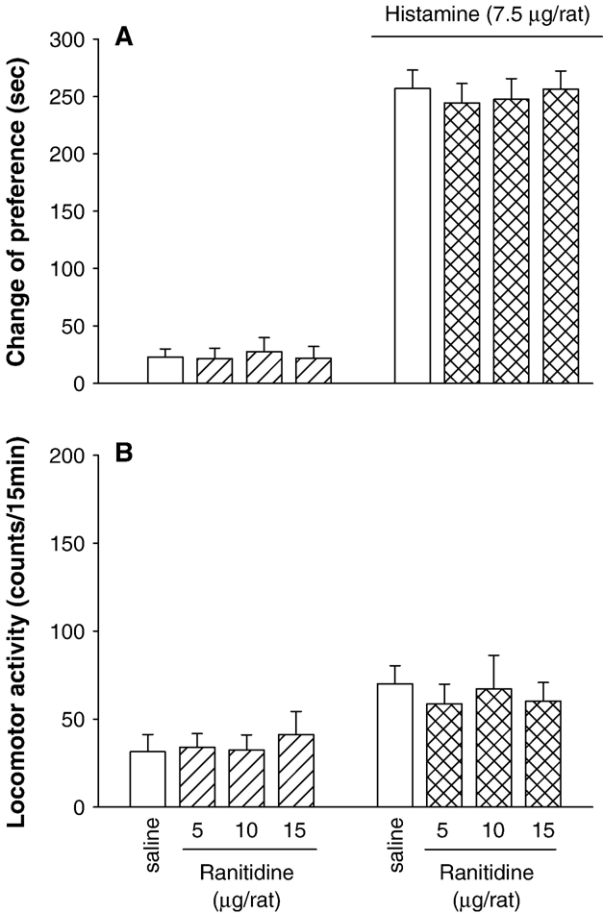

Fig. 3 – The effects of intra-medial septum injection of ranitidine, either alone or in combination with histamine, on the acquisition of a conditioned place preference. The animals received ranitidine (5, 10 and 15 μg/rat) or saline (1 μl/rat) in combination with histamine (7.5 μg/rat) or without histamine, in a 3-day schedule of conditioning. On the test day, the animals were observed for a 15-min period. The change of preference was assessed as the difference between the time spent on the day of testing and the time spent on the day of the preconditioning session. Data are expressed as mean ± SEM of 8 animals per group.

locomotor activity in the testing phase. One-way ANOVA indicated that pyrilamine [$F(3,28)=1.5$, $P>0.05$] or histamine [$F(3,28)=1.6$, $P>0.05$] in the presence or absence of sulpiride did not have any influence on the locomotor activity.

3. Discussion

In the present experiments, we examined the effects of intra-medial septum injections of histaminergic agents on the acquisition of conditioned place preference (CPP) in rats. Rats were injected (intra-medial septum) with histamine (0.5–15 μg/rat, three sessions) using an unbiased conditioned place preference (CPP) paradigm.

Our data indicated that histamine induced a significant CPP, dose dependently. The drug at the doses used also increased locomotor activity in comparison with the control group. One may suggest that histamine indirectly act on dopaminergic system in this site. This may be supported by the reports indicating that neuronal histamine (HA) is able to regulate both reward processes (Cohn et al., 1973; Huston et al., 1997; Rassnick and Kornetsky, 1991) and also dopamine (DA) activity (Dringenberg et al., 1998; Fleckenstein et al., 1993) in the brain. In addition, it is well known that the ascending mesolimbic and mesostriatal dopaminergic pathways may have an important role in processes related to reward, reinforcement and addictive behaviors (Koob, 1992; Olmstead and Franklin, 1997a,b). It has been also suggested that HA can interfere with the uptake of DA and increased levels of extracellular DA (Tuomisto and Tuomisto, 1980). Galosi et al. (2001) reported that HA infusion into the nucleus accumbens can enhance extracellular dopamine levels in the nucleus

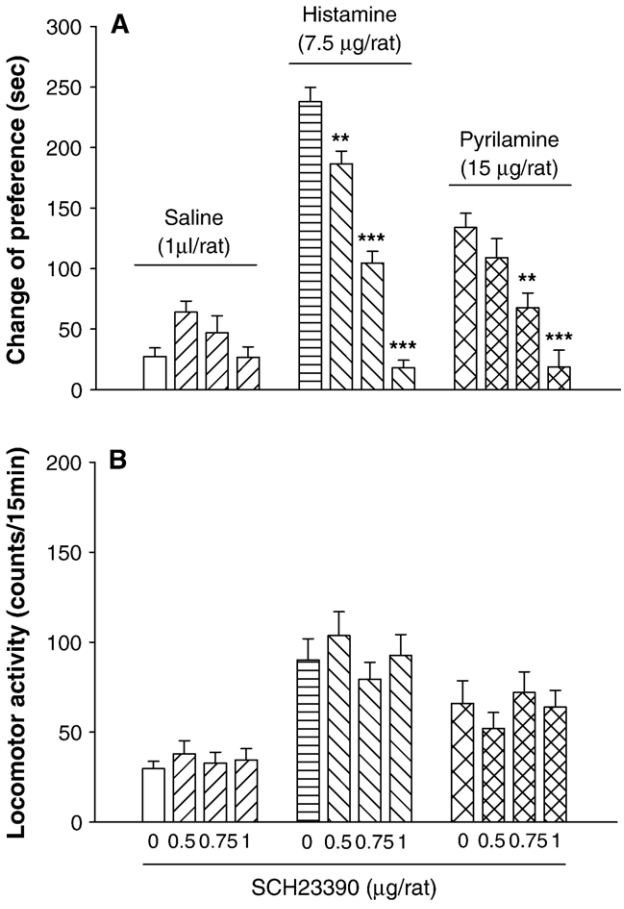

Fig. 4 – The effects of intra-medial septum injection of SCH 23390 on the histamine- or pyrilamine-induced place preference. The animals received SCH 23390 (0, 0.5, 0.75 and 1 μg/rat) immediately before the administration of saline (1 μl/rat), histamine (7.5 μg/rat) or pyrilamine (15 μg/rat), in a 3-day schedule of conditioning. On the test day, the animals were observed for a 15-min period. The change of preference was assessed as the difference between the time spent on the day of testing and the time spent on the day of the preconditioning session. Data are expressed as mean ± SEM of 8 animals per group. $^{**}P<0.01$, $^{***}P<0.001$ different from the respective control group.

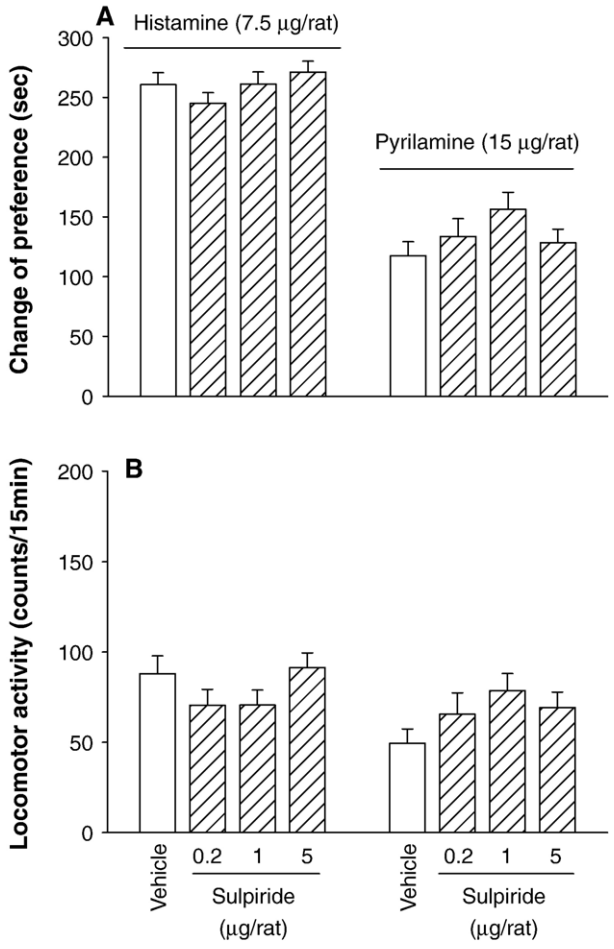

Fig. 5 – The effects of intra-medial septum injection of sulpiride on the histamine- or pyrilamine-induced place preference. The animals received vehicle (1 μl/rat) or sulpiride (0.2, 1 and 5 μg/rat) immediately before the administration of histamine (7.5 μg/rat) or pyrilamine (15 μg/rat), in a 3-day schedule of conditioning. On the test day, the animals were observed for a 15-min period. The change of preference was assessed as the difference between the time spent on the day of testing and the time spent on the day of the preconditioning session. Data are expressed as mean±SEM of 8 animals per group.

accumbens in a dose-dependent way. Thus, in the present study, it is possible that the injection of HA into the medial septum may increase the levels of extracellular DA, which would also lead to induce CPP.

The data showed that co-administration of a histamine H_1 receptor antagonist, pyrilamine with a higher dose of histamine (7.5 μg/rat, intra-medial septum) significantly decreased the histamine response. This response of the antagonist may be due to the blockade of H1 receptors, which raised the possibility that histamine H_1 receptors in the medial septum are involved in the induction of CPP. The present results show that intra-medial septum microinjection of histamine H_2 receptor antagonist ranitidine, in conditioning sessions did not induced any response and also did not alter histamine effect. Thus, involvement of the histamine H_2 receptors in the medial septum in the induction of CPP seems unlikely.

Moreover, the present results also indicate that intra-medial septum microinjection of pyrilamine by itself in conditioning sessions induced place preference and also increased the locomotor activity. These findings support previous studies and demonstrated that the rewarding effects of histamine H_1 receptor antagonists can be conditioned to environmental stimuli, which have previously signaled their administration (Suzuki et al., 1999; Zimmermann et al., 1999). One may suggest that pyrilamine blocks presynaptic histamine receptors and thus its response could be due to histamine release. Since, the antagonist also blocks postsynaptic histamine receptors and postsynaptic H_2 receptors also are not involved in the histamine effect as predicted by ranitidine administration, this hypothesis seems unlikely. However, combined treatment with subeffective doses of histamine and pyrilamine may induce CPP, which needs further experiments.

Considering that several H_1 receptor antagonists inhibit the neuronal uptake of dopamine in synaptosomes (Symchowicz et al., 1971; Tuomisto and Tuomisto, 1980; Young et al., 1988), the place preference produced by the antagonist may be mediated by the activation of the dopaminergic system followed by the inhibition of dopamine uptake (Suzuki et al., 1999). In support of this hypothesis, locomotion which is a dopamine-related behavior also was increased. Furthermore, CPP is a learning paradigm and it may be possible that co-administration of pyrilamine and histamine decreases learning. In support of this hypothesis, there are reports that histamine improves inhibitory and active avoidance conditioning (De Almeida and Izquierdo, 1988; Kamei et al., 1993b), whereas administration of the H_1 receptor antagonists disrupted learning in an active avoidance task (Kamei and Tasaka, 1991; Kamei et al., 1990). Finally, the contradictory responses of pyrilamine remain unclear which needs extensive experiments.

Since, the present data showed that both the injection of histamine and pyrilamine into the medial septum induces CPP and it may be possible that these responses are due to dopaminergic activity. It is also interesting to note that biochemical and behavioral evidence from rodent studies suggests an important role of histaminergic mechanisms in the modulation of dopamine activity in the central nervous system (Boix et al., 1995; De Souza-Silva et al., 1997; Schlicker et al., 1993; Hans et al., 1995) specially in both the mesolimbic and mesostriatal systems (Hans et al., 1995). Therefore, in the present study, the involvement of dopamine D1 or D2 receptor mechanisms on the place preference-induced by histamine or pyrilamine has been studied. Place preferences induced by intra-medial septum injections of histamine or pyrilamine were inhibited by pretreatment with D1 receptor antagonist SCH 233390, but not by D2 receptor antagonist sulpiride, suggesting that place preferences induced by the histaminergic agents may be also mediated by dopamine D1 receptors. Moreover, the data indicated that neither SCH 23390 nor sulpiride in combination with histamine or pyrilamine induced any change on the locomotor activity.

In conclusion, the stimulation of histamine H1 receptors of the medial septum may produce the rewarding effects, which may be mediated through increase in dopaminergic activity. Furthermore, the inhibition of histamine H1 receptors by pyrilamine produced CPP, which was completely inhibited by pretreatment with SCH 23390, which may be due to the activation of dopamine D1 receptors.

4. Experimental procedures

4.1. *Animals*

Male Wistar rats (Pasteur Institute, Tehran, Iran) weighing 210–250 g at the time of the surgery were used. The animals were housed four per cage, in a colony room with a 12/12-h light/dark cycle (7:00–19:00 h lights on) at 22±2 °C. They had free access to food and tap water except during the time of experiments. All animals were allowed to adapt to the laboratory conditions for at least 1 week before surgery and were handled for 5 min/day during this adaptation period. Each animal was used once only. Eight animals were used in each group of experiments. The experiments were carried out during the light phase of the cycle. All procedures were carried out in accordance with institutional guidelines for animal care and use.

4.2. *Surgical and infusion procedures*

The animals were anesthetized with intraperitoneal injection of ketamine hydrochloride (50 mg/kg) plus xylazine (4 mg/kg) and placed in a stereotaxic apparatus, while maintaining the incisor bar at approximately 3.3 mm below horizontal zero to achieve a flat skull position. A mid-saggital incision was made to expose the rat skull. In accordance with previous studies (Rassnick and Kornetsky, 1991) a stainless steel 22-guage cannula was aimed toward the medial septum. The stereotaxic coordinates, according to the atlas of Paxinos and Watson (1987), were 1.2 mm anterior to bregma, 0.1 mm medial lateral and 5.5 mm (1 mm above the site of injection) ventral from dura. The guide cannula was anchored by a jeweler's screw, and the incision was closed with dental cement. After completing the surgery, a dummy inner cannula was inserted into the guide cannula, and left in place until injections were made. The length of dummy cannula matched that of the guide cannula. All animals were allowed to recover for 1 week before behavioral testing began.

4.3. *Injection into the medial septum*

The animals were gently restrained by hand; the dummy cannula was removed from the guide cannula. For intra-medial septum injections of drugs, a 1.0-μl glass Hamilton syringe was used. The injection (inner) cannula (27 gauge), projected a further 1 mm ventral to the tip of the guide, and was attached with polyethylene tubing (0.6 mm internal diameter) to the Hamilton syringe. The injection volume was 1.0 μl for all groups. Injections were made over a 60 s period, and the injection cannula was retained in the guide cannula for an additional 60 s to facilitate the diffusion of the drugs. During the infusion procedure, the experimenter loosely held the animals.

4.4. *Apparatus*

The apparatus is based on that used by Carr and White (1983) with a minor modification and consisted of three wooden compartments. Two of the compartments (A and B) were identical in size (40 cm×30 cm×30 cm) but differed in shading and texture. Compartment A was white with black horizontal stripes 2 cm wide on the walls and also had a textured floor. The other compartment (B) was black with vertical white stripes 2 cm wide and also had a smooth floor. The third compartment (C) was a red tunnel (40 cm×15 cm×30 cm). It protruded from the rear of the two large compartments and connected the entrances to them.

4.5. *Behavioral testing*

4.5.1. *Place conditioning*

Conditioning place preference (CPP) was conducted using an unbiased procedure according to the method of De Fonseca et al. (1995). It consisted of a 5-day schedule with three distinct phases: preconditioning, conditioning and testing.

4.5.1.1. Preconditioning. The animals were placed in the middle of the apparatus, and they were allowed to freely explore the three compartments for the next 15 min. The time spent by the animals in each compartment was recorded. The amount of time spent in each compartment was measured to assess unconditioned preference (the position of the rat was defined by the position of its front paws). In the particular experimental setup used in this study, the animals did not show an unconditioned preference for either of the compartments. Animals were then randomly assigned to one of two groups for place conditioning and a total of eight animals were used for each subsequent experiments.

4.5.1.2. Conditioning. Place conditioning phase started 1 day after the preconditioning phase. This phase consisted of six, 45 min sessions (three saline and three drug pairing). These sessions were conducted twice each day (from day 2 to 4) with a 6 h interval. On each of these days, animals received one conditioning session with drug and one with saline. During these sessions, the animals were confined to one compartment by closing the removable wall. Animals of each group were injected with drug and were immediately confined to one compartment of the apparatus for 45 min. Six hours later, animals were administered saline and confined to the other compartment for 45 min.

Treatment compartment and the order of administration of drug and saline were counterbalanced for each group.

4.5.1.3. Testing. The testing phase was carried out on day 5, 1 day after the last conditioning session. Each animal was tested once only. For testing, the removable wall was raised, and the animals had a free choice in the apparatus for 15 min. The time spent in drug-paired compartment was recorded for each animal and the change of preference was calculated as

the difference (in seconds) between the time spent in the drug-paired compartment on the testing day, and the time spent in this compartment in the preconditioning day. The position of the animal was defined by the position of its forelimbs and head.

4.5.2. *Locomotor testing*

Locomotor activity was measured, based on a method previously used during the testing phase (Belzung and Barreau, 2000; Zarrindast et al., 2002), in a morphine free state. Locomotor testing was carried out on the fifth day of the schedule for rats that received place conditioning, using the CPP apparatus. To measure the locomotor activity, the ground area of the CPP compartments was divided into four equal sized squares. Locomotion was measured as the number of crossings from one square to another during 15 min.

4.6. *Drugs*

The drugs used in the present study were histamine dihydrochloride, the histamine H_1 receptor antagonist pyrilamine maleate, the histamine H_2 receptor antagonist ranitidine hydrochloride (Kimidaru, Iran), the dopamine D_1 receptor antagonist SCH 23390 (R(1)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride), and the dopamine D_2 receptor antagonist sulpiride (Sigma, Poole, UK). All drugs were dissolved in sterile 0.9% saline just before the experiment, except for sulpiride that dissolved in one drop of glacial acetic acid and made up to a volume of 5 ml with sterile 0.9% saline and then diluted to the required concentration. The control animals received either saline or vehicle.

4.7. *Drug treatments*

4.7.1. *Experiment 1. Effect of histamine on the acquisition of CPP*

In this experiment, we established a dose–response function for histamine place conditioning. Six groups of animals were injected with histamine (0.5, 2.5, 5, 7.5, 10 and 15 μg/rat, intra-medial septum) and saline (1 μl/rat, intra-medial septum) on alternate sessions. A separate group of animals was given saline (1 μl/rat, intra-medial septum) only during the conditioning phase in order to confirm that the injections and the conditioning were not affecting the time allotment in the apparatus. This group was used as control. Locomotor activity was also measured in the testing phase.

4.7.2. *Experiment 2. Effect of pyrilamine with or without histamine on the acquisition of CPP*

4.7.2.1. Effect of pyrilamine on the acquisition of CPP. Three doses of the histamine H_1 receptor antagonist, pyrilamine (5, 10 and 15 μg/rat, intra-medial septum) were given to three groups during the conditioning phase. One additional group received saline (1 μl/rat, intra-medial septum) during the conditioning phase and served as a control. All groups were tested 24 h after the conditioning sessions, with no preceding injection. Locomotor activity was also measured in the testing phase.

4.7.2.2. Effect of pyrilamine on the acquisition of histamine-induced place preference. Four groups of animals received saline (1 μl/rat, intra-medial septum) or pyrilamine (5, 10 and 15 μg/rat, intra-medial septum), immediately before the administration of histamine (7.5 μg/rat), during the conditioning sessions. The animals were tested 24 h after the last conditioning session, with no preceding injection. Locomotor activity was also measured during testing.

4.7.3. *Experiment 3. Effect of ranitidine with or without histamine on the acquisition of CPP*

4.7.3.1. Effect of ranitidine on the acquisition of CPP. Three doses of the histamine H_2 receptor antagonist, ranitidine (5, 10 and 15 μg/rat, intra-medial septum) were given to three groups during the conditioning phase. One additional group received saline (1 μl/rat, intra-medial septum) during the conditioning phase and served as a control. All groups were tested 24 h after the conditioning sessions, with no preceding injection. Locomotor activity was also measured in the testing phase.

4.7.3.2. Effect of ranitidine on the acquisition of histamine-induced place preference. Four groups of animals received saline (1 μl/rat, intra-medial septum) or ranitidine (5, 10 and 15 μg/rat, intra-medial septum), immediately before the administration of histamine (7.5 μg/rat), during the conditioning sessions. The animals were tested 24 h after the last conditioning session, with no preceding injection. Locomotor activity was also measured during testing.

4.7.4. *Experiment 4. Effects of SCH 23390 on histamine- or pyrilamine-induced place preference*

Animals received SCH 23390 (0, 0.5, 0.75 and 1 μg/rat, intra-medial septum), immediately before the administration of saline (1 μl/rat), histamine (7.5 μg/rat) or pyrilamine (15 saline μg/rat), during the conditioning sessions. The animals were tested 24 h after the last conditioning session, with no preceding injection. Locomotor activity was also measured during testing.

4.7.5. *Experiment 5. Effects of sulpiride on histamine- or pyrilamine-induced place preference*

Animals received vehicle (1 μl/rat, intra-medial septum) or sulpiride (0.2, 1 and 5 μg/rat, intra-medial septum), immediately before the administration of histamine (7.5 μg/rat) or pyrilamine (15 μg/rat), during the conditioning sessions. The animals were tested 24 h after the last conditioning session, with no preceding injection. Locomotor activity was also measured during testing.

4.8. *Histological verification*

After completion of the experimental sessions, each animal was killed with an overdose of chloroform. Subsequently, 1.0 μl of ink (in accordance with previous studies (Ragozzino and Gold, 1995) was injected into the medial septum by a 27-gauge injection cannula, which projected a further 1 mm ventral to the tip of the guide to aid in histological verification. The brains were removed and perfused with a 10% formalin

solution 10 days before sectioning. Sections were examined to determine location of the cannulae aimed for the medial septum. The cannula placements were verified using the atlas of Paxinos and Watson (1987). Data from rats with cannula placements outside the medial septum were excluded from the analyses.

4.9. *Statistical analysis*

In all experiments, the conditioning scores are expressed as differences in the time spent on the drug-associated side between the preconditioning and the testing phases. Locomotor activities are expressed as crossing of lines in both of the main compartments during the testing phase. Data are expressed as mean ± SEM ($n=8$). Analysis of data was performed using one-way or two-way ANOVA. Following a significant F value, post hoc analyses (Tukey's test) were performed for assessing specific group comparisons. The level of statistical significance was set at $P<0.05$.

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