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Influence of different histamine receptor agonists and antagonists on apomorphine-induced licking behavior in rat

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Abstract

The effects of different histamine receptor agonists and antagonists on apomorphine-induced licking behavior in rats were investigated. Subcutaneous (s.c.) injection of various doses of apomorphine (0.125–1.25 mg/kg) induced licking. The licking response was counted by direct observation and recorded for a 75-min period. Intracerebroventricular (i.c.v.) or intraperitoneal (i.p.) injection of the histamine H_1 or H_2 receptor agonist, HTMT (6-[2-(4-imidazolyl)ethylamino]-*N*-(4-trifluoromethylphenyl) heptanecarboxamide) (50 and 100 μg per rat), or dimaprit (10 and 15 mg/kg, i.p.), respectively, potentiated apomorphine-induced licking, while the histamine H_3 receptor agonist, imetit (5 and 10 mg/kg, i.p.), reduced the licking response induced by apomorphine. Pretreatment with various histamine receptor antagonists, dexchlorpheniramine (30 and 40 mg/kg, i.p.), diphenhydramine (20, 30 and 40 mg/kg, i.p.), famotidine (30 and 40 mg/kg, s.c.) and ranitidine (20, 30 and 40 mg/kg), reduced apomorphine-induced licking, while thioperamide (5 and 10 mg/kg, i.p.) potentiated the apomorphine effect. The effects of HTMT and dimaprit were blocked by dexchlorpheniramine (20 mg/kg, i.p.) and famotidine (20 mg/kg, s.c.), respectively. The inhibitory effect elicited by imetit on apomorphine-induced licking behavior was also abolished in animals treated with thioperamide (2.5 mg/kg, i.p.). The results suggest that histaminergic mechanisms may be involved in the modulation of apomorphine-induced licking behavior.

Keywords: Histamine; Apomorphine; Licking behavior; (Rat)

1. Introduction

Repetitive licking behavior is a stereotyped phenomenon that is correlated with activation of the nigrostriatal system, and is thought to be produced by activation of both postsynaptic dopamine D_1 and D_2 receptors (Costall and Naylor, 1972; Ungerstedt, 1979; Kelly et al., 1975; Zarrindast et al., 1992). In the rat nigrostriatal system, histamine is a modulator of γ-aminobutyric acid (GABA)/dopamine function (Garcia et al., 1997). Stimulation of the histamine H_3 receptor at the terminals of the striatonigral GABA projection neurons inhibits dopamine D_1 receptor-mediated GABA release in substantia nigra pars reticulata slices. It has been reported that unilateral lesioning of nigrostriatal neurons in rat with 6-hydroxydopamine produces an increase in ipsilateral histamine H_3 receptor density in both substantia nigra and striatum, which can be reduced by treatment with the dopamine D_1 receptor agonist, SKF 38393 (1-phenyl-2,3,4,5-tetrahydro-(1*H*)-3-benzazepine-7,8-diol) (Ryu et al., 1994, 1996). There is also good evidence that histamine and histaminic agents change the levels of dopamine and dopamine metabolites in the cortex, nucleus accumbens and striatum via histamine H_1, H_2 and H_3 receptors (Subramanian and Mulder, 1977; Onodera et al., 1992; Fleckenstein et al., 1993; Schlicker et al., 1993; Suzuki et al., 1995) and that, conversely, direct- or indirect-acting dopaminergic agents modulate histamine release in various brain regions such as striatum and hypothalamus (Prast et al., 1993; Ito et al., 1996). These findings suggest that the histaminergic mechanisms may be closely related to the dopaminergic systems, and play an important modulatory role in various behaviors induced by dopaminergic agents. This hypothesis is supported by several findings showing that different histamine receptor agonists or antagonists inhibit or poten-

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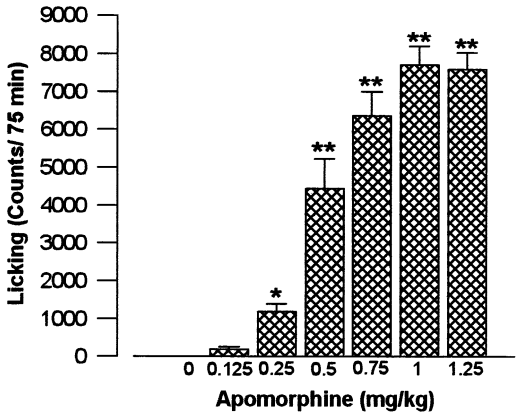

Fig. 1. Licking behavior induced by s.c. injection of different doses of apomorphine (0.125–1.25 mg/kg). Licking response was recorded for a 75-min period. Results are expressed as means + standard error of the mean (S.E.M.) ($n = 7–9$ rats/group). $^{*}P < 0.05$, $^{**}P < 0.001$, different from control group.

tiate methamphetamine- or apomorphine-induced effects: reinforcing, locomotion and climbing behavior in mice (Joshi et al., 1981; Itoh et al., 1984; Masukawa et al., 1993; Clapham and Kilpatrick, 1994; Suzuki et al., 1995). In order to clarify the possible role of the histaminergic mechanism(s) in the modulation of licking behavior, the effects of several histamine receptor agonists and antagonists were studied on the licking behavior induced by the mixed dopamine D_1/D_2 receptor agonist, apomorphine in the rat.

2. Materials and methods

2.1. Animals

All experiments were carried out on male Sprague–Dawley rats from the Pasteur Institute (Iran), 200–250 g body weight. The animals were housed five per plastic cage in an animal room maintained at 21 ± 2°C on a 12-h light/dark cycle (lights on 0700–1900 h). Standard laboratory rat chow (Pars, Iran) and water were available at all times except during the experiments. Each animal was used once only.

2.2. Licking measurement

The rats were placed individually in a glass cylinder (25 cm wide, 25 cm high) and a mirror was arranged in an oblique position under the cylinder to make recording of licking possible. The animals were allowed 30 min to accommodate prior to testing. Immediately after apomorphine administration, the animals were put into the cylinder and the number of licks (protrusion of the tongue against the cylinder wall or floor) was recorded with a hand counter during a 75-min period (Zarrindast et al., 1992).

2.3. Intracerebroventricular (i.c.v.) injection

The i.c.v. injection was performed during short ether anaesthesia, according to the method of Haley and McCormick (1957) with a constant volume of 10 μl. To ascertain the exact point into which drugs were administered, some rats were deeply anesthetized and injected i.c.v. with 10 μl of diluted 1:10 Indian ink and their brains were examined macroscopically after sectioning.

2.4. Drugs

The following drugs were used: *R*(−)-apomorphine HCl (Research Biochemicals, USA), *S*(+)-dexchlorpheniramine maleate (Research Biochemicals), dimaprit dihydrochloride (ICN Biomedicals, UK), diphenhydramine hydrochloride (Research Biochemical), famotidine (Sigma, UK), HTMT dimaleate ((6-[2-(4-imidazolyl)ethylamino]-*N*-(4-trifluoromethylphenyl) heptanecarboxamide), Tocris, UK), imetit dihydrobromide (ICN Biomedicals), ranitidine hydrochloride (Sigma) and thioperamide maleate (ICN Biomedicals). In all cases, the drug doses reported

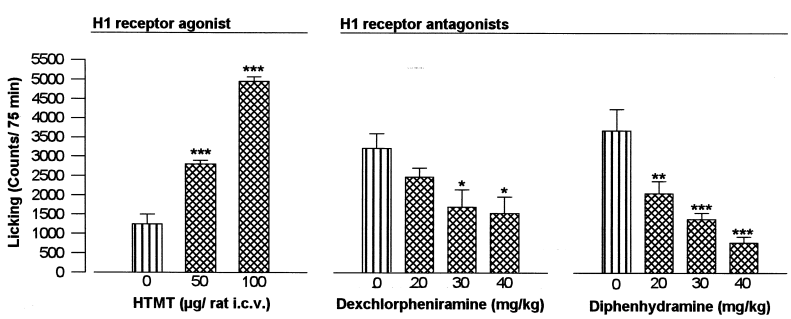

Fig. 2. Effects of HTMT, dexchlorpheniramine and diphenhydramine on apomorphine-induced licking behavior in rats. Animals were injected with HTMT (50 and 100 μg per rat, i.c.v., 20 min before apomorphine), dexchlorpheniramine (20–40 mg/kg, i.p., 30 min before apomorphine), diphenhydramine (20–40 mg/kg, i.p., 30 min before apomorphine) and vehicle (10 μl per rat, i.c.v., 20 min before apomorphine) or saline (1 ml/kg, i.p., 30 min before apomorphine). Results are expressed as means + S.E.M. ($n = 7–9$ rats/group). $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, different from control groups.

Table 1
Effect of dexchlorpheniramine (DEX) alone or in combination with HTMT on apomorphine-induced licking behavior

Treatment (μg, i.c.v. + mg/kg, i.p.)	*n*	Licking (counts/75 min)
Vehicle + saline	7	1310 ± 265
Vehicle + DEX 20	7	1665 ± 238
HTMT 50 + saline	7	2886 ± 112[a]
HTMT 50 + DEX 20	7	1823 ± 125[b]

Animals were injected with either vehicle (10 μl per rat, i.c.v.) in combination with saline (1 ml/kg, i.p.) and dexchlorpheniramine (20 mg/kg, i.p.) or HTMT (50 μg per rat, i.c.v.) in combination with saline and dexchlorpheniramine. HTMT was administered 20 min, dexchlorpheniramine 30 min, vehicle 20 min and saline 30 min before apomorphine (0.5 mg/kg, s.c.) injection. Results are expressed as means ± S.E.M.
[a] $P < 0.001$, different from vehicle/saline group.
[b] $P < 0.001$, different from HTMT/saline group.

are for the base. The drugs were dissolved in saline, except for famotidine, which was dissolved in a drop of acetic acid and HTMT, which was dissolved in a drop of ethanol and then diluted with saline. The vehicle control was acetic acid or ethanol in saline. Drug concentrations were prepared so that the necessary dose could be injected in a volume of 1 ml/kg intraperitoneal (i.p.) or subcutaneous (s.c.). Owing to the reportedly poor ability of trifluoromethyl-phenyl or -toluidide derivatives of histamine to cross the blood–brain barrier (Qiu et al., 1990; Malmberg-Aiello et al., 1998), the i.c.v. route of administration was used for the histamine H_1 receptor agonist, HTMT (Khan et al., 1986; Qiu et al., 1990). For HTMT, the doses were chosen, on a molar basis, as those at which histamine 2HCl exerts its pharmacologic actions on target cells in central nervous system tissue (Chung et al., 1984; Oluyomi and Hart, 1991; Malmberg-Aiello et al., 1994). The doses of other drugs, pretreatment time and route of administration were usually those used previously and shown to be pharmacologically active (Chung et al., 1984; Netti et al., 1984; Rumore and Schlichting, 1985; Oluyomi and Hart, 1991; Malmberg-Aiello et al., 1994; Lamberti et al., 1996; Farzin, 1999).

2.5. Statistical analysis

One-way analysis of variance (ANOVA) followed by the Newman–Keuls multiple comparisons test was used for statistical analysis. Differences with $P < 0.05$ between experimental groups at each point were considered statistically significant. All data were analyzed with the computer program, GRAPHPAD software (V2.01$^+$).

3. Results

3.1. Licking behavior induced by apomorphine

Subcutaneous injection of various doses of apomorphine (0.125, 0.25, 0.5, 0.75, 1 and 1.25 mg/kg) to rats induced dose-dependent licking behavior [$F(6,44) = 59.082$, $P < 0.0001$] (Fig. 1). The maximum response was obtained with 1 mg/kg of the drug. The dose of 0.5 mg/kg of apomorphine was chosen for the induction of licking behavior in subsequent experiments because the ED_{50} value equalled 0.545 mg/kg (obtained by regression analysis).

3.2. Effects of HTMT, dexchlorpheniramine and diphenhydramine on apomorphine-induced licking behavior

In Fig. 2, it can be seen that pretreatment of the animals with HTMT (50 and 100 μg per rat, i.c.v., 20 min before apomorphine) increased apomorphine-induced licking behavior [$F(2,15) = 112.52$, $P < 0.0001$]. However, when the histamine H_1 receptor antagonists, dexchlorpheniramine (20, 30 and 40 mg/kg, i.p.) [$F(3,26) = 3.649$, $P < 0.0255$] and diphenhydramine (20, 30 and 40 mg/kg, i.p.) [$F(3,26) = 11.575$, $P < 0.0001$], were administered 30 min before apomorphine (0.5 mg/kg, s.c.), they dose-relatedly decreased licking behavior (Fig. 2). The effect of HTMT on apomorphine-induced licking behavior was antagonized in animals treated with dexchlorpheniramine (20 mg/kg, i.p., a dose ineffective on licking behavior)

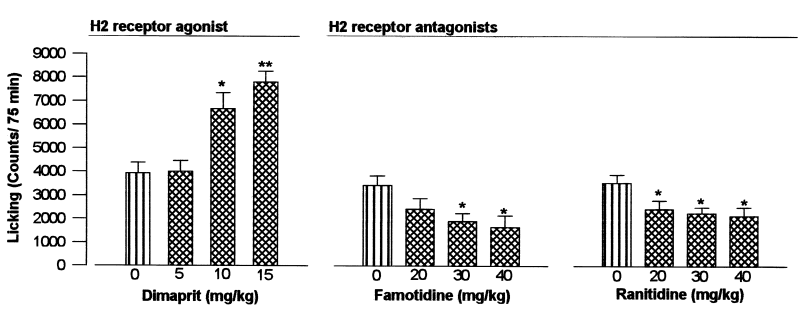

Fig. 3. Effects of dimaprit, famotidine and ranitidine on apomorphine-induced licking behavior in rats. Animals were injected with dimaprit (5–15 mg/kg, i.p.), famotidine (20–40 mg/kg, s.c.), ranitidine (20–40 mg/kg, i.p.), saline (1 ml/kg, i.p.) and vehicle (1 ml/kg, s.c.), 30 min before apomorphine (0.5 mg/kg, s.c.) injection. Results are expressed as means + S.E.M. ($n = 7$–9 rats/group). $^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, different from control groups.

Table 2
Effect of famotidine (FAM) alone or in combination with dimaprit (DIM) on apomorphine-induced licking behavior

Treatment (mg/kg)	*n*	Licking (counts/75 min)
Vehicle + saline	9	3242 ± 665
Vehicle + DIM 10	7	7342 ± 492[a]
FAM 20 + saline	7	2420 ± 470
FAM 20 + DIM 10	7	3475 ± 576[b]

Animals were injected with either vehicle (1 ml/kg, s.c.) in combination with saline (1 ml/kg, i.p.) and dimaprit (10 mg/kg, i.p.) or famotidine (20 mg/kg, s.c.) in combination with saline and dimaprit, 30 min before apomorphine (0.5 mg/kg, s.c.) injection. Results are expressed as means ± S.E.M.
[a] $P < 0.001$, different from vehicle/saline group.
[b] $P < 0.001$, different from dimaprit/vehicle group.

$[F(3,24) = 11.865,\ P < 0.0001]$ (Table 1). In the absence of apomorphine, treatment of rats with HTMT itself did not have any significant effect on the induction of licking behavior (data not shown).

3.3. Effects of dimaprit, famotidine and ranitidine on apomorphine-induced licking behavior

Dimaprit (5, 10 and 15 mg/kg, i.p.) 30 min prior to apomorphine (0.5 mg/kg, s.c.) dose-dependently increased apomorphine-induced licking behavior $[F(3,26) = 14.084,\ P < 0.0001]$ (Fig. 3). When either famotidine (20, 30 and 40 mg/kg, s.c.) $[F(3,26) = 3.635,\ P < 0.0259]$ or ranitidine (20, 30 and 40 mg/kg, i.p.) $[F(3,26) = 4.001,\ P < 0.0181]$ was administered 30 min before apomorphine (0.5 mg/kg, s.c.), licking behavior was significantly decreased (Fig. 3). The effect of dimaprit (10 mg/kg, i.p.) on apomorphine-induced licking was antagonized in animals treated with famotidine (20 mg/kg, s.c., a dose ineffective on licking behavior) $[F(3,26) = 13.647,\ P < 0.0001]$ (Table 2). In the absence of apomorphine, treatment of animals with dimaprit alone did not have any significant effect on the induction of licking behavior (data not shown).

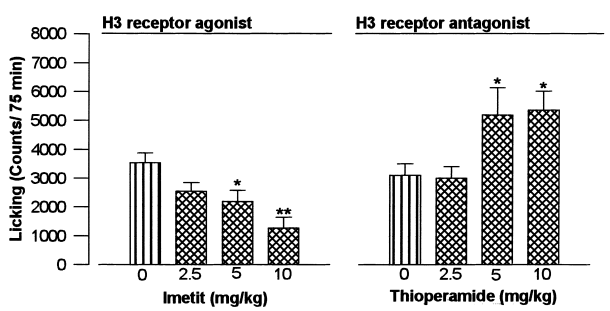

Fig. 4. Effects of imetit and thioperamide on apomorphine-induced licking behavior in rats. Animals were treated i.p. with saline (1 ml/kg), imetit (2.5–10 mg/kg) and thioperamide (2.5–10 mg/kg) 30 min before apomorphine (0.5 mg/kg, s.c.) injection. Results are expressed as means + S.E.M. ($n = 7$–9 rats/group). $^{*}P < 0.05$, $^{**}P < 0.001$, different from control groups.

Table 3
Effect of thioperamide (THI) alone or in combination with imetit (IME) on apomorphine-induced licking behavior

Treatment (mg/kg)	*n*	Licking (counts/75 min)
Saline + saline	9	3545 ± 342
Saline + IME 5	7	1892 ± 389[a]
THI 2.5 + saline	7	2960 ± 395
THI 2.5 + IME 5	7	3475 ± 576[b]

Animals were injected with either saline (1 ml/kg, i.p.) in combination with saline, imetit (5 mg/kg, i.p.) and thioperamide (2.5 mg/kg, i.p.) or thioperamide in combination with imetit, 30 min before apomorphine (0.5 mg/kg, s.c.) injection. Results are expressed as means ± S.E.M.
[a] $P < 0.05$, different from saline/saline group.
[b] $P < 0.05$, different from imetit/saline group.

3.4. Effects of imetit and thioperamide on apomorphine-induced licking behavior

Pretreatment of animals with various doses of imetit (2.5, 5 and 10 mg/kg, i.p., 30 min before apomorphine) $[F(3,26) = 7.385,\ P < 0.001]$ decreased apomorphine-induced licking behavior. However, thioperamide (2.5, 5 and 10 mg/kg, i.p., 30 min before apomorphine) $[F(3,26) = 4.150,\ P < 0.0158]$ increased the licking response induced by apomorphine (Fig. 4). The effect of imetit (5 mg/kg, i.p.) on apomorphine-induced licking behavior was antagonized in animals treated with thioperamide (2.5 mg/kg, i.p., a dose ineffective on licking behavior) $[F(3,26) = 3.160,\ P < 0.0415]$ (Table 3). In the absence of apomorphine, treatment of animals with thioperamide alone did not have any significant effect on the induction of licking behavior (data not shown).

4. Discussion

The present results suggest an involvement of the histaminergic system in the modulation of apomorphine-induced licking behavior. Licking behavior induced by apomorphine was significantly decreased by i.p. administration of the histamine H_1 receptor antagonists, dexchlorpheniramine and diphenhydramine. Most of the work so far published regarding the interactions between the histamine H_1 receptor mechanism(s) and dopaminergic transmission, has been based mainly on the use of histamine H_1 receptor antagonists. For example, striatal dopamine has been reported to increase after peripheral administration of histamine H_1 receptor antagonists (Privou et al., 1998). Interactions between blockade of histamine H_1 receptors and dopaminergic system(s) were also observed in relation to stereotyped behaviors induced by both directly or indirectly acting dopamine agonists. Pretreatment of rats with a histamine H_1 receptor antagonist, promethazine, decreases or increases the intensity of apomorphine- or amantadine-induced stereotyped behaviors, respectively (Balsara et al., 1983). Several studies have also shown that

the histamine H_1 receptor antagonists, dexchlorpheniramine or chlorpyramine, decrease yawning or grooming behavior induced by either apomorphine (Gower et al., 1986) or a dopamine D_1 receptor agonist, SKF 38393 (Skuza et al., 1989), respectively. Therefore, to verify whether the effects of dexchlorpheniramine and diphenhydramine on apomorphine-induced licking behavior are actually due to blockade of histamine H_1 receptors, and not to any other non-specific effects, we investigated the effect of HTMT on apomorphine-induced licking behavior. The present data indicate that the doses of 50 and 100 μg per rat, i.c.v. of the histamine H_1 receptor agonist, HTMT, which did not themselves induce licking behavior, significantly increased the apomorphine-induced licking behavior. Since dexchlorpheniramine (20 mg/kg, i.p.) significantly antagonized the action of HTMT, it may be that histamine H_1 receptor mechanisms are involved in the modulation of apomorphine-induced licking behavior.

The present data also show that the i.p. injection of the doses of 10 and 15 mg/kg of the histamine H_2 receptor agonist, dimaprit (Durant et al., 1977), which did not themselves induce any licking behavior, significantly potentiated the licking response induced by apomorphine. Although dimaprit is thought to be a selective histamine H_2 receptor agonist, it binds to histamine H_3 receptors in the brain and antagonizes histamine H_3 receptor activation (Arrang et al., 1983). Since our results demonstrate that the histamine H_3 receptor antagonist, thioperamide (Hew et al., 1990), potentiates the apomorphine effect, it may be that dimaprit increases apomorphine-induced licking behavior by such a mechanism. The present data also show that both famotidine (30 and 40 mg/kg, s.c.) and ranitidine (20, 30 and 40 mg/kg, i.p.) decreased the apomorphine-induced licking behavior. Interactions between the blockade of histamine H_2 receptors and the dopaminergic system were observed in relation to the induction of rewarding effects (Suzuki et al., 1995). Suzuki et al. (1995) reported that the i.p. injection of zolantidine dose-dependently produced place-preference, which could be abolished by a dopamine D_1 receptor antagonist, suggesting that zolantidine may exert its rewarding effects through the dopaminergic system. Ferrari and Baggio (1985) also reported that the histamine H_2 receptor antagonist, cimetidine, when injected i.p. 15 min before (±)-*N*-*n*-propylnorapomorphine, antagonized dose-dependently the penile erection, stretching and yawning induced by this dopamine receptor agonist in male rats. The results of the above studies suggest that the histamine H_2 receptor mechanisms in various brain regions may play a modulatory role in the licking response induced by apomorphine. This hypothesis is supported by our data showing that the effect elicited by dimaprit on the licking response induced by apomorphine was antagonized in animals treated with famotidine (20 mg/kg, s.c.).

The results of the present study indicate that the selective histamine H_3 receptor agonist, imetit (Garbarg et al., 1992), significantly decreased apomorphine-induced licking behavior. Conversely, the doses of 5 and 10 mg/kg, i.p. of the histamine H_3 receptor antagonist, thioperamide, which did not induce any licking behavior, significantly potentiated the licking response induced by apomorphine. Since thioperamide (2.5 mg/kg, i.p.) significantly antagonized the suppressive action exerted by imetit, it may be that histamine H_3 receptor mechanisms are involved in the modulation of the licking response induced by apomorphine. In autoradiographic studies, histamine H_3 receptors were found to be most dense in telencephalic areas including regions with dopaminergic innervation such as the striatum and substantia nigra (Arrang et al., 1987). Dopamine transmission in these areas is known to be involved in the control of stereotyped behaviors (Costall and Naylor, 1972; Ungerstedt, 1979; Kelly et al., 1975). Ryu et al., (1994, 1996) reported that the histamine H_3 receptors in the striatum and substantia nigra are influenced by tonic dopaminergic inputs, and that denervation of dopaminergic neurons in these regions with 6-hydroxydopamine increases the levels of histamine H_3 receptors, an effect which can be reduced by treatment with the dopamine D_1 receptor agonist, SKF 38393. Ito et al. (1996) also reported that the administration of methamphetamine increases striatal histamine release under the control of dopamine D_2 receptors, which may play an important modulatory role in the methamphetamine-induced stereotyped behavior. It could, therefore, be expected that apomorphine would increase histamine release in striatum. There is a report showing that apomorphine enhances the release of histamine, at least in the hypothalamus (Prast et al., 1993). Histamine levels in the several brain regions are also increased by peripheral administration of the selective histamine H_3 receptor antagonist, thioperamide, but reduced by the selective histamine H_3 receptor agonist, (*R*)-α-methylhistamine, also given peripherally (Arrang et al., 1987). Since histamine inhibits dopamine release in the striatum via presynaptic histamine H_3 receptors (Schlicker et al., 1993), it may account for the ability of imetit or thioperamide to modulate the licking response, acting as histamine H_3 receptor agonist or antagonist, respectively.

In conclusion, we have shown that all three classes of histamine receptors (H_1, H_2 and H_3) may be important in the modulation of apomorphine-induced licking behavior. Further study is required before the precise mechanism of these actions can be identified.

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