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Effects of Putative Dopamine D_3 Receptor Agonists, 7-OH-DPAT, and Quinpirole, on Yawning, Stereotypy, and Body Temperature in Rats

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KURASHIMA, M., K. YAMADA, M. NAGASHIMA, K. SHIRAKAWA AND T. FURUKAWA. *Effects of putative dopamine D_3 receptor agonists, 7-OH-DPAT, and quinpirole, on yawning, stereotypy, and body temperature in rats.* PHARMACOL BIOCHEM BEHAV 52(3) 503–508, 1995.—7-OH-DPAT ((±)-2-(dipropylamino)-7-hydroxy-1,2,3,4-tetrahydronaphthalene) was recently identified as a dopamine receptor agonist having a >100-, 1,000- and >10,000-fold higher affinity for dopamine D_3 than for D_2, D_4 and D_1 receptors, respectively. Quinpirole (LY 171555) has also been reported to have a 113-fold greater affinity for dopamine D_3 receptors than for D_2 receptors. Therefore, we investigated the effects of these putative dopamine D_3 receptor agonists on yawning, stereotypy and rectal temperature in rats (N = 424). 7-OH-DPAT and quinpirole administered subcutaneously (SC) at respective low doses of 10–250 μg/kg and 25–500 μg/kg elicited yawning behavior. The yawning induced by these agents was blocked by spiperone (0.5 mg/kg, SC) and scopolamine (0.5 mg/kg, SC) but was increased by intraperitoneal (IP) administration of pindolol (20 mg/kg). The yawning was also potentiated after treatment with reserpine. 7-OH-DPAT and quinpirole at respective high doses of 0.25 mg/kg (SC) and 0.5 mg/kg (SC) evoked slight stereotypy such as sniffing and licking, and this effect was enhanced by a selective dopamine D_1 receptor agonist, SK&F 38393 (1-phenyl-2,3,4,5,-tetrahydro-(1H)-3-benzazepine-7,8-diol). 7-OH-DPAT (0.5 mg/kg, SC) and quinpirole (0.5 mg/kg, SC) decreased, but SK&F 38393 (10 mg/kg, SC) increased body temperature. However, the hyperthermia induced by SK&F 38393 was interestingly enhanced by 7-OH-DPAT and quinpirole. The present results demonstrate that 7-OH-DPAT and quinpirole evoke yawning at low doses and stereotypy at high doses, and that these agents reduce body temperature but enhance the hyperthermia induced by the dopamine D_1 receptor agonist SK&F 38393.

Yawning behavior Stereotypy Body temperature Dopamine D_3 receptor agonists
Dopamine D_1 receptor agonists 7-OH-DPAT Quinpirole SK&F 38393 Rats

PREVIOUS investigations, including our experimental results, have shown that classical dopamine receptor agonists such as apomorphine and piribedil exert biphasic effects on behavior; i.e., induction of yawning and hypomotility at low doses and that of stereotypy and hypermotility at high doses (27,32,33). The yawning behavior induced by dopamine receptor agonists is blocked by conventional dopamine D_2 receptor antagonists and muscarinic receptor antagonists, without being affected by dopamine D_1 receptor antagonists (13,14,34). On the basis of such findings, the yawning has been proposed to involve dopamine D_2 receptor stimulation and consequent cholinergic activation (32–34).

It has also been reported that concurrent stimulation of both dopamine D_1 and D_2 receptors participates in induction of stereotypy (15,36). In addition, we recently showed that combined administration of a selective dopamine D_1 receptor

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agonist, SK&F 38393 (1-phenyl-2,3,4,5,-tetrahydro-(1H)-3-benzazepine-7,8-diol), and a dopamine D_2 receptor agonist, talipexole (B-HT 920), produced hyperthermia and stereotypy in rats (17,36). These previous findings suggest that there may be a functional link between dopamine D_1 and D_2 receptors, and both of these receptors thereby behave synergistically in induction of stereotypy and regulation of body temperature.

On the other hand, recent gene cloning studies have demonstrated the existence of two families of D_1-like (D_{1A}, D_{1B}/D_5) and D_2-like ($D_{2\ long/short}$, D_3, D_4) receptor sequences (23). Currently, considerable interest is focused on the dopamine D_3 receptors (24). Until recently, quinpirole was believed to be a selective dopamine D_2 receptor agonist but was demonstrated to have a 113-fold greater affinity for dopamine D_3 receptors than that for D_2 receptors following discovery of dopamine receptor subtypes (24). Recently, 7-OH-DPAT ((±)-2-(dipropylamino)-7-hydroxy-1,2,3,4-tetrahydronaphthalene) was also identified as a dopamine receptor agonist having a >100-, >1,000-, and >10,000-fold higher affinity for dopamine D_3 than for D_2, D_4 and D_1 receptors, respectively (10).

The present study was, therefore, undertaken to investigate effects of 7-OH-DPAT and quinpirole, both putative dopamine D_3 receptor agonists, on yawning, stereotypy, and body temperature.

METHOD

Animals

Experimental subjects were 424 naive male Wistar rats (Kyudo Animal Laboratory, Kumamoto, Japan) weighing 200–250 g at the time of testing. Rats were kept in an animal room with a 12L : 12D cycle (lights on at 0700 h). Commercial rat food (CE-2, Clea Japan Ltd.) and tap water were freely available except during the experiments. All experiments were carried out at an environmental temperature of 23 ± 1°C.

Behavioral Observation

Pairs of rats were placed in transparent plastic observation boxes (33 × 30 × 17 cm) containing wood shavings, and allowed to habituate for 15 min prior to drug injection. Yawning is a fixed innate motor pattern characterized by a slow, wide opening of the mouth (28,33). The total number of yawns was counted for 60 min following injection in accordance with our previous reports (13,14,34,35,37). The stereotypy of individual rats was scored for 1 min every 10 min throughout the 90-min observation period after drug administration (36). Two behavioral indices, sniffing and licking, were assessed. For sniffing, both sniffing of air and a substrate were scored. Each behavior was given a rating of "0" if it lasted no longer than 5 s, a "1" if its duration was 6 to 15 s, and a "2" if its total duration in the 1-min interval was longer than 15 s. Rating for licking and sniffing were combined to yield a single stereotypy score, with the maximum score possible being 36 during 90-min observation period. Each rat was tested once only.

Measurement of Temperature

Groups of four rats were placed in plastic observation boxes (33 × 30 × 17 cm) containing wood shavings. Rectal temperature was measured using a digital laboratory thermometer (Physitemp, BAT-12) before and for 24 h after drug administration. The probe was inserted into the animal's rectum to a constant depth of 4 cm and removed after each reading. A change in body temperature (°C) represented a difference from the predrug value.

Administration of Drugs

In rats, saline (1 ml/kg), 7-OH-DPAT (10–250 μg/kg), quinpirole (25–500 μg/kg), or SK&F 38393 (10 mg/kg) was injected subcutaneously (SC) into the neck area alone or in combination with intraperitoneally (IP) administered pindolol at 20 mg/kg. The optimal doses for the induction of yawning were 25 μg/kg for 7-OH-DPAT and 50 μg/kg for quinpirole. To determine the effects of various antagonists on yawning, they were injected at the following times before injection of the yawning inducers: 30 min for saline (1 ml/kg, SC), spiperone (0.5 mg/kg, SC), and scopolamine (0.5 mg/kg, SC); 60 min for pindolol (20 mg/kg, IP); and 24 h for reserpine (5 mg/kg, IP). These drug dosages were selected according to our previous experiments (13,14,17,34–36).

Drugs

The following drugs were used: (±)-2-(dipropylamino)-7-hydroxy-1,2,3,4-tetrahydronaphthalene (7-OH-DPAT) hydrobromide (Research Biochemicals Inc., Natick, MA), quinpirole (LY 171555) hydrochloride (Research Biochemicals Inc.), SK&F 38393 (1-phenyl-2,3,4,5-tetrahydro-(1H)-3-benzazepine-7,8-diol) hydrochloride (Research Biochemicals Inc.), pindolol (Sigma, St. Louis, MO), spiperone (Spiropitan Injection, Eisai, Tokyo, Japan), scopolamine hydrobromide (Nacalai tesque, Kyoto, Japan), and reserpine (Apoplone Injection, Daiichi, Tokyo, Japan). Pindolol was dissolved in tartaric acid solution, followed by subsequent dilution in saline, and the other drugs were dissolved or diluted in saline. All drugs were injected intraperitoneally (IP) or subcutaneously (SC) into the experimental animals as detailed above. Doses were expressed in terms of salts, with the exception of pindolol, spiperone, and reserpine.

Statistical Analysis

Yawning responses, stereotypy scores and changes in body temperature were expressed as mean values ± SEM. Statistical analysis was performed using either two-tailed Student's *t*-test (differences between two groups) or analysis of variance (ANOVA) followed by posthoc comparisons with Dunnett's or Tukey's test, as appropriate.

RESULTS

Yawning Behavior Induced by 7-OH-DPAT and Quinpirole

Rats without treatment and control animals treated with subcutaneous saline yawned only occasionally. 7-OH-DPAT at doses ranging from 10 to 250 μg/kg induced noticeable yawning behavior in the saline-pretreated rats. The dose-response to 7-OH-DPAT of yawning was bell-shaped; the maximal effect was observed at a dose of 25 μg/kg (Fig. 1). Quinpirole (25–500 μg/kg, SC) also produced yawning responses in saline-pretreated rats, with a maximal effect at a dose of 100 μg/kg (Fig. 2). The yawning induced by 7-OH-DPAT or quinpirole was markedly increased by pretreatment with pindolol (20 mg/kg, IP) which per se did not evoke yawning (Figs. 1, 2).

As demonstrated in Table 1, the yawning responses to 7-OH-DPAT (25 μg/kg, SC) and quinpirole (50 μg/kg, SC) were inhibited by pretreatment with either spiperone (0.5 mg/kg, SC) or scopolamine (0.5 mg/kg, SC) which per se did

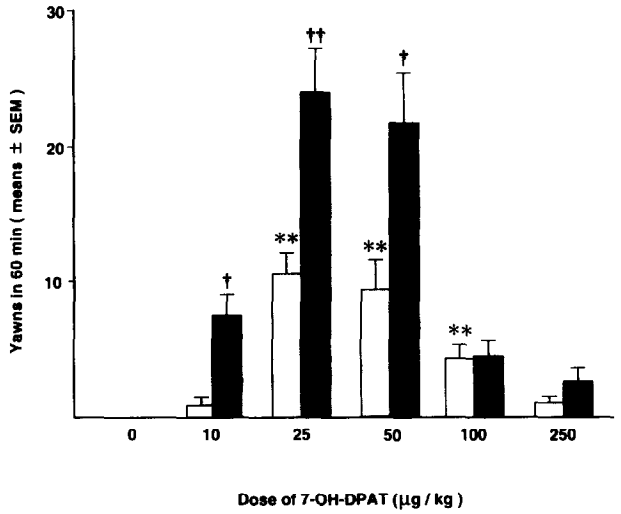

FIG. 1. Dose-responses of yawning to 7-OH-DPAT (10–250 µg/kg, subcutaneous [SC]) in saline- and pindolol-pretreated rats. Saline (1 ml/kg, intraperitoneal [IP]) or pindolol (20 mg/kg, IP) was administered 60 min before 7-OH-DPAT. Saline-pretreated (□), pindolol-pretreated (■). Columns represent means ± SEM (vertical bars) of the number of yawns counted in eight rats during a 60-min observation period. *$p < 0.05$; **$p < 0.01$; significant difference from saline plus saline-injected group, determined by a one-way ANOVA followed by Dunnett's test. † $p < 0.05$; ††$p < 0.01$; significant difference between saline- and pindolol-pretreated groups, determined by Student's t-test.

not elicit yawning. Conversely, the yawning responses were increased after treatment with reserpine (5 mg/kg, IP) or pindolol (20 mg/kg, IP).

Stereotypy Induced by 7-OH-DPAT or Quinpirole

As shown in Fig. 3, 7-OH-DPAT (0.01–0.1 mg/kg, SC) or quinpirole (0.025–0.25 mg/kg, SC) produced virtually no

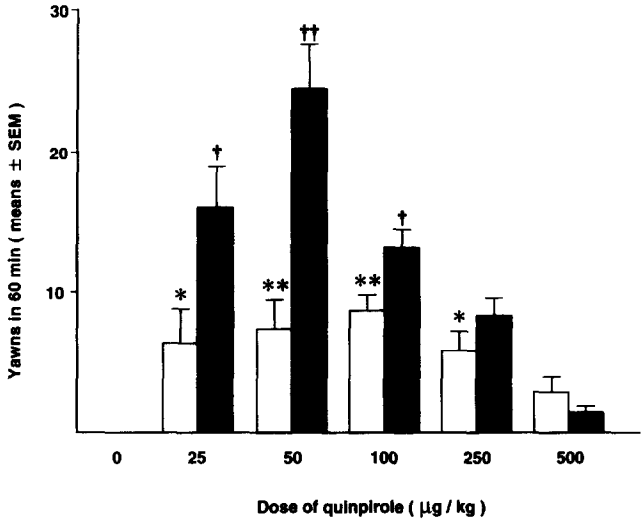

FIG. 2. Dose-responses of yawning to quinpirole (25–500 µg/kg, subcutaneous) in saline- and pindolol-pretreated rats. Further explanations as in Fig. 1.

TABLE 1

EFFECTS OF VARIOUS DRUGS ON YAWNING INDUCED BY 7-OH-DPAT OR QUINPIROLE IN RATS

	Yawns in 60 min (means ± SEM)		
Drugs mg/kg	Saline	7-OH-DPAT	Quinpirole
Saline	0.3 ± 0.2	10.6 ± 1.5*	7.4 ± 1.9*
Spiperone 0.5	0.1 ± 0.1	0.0 ± 0.0‡	0.5 ± 0.3†
Scopolamine 0.5	0.0 ± 0.0	0.4 ± 0.2‡	0.6 ± 0.3†
Reserpine 5	2.1 ± 0.5†	18.0 ± 1.5†	22.9 ± 1.9‡
Pindolol 20	1.0 ± 0.4	24.1 ± 3.2‡	24.5 ± 3.1‡

Various drugs were injected at the following times before 7-OH-DPAT (25 µg/kg, SC) or quinpirole (50 µg/kg, SC): 30 min for saline (1 ml/kg, SC), spiperone (0.5 mg/kg, SC), and scopolamine (0.5 mg/kg, SC); 60 min for pindolol (20 mg/kg, IP); and 24 h for reserpine (5 mg/kg, IP). Values represent means ± SEM of the number of yawns counted in eight rats. *$p < 0.01$, significant difference from saline plus saline-injected group; †$p < 0.05$, ‡$p < 0.01$, significant difference from respective control groups, determined by a one-way ANOVA followed by Dunnett's test.

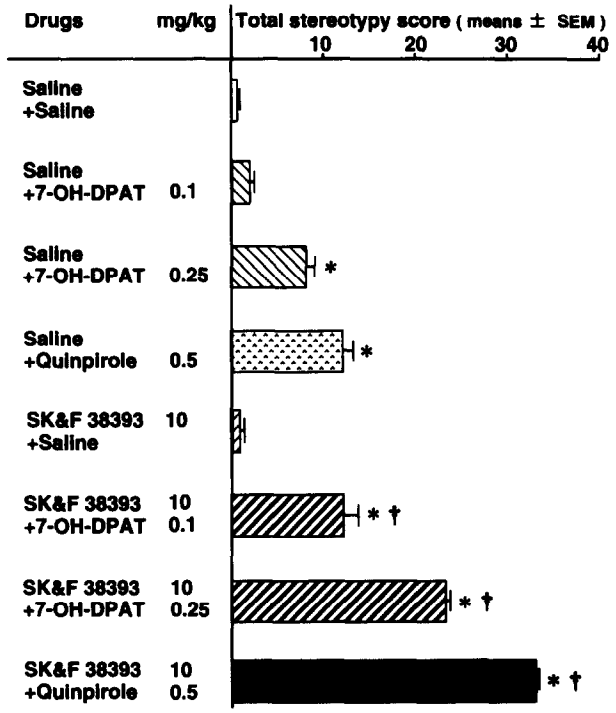

FIG. 3. Stereotypy induced by 7-OH-DPAT or quinpirole administered in combination with either saline or SK&F 38393. 7-OH-DPAT (0.1, 0.25 mg/kg, SC) or quinpirole (0.5 mg/kg, SC) was simultaneously administered with saline or SK&F 38393 (10 mg/kg, SC), and the degree of stereotypy was thereafter scored for 1 min every 10 min and totaled for 90 min. The maximum possible score was 36. Columns represent means ± SEM (horizontal bars) of totaled stereotypy scores from eight rats. *$p < 0.01$; significant difference from saline plus saline-injected group; †$p < 0.01$; significant difference from respective saline plus agonist-injected groups, determined by a two-way ANOVA followed by Tukey's test.

stereotypy at low doses effective in inducing yawning (data not shown) but elicited the behavior at high doses (7-OH-DPAT, 0.25 mg/kg; quinpirole, 0.5 mg/kg). SK&F 38393 did not evoke stereotypy such as sniffing or licking at a dose of 10 mg/kg (SC). The stereotypy evoked by 7-OH-DPAT (0.1, 0.25 mg/kg, SC) or quinpirole (0.5 mg/kg, SC) was markedly potentiated by simultaneous administration of SK&F 38393 (10 mg/kg, SC) (Fig. 3).

Effects of 7-OH-DPAT or Quinpirole on Body Temperature

The mean rectal temperature was 37.1 ± 0.1°C in untreated rats. As shown in Fig. 4, body temperature was unchanged after subcutaneous administration of saline in naive rats. 7-OH-DPAT (0.5 mg/kg, SC) and quinpirole (0.5 mg/kg, SC) significantly reduced body temperature with decreases of −1.1 ± 0.1°C and −1.1 ± 0.2°C, respectively. On the other hand, SK&F 38393 (10 mg/kg, SC) increased body temperature, the hyperthermic effects reaching a maximum with 1.4 ± 0.1°C elevation 1 h after the administration. Interestingly, treatment with either 7-OH-DPAT (0.5 mg/kg, SC) or quinpirole (0.5 mg/kg, SC) enhanced the SK&F 38393 (10 mg/kg, SC) induced hyperthermia with 2.2 ± 0.2°C elevation 1 h after combined treatment with SK&F 38393 plus 7-OH-DPAT and 2.8 ± 0.2°C elevation after SK&F 38393 plus quinpirole. The hyper- or hypothermia recovered within 24 h after drug treatment.

DISCUSSION

Previous biochemical and pharmacological evidence indicated the presence of at least two dopamine receptor subtypes; dopamine D_1 receptors linked positively to adenylate cyclase and dopamine D_2 receptors linked negatively or not linked to adenylate cyclase (8,26,31). Recently, the dopamine receptors have been demonstrated to show greater multiplicity than originally envisaged within the D_1/D_2 nomenclature, the existence of two families of D_1-like (D_{1A}, D_{1B}/D_5) and D_2-like ($D_{2\,long/short}$, D_3, D_4) receptor sequences, from molecular biological and gene cloning studies (23), but their functional roles are still unknown.

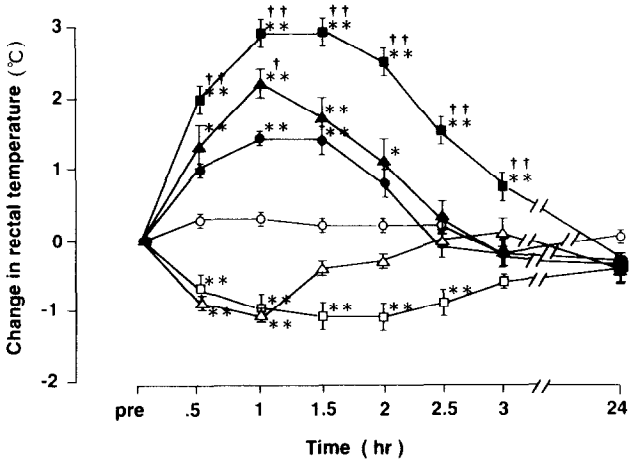

FIG. 4. Changes in body temperature after administration of saline, SK&F 38393, 7-OH-DPAT, or quinpirole given in combination. Drugs were administered concurrently for combined treatment. Points represent means ± SEM (vertical bars) of changes in rectal temperature observed in 8-10 rats. Saline plus saline (1 ml/kg), ○; saline plus 7-OH-DPAT (0.5 mg/kg), △; saline plus quinpirole (0.5 mg/kg), □; SK&F 38393 (10 mg/kg) plus saline, ●; SK&F 38393 (10 mg/kg) plus 7-OH-DPAT (0.5 mg/kg), ▲; SK&F 38393 (10 mg/kg) plus quinpirole (0.5 mg/kg), ■. $*p < 0.05$; $**p < 0.01$; significant difference from saline plus saline-injected group. $\dagger p < 0.05$; $\dagger\dagger p < 0.01$; significant difference from SK&F 38393 plus saline-injected group, determined by a one-way ANOVA followed by Tukey's test.

As mentioned in the introduction, 7-OH-DPAT and quinpirole are putative dopamine D_3 receptor agonists which possess more than 100-fold higher affinities for dopamine D_3 receptors than D_2 receptors (10,24). In addition, the signal transduction mechanism involved in D_3 receptor responses differs from that of its closest homolog, D_2 receptor responses (12). Recently, some behavioral experiments with 7-OH-DPAT have been reported. Daly and Waddington (3) showed that 7-OH-DPAT at a very low dose of 10 μg/kg (SC) reduced spontaneous activity but did not induce yawning at respective doses of 0.01, 0.1, 1, and 10 mg/kg in male Sprague-Dawley rats. On the other hand, Damsma et al. (4) reported that R-(+)-7-OH-DPAT dose-dependently induced yawning at doses ranging from 10 to 1000 nmole/kg and decreased dopamine release in male Wistar rats. Van den Buuse (29) also showed that 7-OH-DPAT (0.01–0.1 mg/kg) dose-dependently induced yawning in spontaneously hypertensive rats (SHR) and Wistar-Kyoto rats (WKY). In the present study, 7-OH-DPAT elicited yawning behavior at doses ranging from 25 to 100 μg/kg in male Wistar rats and the dose-response was bell-shaped with a maximal effect at 25 μg/kg. We have no adequate explanation for the discrepant result reported by Daly and Waddington with regard to inducement of yawning at present, but it may be due, at least in part, to differences in strains, dose-ranges and dose-intervals within the ranges used in the respective studies. Quinpirole (25–250 μg/kg, SC) also evoked yawning in the present study in agreement with previously reported observations (7,11,22). Thus, putative D_3 receptor agonists are capable of inducing yawning. Our previous studies have also shown that conventional dopamine D_2 receptor agonists such as bromocriptine and talipexole induce yawning, and that this effect is blocked by spiperone and scopolamine (13,14,37). Spiperone has been used as a dopamine D_2 receptor antagonist but may not necessarily be selective for dopamine D_2 receptors since respective K_i values are 0.069 and 0.61 nM for D_2 and D_3 receptors (24). In this study, the yawning responses to 7-OH-DPAT and quinpirole were also inhibited by spiperone and scopolamine.

In our previous reports (14,32), the yawning elicited by apomorphine was enhanced after treatment with reserpine. Ståhle (25) has been proposed that autoreceptors are not the mediators of the behavioral effects of dopamine receptor agonists, and that postsynaptic receptors mediate the dopamine receptor agonist-induced yawning. It has also been suggested that endogenous dopamine occupies dopamine D_3 receptors to such an extent that exogenous dopamine agonists may not be able to further activate these sites (21). Accordingly, it is possible that the exogenous dopamine agonists activate dopamine receptors to a greater extent after dopamine depletion by reserpine, although the actual mechanisms are still unclear. We also reported that the blockade of β-adrenoceptors caused by central β-adrenoceptor antagonists, e.g., pindolol and others, but not by peripheral β-adrenoceptor antagonists, facilitates the occurrence of yawning induced by dopamine receptor agonists such as apomorphine and talipexole (B-HT 920) (34,35). Administration of LY-78335 and UK-1187A, phenylethanolamine-*N*-methyltransferase inhibitors, which decrease adrenaline formation without affecting dopamine and noradrenaline

levels in the brain, potentiates the incidence of yawning similarly to β-adrenoceptor blockade (9). Therefore, the central adrenergic neuronal system appears to inhibit yawning via β-adrenoceptors (9). In this experiment, the yawning produced by 7-OH-DPAT or quinpirole was also increased by treatment with reserpine or pindolol.

Stereotypy appears after administration of high doses of mixed D_1/D_2 receptor agonists such as apomorphine and piribedil (32,33). In addition, it was recently reported that concurrent stimulation of both originally envisaged dopamine D_1 and D_2 receptors was required for the appearance of stereotypy (15,36). Moreover, the results of our previous study (36) suggested that high-sensitive dopamine D_2-like receptors having a high affinity for dopamine D_2 receptor agonists are involved in evoking yawning, while low-sensitive D_2-like receptors possessing a low affinity for the agonists participate in induction of stereotypy. In the present study, 7-OH-DPAT and quinpirole elicited virtually no stereotypy at low doses of 10–100 and 25–250 μg/kg (SC), respectively, which were effective in inducing yawning, and evoked slightly but significantly stereotypy at higher respective doses of 250 and 500 μg/kg (SC). These results obtained by quinpirole and SK&F 38393 are in accordance with the previous findings by Eilam et al. (6). Recently, Daly and Waddington (3) reported that 7-OH-DPAT at high doses of 0.1–10 mg/kg (SC) stimulated nonstereotyped sniffing, locomotion, and chewing, which was attenuated by dopamine D_1 receptor antagonists. In this study, SK&F 38393 at a dose of 10 mg/kg did not induce stereotypy such as sniffing or licking in rats. However, the stereotyped behavior produced by 7-OH-DPAT and quinpirole such as sniffing and licking was markedly potentiated by simultaneous administration of the dopamine D_1 receptor agonist SK&F 38393.

The dopaminergic neuronal system also appears to play an important role in central regulation of body temperature in animals (2). Classical dopamine receptor agonists such as apomorphine and bromocriptine have been reported to induce dose-dependent reductions in body temperature in naive rodents, and this effect was blocked by conventional dopamine D_2 receptor antagonists such as haloperidol and sulpiride (16,38). In this study, quinpirole reduced body temperature in rats in accordance with the results from a number of previous experiments on both rats and mice (16,18–20,30). In addition, 7-OH-DPAT similarly reduced body temperature. Accordingly, it is likely that dopamine D_3 and/or D_2 receptors play a role in regulation of body temperature, but we are not able to rule out the possibility of participation of other neuronal mechanisms at present since 7-OH-DPAT has an agonistic profile at α_2-adrenoceptors and 5-HT_{1A} receptors (29).

On the other hand, SK&F 38393 was previously reported to induce dose-dependent increases in body temperature in reserpine-treated mice, and this increase was completely antagonized by conventional dopamine D_1 receptor antagonists (5,30). Moreover, the hypothermia induced by quinpirole was shown to be attenuated by SK&F 38393 in mice (16,19). Thus, previous studies have demonstrated that SK&F 38393 reverses the hypothermia induced by reserpine or quinpirole in mice. We reported previously that SK&F 38393 increased body temperature in naive rats (17), as also shown in the present study. These results are consistent with the recent proposal that stimulation of dopamine D_1 receptors is involved in induction of hyperthermia in rodents as a possible neuronal mechanism (1,30). Interestingly, our recent study also showed that the combined administration of SK&F 38393 and talipexole, a dopamine D_2 receptor agonist, caused not only stereotypy but also marked hyperthermia in rats (17). In the present study, it was also demonstrated that the hyperthermia produced by SK&F 38393 was markedly enhanced by 7-OH-DPAT or quinpirole in rats.

From the present results, it is assumed that dopamine D_3 receptors may collaborate with the D_1 and D_2 receptors envisaged originally in the induction of yawning as well as stereotypy and thermoregulation. However, future studies with as yet unavailable selective dopamine D_3 receptor antagonists may allow further elucidation of the functional role of dopamine D_3 receptors.

In summary, the putative dopamine D_3 receptor agonists 7-OH-DPAT and quinpirole are capable of eliciting yawning responses at low doses and stereotypy at higher doses in rats. These agonists also produce hyperthermia when administered in combination with dopamine D_1 receptor agonists.

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