Pharmacology Biochemistry and Behavior, Vol. 53, No. 4, pp. 903–909, 1996

0091-3057/96 $15.00 + .00

SSDI 0091-3057(95)02096-9

Partial Agonistic Effects of OPC-14597, a Potential Antipsychotic Agent, on Yawning Behavior in Rats

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Received 8 March 1995; Revised 17 July 1995; Accepted 9 August 1995

FUJIKAWA, M., M. NAGASHIMA, T. INOUE, K. YAMADA AND T. FURUKAWA. *Partial agonistic effects of OPC-14597, a potential antipsychotic agent, on yawning behavior in rats.* PHARMACOL BIOCHEM BEHAV **53**(4) 903–909, 1996. – The present experiments were performed to examine the behavioral effects of OPC-14597, which acts on dopamine receptors in rats. OPC-14597 administered subcutaneously (SC) at doses of 0.1–5 mg/kg elicited yawning, as did OPC-4392 (0.5–2 mg/kg, SC) and (−)-3-PPP (2.5–10 mg/kg, SC). These yawning responses were blocked by intraperitoneal (IP) pretreatment with haloperidol (0.5 mg/kg) but were increased by pindolol (20 mg/kg, IP) or reserpine (5 mg/kg, IP), which per se did not elicit yawning. The yawning induced by talipexole, a selective dopamine D_2 receptor agonist, was inhibited by OPC-14597 (0.5–5 mg/kg, SC) and (−)-3-PPP (10 mg/kg, SC). Apomorphine (0.5 mg/kg, SC), a dopamine D_1/D_2 receptor agonist, elicited stereotypy such as sniffing and licking but OPC-14597 (5–20 mg/kg, SC) did not induce this behavior. The stereotypy induced by apomorphine was inhibited not only by haloperidol (0.5 mg/kg, IP) and (−)-3-PPP (10 mg/kg, SC) but also by OPC-14597 (5–20 mg/kg, SC), without being affected by OPC-4392 (2 mg/kg, SC). In 6-hydroxydopamine (6-OHDA)-treated rats, apomorphine (0.5 mg/kg, SC) elicited rotation behavior whereas OPC-14597, OPC-4392 and (−)-3-PPP did not produce this behavior. These findings suggest that OPC-14597 provokes yawning without causing stereotypy and rotation but markedly antagonizes the talipexole-induced yawning and apomorphine-induced stereotypy, and that OPC-14597 thus exerts partial agonistic effects on yawning behavior but antagonistic effects on stereotypy in rats.

Yawning Stereotypy Rotation OPC-14597 (−)-3-PPP β-Adrenoceptor antagonists

THE PRECISE pharmacological mechanisms by which neuroleptics exert their beneficial effects are unknown, but consideration of pharmacological properties of the drugs will provide some clues, because the antipsychotic drugs, despite their variety of chemical structure, share certain effects particularly with respect to dopamine. Neuroleptic drugs in clinical use mainly block the dopamine receptor, but their antidopaminergic effects may also account for the diverse neurological aspects of the syndrome, the parkinsonian and extrapyramidal effects (11,22), though different approaches to avoid side effects related to dopamine antagonist properties are suggested by recent studies, particularly concerning dopamine receptor subtypes (26,27). Accordingly, the neuroleptics that have less side effects, especially less extrapyramidal disturbance, have been still awaited with great interest. Thus, efforts are still being directed at developing drugs that act on the dopamine receptor.

(−)-3-PPP was reported to be a partial dopamine receptor agonist whose intrinsic activity varies according to the location of the receptor, and the agent acts essentially as an antagonist on central postsynaptic dopamine receptors whereas it displays agonistic action on presynaptic dopamine receptors (2,3). OPC-4392, a substituted quinolinone derivative, binds selectively to dopamine D_2 receptors and acts as a dopamine

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agonist at presynaptic autoreceptors related to dopamine synthesis and a dopamine antagonist at postsynaptic D_2 receptors (14,23,40). Furthermore, OPC-14597, another quinolinone derivative, was later synthesized as a more potential antipsychotic drug.

The present experiments were therefore performed to examine the behavioral effects of OPC-14597 on dopamine receptors, as compared with OPC-4392 and 3-PPP.

METHODS

Animals

Male Wistar rats (200–230 g) were obtained from Kyudo Animal Laboratory (Kumamoto, Japan). They were kept in an animal room with a 12 L : 12 D cycle (lights on at 0700 h). Commercial 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 Observations

Pairs of rats were placed in transparent plastic boxes (33 × 30 × 17 cm) containing wood shavings. They were allowed to habituate to the observation boxes for 30 min before drug injection. The total number of yawns was counted for 90 or 60 min following the injection of yawning inducers. The stereotypy of individual rats was observed for 1 min every 10 min up to 60 min after drug administration. The two behavioral indices, sniffing and licking, were assessed. Each symptom was classified into three grades (0–2) by the following criteria: score 0, normal (0–5 s); score 1, discontinuous behavior (6–15 s); score 2, continuous behavior (16–30 s). Stereotypy was assessed by combining the score of two behaviors. The rotation behavior was counted for 60 min after the injection of apomorphine, OPC-14597, OPC-4392, and (−)-3-PPP at least 2 weeks after surgery according to previous reports (5,30).

6-OHDA Lesions

Rats were anesthetized with pentobarbital sodium and placed on a stereotaxic apparatus (Narishige, Japan). An injection needle was stereotaxically positioned into the left neostriatum (anterior: 2.0 mm from bregma, lateral: 3.0 mm from midline, ventricular: 5.0 mm from dura) (21). 6-Hydroxydopamine (6-OHDA) hydrochloride (2 μg/μl of 0.9% saline containing 0.2% ascorbic acid) was microinjected into the striatum at a rate of 1 μl/min for 4 min. The infusion rate was controlled by a Harvard infusion pump (Harvard Apparatus, South Natick, MA) that drove a 10-μl Hamilton syringe connected to the cannula with fine polyethylene tubing (inner diameter = 0.52 mm).

Administration of Drugs

Rats received injections of OPC-14597 (0.1–50 mg/kg, SC), OPC-4392 (0.5–2 mg/kg, SC), (−)-3-PPP (2.5–10 mg/kg, SC), talipexole (0.025 mg/kg, SC), apomorphine (0.5 mg/kg, SC), pindolol (20 mg/kg, IP), haloperidol (0.5 mg/kg, IP), or reserpine (5 mg/kg, IP). Pindolol was injected 60 min and reserpine 24 h prior to the injection of OPC-14597. For the inhibitory effect on yawning or stereotypy, OPC-14597, OPC-4392, (−)-3-PPP, and haloperidol were injected 30 min before talipexole or apomorphine.

Drugs

The following drugs were used: OPC-14597 {7-(4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butyloxy)-3,4-dihydro-2([^{1}H])-quinolinone} (Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan) (Fig. 1), OPC-4392 {7-(3-[4-(2,3-dimethylphenyl)piperazinyl] propoxy)-2([^{1}H])-quinolinone} (Otsuka Pharmaceutical Co.) (Fig. 1), (−)-3-PPP [(−)-3-(hydroxyphenyl)-*N*-*n*-propylpiperidine] hydrochloride (Research Biochemical Inc., Natick, MA), pindolol (Sigma, St. Louis, MO), talipexole (B-HT 920) dihydrochloride (Boehringer Ingelheim, Hyogo, Japan), reserpine (Apoplon Injection, Daiichi, Tokyo, Japan), haloperidol (Serenace Injection, Dainippon, Osaka, Japan), and apomorphine hydrochloride (Sandoz, Basel, Switzerland). OPC-14597 and OPC-4392 were dissolved in an ethanol/water (1 : 1, v/v) solution with subsequent dilution in saline, and both agents were administered subcutaneously (SC) into experimental animals. Pindolol was dissolved in an excess of equimolar tartaric acid solution with subsequent dilution in saline and was injected intraperitoneally (IP) into experimental animals. The other drugs were dissolved or diluted in saline and injected IP or SC into experimental animals as mentioned above. Doses are expressed in terms of salts with the exception of OPC-14597, OPC-4392, pindolol, reserpine, or haloperidol.

Statistical Analysis

Yawning responses and rotation scores were expressed as mean values ± SEM, and statistical analysis for differences between a control and all groups was performed using a one-way analysis of variance (ANOVA) followed by the two-tailed Dunnett's test. Stereotypy scores were expressed as mean values, and nonparametric statistical analysis was done using the two-tailed Mann–Whitney *U*-test.

RESULTS

Yawning Induced by OPC-14597, Talipexole, (−)-3-PPP, and OPC-4392

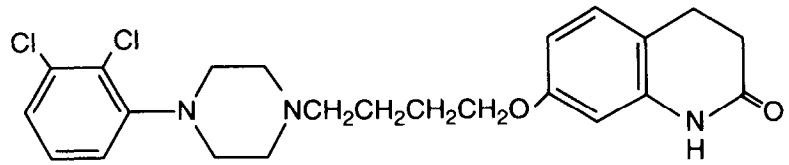
Control rats treated with saline (1 ml/kg, SC) yawned only occasionally. Talipexole (0.025 mg/kg, SC) induced marked yawning behavior. (−)-3-PPP (2.5–10 mg/kg, SC) and OPC-4392 (0.5–2 mg/kg, SC) also elicited yawning behavior (Fig. 2). However, dose-response of yawning to (−)-3-PPP was bell shaped with the maximal effect at 5 mg/kg. OPC-4392 evoked yawning in a dose-dependent manner. As shown in Fig. 3, OPC-14597 (0.1–5 mg/kg, SC) also dose-dependently induced the yawning but the effect was significant at only 5 mg/kg. Thus, OPC-14597 was weaker in inducing yawning than OPC-4392.

Inhibition by OPC-14597 of Talipexole-Induced Yawning

Talipexole (0.025 mg/kg, SC) elicited yawning; the mean number of yawns during 60 min from eight rats was 13.3 ± 2.9 (Fig. 4). The talipexole-induced yawning was markedly inhibited by pretreatment with haloperidol (0.5 mg/kg, IP) or (−)-3-PPP (10 mg/kg, SC). The yawning was also inhibited slightly by OPC-4392 at 2 mg/kg. The behavior was dose-dependently inhibited by OPC-14597 (0.1–5 mg/kg, SC) as well, with similar effects between 0.5 and 5 mg/kg.

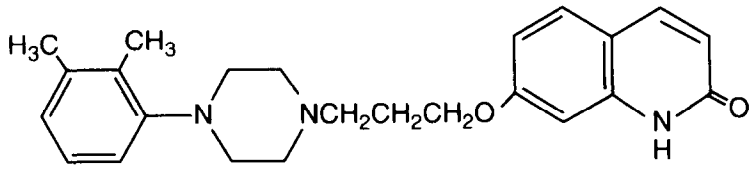
Potentiation of OPC-14597-Induced Yawning by Pindolol or Reserpine

As shown in Fig. 5, the yawning induced by OPC-14597 (0.1–5 mg/kg, SC) was markedly increased by pretreatment



OPC-14597

7-{4-[4-(2,3-Dichlorophenyl)-1-piperazinyl]butyloxy}-3,4-dihydro-2(1H)-quinolinone



OPC-4392

7-{4-[4-(2,3-Dimethylphenyl)-1-piperazinyl]propoxy}-2(1H)-quinolinone

FIG. 1. Chemical structures of OPC-14597 and OPC-4392.

with either pindolol (20 mg/kg, IP) or reserpine (5 mg/kg, IP). Pindolol or reserpine administered alone did not induce yawning.

Effects of OPC-14597 on Stereotypy

Apomorphine (0.5 mg/kg, SC) induced stereotypy such as sniffing and licking; the mean number of episodes of stereotypy during 60 min from eight rats was 13.3 (Fig. 6). However, OPC-14597 (5–20 mg/kg, SC), haloperidol (0.5 mg/kg, IP), (−)-3-PPP (10 mg/kg, SC), and OPC-4392 (2 mg/kg, SC) did not induce stereotypy. The apomorphine-induced stereotypy was markedly inhibited by pretreatment with haloperidol (0.5 mg/kg, IP) and (−)-3-PPP (10 mg/kg, SC). Interestingly, the apomorphine-induced stereotypy was not affected by OPC-4392 (2 mg/kg, SC) but was inhibited in a dose-dependent manner by OPC-14597 at a dose range of 5–20 mg/kg.

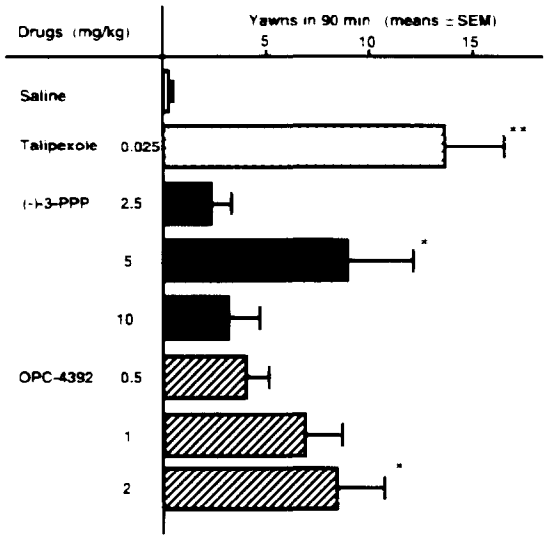


FIG. 2. Yawning induced by talipexole, (−)-3-PPP, and OPC-4392 in rats. The number of yawns was counted for 90 min following injection of saline, talipexole (0.025 mg/kg, SC), (−)-3-PPP (2.5–10 mg/kg, SC), or OPC-4392 (0.5–2 mg/kg, SC). Values are means ± SEM (horizontal lines) of yawns from eight rats. $*p < 0.05$, $**p < 0.01$, significant difference from the saline-injected group, determined by Dunnett's test.

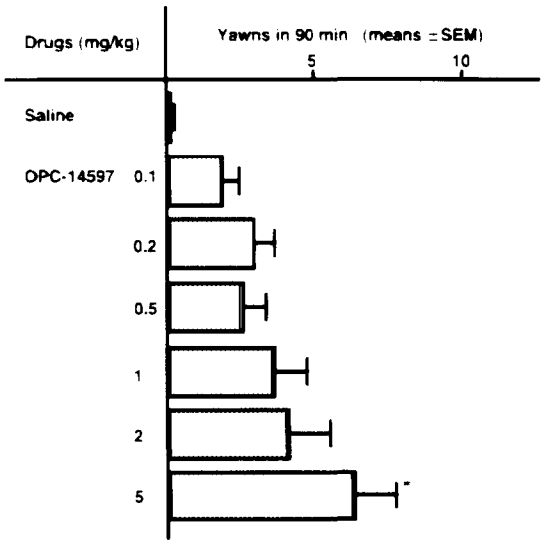


FIG. 3. Dose-response of yawning to OPC-14597 in rats. The number of yawns was counted for 90 min following injection of OPC-14597 (0.1–5 mg/kg, SC). $*p < 0.05$, significant difference from the saline-injected group, determined by Dunnett's test.

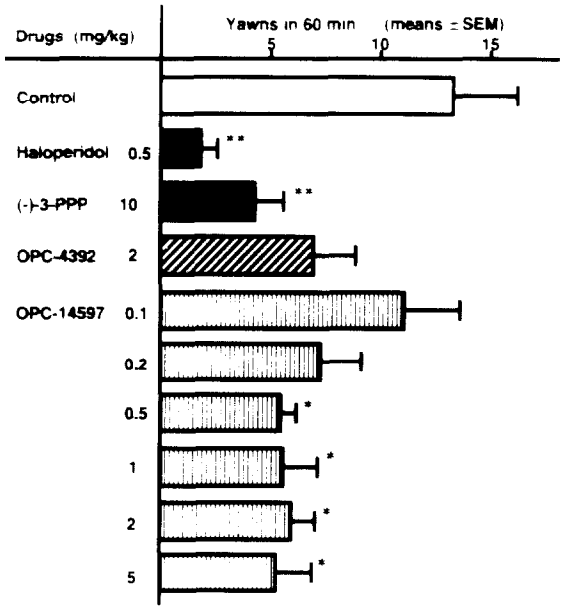


FIG. 4. Inhibitory effects of OPC-14597 on the yawning induced by talipexole in rats. A yawn count was started immediately following the injection of talipexole (0.025 mg/kg, SC). Drugs were given SC 30 min before administration of talipexole. $*p < 0.05$, $**p < 0.01$, significant difference from the control group, determined by Dunnett's test.

Effects of OPC-14597 on Rotation Behavior in 6-OHDA-Lesioned Rats

Treatment with saline (1 ml/kg, SC) had no effect in the control rats with unilateral 6-OHDA-lesions of the nigrostriatal tract. Apomorphine (0.5 mg/kg, SC) markedly induced contralateral rotation behavior (107.2 ± 13.9 turns). However, (−)-3-PPP (5, 10 mg/kg, SC), OPC-4392 (1, 2 mg/kg, SC), and OPC-14597 (5, 10 mg/kg, SC) did not induce the rotation behavior (data not shown).

DISCUSSION

Previous observations have shown the presence of at least two dopamine receptor subtypes: dopamine D_1 receptors linked positively to adenylate cyclase and dopamine D_2 receptors not linked or linked negatively to adenylate cyclase (12,31,35). In addition, the dopamine receptor has recently been divided into more subtypes. The dopamine D_3 receptor is localized to limbic areas of the brain, which are associated with cognitive, emotional, and endocrine functions. It appears to mediate some of the effects of antipsychotic and anti-Parkinson's drugs that were previously thought to interact only with dopamine D_2 receptors (27). 7-OH-DPAT 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 (16). Quinpirole has also been reported to have a 113-fold higher affinity for dopamine D_3 receptors than D_2 receptors (27). The dopamine D_4 receptor gene has high homology to the human dopamine D_2 and D_3 receptor genes. The pharmacological characteristics of this receptor resemble those of dopamine D_2 and D_3 receptors, but its affinity for clozapine is one order of magnitude higher (34). OPC-14597 was recently proposed to possess the following rank order of receptor affinity; $D_2 > D_3 > D_4 > D_{1A} > D_{1B}$ (26), indicating that OPC-14597 acts predominantly on dopamine D_2 receptors.

Apomorphine and piribedil, dopamine D_1/D_2 receptor agonists, exerted biphasic effects on behavior (i.e., inducing yawning and hypomotility at low doses, and stereotypy and hypomotility at high doses) (4,32,36,37). Furthermore, our previous studies found that talipexole and SND 919, dopamine D_2 receptor agonists, markedly induced yawning but did not cause or induced only slight stereotypy even at larger doses, and that the yawning induced was inhibited by the selective dopamine D_2 receptor antagonist, spiperone, and the muscarinic receptor antagonist, scopolamine, but was unaffected by the selective dopamine D_1 receptor antagonist, SCH 23390 (6,18,19,36,41). These findings suggest that the yawning is mediated via stimulation of dopamine D_2 receptors and consequent cholinergic activation.

In the present study, OPC-14597, OPC-4392, and (−)-3-PPP induced yawning as did talipexole. However, the dose-response to (−)-3-PPP was bell shaped whereas those to OPC-4392 and OPC-14597 were dose dependent, OPC-4392 being more effective in inducing yawning. On the other hand, the talipexole-induced yawning was markedly inhibited by pretreatment with haloperidol, a dopamine receptor antagonist, or (−)-3-PPP, a partial dopamine receptor agonist, whereas the yawning was not significantly inhibited by OPC-4392. The yawning was also inhibited in a dose-dependent manner by OPC-14597 at doses of 0.1–0.5 mg/kg, but the inhibition reached almost a maximum even at higher doses of 0.5–5 mg/kg, presumably because OPC-14597 exerted both antagonistic and agonistic activities. Thus, OPC-14597 exhibits

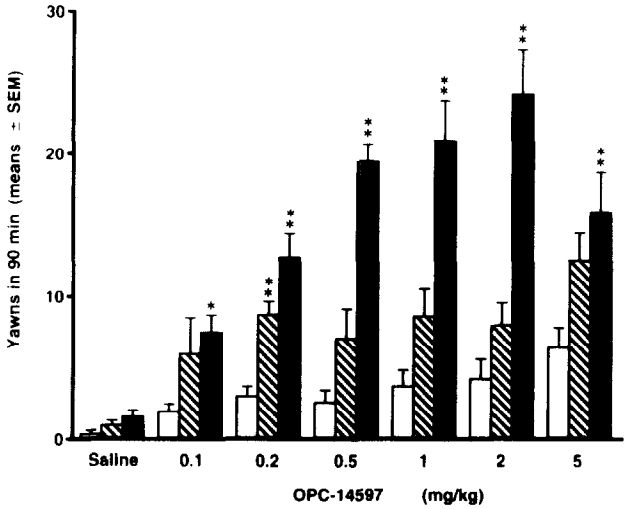


FIG. 5. Potentiation of OPC-14597-induced yawning by pindolol or reserpine in rats. The number of yawns was counted for 90 min following injection of OPC-14597 (0.1–5 mg/kg, SC). Pindolol (20 mg/kg, IP) or saline (1 ml/kg, IP) was administered 60 min and reserpine (5 mg/kg, IP) 24 h before OPC-14597. Open columns: saline-pretreated, hatched columns: pindolol-pretreated, striped columns: reserpine-pretreated. Columns represent means ± SEM (vertical lines) of the number of yawns counted during a 90-min observation period in 8–12 rats. $*p < 0.05$, $**p < 0.01$, significant difference from saline plus OPC-14597-injected respective control groups, determined by Dunnett's test.

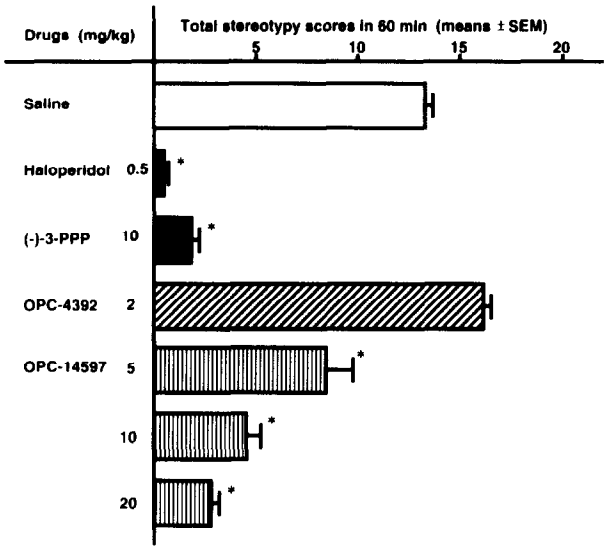


FIG. 6. Inhibitory effects of OPC-14597 on the stereotypy induced by apomorphine in rats. Each rat was scored for degree of stereotypy every 10 min after SC injection of apomorphine (0.5 mg/kg) and each score was accumulated for 60 min. Saline, haloperidol (0.5 mg/kg), (−)-3-PPP (10 mg/kg), OPC-4392 (2 mg/kg), or OPC-14597 (5–20 mg/kg) was injected 30 min prior to injection of apomorphine. Values are means of the final accumulated scores of stereotypy from 8–14 rats. $*p < 0.05$, $**p < 0.01$, significant difference from the saline-injected control group, determined by Mann–Whitney *U*-test.

weaker agonistic and stronger antagonistic and OPC-4392 stronger agonistic and weaker antagonistic effects on dopamine D_2 receptors involved in the yawning behavior. We recently found that putative dopamine D_3 receptor agonists, 7-OH-DPAT (10–250 μg/kg) and quinpirole (25–500 μg/kg), elicited yawning but the behavior induced by these agents was strongly blocked by spiperone, a dopamine D_2 receptor antagonist (15), suggesting the participation of dopamine D_2 receptors in inducing yawning. Recently, clozapine has been reported to be a dopamine D_4 receptor antagonist (34); however, the effects of clozapine on yawning have not been presented.

Previous studies have shown that yawning responses to dopaminergic agonists and cholinergic agents are increased after treatment with β-adrenoceptor antagonists such as pindolol and propranolol (13,38). The potentiation is elicited by central β-adrenoceptor blockers that can reach the brain through the blood-brain barrier, but not by peripheral β-adrenoceptor blockers, carteolol and atenolol, indicating that potentiation by β-adrenoceptor blockers occurs in the brain (38). Moreover, we previously noted that the yawning elicited by apomorphine was enhanced after treatment with reserpine (19,36). Stahle (28) has proposed that autoreceptors are not the mediators of behavioral effects of dopamine receptor agonists and postsynaptic receptors thereby mediate the dopamine agonist-induced yawning, and that exogenous agonists may further activate these sites (24). Accordingly, the exogenous dopamine agonists may activate more postsynaptic dopamine receptors when supersensitivities of dopamine receptor occur after reserpine. In the present study, the yawning induced by OPC-14597 was potentiated by treatment with pindolol or reserpine.

Stereotypy appears after administration of high doses of D_1/D_2 receptor agonists, apomorphine and piribedil (36,37). In addition, concurrent stimulation by both dopamine D_1 and D_2 receptors has recently been confirmed to be required for the appearance of stereotypy (10,17,20,39). In the present study, the apomorphine-induced stereotypy was markedly inhibited by pretreatment with haloperidol and (−)-3-PPP. The stereotypy was not affected by OPC-4392 but was inhibited in a dose-dependent manner by OPC-14597, which did not induce this behavior. These findings suggest that OPC-14597, but not OPC-4392, exerts antagonistic effects on postsynaptic dopamine receptors which are responsible to elicit stereotypy.

After unilateral 6-OHDA lesions, the dopamine D_1 and D_2 receptor agonists, like apomorphine, induce contralateral rotation behavior (1,7–9,25). In the present study, OPC-14597, OPC-4392, and (−)-3-PPP did not cause rotation behavior in 6-OHDA-lesioned rats. These agents may lack agonistic effects on postsynaptic dopamine D_2 receptors that are involved in evoking rotation.

In our previous study, apomorphine induced yawning at smaller doses and stereotypy at larger doses (33). Moreover, talipexole, a selective dopamine D_2 receptor agonist, induced only yawning (39). Yawning and suppression of exploration induced by dopamine agonists have been proposed to be mediated by postsynaptic dopamine receptors, but not by presynaptic autoreceptors, because the change in extracellular level of dopamine is not related to the behavior (28,29). Besides, we have proposed that dopamine D_2 receptors involved in yawning behavior have a high sensitivity for dopamine receptor agonists similar to that of dopamine D_2 autoreceptors and pituitary lactotroph dopamine D_2 receptors and seem not to be involved in the stereotypy behavior (39). In fact, OPC-14597 activates dopamine D_2 autoreceptors because the agent dose-dependently inhibited tyrosine hydroxylase activity stimulated by γ-butyrolacton or reserpine (Kikuchi et al., personal communication). In this study, OPC-14597 evoked yawning without inducing stereotypy but antagonized talipexole-induced yawning and apomorphine-induced stereotypy. Moreover, in our recent study (unpublished observation), the estrogen-induced hyperprolactinemia, which involves hyperactivation of D_2 receptor by an increased level of dopamine in the hypophyseal portal blood, was inhibited by talipexole but was enhanced by haloperidol. Under such experimental conditions, the hyperprolactinemia was enhanced by OPC-14597. On the other hand, the hyperprolactinemia induced 5 h after reserpine, which involves hypoactivation of dopamine D_2 receptors by a decreased level of dopamine in the blood, was inhibited by talipexole but was increased by haloperidol. The hyperprolactinemia produced 5 h after reserpine was reduced by OPC-14597. Our recent findings thus indicate that OPC-14597 has a mixed agonist/antagonist profile on dopamine D_2 receptors located at lactotroph cells and exerts an antagonistic or agonistic action depending on the preexisting tone of dopaminergic activities.

The present findings demonstrate that OPC-14597 induces yawning without causing stereotypy and rotation but antagonizes the talipexole-induced yawning and apomorphine-produced stereotypy in rats by exerting partial agonistic effects on yawning and antagonistic effects on stereotypy.

ACKNOWLEDGEMENT

The authors are grateful to Otsuka Pharmaceutical Company (Tokyo, Japan) for the gift of OPC-14597 and OPC-4392.

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