Biphasic Effects of D3-Receptor Agonists, 7-OH-DPAT and PD128907, on the D1-Receptor Agonist-Induced Hyperactivity in Mice

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ABSTRACT—Effects of D3-receptor agonists, 7-OH-DPAT and PD128907, on the D1-receptor agonist SKF81297-induced hyperactivity in mice were examined. 7-OH-DPAT and PD128907 significantly suppressed the SKF81297-induced hyperactivity at low doses, but significantly potentiated the hyperactivity at high doses. These D3-agonists alone had no effect on the motor activity. A σ-receptor agonist that reduces dopamine release had no effect on the SKF81297-induced hyperactivity. These results suggest that lower doses of 7-OH-DPAT and PD128907 may negatively influence the D1-receptor mediated behaviors via postsynaptic D3-receptors. On the other hand, higher doses of these compounds may positively influence these behaviors via D2- or D3-receptors.

Keywords: D1-receptor agonist, D3-receptor agonist, Motor activity

There are two superfamilies of dopamine receptors, designated D1-like (D1a, D1b) and D2-like (D2a, D2b, D3, D4) receptors by their sequence and biochemical and pharmacological functions (1). The D1-like receptors are coupled positively to adenylate cyclase, but D2-like receptors are negatively coupled to the enzyme. Recent studies have indicated that selective D1-agonists and D2-agonists act synergistically in an expression of stereotypy and the rewarding effects, suggesting that the interactions between D1- and D2-receptors may play an important role in the expression of dopamine-mediated multiple behaviors (2, 3). However, the interactions between D1- and D2-receptors in the dopamine-mediated behavior remains unclear.

Activation of D2-receptors induces hyperlocomotion in rodents, while D2- and D3-receptor agonists show biphasic effects on locomotor activity, depending on the doses used (4, 5). It is well-established that the locomotor suppression by the low doses of D2-agonists is considered to be the reflection of a preferential stimulation of presynaptic dopamine autoreceptors, resulting in a reduction of dopamine synthesis and release. On the other hand, the behavioral suppression induced by D3-receptor agonists does not always coincide with the reduced dopamine release and synthesis (6, 7). Thus, the mechanism of the behavioral suppression induced by D3-receptor agonists may be different from that by D2-receptor agonists.

In the present study, the effects of the D3-receptor agonists, 7-OH-DPAT and PD128907, on D1-receptor agonist SKF81297-induced hyperactivity were examined. Previous studies demonstrated that σ-opioid receptor agonists attenuate the dopamine-related behaviors by the inhibition of dopamine release (8, 9). Therefore, the effects of the σ-opioid receptor agonist U50,488H on the SKF81297-induced hyperactivity were also examined.

Male ddY mice (Nihon SLC, Atsugi) were used for the following experiments. The mice were housed at a room temperature of 20–25°C with a 12-hr light-dark cycle (lights on at 7:00 AM). Food and water were available ad libitum. The drugs used in the present study were (±)-6-chloro-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepin hydrobromide (SKF81297), (±)-7-hydroxy-N,N-di-n-propyl-2-aminotetralin hydrobromide (7-OH-DPAT), (+)-(4aR,10bR)-3,4,4a,10b-tetrahydro-4-propyl-2H,5H-[1]benzopyrano-[4,3-b]1,4-oxazin-9-ol hydrochloride (PD128907) and trans-(±)-3,4-dichloro-N-methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-benzeneacetamide (U50,488H) methane sulfonate. All drugs were purchased from Research Biochemicals, Inc. (Natick, MA, USA) and dissolved in saline. All the following procedures were conducted in accordance with the guiding principles for the care and use of laboratory animals by the Japanese Pharmacological Society and with the guidelines of animal care in our laboratories, as approved by the Meiji...
Seika Pharmaceutical Research Center Committee on animal care and use. The motor activity of mice was measured in an open cubic transparent plastic box (30 × 30 × 30 cm) placed on an Animex apparatus (Muromachi Kikai, Tokyo) in a sound-proof box to avoid the circumstantial effects. The data of locomotor activity was collected and analyzed with a personal computer. After the administration of each drug, the animal was individually placed into the cubic box for 35 min. To neglect initial explorative behavior, the record started 5 min later. 7-OH-DPAT (s.c.) and PD128,907 (s.c.) were injected just before placing the animal into the box, and SKF81297 (i.p.) and U50,488H (s.c.) were injected 20 min and 30 min before the placing it in the box respectively. Data are expressed as the mean with S.E.M. One-way analysis of variance (ANOVA) followed by Dunnett’s t-test were used for a statistical analysis.

SKF81297 increased motor activity in a dose-dependent manner, and significant increases were observed around doses of 3.2–10 mg/kg (Fig. 1). The lower doses of 7-OH-DPAT and PD128,907 significantly suppressed the SKF81297 (3.2 mg/kg)-induced hyperactivity, but both drugs potentiated the hyperactivity at higher doses (Fig. 2), while 0.032–1.0 mg/kg 7-OH-DPAT and 0.1–3.2 mg/kg PD128,907 alone had no effect on the motor activ-

![Graph](image1)

Fig. 1. Effect of SKF81297 on motor activity in mice. Each column represents the mean total counts with S.E.M. of 6–7 animals. **P<0.01 vs saline control.

![Graph](image2)

Fig. 2. Effects of 7-OH-DPAT, PD128,907 (A) and U50,488H (B) on SKF81297 (3.2 mg/kg)-induced hyperactivity in mice. Each column represents the mean total counts with S.E.M. of 5–9 animals. *P<0.05 vs SKF81297 control. **P<0.01 vs SKF81297 control.
ity (Fig. 3A). On the other hand, U50,488H (2 mg/kg) showed no effect on the SKF81297-induced hyperactivity (Fig. 2B) and the spontaneous locomotor activity (Fig. 3B).

Previous reports demonstrated that a D3-receptor agonist alone produces biphasic effects on motor behaviors and motivational effects in rodents (6, 7, 10, 11). Furthermore, 7-OH-DPAT can modify morphine- or cocaine-induced dopamine-related behaviors (12, 13). In the present study, we could not find any biphasic effects by the tested D3-receptor agonists, 7-OH-DPAT and PD128907 alone, but these D3-receptor agonists were found to have biphasic effects on the SKF81297-induced hyperlocomotion. The difference between previous results and the present results may be attributable to differences in the light condition, measurement method of motor activity (photocell counter versus animex) or dose ranges. Consistent with our data, Suzuki et al. (12) showed that 7-OH-DPAT (0.01–0.3 mg/kg) had no effect on the locomotor activity measured by an ambulometer in mice.

The dopaminergic (especially mesolimbic) system plays an important role in the motor behavior and motivational effects. D1-receptor agonists stimulate the postsynaptic D1-receptors, resulting in an increase in locomotor activity (2). On the other hand, recent papers demonstrated that D3-receptors are particularly distributed in the limbic area and suggested that this receptor subtype may function as a dopamine autoreceptor (7, 14). Low doses of 7-OH-DPAT produce hypolocomotion and aversive effects, and they attenuated morphine-induced hyperlocomotion in rodents (6, 7, 10–13). Nevertheless, the behavioral suppression induced by D3-receptor agonists does not always coincide with the reduction of dopamine release and synthesis (6, 7). Thus, the mechanisms of D3-receptor agonists-induced hypoactivity remains unclear.

If the suppressive effect of a D3-receptor agonist on the SKF81297-induced hyperlocomotion was mediated by the reduction of dopamine release via dopamine autoreceptors, U50,488H would also be expected to suppress the SKF81297-induced hyperactivity because it suppresses dopamine release from the nucleus accumbens and attenuates the morphine-induced dopamine-related behaviors (8, 9). However, the SKF81297-induced hyperactivity was not suppressed by U50,488H. Thus, SKF81297-induced hyperactivity may not be affected by the decrease of dopamine release from dopaminergic neurons. These results suggest that the postsynaptic D3-receptors play a much greater role than presynaptic D3-receptors in the inhibitory effects of 7-OH-DPAT and PD128907 on SKF81297-induced hyperactivity.

Starr and Starr (15) demonstrated that a combination of the D1-receptor agonist SKF38393 and 7-OH-DPAT caused an increase of locomotor activity under a particular condition such as reserpine treatment, but not in naive mice. In the present study, however, high doses of D3-receptor agonists potentiated the SKF81297-induced hyperlocomotion in naive mice. These discrepancies between the present results and previous findings (15) in
naive mice may depend on the fact that SKF81297 is a full agonist, while SKF38393 is a partial agonist. The weak behavioral stimulant effects of SKF38393 are often related to its partial agonist activity and may not completely account for the functional capacity of D1-receptors (2). On the other hand, an in vitro study demonstrated that 7-OH-DPAT and PD128907 had affinities to D2- and D3-receptors at higher concentrations (7). The D2-receptor agonists enhance the D1-receptor agonist-induced stereotypy and rewarding effects (2, 3). Therefore, we cannot exclude the possibility that the potentiation of SKF81297-induced hyperactivity by 7-OH-DPAT and PD128907 depends on their D2-agonistic, but not D3-agonistic profile. 7-OH-DPAT or PD128907, however, potentiated the SKF81297-induced hyperactivity at lower doses than the doses of D3-receptor agonists used in the previous reports (6, 7, 10–12). We could not clarify which receptor (D2- or D3-) plays a major role in the potentiation of SKF81297-induced hyperactivity by 7-OH-DPAT and PD128907. More selective D2-receptor agonists or antagonists are necessary to elucidate the role of D3-receptors in the dopamine-related behaviors.

In summary, the results of the present study suggest that low doses of 7-OH-DPAT and PD128907 suppress the SKF81297-induced hyperactivity via post synaptic D3-receptors, while both drugs significantly potentiate the hyperactivity at high doses via D2- or D3-receptors.

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