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Involvement of D_1 and D_2 Dopamine Systems in the Behavioral Effects of Cocaine in Rats

I. USHIJIMA, M. A. CARINO AND A. HORITA[1]

Department of Pharmacology, School of Medicine, University of Washington, Seattle, WA 98195

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USHIJIMA, I., M. A. CARINO AND A. HORITA. *Involvement of D_1 and D_2 dopamine systems in the behavioral effects of cocaine in rats.* PHARMACOL BIOCHEM BEHAV **52**(4) 737-741, 1995.—Cocaine (5-40 mg/kg, intraperitoneally) enhanced locomotion and rearing accompanied with head circling and body shaking. Although at 40 mg/kg typical stereotypy licking occasionally appeared, 40% of the rats died. At doses that did not affect physiologic locomotion and rearing, the D_1-receptor antagonist SCH23390 but not D_2 antagonist raclopride inhibited locomotion and rearing stimulated by cocaine (20 mg/kg). All behavioral responses of cocaine were abolished with increasing doses of raclopride and SCH23390. Sulpiride, a D_2 antagonist, exerted a biphasic effect on locomotor activity (i.e., a low dose of sulpiride increased and a high dose decreased cocaine-induced locomotor activity). Sulpiride enhanced head circling, body shaking, and increases of rearing induced by cocaine. D_2-receptor agonists quinpirole and bromocriptine inhibited these responses, presumably by activating the typical stereotyped behaviors such as sniffing at low doses, and licking and gnawing at high doses. The lowest dose of bromocriptine inhibited all behaviors induced by cocaine without producing typical stereotyped behaviors in itself. SK&F38393, a D_1-receptor agonist, in combination with cocaine did not induce typical stereotypy, which results in a synergistic effect of D_1 and D_2-receptor activities. The increases of locomotion and rearing, head circling, and body shaking induced by cocaine may involve the indirect activation of postsynaptic D_1 and D_2 receptors, presumably via dopamine release, resulting from inhibition of the presynaptic D_2 receptors. These results also provide evidence that the indirect stimulation of postsynaptic D_2 receptors by cocaine (20 mg/kg) is insufficient to induce stereotyped behaviors, and that the role of dopamine D_1 receptors in mediating the behavioral actions of acute cocaine appears to be more important than that of D_2 receptors. Our results also suggest that bromocriptine may be useful for the treatment of acute cocaine poisoning.

Cocaine Locomotion Stereotypy D_1 and D_2 systems Rats

COCAINE has several different pharmacologic actions in the CNS. It is an inhibitor of dopamine uptake (an indirect-acting dopamine receptor agonist) and a local anesthetic. Cocaine at higher blood concentrations produces apprehension, anxiety, delirium, and schizophrenic-like psychoses in the human (17,31). Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats (4). Cocaine at higher doses produces hyperlocomotion and stereotyped behaviors in animals. The predominant cocaine-induced behaviors shift from those of hyperlocomotion to stereotyped behaviors with increasing dose or number of injections (18). Psychomotor stimulants generally increase the availability of catecholamines at CNS synapses by increasing release, decreasing reuptake, and/or inhibiting metabolism of catecholamines (11,30). The psychotropic effects of cocaine are usually attributed to its ability to block the reuptake of dopamine into mesocortical or mesolimbic neurons, rather than to its ability to block the reuptake of serotonin and norepinephrine (5). The psychomotor stimulant effects of cocaine are prevented by pretreatment with reserpine, a monoamine-depleting agent, or dopamine (DA)-receptor antagonists (21,29). Thus, the euphorigenic property of cocaine is thought to be related to its ability to indirectly enhance dopaminergic function.

DA receptors are of two types, D_1 and D_2. DA as a transmitter substance can influence the postsynaptic neurons in two distinct ways. Acting on D_1 receptors, it activates adenyl cyclase and increases cyclic AMP (9). In the striatum, activation of D_2 receptors inhibits adenyl cyclase activity, counteracting the effect of D_1 receptor activation (23), but this counteraction is absent in the nucleus accumbens (24). Evidence suggests that D_1 and D_2 receptors can interact in either a synergistic or opposing fashion. Dopamine D_1- and D_2-receptor agonists are behaviorally ineffective by themselves, but inter-

[1] Requests for reprints should be addressed to A. Horita, Department of Pharmacology, SJ-30, School of Medicine, University of Washington, Seattle, WA 98195.

act synergistically to stimulate locomotion and to induce stereotypy (1); locomotion depends on the activation of the D_1 receptor (22), and oral stereotyped behaviors such as licking and gnawing depend on the activation of the D_2 receptors (1,27,28). Selective D_2-receptor agonists cannot reverse the akinesia produced by reserpine unless D_1 receptors are concurrently stimulated by D_1-receptor agonists (6,8,32). On the other hand, the antinociceptive effect of cocaine in rats is modified in an opposite manner by the dopamine receptor agonists (i.e., the D_1 agonist increases and D_2 agonist decreases the antinociceptive effect). These effects of DA agonists are reversed by their respective antagonists. Because of this opposing nature of the D_1 and D_2 systems, it was suggested that these two receptor subtypes are independent of each other in influencing cocaine-induced antinociception (26). This study was designed to clarify whether some of the behavioral effects of cocaine are altered by pretreatment with DA D_1 receptor antagonist (SCH23390), D_1-receptor agonist (SK&F38393), D_2-receptor antagonists (raclopride and sulpiride), or D_2-receptor agonists (quinpirole and bromocriptine).

METHODS

Animals

Healthy male Sprangue-Dawley rats (250–310 g) were permitted food and water ad lib except during trials. All trials and breeding were carried out at an environmental temperature of 24 ± 1°C with a 12 L : 12 D cycle. All experiments were carried out at 900–1200 h.

Measurement of Behaviors

Locomotor activity (ambulation), rearing, stereotypy (sniffing, licking, gnawing, head circling), and body shaking in rats were measured using an open-field apparatus. The open-field chamber was 1 × 1 × 0.6 m, and the floor was divided into nine segments. Five minutes after the animal was placed in the center of the floor, each behavioral response was recorded every 10 min for 60 min.

Locomotor activity. The number of segments on the floor traversed by the rat was recorded.

Other behavioral responses. Each pattern of behavioral response such as sniffing, licking, gnawing, and head circling was scored: i.e., 0 = absent; 1 = mild or discontinuous (0–10 s); 2 = continuous (10–20 s); and 3 = marked continuous (20–30 s). When marked continuous behavior was 30–40 s, 40–50 s, and 50–60 s, the score was counted as 4, 5, and 6, respectively. The frequency of rearing and body shaking responses was counted every 10 min for 60 min.

Administration of Drugs

Rats given intraperitoneal (IP) doses of 5–40 mg/kg cocaine or 1 ml/kg saline were monitored for the appearance of the various behavioral responses (Fig. 1). To examine the influence of DA antagonists on behavioral responses, we injected cocaine (20 mg/kg, IP) 10 min after SCH23390 (0.01 and 0.1 mg/kg) or raclopride (0.01 and 0.1 mg/kg), or 15 min after sulpiride (10 and 50 mg/kg). For the agonist interaction studies we administered cocaine 10 min after quinpirole (0.1 and 1.0 mg/kg), bromocriptine (2, 5 and 20 mg/kg), or SK&F38393 (5 mg/kg).

Drugs

The drugs used were cocaine hydrochloride (Sigma, St. Louis, MO), SCH23390 (RBI, Natick, MA), sulpiride (RBI), SK&F38393 (RBI), raclopride (Astra Läkemedel AB, Södertälije, Sweden), quinpirole hydrochloride (RBI), and bromocriptine mesylate (Sandoz, AG, Basle, Switzerland).

SK&F38393 and quinpirole were dissolved in ethanol (0.1 ml) and subsequently diluted with saline (10 ml). Sulpiride and bromocriptine were suspended in 3% Tween 80 solution. All other drugs were dissolved in saline. These drugs were injected IP in a volume of 1 ml/kg. Doses are expressed as authentic substances.

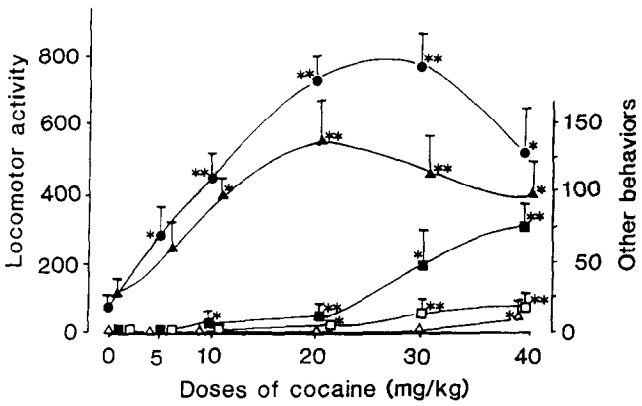

FIG. 1. Dose responses to cocaine-induced behaviors. Each value is the mean ± SEM. Locomotor activity (●), rearing (▲), head circling (■), sniffing (□), licking (△): $*p < 0.05$, $**p < 0.002$, significant difference from saline group (0).

Statistics

Locomotor activity was expressed as mean values. Statistical analysis was done using Kruskal-Wallis one-way analysis of variance (ANOVA) and Newman-Keuls one-way test for locomotor activity, and Mann-Whitney *U*-test for other behavioral responses. The level of significance chosen was $p < 0.05$.

RESULTS

Behavioral Responses Induced by Cocaine

As shown in Fig. 1, rats given cocaine (5–20 mg/kg) showed an increased locomotor or rearing activities in a dose-dependent manner, as compared with saline-injected rats. Locomotion was maximal 0–10 min and rearing 10–20 min after administration. Cocaine (20–40 mg/kg) induced dose-related head circling, body shaking, and sniffing, whereas typical stereotypy (oral stereotypy) such as biting and gnawing was absent. At 40 mg/kg, licking was seen occasionally, but four of 10 rats died. These behaviors were not observed in saline-injected rats.

Effects of DA D_1- and D_2-Receptor Antagonists on Cocaine-Induced Behavioral Responses

As summarized in Table 1, SCH23390 (0.01 mg/kg) and raclopride (0.01 mg/kg) did not inhibit natural locomotor activity and rearing responses in saline-treated rats. However, these responses stimulated by cocaine (20 mg/kg) were inhibited by SCH23390 (0.01 and 0.1 mg/kg) and raclopride (0.1 mg/kg), but not raclopride (0.01 mg/kg). The blocking effects of SCH23390 and raclopride on cocaine-stimulated locomotor activity and rearing responses were dose-dependent. SCH23390

TABLE 1

EFFECTS OF D_1 AND D_2 ANTAGONISTS ON BEHAVIORS INDUCED BY COCAINE

Drugs (mg/kg)	Locomotion	Rearing	Head Circling	Body Shaking	(N)
Saline + saline	63.3 ± 11.4	29.0 ± 8.2	0.0 ± 0.0	0.0 ± 0.0	(6)
Saline + cocaine (20)	735.8 ± 67.9‡	138.8 ± 38.9‡	8.4 ± 2.5‡	3.9 ± 0.9*	(10)
SCH23390 (0.01) + saline	52.4 ± 14.2	21.2 ± 5.3	0.0 ± 0.0	0.0 ± 0.0	(6)
SCH23390 (0.1) + saline	3.8 ± 2.6*	2.3 ± 1.7*	0.0 ± 0.0	0.0 ± 0.0	(6)
SCH23390 (0.01) + cocaine	265.3 ± 45.4†	50.2 ± 11.3†	2.2 ± 0.1†	0.0 ± 0.0†	(6)
SCH23390 (0.1) + cocaine	5.8 ± 3.4§	3.8 ± 1.8§	1.3 ± 0.5†	0.0 ± 0.0†	(6)
Raclopride (0.01) + saline	45.9 ± 17.3	20.7 ± 4.3	0.0 ± 0.0	0.0 ± 0.0	(6)
Raclopride (0.1) + saline	0.6 ± 0.2§	0.0 ± 0.0‡	0.0 ± 0.0	0.0 ± 0.0	(6)
Raclopride (0.01) + cocaine	696.2 ± 38.1	94.8 ± 10.2	8.8 ± 3.2	3.0 ± 0.8	(6)
Raclopride (0.1) + cocaine	73.8 ± 10.5§	0.5 ± 0.2§	2.5 ± 0.0§	1.7 ± 0.4†	(8)
Sulpiride (10) + saline	75.3 ± 35.2	32.4 ± 12.3	0.0 ± 0.0	0.0 ± 0.0	(6)
Sulpiride (50) + saline	44.7 ± 31.7	30.2 ± 11.5	0.0 ± 0.0	0.0 ± 0.0	(6)
Sulpiride (10) + cocaine	1342.3 ± 82.4†	275.3 ± 55.1†	58.5 ± 18.2§	21.5 ± 8.3§	(10)
Sulpiride (50) + cocaine	480.9 ± 39.9†	232.6 ± 45.5†	50.2 ± 14.1§	18.9 ± 5.2§	(10)

Respective behaviors were observed for 60 min. Each value is the mean ± SEM.
,†$p < 0.05$, ‡,§$p < 0.002$, significant difference from saline (,†) and cocaine (†,§).

(0.01 and 0.1 mg/kg) and raclopride (0.1 mg/kg but not 0.01 mg/kg) also blocked head circling and body shaking responses induced by cocaine (20 mg/kg).

Although sulpiride at 10 and 50 mg/kg did not affect locomotor or rearing activity in control animals, at 10 mg/kg it significantly increased total locomotion produced by cocaine. At 50 mg/kg sulpiride significantly reduced the response to below that produced in saline plus cocaine-treated animals. The inhibitory effect of high-dose sulpiride appeared gradually over a 30-min period. Furthermore, the drug potentiated head circling and body shaking and increased rearing responses induced by cocaine. SCH23390 (0.1 mg/kg) and raclopride (0.1 mg/kg, IP) diminished all behavioral responses induced by cocaine.

Effects of D_1- and D_2-Receptor Agonists on Cocaine-Induced Behavioral Responses

As shown in Table 2, pretreatment with SK&F38393 (5 mg/kg) did not affect hyperlocomotion but increased the rearing response activated by cocaine (20 mg/kg). SK&F38393 (5 mg/kg) in combination with cocaine (20 mg/kg) slightly increased sniffing but did not produce oral stereotypy, such as licking and gnawing activities.

Quinpirole (0.1 and 1.0 mg/kg) and bromocriptine (2-20 mg/kg) dose-dependently inhibited locomotor activity stimulated by cocaine (20 mg/kg) and abolished cocaine-stimulated rearing as well as natural rearing responses. Quinpirole (0.1 and 1.0 mg/kg), bromocriptine (5 and 20 mg/kg), or cocaine (20 mg/kg) alone did not induce typical stereotypy such as sniffing, licking, gnawing, and biting, but the combination of cocaine and quinpirole (0.1 mg/kg) or bromocriptine (5 mg/kg) produced sniffing, whereas licking and gnawing responses were observed only with higher doses of quinpirole (1 mg/kg) or bromocriptine (20 mg/kg). The lowest dose of bromocriptine (2 mg/kg) in combination with cocaine (20 mg/kg) did not produced typical stereotypy.

SK&F38393 (5 mg/kg) alone did not induce hyperlocomotor activity or typical stereotypy. The scores were similar to those of saline-injected control rats. The only prominent effect of SK&F38393 was the production of frequent episodes of intense grooming and preening behaviors. Quinpirole (0.1 and 1.0 mg/kg) alone did not produce consistent licking, biting, or gnawing. SK&F38393 combined with quinpirole (0.1 mg/kg) produced hyperlocomotion and sniffing, and with 1.0 mg/kg, oral stereotypy such as licking and gnawing (Table 2).

DISCUSSION

In this study, cocaine (5-20 mg/kg, IP) increased locomotor activity and rearing responses accompanied with head movement (head circling) and body shaking responses in a dose-dependent manner. Cocaine at these doses did not produce typical stereotyped behaviors such as sniffing, licking, gnawing, and biting. The locomotor effects are mediated primarily via the dopaminergic system in mesolimbic areas (nucleus accumbens and tuberculum olfactorium), whereas the stereotyped behaviors are mediated mainly via that in the nigrostriatal areas (2,10). The action of cocaine on the dopaminergic system in mesolimbic areas may be more potent than that in nigrostriatal areas, because cocaine prefers to induce hyperlocomotion rather than stereotypy. The treatments with SCH23390, a selective D_1 DA-receptor antagonist, and raclopride, a specific D_2-receptor antagonists, significantly reduced the effects of cocaine on locomotor activity. These results imply that the stimulatory effects of cocaine on locomotor activity involve the activation of both D_1 and D_2 receptors. Sulpiride, which is well known as a D_2 antagonist, exerted biphasic action in cocaine-stimulated locomotor activity [i.e., an increase at a lower dose (10 mg/kg), but a decrease at higher dose (50 mg/kg)]. Sulpiride, which has been hypothesized to have a higher affinity for the presynaptic than for the postsynaptic D_2 receptor (20), could antagonize apomorphine sedation by preferential blockade of DA autoreceptors, suggesting that a low dose of sulpiride could release DA from the presynaptic nerve ending. Because an intrastriatal injection of sulpiride evokes catalepsy, which is the result of blockade of striatal postsynaptic DA D_2 receptors (16), it may be surmised that the peripheral administration of sulpiride initially inhibits the autoregulatory presynaptic DA D_2 receptors, and then as more drug enters the brain, gradually inhibits postsynaptic D_2 receptors.

TABLE 2

EFFECTS OF D_1 AND D_2 RECEPTOR AGONISTS ON BEHAVIORS INDUCED BY COCAINE

Drugs (mg/kg)	Locomotion	Rearing	Head Circling	Body Shaking	Sniffing	Licking	Gnawing	(N)
Saline + saline	63.3 ± 11.4	29.0 ± 8.2	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	(6)
Saline + cocaine (20)	735.8 ± 67.9‡	138.8 ± 38.9‡	8.4 ± 2.5‡	3.9 ± 0.9*	0.8 ± 0.0*	0.0 ± 0.0	0.0 ± 0.0	(10)
SKF38393 (5) + saline	73.5 ± 13.0	49.3 ± 12.5	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	(6)
SKF38393 (5) + cocaine	714.8 ± 63.4	233.3 ± 75.1†	5.2 ± 1.8	1.4 ± 0.8	0.4 ± 0.1	0.0 ± 0.0	0.0 ± 0.0	(6)
Quinpirole (0.1) + saline	65.4 ± 15.1	0.0 ± 0.0‡	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	(6)
Quinpirole (1) + saline	48.2 ± 14.3	0.0 ± 0.0‡	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	(6)
Quinpirole (0.1) + cocaine	317.2 ± 45.3†	0.0 ± 0.0§	0.0 ± 0.0§	0.0 ± 0.0§	36.5 ± 11.8§	0.0 ± 0.0	0.0 ± 0.0	(8)
Quinpirole (1) + cocaine	225.2 ± 24.2†	0.0 ± 0.0§	0.0 ± 0.0§	0.0 ± 0.0§	32.3 ± 9.9§	32.5 ± 8.7§	19.2 ± 3.2§	(8)
Bromocriptine (2) + saline	56.2 ± 10.3	0.0 ± 0.0‡	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	(6)
Bromocriptine (5) + saline	45.1 ± 9.2	0.0 ± 0.0‡	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	(6)
Bromocriptine (20) + saline	10.3 ± 2.4*	0.0 ± 0.0‡	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	(6)
Bromocriptine (2) + cocaine	135.4 ± 21.3§	0.0 ± 0.0§	0.0 ± 0.0§	0.0 ± 0.0§	0.0 ± 0.0†	0.0 ± 0.0	0.0 ± 0.0	(8)
Bromocriptine (5) + cocaine	123.6 ± 18.3§	0.0 ± 0.0§	0.0 ± 0.0§	0.0 ± 0.0§	2.8 ± 0.5†	0.0 ± 0.0	0.0 ± 0.0	(8)
Bromocriptine (20) + cocaine	95.2 ± 15.4§	0.0 ± 0.0§	0.0 ± 0.0§	0.0 ± 0.0§	1.4 ± 0.4†	14.4 ± 7.8§	10.3 ± 4.2§	(8)
SKF38393 + quinpirole (1)	315.2 ± 50.2*	0.0 ± 0.0‡,‖	0.0 ± 0.0	0.0 ± 0.0	48.2 ± 8.5‡,‖	39.1 ± 9.5‡,‖	6.2 ± 2.1‡,‖	(6)

,†$p < 0.05$, ‡,§, ‖$p < 0.002$, significant difference from saline (,‡), cocaine (†,§) and SKF38393 (‖), $n = 6$-10.

A new D_2 antagonist, raclopride, whose chemical structure is similar to that of sulpiride, has been reported to have a relatively high affinity for D_2 receptors. Its affinity for D_1 receptors is as low as that of sulpiride (12,15). Sulpiride, however, enhanced the increased rearing, head circling, and body shaking induced by cocaine, but raclopride blocked these behaviors, suggesting that the affinity of these drugs on the two D_2-type receptors (pre- and postsynaptic D_2 receptors) may be different. It seems that the inhibitory effect of sulpiride on the presynaptic D_2 receptor is more potent than that on the postsynaptic D_2 receptors, whereas that of raclopride is the opposite. Alternatively, the difference between the sulpiride and raclopride effects may be explained on a pharmacokinetic basis rather than a pharmacodynamic one (sulpiride does not cross the blood-brain barrier as easily as raclopride).

The increased rearing, head circling, and body shaking induced by cocaine were completely blocked by SCH23390, quinpirole, and bromocriptine, as well as raclopride. The rearing, preening, and grooming behaviors were enhanced by the selective D_1-receptor agonist SK&F38393, which by itself can induce these behaviors (1,14), whereas D_2-receptor agonists quinpirole and bromocriptine completely blocked these responses. The behavioral difference between cocaine and SK&F38393 effects is that cocaine but not SK&F38393 alone induced head circling and body shaking. Accordingly, cocaine-induced behaviors may involve the indirect activation of postsynaptic D_1 receptors rather than the D_2 receptors. Because quinpirole and bromocriptine activate pre- and postsynaptic DA D_2 receptors, the inhibitory effects of these drugs on rearing, head circling, and body shaking may be due to the blockade of DA release, presumably via the activation of the presynaptic rather than the postsynaptic D_2 receptors.

There are reports that bromocriptine is also effective in attenuating acute cocaine addiction (7) and euphoria (25). In this study, the main behavioral responses of cocaine in rats seem to be hyperlocomotion and increases of rearing and head circling, which are inhibited with low doses of bromocriptine, which is not in itself behaviorally active. DA D_2-receptor agonist quinpirole decreases the antinociceptive effect of cocaine and the decreasing effect is reversed by its antagonist, although both D_2 agonists and antagonists are without activity by themselves (26). Bromocriptine also acutely antagonized cocaine-induced behavioral arousal and depression at doses that are not active in themselves (3). However, any possible therapeutic benefits of the acute administration of bromocriptine in cocaine abuse are not likely to be the direct result of modulation of the acute effects of cocaine (19).

Memo et al. (13) reported that in the striatum and nucleus accumbens, both spiperone-binding site and dopamine-sensitive adenyl cyclase (D_1-receptor stimulation) were increased after acute cocaine administration. These results suggest that the stimulatory effects of acutely administered cocaine on locomotor activity may be mediated mainly via the activation of D_1 receptors, although D_2-receptor activity is also necessary.

In this study, cocaine-induced hyperlocomotor activity was inhibited by quinpirole (0.1 and 1.0 mg/kg) and bromocriptine (5 and 20 mg/kg) and was replaced by typical stereotyped behaviors such as sniffing, licking, and gnawing. Bromocriptine (2 mg/kg) inhibited all behavioral responses of cocaine without inducing typical stereotypy. SK&F38393 in combination with cocaine did not induce these typical stereotyped behaviors, which resulted in the synergistic effect of D_1- and D_2-receptor activities (1,32). The ability of DA-receptor agonists to induce these behaviors may depend on the potency and ratio of D_2 vs. D_1 receptor activity (27,28). It is well known that

the D_1 receptors have a D_2 enabling role in locomotor activity (22). Even though a high dose of 40 mg/kg cocaine slightly induced sniffing and licking, 40% of the rats died, which indicated that this was a toxic dose. These results suggest that the indirect stimulation of postsynaptic D_2 receptors by cocaine (20 mg/kg) was insufficient to produce stereotyped behaviors. The behavioral action of cocaine seems to be greater via activation of D_1 receptors than that of D_2 receptors.

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