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RAPID COMMUNICATION

D_1 Dopamine Receptors in the Nucleus Accumbens Modulate Cocaine Self-Administration in the Rat

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MALDONADO, R., P. ROBLEDO, A. J. CHOVER, S. B. CAINE AND G. F. KOOB. *D_1 dopamine receptors in the nucleus accumbens modulate cocaine self-administration in the rat.* PHARMACOL BIOCHEM BEHAV **45**(1) 239–242, 1993.—Previous work using systemic injections of dopamine receptor antagonists has established that dopamine D_1 receptors may have a role in cocaine self-administration. The purpose of the present study was to test the hypothesis that these effects were mediated by dopamine D_1 receptors in the region of the nucleus accumbens. Animals were trained to perform operant responses to self-administer cocaine via an IV catheter on a fixed-ratio 5 (FR 5) schedule of reinforcement. SCH23390, a selective D_1 dopamine antagonist, significantly increased the self-administration of cocaine when injected into the nucleus accumbens. This increase in self-administration is thought to reflect decreases in the magnitude of the reinforcer, similar to the increase observed when the dose of cocaine is reduced. Similar doses of SCH23390 injected into the posterior caudate nucleus failed to alter cocaine self-administration. These data suggest that D_1 receptors in the nucleus accumbens are important for the reinforcing properties of cocaine.

Cocaine Self-administration SCH23390 D_1 dopamine receptors Rat

IV self-administration studies strongly suggest that dopaminergic mechanisms are involved in the reinforcing properties of psychomotor stimulants. It is well known that systemic injections of low doses of both D_1 and D_2 dopaminergic antagonists will increase responding for IV injections of cocaine (2, 3,9,15). This increase in self-administration behavior is thought to be a compensatory mechanism for decreases in the magnitude of the reinforcer, similar to the increase observed when the dose of the self-administered stimulant is reduced (8). Moreover, it has been reported that dopamine agonists function as positive reinforcers in the monkey (4) and rat (16). Finally, lesion studies suggest that the dopaminergic system in the nucleus accumbens plays a critical role as a neuroanatomic substrate for cocaine reinforcement in the rat (8,14). The purpose of the following study was to test the hypothesis that D_1 dopamine receptors in the nucleus accumbens mediate the reinforcing actions of cocaine by evaluating the effects of local intracerebral administration of the selective D_1 dopaminergic antagonist SCH23390 (7) on the self-administration of cocaine in the rat.

METHOD

Fourteen male albino Wistar rats weighing 260–300 g (Charles River, Kingston, Ontario) were used in this study. Animals were housed in groups of three and maintained in a temperature- and light-controlled environment. Rats had free access to food and water except during self-administration sessions. They were maintained on a 12 L : 12 D cycle and tested during the light phase. Rats were anesthetized with halothane and a silastic catheter was implanted in the jugular vein as previously described (13). Animals were then trained

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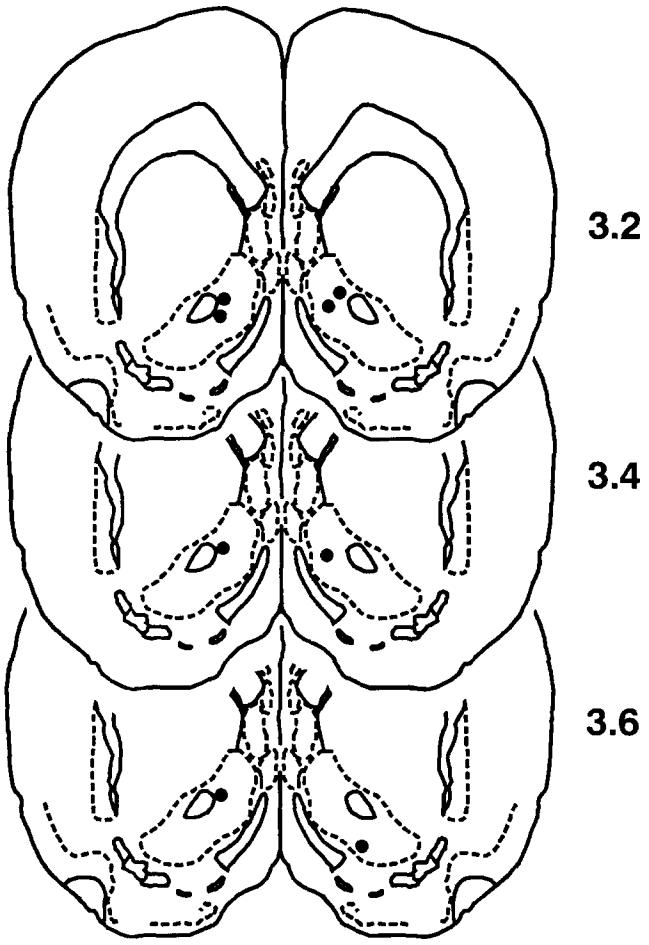

FIG. 1. Coronal sections based on the atlas of Pellegrino et al. (11), (bregma coordinates A: +3.2-3.6). Each black point corresponds to a final site of injection into the nucleus accumbens of an individual rat with cannulae aimed at the nucleus accumbens. Injections were bilateral through indwelling cannulae guides located 3 mm above the site of injection.

in operant chambers with extendable levers on a fixed-ratio 5 (FR 5) schedule of reinforcement. Completion of the FR 5 resulted in an IV injection of 0.25 mg cocaine (Sigma Chemical Co., St. Louis, MO) dissolved in 0.1 ml saline (a dose of approximately 0.75 mg/kg/injection) administered over a period of 4 s. The duration of each self-administration session was 3 h during training and testing. Following completion of training, rats were stereotaxically implanted with bilateral chronic-indwelling stainless steel guide cannulae (23 ga) aimed at the nucleus accumbens (with the tooth bar +5.0 mm: AP +3.2 from bregma, ML ±1.7, DV −7.8) (11) or posterior caudate (with the skull flat: AP −0.9 from bregma, ML ±4.4, DV −6.4) (10). The guides were implanted 3 mm above these injection sites. A recovery period of at least 3 days was given prior to testing. Rats were then given access to cocaine in daily 3-h sessions until baseline rates of self-administration (three consecutive sessions with less than ±10% variation in total number of injections self-administered) were established. Microinjections of the dopaminergic antagonist SCH23390 were administered through 30-ga internal cannulae that were inserted such that the tip extended 3 mm below the guide

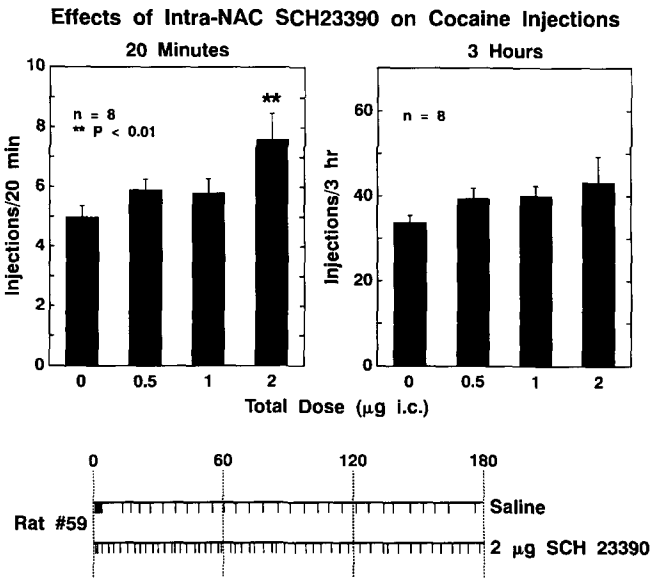

FIG. 2. Effects of local intracerebral administration of SCH23390 into the nucleus accumbens on IV cocaine self-administration. The abscissa represents the different intra-accumbens treatments. The ordinate expresses the number of injection ± S.E.M. for each group (n = 8). **p < 0.01 vs saline group (Dunnett's t-test). Left panel: total number of injections for the first 20 min of the session. Right panel: total number of injections for the whole 3-hour period. Bottom panel: self-administration record for a representative animal who received saline or 2 µg of SCH23390 immediately prior to the cocaine self-administration session.

cannulae. The injection volume for the bilateral injections was 0.3–0.5 µl per side and was injected over 70 s. The injection cannulae were left in place for an additional minute to allow for diffusion away from the cannulae tip. All doses were administered using a Latin square design to counterbalance the order of doses. In addition, a minimum of 2 days of baseline self-administration separated each treatment with SCH23390. Each subject received all doses of SCH23390, and statistical analyses were carried out using a within-subject analysis of

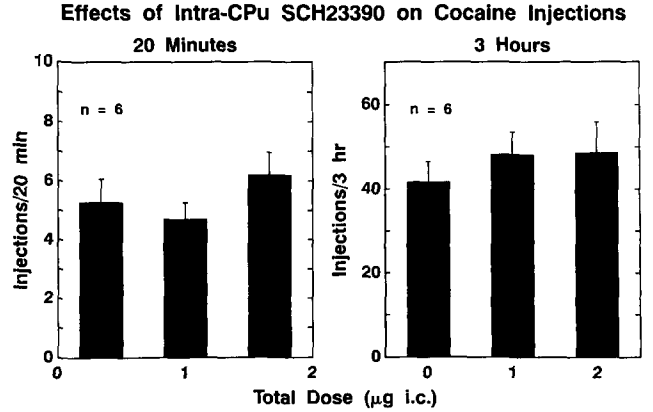

FIG. 3. Effects of local intracerebral administration of SCH23390 into the posterior caudate nucleus on IV cocaine self-administration (n = 6). Other details as in Figure 2.

variance with repeated measures on dose. Individual means comparisons were made using Dunnett's *t*- a posteriori test. SCH23390 maleate (Schering, Kenilworth, NJ) was dissolved in distilled water. Doses are expressed as total dose/brain, for example, total bilateral dose.

RESULTS

Intraaccumbens administration (see Fig. 1 for injection sites) of the selective D_1 dopamine receptor antagonist, SCH23390, induced a dose-dependent increase in responding for cocaine during the first 20 min of the session, $F(3, 24) = 4.95, p < 0.01$. The effect observed over the entire 3-h session after the administration of SCH23390 was not statistically significant, $F(3, 24) = 1.05$, n.s., due to the increased variability; several rats decreased responding completely for brief periods. The pattern of responding after intraaccumbens SCH23390 injection in general retained a regular interinjection interval, similar to saline-injected control animals during the 3 h of the self-administration session, and no extinction-like pattern was observed (see Fig. 2). Thus, the increase in the number of injections at the high dose reflects a decrease in the interinjection interval as is observed when the dose of cocaine is reduced.

Local intracerebral injection of SCH23390 into the posterior caudate nucleus failed to significantly increase cocaine self-administration (see Fig. 3) during the first 20 min, $F(2, 12) = 3.68$, n.s., or over the entire 3-h session, $F(2, 12) = 3.85$, n.s. The trend toward increases in the number of cocaine injections self-administered were not as dramatic as observed with the intraaccumbens injections at either the 20-min or 3-h interval.

DISCUSSION

It is now well documented that systemic administration of both D_1 and D_2 dopamine antagonists alters the rate of IV cocaine self-administration in rats (2,3,9,15) and monkeys (1). The present results show that the selective D_1 dopamine antagonist SCH23390 locally injected into the nucleus accumbens also increases cocaine self-administration in rats, without modifying the overall pattern of self-administration, except by decreasing the interinjection interval. The increase in cocaine self-administration can be interpreted as a decrease in the reinforcing properties of cocaine, similar to the rate increase observed when the dose of self-administered cocaine is reduced. The increase in cocaine self-administration following microinjections of SCH23390 was significant at 20 min but not 3 h, suggesting that the drug may diffuse away from the nucleus accumbens, where it produces its most robust effect. The trend toward increased responding over 3 h following SCH23390 injections into the posterior caudate nucleus may reflect spread of this lipophilic drug throughout the neuraxis.

Although there is some evidence to suggest that areas outside the nucleus accumbens may be involved in the rewarding properties of cocaine (5), the present data support previous findings suggesting an important role of the dopaminergic system in the nucleus accumbens in the expression of cocaine's rewarding properties (8). 6-Hydroxydopamine (14) or kainic acid (17) lesions of the nucleus accumbens and 6-hydroxydopamine lesions of the ventral tegmental area (13) decrease self-administration of cocaine in rats. Further, rats will self-administer amphetamine directly into the nucleus accumbens (6).

In the present study, the increases in cocaine self-administration observed after SCH23390 injections were dependent upon the dose of antagonist used. Identical effects were not observed after intracerebral injection of these doses into the posterior caudate nucleus, suggesting that dopamine receptors in the region of the nucleus accumbens are an important substrate mediating the effects of cocaine that produce its reinforcing actions. The results of the present study are consistent with an earlier report using the selective D_2 antagonist spiroperidol (12). In that report, spiroperidol dose dependently increased cocaine self-administration when injected into the nucleus accumbens but not the caudate nucleus. Together, these results suggest that both dopamine D_1 and D_2 receptors in the region of the nucleus accumbens are involved in mediating the reinforcing actions of cocaine.

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