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BRIEF COMMUNICATION

Cocaine Self-Administration Is Increased by Both D1 and D2 Dopamine Antagonists

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CORRIGALL, W. A. AND K. M. COEN. *Cocaine self-administration is increased by both D1 and D2 dopamine antagonists.* PHARMACOL BIOCHEM BEHAV 39(3) 799–802, 1991.—Rats were trained to self-administer cocaine on a fixed-ratio 5 schedule of reinforcement with a 1-min time-out period following each infusion. Cocaine was available at doses of either 0.1, 0.3 or 1.0 mg/kg/infusion. A low dose (3 μg/kg) of the D1 antagonist SCH23390 caused an increase in cocaine self-administration which was more prominent at higher, as compared to lower, doses of cocaine. Higher doses of SCH23390 generally caused decreases in self-administration which may in part be due to the response-decreasing properties of this agent. The D2 antagonist spiperone generally caused an increase in self-administration of cocaine. These data suggest that cocaine reinforcement depends upon both D1 and D2 receptor subtypes.

Cocaine Self-administration D1 dopamine antagonists D2 dopamine antagonists

IT is now well established that brain dopamine systems are prominently involved in the reinforcing effects of cocaine [e.g., see review in (5)]. A portion of the evidence in support of a role for dopamine in cocaine reinforcement consists of numerous demonstrations that treatment with dopamine antagonists will produce transient increases in cocaine self-administration [e.g., (4)], interpreted as reflecting a compensatory increase in cocaine self-administration consequent to the reduction in its reinforcing effects. More recently, with increasing knowledge of dopamine receptor systems, some experiments have sought to determine the effects on cocaine self-administration of treatment with antagonists selective for the D1 and D2 subtypes. However, concordant results have not always been obtained in these studies. For example, although most studies have reported that the D1 antagonist SCH23390 produces decreases in the rate of responding for a number of reinforcers, including cocaine [e.g., (3, 7, 8)], SCH23390 has been reported to increase cocaine self-administration in rats (6). Similarly, the D2 antagonist pimozide has been reported both to generally increase (7) and to decrease (8) cocaine self-administration; these latter differences may be due to differences in the schedule of reinforcement used.

The objective of the present experiment was to extend research into the effects of D1 and D2 antagonists on cocaine self-administration. Rats trained to self-administer cocaine at three different doses were treated with a range of doses of a D1 and a D2 antagonist in order to obtain a complete picture of the effects of these antagonists on cocaine reinforcement.

METHOD

Self-Administration

Subjects were 24 male, Long-Evans rats (Charles River, Lachine, Quebec), divided into 3 experimental groups, one for each of 3 doses of cocaine to be studied. Animals were drug naive prior to the start of surgical or training procedures and were housed in a reversed light:dark cycle colony room (lights off between 0700 and 1900 hours). Prior to the start of experimental procedures, animals were maintained in a free-feeding state and weighed approximately 300 g.

Techniques for training and surgery were similar to those that we have used previously (1,2). Animals were deprived of food for a short period (24–48 h), and trained to press a lever on a continuous reinforcement (CRF) schedule for food pellets (45 mg). Once trained, animals were fed their daily nutritional requirement of approximately 20 g of standard rat chow as a single meal. After recovery of body weight, each animal was surgically prepared with a chronic intravenous catheter implanted in the jugular vein; the catheters exited between the scapulae. Surgery was performed under anesthesia induced by acepromazine maleate (10 mg/kg IP) and ketamine hydrochloride (100 mg/kg IM). Animals were allowed to recover for a period of 3–7 days before drug self-administration sessions were begun.

Access to cocaine was initially on a CRF schedule with a 1-minute signalled time-out (TO) period following each drug in-

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fusion. During the TO, responding was recorded but did not lead to drug delivery. Over a period of two to three weeks the response requirements were increased to the final value of fixed-ratio 5 (FR5); the TO remained at 1 min. Acquisition of self-administration occurred at a unit dose of cocaine of 0.3 mg/kg/infusion. The cocaine dose was changed to 0.1 mg/kg/infusion in one of the groups following acquisition, and to 1.0 mg/kg/infusion in another.

Self-administration sessions were carried out in operant chambers equipped with two levers. Responding on one of the levers resulted in drug delivery when schedule requirements were met, while responding on the other lever was recorded but was never reinforced. Self-administration sessions were 60 min in duration and occurred once daily Monday through Friday.

Pretreatments with dopamine antagonists were done acutely, with each dose of antagonist administered once. SCH23390 was used as D1 antagonist and spiperone as D2 antagonist. Pretreatments were carried out a maximum of two days each week (Tuesday and Friday). Injections were given subcutaneously (SC) in a volume of 1 ml/kg, and in a nonsystematic fashion. For the D1 antagonist SCH23390, injections were given 30 min before the start of self-administration sessions, whereas for the

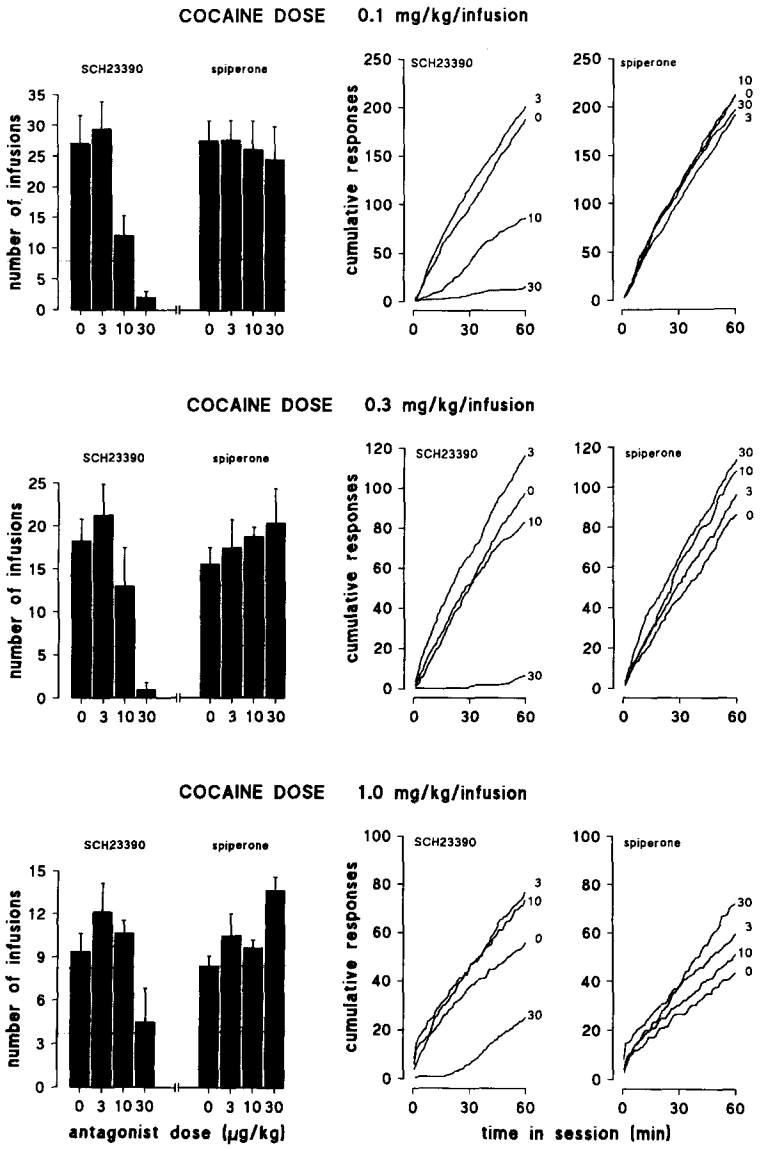

FIG. 1. Left-hand side. Number of cocaine infusions obtained in 1 h self-administration sessions after treatment with various doses of the dopamine antagonists SCH23390 and spiperone. Bars indicate one standard error of the mean. Right-hand side. Average cumulative response records for the same subjects. A different group of animals was treated at each dose of cocaine; at a given dose of cocaine, the same sample (n = 8) received all treatments.

D2 antagonist spiperone, injections were given 60 min prior to the start of the sessions. Doses of 0, 3, 10, and 30 μg/kg were tested for spiperone and SCH23390.

Drugs and Solutions

The following drugs were used: cocaine hydrochloride (B.D.H.), and SCH23390 hydrochloride and spiperone (both from Research Biochemicals, Inc.). Cocaine solutions were prepared in saline and passed through a 0.22 μm filter to sterilize them prior to use. For self-administration, the solution concentrations were 1, 3, and 10 mg/ml, to yield unit doses of 0.1, 0.3, and 1.0 mg/kg/infusion, respectively (each unit infusion was 0.1 ml/kg in volume, delivered in an infusion time of approximately 1 s). Dopamine antagonists were administered SC in a volume of 1 ml/kg. SCH23390 was dissolved in sterile saline, and its vehicle control, i.e., the zero dose, was saline. Spiperone was dissolved in 0.1 ml of 0.1 N tartaric acid for each 10 ml of solution, and diluted to volume with sterile saline; the vehicle control in this case was tartaric acid in saline, at the same concentration as in the antagonist solutions. Values for doses and concentrations for all compounds refer to the base.

Analysis

For each dose of cocaine, 8 subjects were studied, and all antagonist treatments were tested in each of the 8 subjects. Data are presented as the mean and standard error of the mean for each dose or treatment condition. Statistical comparisons were done by means of analysis of variance (ANOVA) for repeated measures, with post hoc tests as appropriate.

It was advantageous to examine response patterns during treatment sessions. To do this, the cumulative number of lever presses in each 1-minute time period were averaged across subjects. Average cumulative records for treatments with the antagonists and their vehicles were compared to determine changes in response patterns after treatment.

RESULTS AND DISCUSSION

The dose-response relationship for cocaine self-administration in this experiment can be seen by comparing the number of infusions obtained when vehicle treatments were done (i.e., zero doses of the antagonists; Fig. 1, left-hand side). The 0.1 mg/kg unit dose of cocaine represents essentially the lowest dose of cocaine that maintains self-administration behavior with the schedule used here; at a unit dose one-half logarithmic step lower (0.03 mg/kg), responding is not different from that obtained when saline is substituted for cocaine [see (1)].

The effects of treatment with dopamine antagonists on cocaine self-administration were dependent on doses of both the antagonists and of cocaine (Fig. 1, left-hand side), although the overall trend in the effect of each antagonist was consistent across the three doses of cocaine examined. In the case of SCH23390, there were biphasic effects on cocaine self-administration. The lowest dose of the antagonist (3 μg/kg) tended to produce an increase in the number of cocaine infusions obtained (Fig. 1, left-hand side), due to a small but sustained elevation of responding throughout the self-administration sessions (Fig. 1, right-hand side). In contrast, higher doses of SCH23390 generally resulted in a decrease in the number of cocaine infusions obtained by the rats as compared to treatment with saline vehicle. At 10 μg/kg of SCH23390 the effects were dependent upon the dose of cocaine; at 0.1 and 0.3 mg/kg cocaine, responding was reduced by 10 μg/kg SCH23390, whereas at 1.0 mg/kg cocaine responding was essentially unaffected after this same dose of antagonist. However, at the highest dose of SCH23390 (30 μg/kg), there was a marked reduction in the number of cocaine infusions obtained, irrespective of the dose of cocaine (Fig. 1, left-hand side); this was due primarily to a complete cessation in responding for the first 20–30 minutes of the treatment sessions, before animals had sampled cocaine (Fig. 1, right-hand side).

Analysis of variance for repeated measures showed that there were statistically significant effects of SCH23390 at all doses of cocaine [at 0.1 mg/kg/infusion cocaine, $F(3,21)=21.84$, $p<0.0001$; at 0.3 mg/kg/infusion cocaine, $F(3,21)=11.04$, $p<0.0005$; at 1.0 mg/kg/infusion cocaine, $F(3,21)=5.01$, $p<0.01$]. Post hoc tests showed that the increase in cocaine self-administration was significant at the 1.0 mg/kg unit dose, $t(7)=3.27$, $p<0.05$, but not at other cocaine doses. This latter effect is consistent with the interpretation that, at a low dose, the D1 antagonist SCH23390 produces an attenuation of the reinforcing effects of cocaine, which in turn results in a compensatory increase in responding for the drug. These observations also suggest that, at higher doses, SCH23390 has direct, response rate-decreasing effects in rats, a conclusion supported by our previous findings that the same doses of SCH23390 also produce a cessation of responding for both food and intravenous nicotine (3).

Unlike the D1 antagonist, spiperone did not produce biphasic effects over the dose range examined in this research, nor was there any indication that spiperone had direct, rate-decreasing effects. At the lowest dose of cocaine examined (0.1 mg/kg/infusion), spiperone had little effect on either the number of cocaine infusions obtained by the rats or the pattern of responding during the treatment sessions (Fig. 1). At higher unit doses of cocaine (0.3 and 1.0 mg/kg/infusion), spiperone increased the rate of responding for cocaine generally throughout the session (Fig. 1, right-hand side), leading to an increase in the number of cocaine infusions received (Fig. 1, left-hand side). The effect of spiperone on the number of infusions received was significant at the 1.0 mg/kg unit dose of cocaine, $F(3,21)=9.53$, $p<0.001$, but not at the lower doses of cocaine. Like the low-dose effects of SCH23390, the increase in cocaine self-administration after treatment with spiperone can be interpreted as arising from an effect of the antagonist on reinforcement processes.

Comparison of these data to previous research confirms that the effects of SCH23390 on cocaine self-administration depend strongly on the schedule of reinforcement used. In the only previous study which has been carried out using rodents, SCH23390, at doses up to 30 μg/kg, produced increases in the self-administration of cocaine at 0.75 mg/kg/infusion (6). The only substantive difference between that study and the present one was the absence of a time-out period in the former. (Although 0.75 mg/kg/infusion was not examined in the present study, cocaine doses both higher and lower were tested, and their effects were qualitatively similar at both doses.) It is apparent that recovery of responding after high doses of SCH23390 occurs to a greater degree when high doses of cocaine are available (for example, compare the recovery after 30 μg/kg SCH23390 at 1.0 and 0.3 mg/kg/infusion cocaine). Therefore, the absence of a time out period in the report by Koob et al. (6) may have contributed to the absence of a decrease in cocaine self-administration following SCH23390, since subjects could obtain a greater number of infusions of cocaine in a given time. It should be noted, however, that both cocaine self-administration and food-maintained responding in monkeys (7,8), as well as nicotine self-administration and responding for food by rats (3), are decreased by SCH23390, confirming our observation that this compound can have severe rate-decreasing effects.

Previous findings with respect to the effects of D2 antagonists on cocaine self-administration may also be reconciled on the basis of the schedule of reinforcement used. For example, in

primates, studies using pimozide as the D2 antagonist have found both increases (7) and decreases (8) in cocaine self-administration after treatment. These differences may be due to the presence of a time out in one study (8) and not in the other (7). However, in the latter study an additional factor may be that cocaine self-administration was maintained at the maximal level for each subject; that is, the cocaine dose was selected for each subject to produce maximal responding. It is possible that this design contributed to the generation of rate decreases in treatment. Indeed, with the schedule of reinforcement used in the present study, maximal responding is maintained by the 0.1 mg/kg unit dose of cocaine, and at this dose spiperone treatment did produce a small tendency toward a reduction in cocaine self-administration. With rodents, cocaine self-administration has been reported to be increased only at 10 μg/kg spiperone, whereas higher doses produced response decreases (6). However, this biphasic effect may also be the result of the schedule of reinforcement; in the absence of a time-out period, self-administration is likely to be maximal at a given dose, and therefore once again decreases may be more probable as a result of antagonist treatment.

It is interesting to note that the largest effects of the antagonists, and the only statistically significant ones, occurred at the highest dose of cocaine. This raises the possibility that the antagonists are acting on cocaine mechanisms other than reinforcement. For example, increases in self-administration after treatment with the antagonists could be due in whole or in part to blockade of the rate-decreasing effects of cocaine. The degree of tolerance which develops to these effects during chronic cocaine self-administration is not known. Use of a time-out period reduces the possibility that antagonism of the rate-altering effects of cocaine contributes to the present observations, since drug infusions are necessarily separated in time. Furthermore, inspection of the cumulative records shows that increases in self-administration are frequently present from the start of treatment sessions, indicating that antagonist effects are not dependent upon an accumulation of cocaine.

The present data extend previous studies, and show that treatment with either a D1 or a D2 antagonist can produce increases in cocaine self-administration. The findings suggest that each of these receptor subtypes may play a role in mediating the reinforcing properties of cocaine.

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