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Discriminative Stimulus Effects of Cocaine in Squirrel Monkeys: Lack of Antagonism by the Dopamine D_2 Partial Agonists Terguride, SDZ 208-911, and SDZ 208-912[1]

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SPEALMAN, R. D. *Discriminative stimulus effects of cocaine in squirrel monkeys: Lack of antagonism by the dopamine D_2 partial agonists terguride, SDZ 208-911, and SDZ 208-912.* PHARMACOL BIOCHEM BEHAV **51**(4) 661–665, 1995.– The effects of cocaine alone and after pretreatment with the dopamine D_2 partial agonists terguride, SDZ 208-911, and SDZ 208-912 were determined in squirrel monkeys trained to discriminate cocaine from saline using a two-lever drug discrimination procedure. When tested alone, cocaine engendered dose-related increases in the percentage of responses on the cocaine-associated lever, reaching virtually exclusive cocaine-appropriate responding after a dose of 1.0 mg/kg. Pretreatment with terguride (0.003–0.03 mg/kg), SDZ 208-911 (0.001–0.01), and SDZ 208-912 (0.003–0.018 mg/kg) did not consistently alter the discriminative stimulus effects of cocaine. Although some doses of each D_2 partial agonist either increased (notably SDZ 208-911) or decreased (notably SDZ 208-912) the level of cocaine-appropriate responding engendered by low to intermediate doses of cocaine, none of the drugs reduced the percentage of cocaine-appropriate responses engendered by 1.0 mg/kg cocaine. The results do not support the view that terguride, SDZ 208-911, or SDZ 208-912 would serve as functional antagonists of the subjective effects of cocaine.

Cocaine D_2 partial agonists Terguride SDZ 208-911 SDZ 208-912 Drug discrimination Cocaine abuse Squirrel monkeys

TERGURIDE, SDZ 208-911, and SDZ 208-912 are dopamine (DA) D_2 agonists with low intrinsic activity (i.e., partial agonists) (7,22). Based on a number of biochemical, behavioral and electrophysiological assays, each of these drugs has been estimated to be less than half as effective as DA in stimulating D_2 receptor activity (7,14,21,22). Moreover, as would be expected for partial agonists (2,5), each compound has been found to function as a DA antagonist under certain conditions. All three drugs, for example, reduce the inhibitory effects of DA agonists on the firing of DA neurons in the substantia nigra pars compacta and ventral tegmentum (1,17,21) and attenuate DA agonist-induced hyperactivity and stereotypy in rodents (3,6,7,22). In addition, SDZ 208-911 has been reported to alter cocaine self-administration in rats (18), and both terguride and SDZ 208-912 have been found to block the discriminative stimulus (DS) effects of amphetamine in this species [(8,9,) but see (3)]. Such findings have prompted speculation that D_2 partial agonists might have a role in the pharmacotherapy of stimulant abuse by counteracting the behavioral effects of cocaine or amphetamine. To date, however, little information is available concerning interactions between D_2 partial agonists and stimulants in either humans or nonhuman primates.

The purpose of this study was to investigate the possible cocaine antagonist effects of terguirde, SDZ 208-911, and SDZ 208-912 in squirrel monkeys trained to discriminate co-

[1] Animals used in this study were maintained in accordance with the guidelines of the Committee on Animals of the Harvard Medical School and of the Guide for Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council, Department of Health, Education and Welfare, Publication No. (NIH)85-23, revised 1985.

caine from vehicle. Previous studies have shown that cocaine discrimination procedures are sensitive techniques for detecting cocaine antagonist effects of drugs in monkeys (12,20) and provide relevant information for preclinical assessment of candidate therapeutics for cocaine abuse (11,19,23). To facilitate comparison with other DA compounds, terguride, SDZ 208-911, and SDZ 208-912 were studied using protocols identical to those used previously to characterize the effects of D_2 full agonists and antagonists (20). The results show that, in contrast to D_2 antagonists, none of the D_2 partial agonists consistently blocked the DS effects of cocaine.

METHOD

Subjects

Four adult male squirrel monkeys (*Saimiri sciureus*) were studied in daily experimental sessions (Monday–Friday). Between sessions, the monkeys lived in individual home cages where they had unlimited access to water. Each monkey was maintained at approximately 85% of its free-feeding weight (0.74–0.85 kg) by adjusting its access to food (PMI Monkey Diet, fresh fruits and vegetables) in the home cage. All monkeys previously had served as subjects in cocaine discrimination experiments and had been tested with several DA agonists and antagonists (20).

Apparatus

During experimental sessions, the monkeys were seated in a Plexiglas chair identical to the one described by Spealman et al. (20). Two response levers (BRS/LVE, model 121-05) were mounted 15 cm apart on the wall of the chair in front of the monkey. A press of either lever with a minimum downward force of 0.25 N and was recorded as a response. Food pellets (Noyes, 190 mg, Formula L) could be delivered to a tray located between the levers, and light bulbs mounted above the levers could be illuminated during the fixed-ratio (FR) components described below. The chair was enclosed in a ventilated, sound-attenuating chamber, which was provided with white noise to mask extraneous sounds.

Drug Discrimination Procedure

All monkeys previously had been trained to discriminate cocaine (0.30 mg/kg for three subjects; 0.56 mg/kg for the fourth) from vehicle (20). Briefly, after IM injection of cocaine, 10 consecutive responses (FR 10) on one lever produced food, whereas after injection of vehicle (0.9% saline), 10 consecutive responses on the other lever produced food. Responses on the inappropriate lever (e.g., the saline-associated lever when cocaine was injected) reset the FR requirement. Training sessions consisted of a variable number of components (n = 1–4) of the FR schedule. Each component ended after the completion of 10 FRs or 10 min, whichever occurred first. A 10-min time-out period, during which the lights were off and responses had no programmed consequences, preceded each component. In most training sessions, saline was injected during the 5th min of each time-out period preceding the first $n - 1$ components (e.g., the first three components of a four-component session) and cocaine was injected during the 5th min of the time-out period preceding the last component of the session. Periodically, saline was injected during every time-out period of a training session to prevent an invariant association between the last component and cocaine. Training under this procedure continued until a criterion of $\geq$ 90% of responses on the injection-appropriate lever was met consistently from session to session.

Drug Testing Procedure

Drug test sessions were conducted once or twice per week, with training sessions held on intervening days. Test sessions were scheduled only if performance during at least four of the preceding five training sessions met criterion. Test sessions consisted of four FR components, each preceded by a 10-min time-out period. In each component, completion of 10 consecutive responses on either lever produced food. The effects of cocaine were determined using a cumulative dosing procedure described previously (20). Briefly, either four incremental doses of cocaine or, in separate test sessions, saline followed by three incremental doses of cocaine were injected i.m. during time-out periods that preceded the four sequential components of the session. The effects of cocaine after pretreatment with terguride (0.003, 0.01, and 0.03 mg/kg), SDZ 208-911 (0.001, 0.003, and 0.01 mg/kg) and SDZ 208-912 (0.003, 0.01, and 0.018 mg/kg) were determined by injecting the latter drugs IM 10 min before the first component of the session and then administering cumulative doses of cocaine during the session as outlined above. The doses of terguride, SDZ 208-911, and SDZ 208-912 used in these experiments were selected on the basis of previous studies in monkeys [(13,16), unpublished observations] and typically were one to two orders of magnitude lower than the doses used in behavioral experiments with rodents [cf. (3,6,8,9)]. Cumulative dose–response functions for cocaine alone were determined on two or three occasions in each monkey at various times during the experiment and cumulative dose–response functions for cocaine after pretreatment with each dose of the D_2 partial agonists were determined twice in each of three (experiments with SDZ 208-911 and SDZ 208-912) or four monkeys (experiments with terguride).

For analysis of drug effects, the percentage of responses on the cocaine-associated lever was computed in each component of a test session by dividing the number of responses on that lever by the total number of responses on both levers. The rate of responding was computed in each component by dividing the total number of responses in a component (regardless of lever) by the total component duration.

Drugs

Cocaine hydrochloride (NIDA, Rockville, MD), terguride hydrogen maleate (RBI, Natick, MA), SDZ 208-911 {*N*-[(8-α)-2,6-dimethylergoline-8-yl]-2,2-dimethylpropanamide} methanesulfonate and SDZ 208-912 {*N*-[(8-α)-2-chloro-6-methylergoline-8-yl]-2,2-dimethylpropanamide} methanesulfonate (Sandoz, Basle, Switzerland) were dissolved in sterile distilled water containing small amounts of 95% ethanol and 0.1 N HCl as required and then diluted to the desired concentrations with 0.9% saline solution. All drugs were injected into the calf or thigh muscle of either leg in a volume of 0.3 ml/kg body weight or less.

RESULTS

Control Performance and Effects of Cocaine

During training sessions that preceded drug test sessions, individual monkeys made an average of $\geq$95% responses on the cocaine-associated lever after injection of the training dose of cocaine and $\leq$4% responses on the cocaine-associated lever after injection of saline. Averaged for the group of four mon-

keys, the rate of responding after the training dose of cocaine (2.1 ± 0.3 SEM responses/s) was comparable to the rate after saline (1.9 ± 0.2 responses/s).

When tested alone, cocaine engendered dose-related increases in the percentage of responses on the cocaine-associated lever, reaching virtually exclusive cocaine-appropriate responding after a dose of 1.0 mg/kg in all subjects (Fig. 1, unfilled circles in each panel). Injection of saline during test sessions engendered little or no cocaine-appropriate responding in any monkey (unfilled circles above S). Cocaine had no systematic effect on the average rate of responding except after the highest dose (1.0 mg/kg), which decreased the average response rate by 50% or more (Fig. 1, lower panels).

Effects of Terguride, SDZ 208-911, and SDZ 208-912

Pretreatment with most doses of terguride (0.003–0.03 mg/kg), SDZ 208-911 (0.001–0.01 mg/kg), and SDZ 208-912 (0.003–0.018 mg/kg) resulted in only modest changes in the dose-response function for the DS effects of cocaine (Fig. 1, top panels). Although one or more doses of each compound reduced to some degree the percentage of cocaine-appropriate responses engendered by 0.3 mg/kg cocaine (the training dose of cocaine for most subjects), the changes were notable (37–49% average reduction) only after pretreatment with doses of SDZ 208-912 ≥ 0.01 mg/kg. None of the drugs attenuated the DS effects of a higher dose of 1.0 mg/kg cocaine: after pretreatment with low to intermediate doses of terguride (0.003 mg/kg), SDZ 208-911 (0.001 and 0.003 mg/kg), or SDZ 208-912 (0.003 and 0.01 mg/kg), this dose of cocaine continued to engender nearly exclusive responding on the cocaine-associated lever, whereas after pretreatment with higher doses of terguride (0.01 and 0.03 mg/kg), SDZ 208-911 (0.01 mg/kg), or SDZ 208-912 (0.018 mg/kg), responding was markedly reduced or eliminated in all subjects (Fig. 1, bottom panels). The severe rate-decreasing effects of these latter dose combinations precluded meaningful evaluation of the distribution of responses on the two levers.

Some doses of terguride, SDZ 208-911, and SDZ 208-912 also tended to increase the percentage of cocaine-appropriate responses engendered by low doses of cocaine (0.03 or 0.1 mg/kg). However, with the exception of certain combinations of cocaine and SDZ 208-911 (notably 0.1 mg/kg cocaine after pretreatment with 0.01 mg/kg SDZ 208-911), these increases were relatively small and not observed consistently from monkey to monkey. When tested in combination with saline, none of the D_2 partial agonists engendered substantial cocaine-appropriate responding even after doses that markedly reduced the response rate (Fig. 1, filled symbols above S).

DISCUSSION

The present results provide little evidence for functional antagonism of the DS effects of cocaine by terguride, SDZ

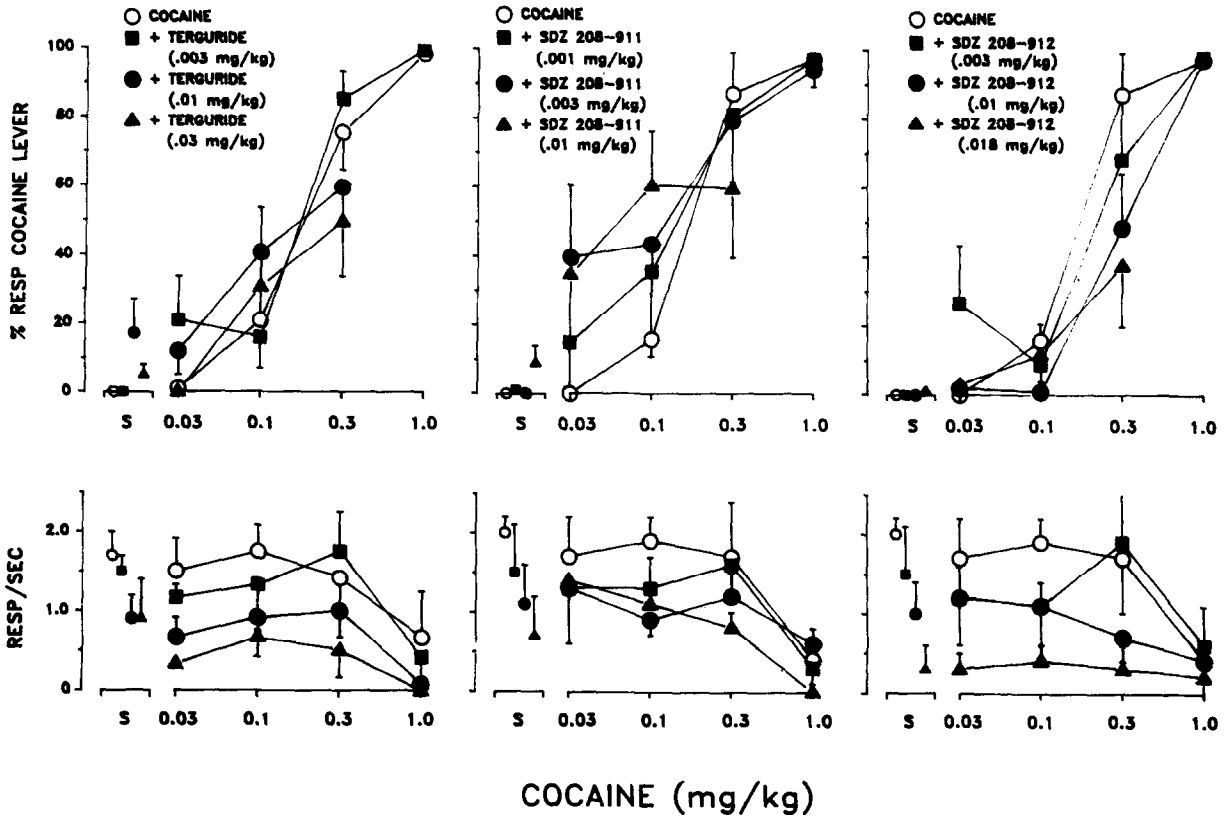

FIG. 1. Effects of cocaine alone (unfilled symbols) and after pretreatment with terguride, SDZ 208-911, and SDZ 208-912 (filled symbols) in squirrel monkeys trained to discriminate cocaine (0.3 or 0.56 mg/kg) from saline. Abscissae: cumulative dose of cocaine, logarithmic scale. Ordinates: percentage of cocaine-appropriate responses (top panels) and response rate (bottom panels). Points above S show the effects of saline (unfilled symbols) or saline after pretreatment with the D_2 partial agonists (filled symbols). Data are means ± SEM for groups of three or four monkeys.

208-911, or SDZ 208-912 despite the use of up to a 10-fold range of doses of the D_2 partial agonists in combination with a 30-fold range of doses of cocaine. The most notable exception was a 37–49% reduction in cocaine-appropriate responding engendered by an intermediate dose of cocaine (0.3 mg/kg) after pretreatment with high doses of SDZ 208-912 ($\geq$ 0.01 mg/kg). Although this reduction undoubtedly reflects the influence of SDZ 208-912 pretreatment, there was no indication that SDZ 208-912 similarly altered the DS effects of a higher dose of cocaine, nor did it block the cocaine-induced decreases in response rate. This general type of finding (i.e., incomplete attenuation of DS effects without concomitant attenuation of rate-decreasing effects) has been interpreted as being more indicative of a perceptual masking phenomenon (i.e., the obscuring of one stimulus by another) than of true pharmacological antagonism (10,24).

The overall failure of the D_2 partial agonists to block the effects of cocaine in the present study appears at odds with a recent report that SDZ 208-911 can significantly alter the IV self-administration of cocaine in rats (18). These seemingly disparate results might be due to several factors, including differences in species, route of administration, and other procedural details, but conceivably could reflect a selective antagonism of the reinforcing vs. subjective effects of cocaine. Additional studies obviously will be required to evaluate this possibility. The present results also are somewhat surprising in light of reports that terguride and SDZ 208-912 can block the DS effects of another abused stimulant, amphetamine, in rats (8,9). Although species and procedural differences again might account for the different findings, it is possible that D_2 partial agonists are more effective in counteracting the DS effects of amphetamine than of cocaine. Terguride, SDZ 208-911, and SDZ 208-912 also have been found to attenuate other amphetamine-induced behaviors, including hyperactivity and stereotypy in rats (6).

In addition to their effects at dopamine D_2 receptors, terguride, SDZ 208-911, and SDZ 208-912 have appreciable affinity for 5-HT_{1A} and 5-HT_2 serotonin receptors as well as α_1 and α_2 adrenoceptors, where they appear to function as either antagonists or partial agonists (7,21). Such actions undoubtedly contribute to the overall profile of behavioral effects induced by these drugs (6,21) and may have influenced their interaction with cocaine. Thus, although terguride, SDZ 208-911 and SDZ 208-912 did not consistently block the effects of cocaine in the present study, it is possible that antagonism of cocaine's DS effects might eventually be achieved by partial agonists with greater D_2 receptor selectivity. Whether or not terguride, SDZ 208-911, or SDZ 208-912 might have a place in the pharmacotherapy of cocaine abuse is unknown, but to the extent that the present findings in monkeys are applicable to humans, they would not be expected to block cocaine's subjective effects. It is noteworthy, however, that cocaine abusers typically administer the drug in binges either intranasally or by inhalation, whereas cocaine was administered acutely by the IM route in this study. Such differences clearly restrict generalizations that can be made from the present findings to humans.

In contrast to the limited effects of the D_2 partial agonists in the present study, D_2 receptor *antagonists* have been found to attenuate the DS effects of cocaine in squirrel monkeys under conditions identical to those used in the present study (19,20). These different findings with D_2 partial agonists, on the one hand, and D_2 antagonists, on the other, imply that blockade of the DS effects of cocaine may require a greater inhibition of D_2 receptor activity than can be achieved with partial agonists. This interpretation is consistent with the recent findings of Nielsen and Andersen (15), who showed that nearly complete blockade of D_2 receptors, as measured by in vivo radioligand binding, was necessary to antagonize various amphetamine- or methylphenidate-induced behaviors in rodents. Interestingly, in that same study, comparable antagonism of amphetamine- or methylphenidate-induced behaviors typically was observed with considerably lower levels (40–70%) of D_1 receptor blockade, a finding compatible with recent observations that D_1 partial agonists can be nearly as effective as D_1 antagonists in attenuating the DS effects of cocaine in monkeys (4,19). The relevance of these findings for the pharmacotherapy of cocaine abuse is currently being investigated.

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