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BRIEF COMMUNICATION

Failure of Cholecystokinin Antagonists to Modify the Discriminative Stimulus Effects of Cocaine

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SPEALMAN, R. D. *Failure of cholecystokinin antagonists to modify the discriminative stimulus effects of cocaine.* PHARMACOL BIOCHEM BEHAV 43(2) 613–616, 1992.—Enhancement of brain dopamine (DA) activity is believed to be an important mechanism underlying the discriminative stimulus effects of cocaine in animals and the subjective effects of cocaine in people. Cholecystokinin (CCK) receptors, which are colocalized with DA receptors in several brain regions, have been implicated as modulators of DA activity, leading to speculation that CCK-based drugs might be developed as therapeutics for cocaine abuse. In the present study, the effects of cocaine alone and after pretreatment with the selective CCK_A antagonist devazepide and the selective CCK_B antagonist CI 988 were determined in squirrel monkeys trained to discriminate cocaine (1.0 mg/kg) from saline. When tested alone, cocaine engendered dose-related increases in the percentage of cocaine-appropriate responses, reaching virtually exclusive responding on the cocaine-associated lever after doses of 1.0 mg/kg or greater. Pretreatment with a wide range of doses of either devazepide (0.01–3.0 mg/kg) or CI 988 (0.3–30 mg/kg) did not systematically alter the discriminative stimulus effects of any dose of cocaine. The results do not support a role for CCK antagonists in the pharmacotherapy of cocaine abuse.

Cocaine Devazepide CI 988 Cholecystokinin antagonists Drug discrimination Squirrel monkeys

THE widespread illicit use of cocaine has intensified efforts to characterize the neurochemical basis for cocaine's behavioral effects and identify potential pharmacotherapies for cocaine addiction. Previous research has established that cocaine acts as an indirect dopamine (DA) agonist by binding to specific recognition sites associated with the DA transporter (14,17,20) and inhibiting the uptake of DA into presynaptic terminals (8,16). Recent studies have linked these neurochemical actions to various behavioral effects of cocaine in monkeys (1, 15,20,24), and several compounds with the capacity to alter DA neurotransmission have been proposed as candidate therapeutics for cocaine abuse (13,21,23). Among these drugs are cholecystokinin (CCK) antagonists, some of which have been found to modulate DA neuronal activity in vitro and to bind to CCK receptors in DA-rich brain regions implicated in cocaine abuse [cf. (3,7,26)].

The purpose of the present study was to investigate the possible cocaine-modulating effects of selective CCK antagonists in squirrel monkeys trained to discriminate cocaine from vehicle. Previous studies have shown that cocaine discrimination procedures are sensitive techniques for detecting both cocaine-antagonist and cocaine-mimetic effects of drugs in monkeys and provide relevant information for preclinical evaluation of candidate therapeutics for cocaine abuse (13, 15,23). In the present study, a 60-fold or greater range of doses of the selective CCK_A antagonist devazepide (2) and the selective CCK_B antagonist CI 988 (12) was studied in combination with saline and a full range of discriminable doses of cocaine.

CCK antagonists previously have been reported to modulate satiety mechanisms and alter food intake in rodents (6,9,26). It is not known whether either devazepide or CI 988 can similarly modulate the anorectic effects of cocaine in monkeys, but such actions might be expected to complicate

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.

interpretation of drug discrimination experiments in which behavior is maintained by food delivery. To circumvent this potential problem, responding in the present study was maintained by termination of a stimulus associated with shock (18) rather than by presentation of food. The results show that under these conditions neither devazepide nor CI 988 systematically modify the discriminative stimulus effects of cocaine.

METHOD

Subjects

Three adult male squirrel monkeys (*Saimiri sciureus*) were studied in daily experimental sessions (Monday–Friday). Between sessions, monkeys lived in individual home cages where they had unrestricted access to water and received a nutritionally balanced diet of Purina Monkey Chow, fresh fruits, and vegetables. Their weights were maintained at approximate ad lib values of 0.9–1.1 kg.

Apparatus

During experimental sessions, monkeys were seated in a Plexiglas chair described previously (22). Two response levers were mounted 15 cm apart on the front wall of the chair and white lights could be illuminated while the fixed-ratio (FR) schedule (see below) was in effect. A press of either lever with a minimum downward force of 0.25 N produced an audible click and was recorded as a response. Brief, low-intensity electrical stimulation (200 ms, 3 mA) could be delivered through brass electrodes, which rested on a shaved portion of the monkey's tail. Electrode paste ensured a low-resistance contact between the electrodes and the tail. The chair was enclosed in a ventilated, sound-attenuating chamber provided with white noise to mask extraneous sounds.

Discrimination Training

Monkeys initially were trained to respond under an FR schedule of stimulus-shock termination (18). In the presence of a white light, shocks were scheduled at 30-s intervals. The completion of 10 responses (FR 10) terminated the white light and the schedule of shock delivery and started a 30-s timeout. During the timeout, the white light was off and responses had no programmed consequences. If the FR 10 requirement was not met, the timeout was started automatically following the third shock. During this initial phase of training, only one lever was present at a time and its position (left or right) was changed irregularly from day to day.

After responding under the FR schedule developed, monkeys were trained to respond differentially on the two levers depending upon whether cocaine (1.0 mg/kg, IM) or saline was injected. After injection of cocaine, 10 consecutive responses on one lever (left for monkey S-371; right for monkeys S-6 and S-123) terminated the stimulus associated with shock, whereas after injection of saline 10 consecutive responses on the other lever terminated the stimulus. Responses on the inappropriate lever (e.g., the saline-associated lever after injection of cocaine) reset the FR requirement. Both levers were present at all times during discrimination training.

Daily training sessions consisted of a variable number (n = 1–4) of components of the FR schedule as described previously (22). Each component ended after completion of 10 FRs or 15 min, whichever occurred first, and each was preceded by an extended (10-min) timeout period. During most sessions, saline was injected during the timeout periods preceding the first n-1 components and cocaine was injected before the nth component of the session. Periodically, saline was injected before all components of a training session to prevent an invariant association between the last component and cocaine. The number of components per session was varied randomly from day to day with the restriction that each number occur equally often in a block of 20 sessions. Discriminative training continued until a criterion of at least 90% of responses were made on the injection-appropriate lever (total training: 58–81 sessions).

Drug Testing

Drug test sessions were conducted once or twice per week, with training sessions on intervening days. Testing was 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 timeout period. In each component, the completion of 10 consecutive responses on either the left or right lever terminated the stimulus associated with shock. The effects of cocaine alone and after pretreatment with the CCK antagonists were determined using a cumulative dosing procedure described previously (22). Briefly, incremental doses of cocaine were injected during the fifth minute of the 10-min timeout periods that preceded sequential FR components, permitting a four-point cumulative dose-effect curve to be determined in a single session. Up to five different doses of cocaine were studied by administering overlapping ranges of cumulative doses during test sessions on different days. Saline was included as the first injection in at least one of these test sessions. The effects of cocaine alone were studied on two or three occasions in each monkey at different times during the course of the study. Cocaine after pretreatment with each dose of devazepide (0.01–3.0 mg/kg) or CI 988 (0.3–30 mg/kg) was studied once or twice in each monkey. Devazepide (also designated MK 329 and L-364,718, Merck, Sharpe and Dohme Research Laboratories) was suspended in sterile distilled water to which few drops of Tween-80 were added. CI 988 (also designated PD 134308, Parke-Davis Research Unit) and cocaine HCl (National Institute on Drug Abuse) were dissolved in 0.9% saline solution.

RESULTS

When tested alone, cocaine engendered dose-related increases in the percentage of cocaine-appropriate responses, with doses of 1.0 and 1.8 mg/kg resulting in virtually exclusive responding on the cocaine-associated lever (Fig. 1, open circles, top panels). Injection of saline during test sessions engendered little or no cocaine-appropriate responding in any monkey (solid symbols above S). With the exception of the highest dose, which slightly reduced the rate of responding, cocaine had no marked effect on response rate (bottom panels).

Pretreatment with either devazepide (0.01–3.0 mg/kg) or CI 988 (0.3–30 mg/kg) did not systematically alter the discriminative stimulus effects of cocaine (Fig. 1, solid symbols, top panels) and did not markedly affect the rate of responding (bottom panels). Although some doses of devazepide (e.g., 3.0 mg/kg) and CI 988 (e.g., 10 mg/kg) reduced the percentage of cocaine-appropriate responses engendered by an intermediate

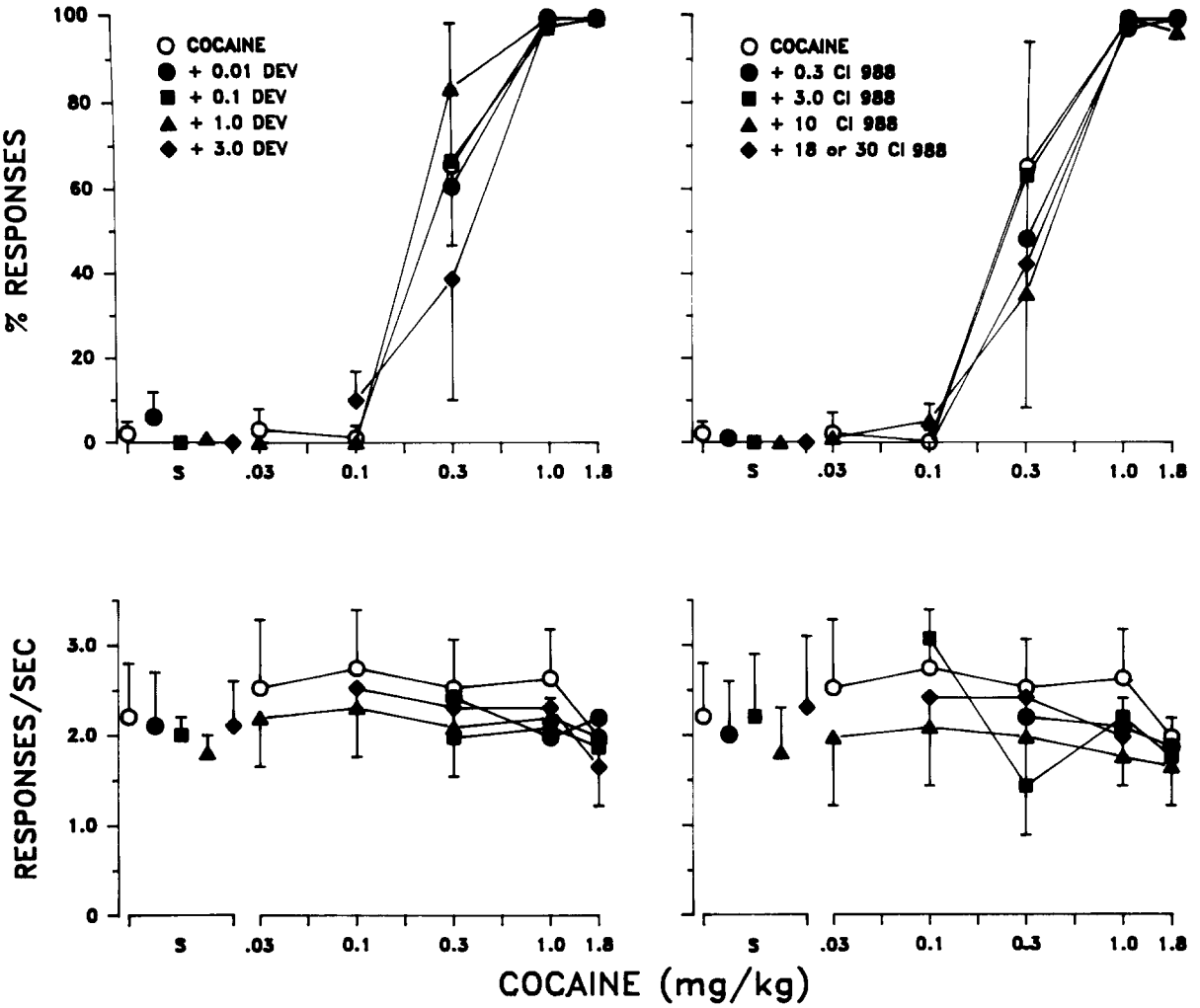

FIG. 1. Effects of cocaine alone (○) and after pretreatment with the selective CCKA antagonist devazepide (●, ■, ▲, ♦; left panels) and the selective CCKB antagonist CI 988 (●, ■, ▲, ♦; right panels) in monkeys trained to discriminate cocaine from saline. Ordinates: percentage of responses on the cocaine-associated lever (top panels) and response rate (bottom panels). Points at S show effects of saline or saline after pretreatment with the CCK antagonists. Points are means based upon three monkeys; brackets show ± SD. The highest dose of CI 988 was 30 mg/kg in two monkeys and 18 mg/kg in the third due to limited drug supply.

dose of cocaine (0.3 mg/kg), almost exclusive cocaine-appropriate responding was still observed following the training dose (1.0 mg/kg) in combination with each dose of devazepide or CI 988. Neither devazepide nor CI 988 engendered appreciable cocaine-appropriate responding when studied in combination with saline (solid symbols above S).

DISCUSSION

Previous studies identified the existence of CCK receptors in several DA-rich brain regions implicated in the behavioral effects and abuse of cocaine (4,11,25,26). The colocalization of CCK and DA receptors in these regions, coupled with the modulatory effects of CCK-based drugs on DA neuronal activity (3,7,26), has prompted speculation that CCK receptor ligands might be developed as novel therapeutics for drug abuse. To help evaluate this possibility, the present study investigated the capacity of selective CCK_A and CCK_B antagonists to modify the discriminative stimulus effects of cocaine in monkeys. Over at least a 60-fold range of doses, however, there was no indication that either devazepide or CI 988 systematically altered the effects of cocaine, and neither drug produced marked changes in the shape or position of the cocaine dose-response function. To the extent that the findings in monkeys are applicable to humans, these results suggest that CCK_A and CCK_B antagonists would have little influence on the subjective effects of cocaine in people.

It is unlikely that the failure to observe systematic interactions between cocaine and the CCK antagonists in the present study was the result of using inadequate doses of devazepide or CI 988. In this regard, both drugs bind with nanomolar affinity to their respective CCK receptor subtypes and appear to have good CNS bioavailability after peripheral administration (2,12,19,26). Moreover, at doses considerably lower than the highest doses studied here devazepide and CI 988 have been found to antagonize the in vivo effects of CCK, potenti-

ate opioid analgesia, and induce anxiolytic-like effects in rodents or monkeys (2,12,26).

Although the CCK antagonists showed no tendency to alter the effects of cocaine in the present study, recent reports suggest that devazepide and other CCK_A antagonists can modulate the behavioral effects of morphine (26). Dourish et al. (5), for example, found that devazepide attenuated the development of morphine tolerance in rats and Higgins et al. (10) reported that devazepide blocked morphine-conditioned place preference. Such findings might indicate a role for CCK_A antagonists in the treatment of opiate or dual cocaine-opiate (speedball) abuse. Whether devazepide or other CCK antagonists are, in fact, capable of modifying the subjective effects of opiates has not yet been determined.

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