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CGS 10746B, a Novel Dopamine Release Inhibitor, Blocks the Establishment of Cocaine and MDMA Conditioned Place Preferences

EDWARD J. BILSKY,* MICHAEL J. MONTEGUT,† MICHAEL L. NICHOLS‡ AND LARRY D. REID†

*Department of Biological Sciences, University of Northern Colorado, Greeley, CO 80639
†Laboratory for Psychopharmacology, Rensselaer Polytechnic Institute, Troy, NY 12180
‡Molecular Neurobiology Laboratory, VA Medical Center, Minneapolis, MN 55417

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BILSKY, E. J., M. J MONTEGUT, M. L. NICHOLS AND L. D. REID. *CGS 10746B, a novel dopamine release inhibitor, blocks the establishment of cocaine and MDMA conditioned place preferences.* PHARMACOL BIOCHEM BEHAV **59**(1) 215–220, 1998.—Cocaine and methylenedioxymethamphetamine (MDMA), two drugs self-administered by humans and laboratory animals, have previously been shown to produce conditioned place preferences (CPPs) among rats, an index of drug-reward relevant events. Both of these agents increase functional levels of dopamine that may be critical to their rewarding properties. Here, the effects of doses of CGS 10746B, an agent reported to attenuate the release of dopamine without occupying dopamine receptors, are assessed on cocaine and MDMA's ability to produce a CPP. CGS 10746B dose dependently blocked the establishment of a MDMA CPP. A 30 mg/kg dose of CGS 10746B, which completely blocked the MDMA CPP, also blocked the establishment of a cocaine CPP. Release of dopamine appears critical to the ability of these agents to establish a CPP. © 1998 Elsevier Science Inc.

Methylenedioxymethamphetamine MDMA Cocaine CGS 10746B Dopamine release Conditioned place preference Affect Reward

PSYCHOSTIMULANTS such as cocaine and methylenedioxymethamphetamine (MDMA) are widely abused substances. Despite intense research, the biochemical actions that support the self-administration of these compounds are still not completely understood. There is, however, substantial in vivo and in vitro evidence for the dopamine hypothesis of psychostimulant reward (8,35). The theory builds on studies using direct electrical stimulation of the brain in freely moving animals, and the administration of specific dopamine agonists and antagonists, neurotoxins and site-directed injections. Collectively, the results support the critical role of dopaminergic elements of the medial forebrain bundle (MFB) in the processes of positive reinforcement (8,20,23,26), including that associated with addictive drugs. A version of the theory states that addictive stimulants increase the functional availability of dopamine mimicking the heightened activity of dopaminergic elements achieved by direct electrical stimulation of the MFB and, ordinarily, achieved by adaptive acts such as moving toward food when hungry (25). The conscious manifestation of such activity is presumably some increment in positive mood, pleasure, or positive affect.

Testing for conditioned place preferences (CPP) is one of the procedures that have contributed to new theories of drug use [e.g. (4,6,7,9,28)]. Testing, for example, is done in an undrugged state so that antagonists that might interfere with motor skills can still be assessed. Furthermore, when antagonists of particular neurochemical systems produce an aversive state, that can be detected; and, methods can be implemented to separate nonspecific aversive effects from more relevant effects (6).

The current study uses the CPP procedures to assess the effects of CGS 10746B (CGS), an agent that reportedly attenuates the release of dopamine without binding to synaptic dopamine receptor sites (1,36), on the reinforcing effects of

Requests for reprints should be addressed to Edward J. Bilsky, Ph.D., Department of Biological Sciences, University of Northern Colorado, Greeley, CO 80639, e-mail: ejbilsk@bentley.univnorthco.edu

MDMA and cocaine. CGS, therefore, can be used to ask whether or not dopamine release is critical to a relevant aspect of an addictive stimulant (11,13,31).

EXPERIMENT 1

The "designer" drug MDMA has become popular among young adults willing to take illicit drugs. The compound produces a variety of biochemical effects including increased synaptic levels of measured dopamine and serotonin in laboratory animals [for a review, see (22)]. MDMA is also self-administered (2,17), lowers the threshold for intracranial reinforcement associated with stimulation of the MFB (15), and can establish a CPP (5,29). The results from these converging operations support the idea that MDMA's effects are rewarding. There remains, however, questions of how MDMA produces its rewarding effects.

After having established that injections of MDMA reliably set the conditions for producing a CPP (5), we showed that an antagonist at 5-HT_3 receptors blocked MDMA's CPP (7). One possible consequence of administration of 5-HT_3 antagonists is an attenuation of dopamine release (12). If CGS attenuates the ability of MDMA to establish a CPP, as does the 5-HT_3 antagonist, then there will be converging evidence supporting the idea that the release of dopamine is critical to MDMA's place preference. Consequently, we assessed the ability of CGS to modify a MDMA CPP.

METHOD

Subjects

Seventy-two experimentally naive, male Sprague–Dawley rats (Taconic Farms, Germantown, NY) were used in this assessment. Rats weighed between 175 and 200 g upon their arrival at the laboratory. They were housed individually in standard hanging metal cages in a windowless vivarium maintained at 22°C with 12 h of artificial light a day (lights on at 0700 h). Food (standard laboratory chow) and water were always available in the rat's home cages.

Drugs

MDMA was dissolved in physiological saline and administered in a dose of 6.3 mg/kg body weight, a dose previously shown to produce a reliable CPP in our apparatus (5,7). CGS 10746B, 5-(4-methyl-1 piperazinyl)-imidazo[2,1-b] [1,3,5] benzothiadiazepine maleate (Ciba-Geigy Corporation, Summit, NJ) was dissolved by adding a few drops of 0.1 M hydrochloric acid (HCl) and a small amount of water to the powder, adjusting the pH to 7 with NaOH and bringing the solution to volume in physiological saline. Doses of 3.0, 10.0, and 30.0 mg/kg were administered.

Injections of MDMA, or its placebo (saline), were administered subcutaneously, 10 min before conditioning. CGS, or its placebo (a small amount of HCl and NaOH in physiological saline), were injected intraperitoneally 30 min before conditioning. All injections were in a volume of 1 ml/kg. Injection times were based upon previous research indicating that the drug's effects would be extant during conditioning (6,30).

Apparatus

The apparatus, described in detail elsewhere (24), consisted of 12 nearly identical alleys, each housed in a sound attenuating outer shell. Each alley was divided into two equal halves having distinct visual (solid gray or black and white striped sides) and textural cues (flooring made of steel rods running either parallel or perpendicular to the length of the alley). A wooden barrier, with sides painted to match the respective halves of the alley, was used to separate the distinct environments. An alley tilted slightly when a rat moved to either side of a center support, completing a circuit that was monitored by software of a personal computer.

Each side of the alley had an adjustable light bulb overhead. The amount of reflected light on each side of the alley was adjusted so that the side of putative conditioning was slightly brighter than the alternate side.

Procedure

Upon arrival at the laboratory, all rats were individually housed in their home cages. On the following day, rats began a 3-week schedule of habituation, conditioning, and testing. All procedures took place between 0900 and 1300 h.

Days 1–5 comprised the handling phase of the experiment in which rats were habituated to the general procedures. Rats were weighed daily, as they were on every day of the formal experiment, and placed into a mobile cart (12 cages/cart, one rat/cage). The cart was then wheeled into the room of the apparatus where each rat was handled briefly before being returned to its home.

On days 6–7, each rat was placed into its respective alley and allowed access to either side for 30 min. The time spent on the side of putative conditioning was recorded on day 7 and served as a baseline measure and was used to assign subjects to groups. Rats were subsequently assigned so that each group had (a) the same number of subjects ($n = 10$), (b) roughly equal mean times on putative side of conditioning, and (c), the same number of rats assigned the gray or striped side as side of putative conditioning. A treatment was then randomly assigned to each of the groups (Table 1). On days 8–9, rats were given no special treatment.

Formal conditioning began on day 10 with rats being given their two assigned injections (Table 1) before being placed into their side of putative conditioning for 30 min. These procedures were repeated on days 11–12. On day 13, rats received two injections (Table 1) and were placed into the alternate side of the alley. Following 3 additional days of no special treatment (days 14–16), the procedure of 3 days of putative conditioning and 1 day of alternate conditioning was repeated (days 17–20). Rats were tested for place preferences on the following day (day 21).

Data Reduction and Statistics

The design of the assessment conforms to a 6 by 2 by 2 ANOVA for repeated measures having factors of groups (Table 1), side of putative conditioning (gray or striped), and tests (baseline and test), respectively. Because the factor of side failed to be a reliable source of variance by itself or to interact with the other factors ($ps > 0.41$), it was subsequently dropped from further analyses. Furthermore, because rats were assigned to groups based on their baseline scores (and, therefore, on average did not differ) and these scores were as expected (approximately a 42% preference for putative side), consideration of baseline scores were not considered in the final analyses.

Further analyses revealed no differences between the saline control and the CGS control groups at either baseline or test ($ps > 0.90$). Because the best indicator of what the other rats would do, without a conditionable effect of drugs, are the scores associated with the two control groups, the data of

TABLE 1

GROUP ASSIGNMENTS AND SCHEDULES OF DRUG ADMINISTRATION

Group	Putative	Alternate
Saline control	Saline/saline	Saline/saline
CGS control	CGS 10746B 30.0/saline	CGS 10746B 30.0/saline
MDMA control	Saline/MDMA	Saline/saline
MDMA/CGS 3.0	CGS 10746B 3.0/MDMA	CGS 10746B 3.0/saline
MDMA/CGS 10.0	CGS 10746B 10.0/MDMA	CGS 10746B 10.0/saline
MDMA/CGS 30.0	CGS 10746B 30.0/MDMA	CGS 10746B 30.0/saline

Putative refers to the injections each group received prior to being placed on the putative side of conditioning while alternate refers to the injections administered prior to being placed on the other side. The label to the left of the slash is the type of injection administered first. The labels correspond to the following injections: saline (the vehicle of CGS 10746B and MDMA; MDMA at a dose of 6.3 mg/kg, SC; and CGS 10746B with the numbers referring to doses in mg/kg, IP.

these two groups were collapsed into one group. Furthermore, as expected, the control groups did not exhibit any gross change in preferences between baseline and test (ps $>$ 0.80). With these conditions met, the relevant data assessing CGS's effects on a MDMA CPP conformed to a one-way ANOVA across the preference scores of the test.

RESULTS AND DISCUSSION

The results are depicted in Fig. 1. An ANOVA of the data of Fig. 1 yields an $F(4, 67) = 2.98$, $p = 0.025$. A comparison of the scores of the control group and the MDMA group indicated that the group conditioned with MDMA preferred the side where MDMA's effects were experienced, $t(34) = 2.76$, $p = 0.009$, replicating previous research (5,7). The low dose of CGS had a slight effect on MDMA's ability to establish a positive CPP; but that group's mean score is neither reliably different from the group getting MDMA (plus placebo) on side of putative conditioning, $t(22) = 1.27$, $p = 0.22$, nor the control group, $t(34) = 1.33$, $p = 0.19$. The two higher doses of CGS (10.0 and 30.0 mg/kg) apparently blocked the establishment of a MDMA CPP. The mean scores of these two groups getting MDMA in combination with one of the higher doses of CGS are very similar to those of the control group (ps $>$ 0.45). Furthermore, t-tests comparing the MDMA group with the MDMA/CGS10 and MDMA/CGS30 groups, yields ts(22) = 2.22 and 3.38, ps = 0.037 and 0.003, respectively.

MDMA is capable of establishing a positive CPP [this experiment and (5,7,29)]. These data support the conclusion that MDMA's ability to establish a positive CPP is blocked by doses of CGS, an agent attenuating the release of dopamine (1). CGS's effects were paired with both sides of the alley and, therefore, any nonspecific effects are apt to be conditioned to each side of the alley. This is reflected in the mean score of the CGS control group which was no different than the saline control group.

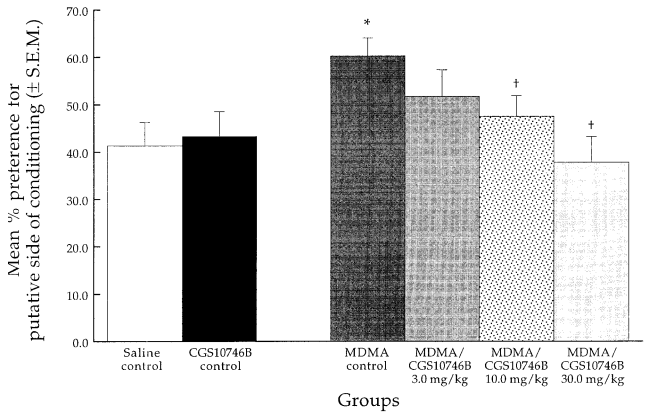

FIG. 1. Test scores are depicted as mean % time spent on side of putative conditioning. Groups are labeled according to the two injections they received on day of putative conditioning, e.g., MDMA/CGS10746B 30 mg/kg refers to the group that received conditioning with 6.3 mg/kg MDMA in combination with a 30.0 mg/kg dose of CGS (see Table 1). An asterisk (*) indicates a reliable difference from the saline and CGS control groups ($p < 0.05$). A dagger (†) indicates a reliable difference from the MDMA control group. Bars represent standard errors of the mean.

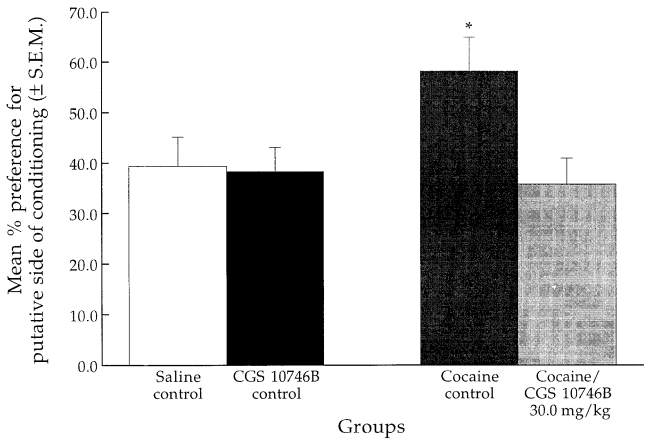

FIG. 2. Test scores are depicted as mean % time spent on side of putative conditioning for each group. Groups are labeled according to the injections they received on day of putative conditioning, e.g., Cocaine/CGS10746B 30 mg/kg refers to the group that received conditioning with cocaine in combination with a 30.0 mg/kg dose of CGS 10746B (see Table 2). An asterisk indicates a reliable difference from the saline and CGS control groups as well as the cocaine/CGS group ($p < 0.05$). Bars represent standard errors of the mean.

EXPERIMENT 2

Although it seems as if there is a consensus that higher functional levels of dopamine are critical to cocaine's ability to sustain its own use, there are a number of findings that are not concordant with the apparent consensus. Several reports have demonstrated that dopamine antagonists, or 6-hydroxydopamine lesions of the nucleus accumbens, fail to block cocaine place preferences (18,33). Furthermore, intraaccumbens infusions of cocaine do not produce a place preference (14). There may also be contributions from cocaine's effects on serotonergic and noradrenergic systems [for a review see (26)]. It is, therefore, of interest to test the hypothesis that cocaine's reinforcing capacity is dependent upon the CGS-sensitive release of dopamine. Consequently, we instituted procedures similar to those of Experiment 1 except cocaine was used rather than MDMA.

METHOD

Forty-eight rats similar to those described in Experiment 1 were used in this assessment. CGS, in a dose of 30.0 mg/kg, was administered as in Experiment 1. Cocaine HCl (Sigma) was dissolved in physiological saline and administered SC in doses from 5.0 to 11.0 mg/kg body weight. Cocaine or its placebo (physiological saline) were administered 10 min before conditioning.

The procedures used here are similar to those in Experiment 1 through day 21. Cocaine (5 mg/kg) was administered to two of the groups on each of the first 6 days of putative conditioning. Injection-schedules are presented in Table 2 . Based on the results of the first test, it was decided to further condition and test each of the groups. Following 2 days of no special treatment (days 22–23), rats continued a cycle of conditioning consisting of 3 days of putative (days 24–26) and 1 day of alternate (day 27) conditioning followed by a test (day 28) and 2 days of no special treatment (days 29–30). The cycle was repeated once more (days 31–35) for a total of three tests. Beginning on day 24 the dose of cocaine was increased by 1.0 mg/kg across each of the putative days of conditioning. For example, on day 33 (the last day of conditioning on putative side) each of the cocaine groups received 11 mg/kg cocaine.

Data Reduction and Statistics

The data reduction and statistics follow the same pattern as outlined for Experiment 1. An analysis of the baseline and test 1 data failed to reveal any reliable sources of variance ($ps > 0.05$) associated with drug administration. Based on these results, it was decided to further condition rats with increasingly larger doses of cocaine in an effort to condition a cocaine place preference. A one-way ANOVA of test 2 scores yielded an F-value of $F(3,44) = 2.60$, $p = 0.06$, so, we engaged further conditioning. The relevant data (test 3 scores) conform to a one-way ANOVA.

TABLE 2

GROUP ASSIGNMENTS AND SCHEDULES OF DRUG ADMINISTRATION

Group	Putative	Alternate
Saline control	Saline/saline	Saline/saline
CGS control	CGS 10746B/saline	CGS 10746B/saline
Cocaine control	Saline/cocaine	Saline/saline
Cocaine/CGS 10746B	CGS 10746B/cocaine	CGS 10746B/saline

Group assignments and schedules of drug administration for the assessment are depicted as in Table 1. The cocaine dosing regimen is given in the text. The CGS 10746B compound was given via the IP route at a dose of 30.0 mg/kg.

RESULTS AND DISCUSSION

The ANOVA of test 3 scores (Fig. 2) indicated that group's mean scores differed reliably from each other, $F(3, 44) = 3.25$, $p = 0.03$. A Student's t-test between the saline and cocaine groups yielded a $t(22) = 2.10$, $p < 0.05$, indicating that cocaine produced a CPP. Further t-tests between the saline and CGS controls and between CGS control and the cocaine/CGS group indicated no reliable differences among groups ($ps > 0.7$). The data, therefore, lead to the suggestion that CGS blocks cocaine's ability to establish a CPP.

Conditioned place aversions have been reported following systemic or central administrations of CGS (10,32). Taking this into account, CGS was administered on both sides of the alley. It is doubtful, therefore, that the results are due to the aversive properties of CGS. With an unselected group of Sprague–Dawley rats, we sometimes achieve a positive CPP with 5.0 mg/kg doses of cocaine with very few pairings of cocaine's effects with the side of putative conditioning (unpublished data). More often, however, it takes larger doses of cocaine or more extensive pairings to achieve a reliable CPP with cocaine (as it did with these subjects). It seems that with every group of 10 to 12 rats that are given cocaine, there are some rats that do not show positive effects from cocaine, as indexed by a place preference. In fact, a small number of each group (say one or two) seem to averse the effects of cocaine. Consequently, there is a possibility that the group receiving cocaine and CGS had, by chance, a larger than usual number of rats that did not find cocaine's effects positive and that the low mean scores of the cocaine-CGS group reflect a potential selection error rather than CGS's ability to attenuate cocaine's effects. This is an unlikely possibility because (a) groups were randomly assigned and there is no reason to suppose that any systematic factor separated the group receiving cocaine and cocaine plus CGS; (b) the mean score of the cocaine plus CGS group is actually slightly lower than the saline group, and in almost all groups that we have tested with cocaine the mean score of the cocaine group is higher than that of placebo controls; and (c) there were no high scores among the cocaine-CGS30 group. Provided that CGS does indeed block release of dopamine, it is probable that cocaine's ability to produce a CPP is dependent upon release of dopamine.

GENERAL DISCUSSION

A reasonable conclusion that might be drawn is that release of dopamine is necessary for both MDMA and cocaine to produce effects that establish a CPP. Such a conclusion is compatible with the theory that addictive stimulants achieve their salient effects by increasing functional levels of dopamine. The increase in functional levels of dopamine, following cocaine administration, are thought to be mediated by cocaine's interference with the dopamine transporter (26,27). These data indicate that a CGS 10746B-sensitive release of dopamine may be necessary for the reinforcing actions of cocaine and MDMA. It would be of interest to further assess the actions of CGS 10746B on a place preference established with a direct acting dopamine agonist such as apomorphine.

The proposed role of dopamine in the manifestation of the reinforcing properties of cocaine and other addictive agents is likely an oversimplification of a dynamic process (19). For example, cocaine has been shown to interact with serotonergic

and noradrenergic systems (26). Furthermore, there is some evidence to suggest that serotonin receptor subtypes may mediate dopamine synthesis and release (12). To complicate the possible interactions, work with serotonergic antagonists has provided differential effects on measures of cocaine reinforcement (16,21,34). The use of more selective antagonists, or molecular manipulations (e.g., antisense oligodeoxynucleotides or gene knockout) that target the cloned dopamine and serotonin receptor subtypes, may provide additional information [see (3)].

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