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Chlordiazepoxide Alters Intravenous Cocaine Self-Administration in Rats[1]

NICK E. GOEDERS,[2] MARCIA A. McNULTY, SERENE MIRKIS AND KEVIN H. McALLISTER

Department of Pharmacology & Therapeutics, Louisiana State University Medical Center 1501 Kings Highway, Shreveport, LA 71130-3932

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GOEDERS, N. E., M. A. McNULTY, S. MIRKIS AND K. H. McALLISTER. *Chlordiazepoxide alters intravenous cocaine self-administration in rats.* PHARMACOL BIOCHEM BEHAV **33**(4) 859–866, 1989.—This investigation was designed to examine the effects of benzodiazepines on intravenous cocaine self-administration in rats. Pretreatment with low doses of the benzodiazepine receptor agonist, chlordiazepoxide (0.3 to 1.0 mg/kg, IP), resulted in small but nonsignificant increases in drug intake with 0.5 mg/kg cocaine, while higher doses (10 mg/kg, IP) significantly decreased drug intake in all rats tested. The effects of chlordiazepoxide on self-administration were attenuated when the concentration of cocaine was increased to 1.0 mg/kg, suggesting that chlordiazepoxide was opposing rather than augmenting the pharmacological actions of cocaine. Pretreatment with the benzodiazepine receptor antagonist, Ro 15-1788 (1.0 to 10 mg/kg, IP), had no effect on self-administration, suggesting that the reinforcing properties of cocaine do not result from direct interactions with benzodiazepine receptors. The results of this investigation demonstrate that chlordiazepoxide alters intravenous cocaine self-administration in rats. Although additional research will be necessary to confirm these data, the results of this investigation suggest that chlordiazepoxide may decrease the reinforcing efficacy of cocaine through indirect actions on dopaminergic neuronal activity potentially mediated through GABAergic mechanisms via benzodiazepine receptor activation.

Cocaine Self-administration Benzodiazepine Chlordiazepoxide Reinforcement

THE chronic nonmedical use of cocaine has continued to increase during the last decade despite numerous drug-related health problems and severe penalties associated with the possession and the sale of the drug (11,22). Unfortunately, however, there is no clear-cut consensus among health care professionals regarding optimal treatment strategies for cocaine abuse (27, 30, 42). Since chronic cocaine use has not historically been assumed to produce prolonged physiological withdrawal symptoms upon discontinuation, most current treatments generally consist of psychological therapy aimed at modifying addictive behaviors (27). The increase in the number of people suffering from cocaine dependence who have requested medical assistance for withdrawal has resulted in a number of investigations attempting to develop more satisfactory treatment strategies. The introduction of pharmacological interventions to increase the probability of successful cocaine abstinence has, therefore, only recently been investigated (59).

Benzodiazepines are often employed clinically for the medical complications associated with acute cocaine toxicity and can be used to manage symptoms associated with withdrawal. Convulsions may be manifested following acute cocaine intoxication, and these seizures can be treated with intravenous diazepam (26,71), but not dilantin (71). Major symptoms associated with cocaine withdrawal often include severe agitation, anxiety and restlessness (11, 71, 80). In addition, cocaine has been reported to precipitate episodes of panic attack (2) in as many as 64% of chronic cocaine users (77). In many of these cases, panic disorder only appeared to occur after the chronic use of cocaine, suggesting that the drug may have been a precipitating and causative factor in a neurobiologically vulnerable host (2). However, while diazepam can be used to treat cocaine-induced anxiety (71,80), benzodiazepines are not usually recommended as the treatment of first choice for cocaine withdrawal because the use of these drugs could result in a secondary dependence (80).

The drug self-administration paradigm has been utilized by a number of laboratories to investigate the reinforcing properties of drugs (51, 68, 83). Since a wide variety of the psychoactive substances that are self-administered by humans also serve as reinforcers in rats, drug self-administration by animals is thought to reflect potential abuse liability in humans (10,39). This laboratory self-administration model has conclusively demonstrated that cocaine can serve as a potent reinforcer in humans as well as nonhuman animals (22, 38, 82), and this methodology was used in this investigation to determine the effects of benzodiazepines on cocaine reinforcement since many of the clinical manifestations associated with cocaine-induced intoxication and withdrawal can be treated with these drugs. Chlordiazepoxide pretreatment was

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[2]Requests for reprints should be addressed to Nick E. Goeders, Ph.D., Department of Pharmacology & Therapeutics, Louisiana State University Medical Center, P.O. Box 33932, Shreveport, LA 71130-3032.

used to examine the effects of a benzodiazepine receptor agonist on intravenous cocaine self-administration in rats. The benzodiazepine receptor antagonist, Ro 15-1788, was tested to determine whether the reinforcing properties of cocaine were mediated through direct interactions with benzodiazepine receptors or whether chlordiazepoxide altered cocaine self-administration through other mechanisms.

METHOD

Subjects

Sixteen experimentally-naive adult male inbred rats originally developed from the Fischer 344 strain and weighing between 275–325 g at the beginning of the study were used. Fourteen rats were trained with 0.5 mg/kg/infusion cocaine hydrochloride, and four of these rats were retrained with 1.0 mg/kg/infusion cocaine following testing with chlordiazepoxide. Two additional rats were only trained with 1.0 mg/kg/infusion cocaine. The animals were housed in individual cages in a temperature- and light-controlled animal care facility on a reversed 12-hour light/dark cycle. Since the rats were tested during one of three daily sessions, light onset occurred at either 7:00 p.m., 10:00 p.m. or 2:00 a.m. The rats had continuous access to food (Purina Rat Chow) and water containing 0.01% tetracycline as prophylactic against infections.

Surgical Procedures

Each rat was implanted with a chronic indwelling jugular catheter using previously described methods (78,79) under sodium pentobarbital anesthesia (50 mg/kg, IP) with methylatropine sulfate pretreatment (10 mg/kg, IP). The catheter (0.76 mm o.d. × 0.25 mm i.d., polyvinylchloride tubing) was inserted into the right posterior facial vein and pushed down into the jugular vein until it terminated outside the right atrium. The catheter was anchored to tissue in the area and continued subcutaneously to the back where it exited just posterior to the scapulae through a plastic harness that was implanted under the skin for attachment of a leash. The stainless steel needle tubing-spring leash was attached to the subcutaneous harness to protect the catheter, which was connected to a leak-proof fluid swivel (9) suspended above the cage and connected to a motor-driven syringe. The swivel and leash assembly was counter-balanced to permit relatively unrestrained movement of the animal. Following surgery, the animals were injected with sterile penicillin G procaine suspension (75,000 units, IM) and were allowed a minimum of four days to recover from surgery.

Apparatus

Each animal was housed in a galvanized steel/wire self-administration cage (26 × 18 × 18 cm). The animals were housed in groups of three in ventilated, sound-attenuating enclosures where they received automatic injections of heparinized saline (0.2 ml) every two hours to maintain the patency of the catheters. For behavioral testing, the catheter was disconnected from the syringe at a joint located above the fluid swivel, and the entire self-administration cage, swivel and counter-balance assembly was transferred to an individual ventilated, sound-attenuating testing enclosure. The catheter was attached to a motor-driven syringe located above the testing chamber, and a response lever mounted 6 cm above the floor and 3 cm from the left wall and a red stimulus light mounted 2 cm above the lever were installed in each cage. The testing enclosure also contained a house light mounted above the self-administration cage and a tone source located on the right wall of the enclosure.

Experimental Procedure

Subjects were trained to self-administer cocaine during daily 2.5-hour sessions five days per week. Initially, the rats were trained under a continuous schedule of reinforcement where each lever press resulted in an intravenous infusion of cocaine (0.5 or 1.0 mg/kg/infusion in 0.2 ml delivered over 4.9 sec). The response requirement was gradually increased to a fixed-ratio 4 limited hold 300-sec schedule (FR4 LH300) where cocaine delivery was contingent on the animal responding three additional times within 5 minutes from the first response. If the limited hold elapsed before the animal pressed the lever four times, then the ratio was reset. This limited hold contingency was added to the behavioral program to decrease the probability that accidental depressions of the response lever from normal movement about the cage would result in cocaine presentations. In addition, this contingency was used to evaluate whether drug pretreatment would affect the ability of the animals to respond under this schedule. Illumination of the red stimulus light indicated the availability of cocaine infusions. Following the successful completion of the response requirement, the red stimulus light was extinguished, the house light was illuminated and a tone was presented for 20 seconds. During this 20-sec timeout period, responses were counted but had no scheduled consequences. Successful training was determined when the number of infusions per session varied less than 10% and the limited hold did not elapse for three consecutive sessions.

Testing sessions were then conducted each Tuesday and Friday provided that training criteria were met on consecutive Thursdays. The animals were injected intraperitoneally with chlordiazepoxide hydrochloride (0, 0.3, 0.56, 1.0, 3, 5.6, 10, 17 or 30 mg/kg) or Ro 15-1788 (0, 1, 3, 5.6 or 10 mg/kg) fifteen minutes before the start of the training session while still in the housing enclosure. Following the fifteen-minute pretreatment period, the animals were tested for cocaine self-administration as described above for the training sessions. The doses of each drug were tested in a random order, and each dose was tested at least twice. To determine whether cocaine presentations were indeed maintaining responding, saline was substituted for cocaine during at least two test sessions each in these animals.

Drugs

Cocaine hydrochloride (Mallinckrodt) and chlordiazepoxide hydrochloride (Sigma) were dissolved in a bacteriostatic 0.9% sodium chloride solution (Elkins-Sinn, Inc.) containing 0.83 USP units/ml of sodium heparin. Ro 15-1788 (ethyl-8-fluoro-5,6-dihydro-5-methyl-6-oxo-4H-imidazo[1,5a]-[1,4]benzodiazepine-3-carboxylate; Hoffmann-La Roche, Inc.) was suspended in a 2% carboxymethyl cellulose solution containing 0.1% Tween 80. Cocaine presentations consisted of a 0.2 ml intravenous infusion delivered over 4.9 sec concurrently with a 20-sec tone and house light presentation. Chlordiazepoxide and Ro 15-1788 were delivered intraperitoneally in a volume of 1 ml/kg fifteen minutes prior to the start of the experimental session.

Data Analysis

The number and distribution of cocaine injections self-administered in test sessions were used for data analysis. The effects of chlordiazepoxide or Ro 15-1788 pretreatment on cocaine self-administration were compared to the effects obtained during vehicle-control sessions. The significance of the differences in drug intake between test and vehicle-control sessions was deter-

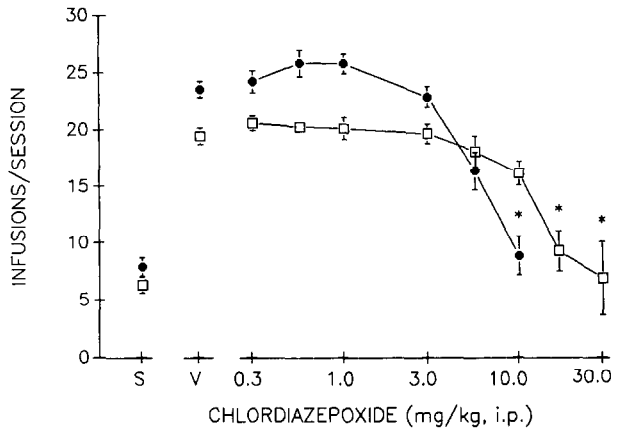

FIG. 1. Effects of chlordiazepoxide pretreatment (15 min) on intravenous cocaine self-administration expressed as the total number of infusions delivered per 2.5-hour session. Points are the mean ± SEM for double determinations in each rat. The closed circles represent drug intake with 0.5 mg/kg/infusion cocaine (n = 14) and the open squares represent intake with 1.0 mg/kg/infusion cocaine (n = 6). Points above S represent the effects of substituting saline for cocaine, while points above V represent the effects of pretreatment with the appropriate vehicle. Low doses of chlordiazepoxide resulted in small but nonsignificant increases in drug intake while higher doses significantly reduced self-administration in all rats tested. *$p<0.01$.

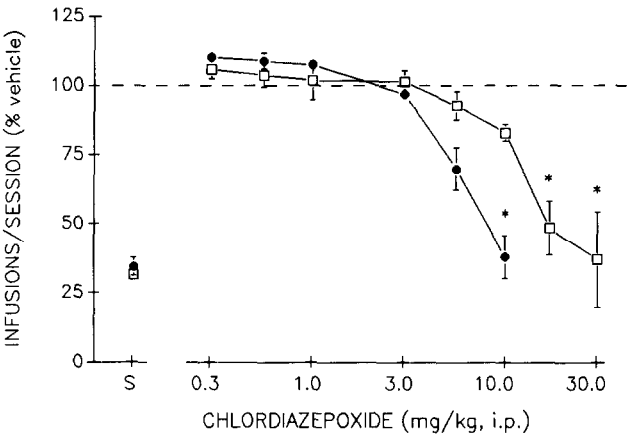

FIG. 2. Effects of chlordiazepoxide pretreatment on intravenous cocaine self-administration plotted as the percentage of drug intake following vehicle pretreatment (100%). The legend for this figure is the same as for Fig. 1. Low doses of chlordiazepoxide resulted in small but nonsignificant increases in drug intake, while the 10 mg/kg dose significantly decreased self-administration with 0.5 mg/kg cocaine (closed circles). The dose response curve for chlordiazepoxide was significantly shifted to the right when the dose of cocaine was increased to 1.0 mg/kg (open squares), suggesting that chlordiazepoxide was attenuating rather than augmenting the pharmacological effects of cocaine. *$p<0.01$.

mined with an analysis of variance followed by Tukey's comparisons among treatment means. Test sessions were conducted each Tuesday and Friday provided that training criteria were met on consecutive Thursdays, which were used to determine baseline levels of drug intake.

RESULTS

All rats self-administered cocaine under baseline conditions with stable rates of responding obtained under the FR4 LH300 schedule of reinforcement within two to three weeks. The average intake of the lower dose of cocaine (0.5 mg/kg) ranged between 20 and 29 injections per session (3.4 to 4.9 mg/session), while the intake of the higher dose (1.0 mg/kg) ranged between 17 and 22 injections per session (5.8 to 7.5 mg/session). Although there was some variability between subjects in baseline drug intake, within subject variability was remarkably stable over the course of the experiment. When saline was substituted for cocaine, drug intake decreased to 7.9 ± 0.8 and 6.3 ± 0.7 infusions/session for animals trained with 0.5 mg/kg and 1.0 mg/kg cocaine, respectively (Fig. 1). Typically, there would be a burst of responding during the first 10 to 30 minutes of the session followed by little or no responding for the remainder of the testing period. The dose-related changes in self-administration as well as the decrease in drug intake and extinction-like patterns of responding observed during saline substitutions clearly indicated that responding was maintained by cocaine presentations in this experiment.

The effects of chlordiazepoxide pretreatment on cocaine self-administration are presented in Fig. 1. Low doses of chlordiazepoxide (0.3 to 1.0 mg/kg) resulted in small but nonsignificant increases in drug intake, while 10 mg/kg chlordiazepoxide significantly decreased drug intake only in rats trained with 0.5 mg/kg cocaine. The dose-response curve for chlordiazepoxide was therefore effectively shifted to the right with the higher cocaine dose (1.0 mg/kg), and these data are plotted as the percentage of vehicle responding for clarity (Fig. 2). Higher concentrations of chlordiazepoxide (17 to 30 mg/kg) were therefore required to produce significant decreases in intake with this dose of cocaine since the dose of chlordiazepoxide (10 mg/kg) that decreased intake with 0.5 mg/kg cocaine no longer resulted in a significant reduction in drug intake. These data suggest that the effects of chlordiazepoxide on self-administration were attenuated or reversed by increasing the concentration of cocaine. The initial training dose of cocaine did not appear to alter the effects of chlordiazepoxide on drug intake since chlordiazepoxide resulted in similar effects with the higher dose of cocaine when the rats were trained with either this or the lower dose.

Event records depicting the effects of chlordiazepoxide on the patterns of self-administration for a representative rat (106E) are presented in Fig. 3. Chlordiazepoxide decreased the number of infusions per session in a dose-related manner without affecting the ability of the animal to respond or to complete the response requirement. In addition, chlordiazepoxide did not affect the number of limited holds that elapsed per session at any dose tested (Table 1), providing further support that the drug did not alter the ability of the animals to respond under the requirements of the schedule. In contrast to the effects of chlordiazepoxide, pretreatment with Ro 15-1788 had little or no effect on cocaine self-administration (Fig. 4), suggesting that cocaine reinforcement did not result from direct interactions of the drug with benzodiazepine receptors.

DISCUSSION

The results of this investigation demonstrate that chlordiazepoxide pretreatment can alter intravenous cocaine self-administration in rats. Low doses of chlordiazepoxide resulted in nonsignificant trends toward increased responding while higher doses significantly decreased intake suggesting that chlordiazepoxide decreased the reinforcing efficacy of cocaine. The decrease in drug intake observed with higher doses is probably not due to a debilitating effect of chlordiazepoxide on the ability of the animals to respond since the response requirement was effectively com-

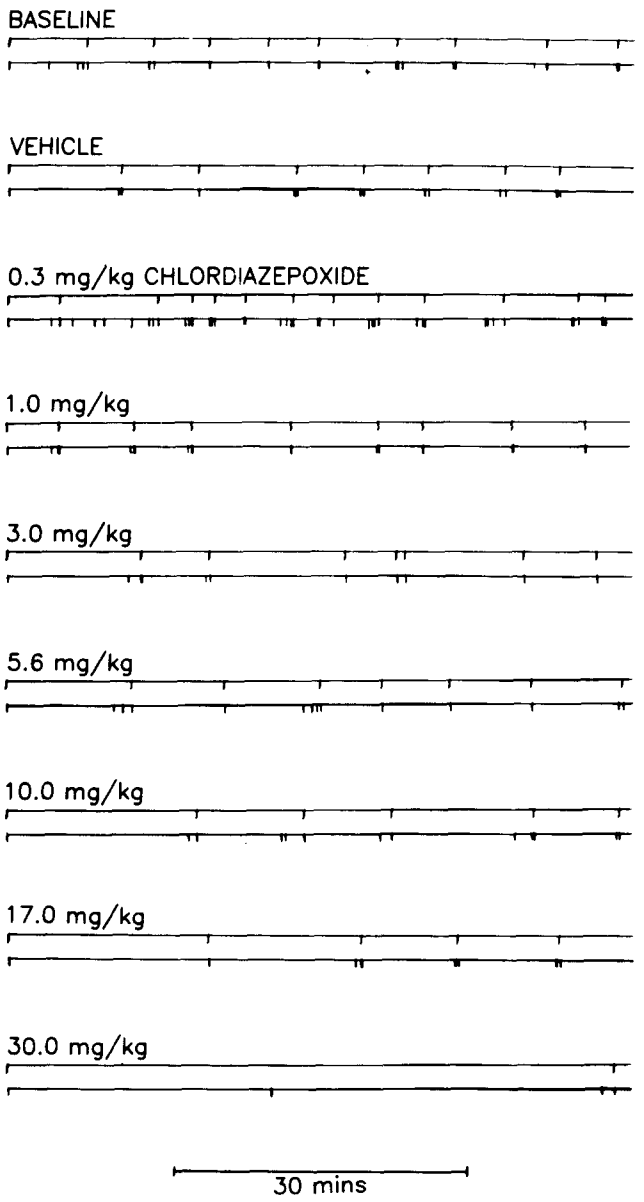

FIG. 3. Event records depicting the effects of chlordiazepoxide pretreatment on cocaine self-administration (1.0 mg/kg/infusion) selected from a representative rat (106E). The upper trace from each pair of lines indicates cocaine infusions, and the lower trace represents lever presses. Low doses of chlordiazepoxide decreased the interval between infusions and increased drug intake while higher doses decreased the number of infusions delivered per session without affecting the ability of the animal to respond under the requirements of the schedule.

pleted when responding was initiated. Furthermore, the dose of chlordiazepoxide (10 mg/kg, IP) that resulted in a maximal decrease in responding with the lower cocaine concentration (0.5 mg/kg) either has no effect or increases response rates under other conditions. For example, similar doses of chlordiazepoxide have been reported to increase responding in conflict or punishment paradigms in rats (20, 31, 54) and pigeons (7) without affecting performance by nonpunished control animals. In addition, chlordiazepoxide either increases responding or has little or no effect on the response rates of squirrel monkeys responding under a variety of operant schedules of reinforcement (6, 70, 76). These data suggest that the concentrations of chlordiazepoxide studied in this investigation did not reduce drug intake through nonspecific effects on response rates.

An alternative explanation could be postulated that the effects reported in this investigation may be related to a chlordiazepoxide-induced potentiation of the unconditioned effects of cocaine. According to this hypothesis, the decrease in response rates observed following large doses of cocaine may be the result of unconditioned behavioral effects of previously self-administered cocaine (4, 50, 81) so that large doses of cocaine would directly suppress the ongoing rate of cocaine-maintained responding (82). Theoretically, chlordiazepoxide pretreatment could result in an additive increment in the unconditioned effects of cocaine resulting in the decrease in drug intake observed in this investigation. Indeed, complex behavioral and neuropharmacological interactions between benzodiazepines and psychomotor stimulants have been reported. Amphetamine and cocaine augment the effects of chlordiazepoxide and diazepam on response rates in conflict (45), avoidance (63,65) and punishment (7,23) paradigms at doses which have little or no effect alone. In addition, chlordiazepoxide has been reported to enhance the stimulatory effects of amphetamine (64,66) or cocaine (17) on locomotor activity in mice. However, the data presented in this investigation do not support the theory that chlordiazepoxide augmented the rate decreasing effects of self-administered cocaine. While higher doses of chlordiazepoxide decreased drug intake, these effects were reversed when the cocaine dose was increased, suggesting an attenuation rather than a potentiation of the effects of the benzodiazepine. If the combination of chlordiazepoxide and self-administered cocaine was resulting in an additive increment in the unconditioned rate decreasing effects of the drug, then higher cocaine concentrations should have resulted in a further decrease in drug intake. Since drug intake actually increased when the cocaine dose was raised, these data suggest that chlordiazepoxide was opposing rather than augmenting the pharmacological actions of cocaine.

Cocaine results in a number of neurochemical effects in the central nervous system which may be involved in its reinforcing properties (48,82) and which may account, in part, for a cocaine-induced state of physical addiction (12,60). Although the effects of cocaine on neurotransmission are complex, the primary neurochemical action appears to be an inhibition of biogenic amine neurotransmitter uptake into presynaptic nerve endings, resulting in an increased synaptic concentration of these neurotransmitters. For example, cocaine decreases the reuptake of norepinephrine (19,35), dopamine (36, 44, 47) and serotonin (74), with no effect on release except at high concentrations (15,72). While it has yet to be conclusively determined whether or not these effects on neurotransmission are directly involved in the neuronal events responsible for the reinforcing properties of cocaine, intravenous self-administration experiments in nonhuman animals suggest a role for dopaminergic neurons (82). Cocaine-maintained responding by rats and rhesus monkeys is increased in a dose-related manner after the systemic administration of the dopaminergic receptor antagonists pimozide (16), haloperidol (14), alpha-flupenthixol (21) and sulpiride (58), suggesting an attenuation of reinforcing efficacy. Moreover, 6-hydroxydopamine lesions of the nucleus accumbens disrupt cocaine self-administration (55,56) as do similar lesions of the ventral tegmental area where the cell bodies for the mesolimbic/mesocortical dopaminergic neuronal system are localized (57). However, while dopaminergic receptor antagonists may modify the behavioral actions of cocaine, the doses required to reduce the reinforcing properties of the drug probably also reduce other behaviors as well (82). In fact, while the neuroleptics chlorpromazine and haloperidol have been reported to be effective in the management of cocaine-induced paranoia and delusional episodes as well as auditory and visual

TABLE 1

EFFECTS OF CHLORDIAZEPOXIDE ON THE NUMBER OF LIMITED HOLDS ELAPSED*

Cocaine (mg/kg/ infusion)	Chlordiazepoxide (mg/kg, IP)								
	0	0.3	0.56	1.0	3.0	5.6	10.0	17.0	30.0
0.5	2.4 ±1.0	3.2 ±0.9	2.3 ±0.8	0.7 ±0.4	1.9 ±0.8	2.1 ±0.6	1.7 ±0.5	ND	ND
1.0	1.4 ±0.8	1.0 ±0.6	0.8 ±0.5	0.7 ±0.4	0.4 ±0.3	0.7 ±0.7	1.3 ±0.7	2.1 ±0.9	1.4 ±0.6

*Points are the mean ± SEM for double determinations with n = 14 (0.5 mg/kg/infusion) or n = 6 (1.0 mg/kg/infusion cocaine).
ND: no data collected.

hallucinations (42,80), these drugs have little or no effect on cocaine euphoria and cocaine administration in humans (28) and may actually increase subjective reports of "cocaine craving" (12).

Even though neuroleptic agents appear to be ineffective in the maintenance of cocaine abstinence in humans, the most promising pharmacological strategies currently under investigation for the treatment of the nonmedical use of cocaine have focused almost entirely on direct manipulations of dopaminergic, serotonergic or noradrenergic neuronal activity. Treatment with the dopamine agonists amantadine (75) or bromocriptine (13,75) has been reported to be effective in alleviating the symptoms of cocaine withdrawal in patients experiencing severe craving. This treatment strategy is based on the hypothesis that cocaine-induced dopamine depletion and the subsequent supersensitivity of postsynaptic dopaminergic receptors may underlie the dysphoric aspects of cocaine abstinence (12). Other pharmacotherapies currently under investigation involve the use of drugs commonly used to treat affective disorders. The tricyclic antidepressant desipramine (8, 27, 32) and the atypical antidepressant trazodone (61) have each been reported in open clinical trials to be effective in reducing cocaine craving and promoting abstinence. While these data

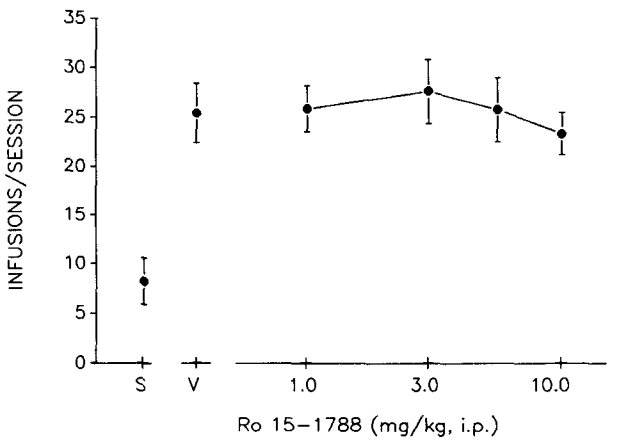

FIG. 4. Effects of Ro 15-1788 pretreatment (15 min) on intravenous cocaine self-administration (0.5 mg/kg/infusion) presented as the total number of infusions delivered per 2.5-hour session. Points are the mean ± SEM for double determinations in 5 rats. Points above S represent the effects of substituting saline for cocaine while points above V indicate the results of pretreatment with the appropriate drug vehicle. Ro 15-1788 pretreatment had little or no effect on self-administration.

appear to suggest that antidepressant drug therapy may only be alleviating an underlying depression that predisposes certain individuals to drug dependence (40), results from these investigations suggest that these drugs are useful whether depressive symptomatology is present or not (27). Therefore, treatment with antidepressants may reverse certain cocaine-induced neurobiological alterations potentially involving β-noradrenergic receptor systems (5) or serotonin depletion (73). However, while antidepressants such as desipramine have been reported to result in a decrease in the symptomatology associated with cocaine withdrawal, two to three weeks of treatment are often necessary before these effects become apparent (27). During this two- to three-week period, intense cocaine craving can occur and result in a relapse to persistent drug use (29), which suggests that more effective and efficient pharmacotherapy during this period may be critical for some individuals.

The mechanisms through which chlordiazepoxide produced the effects on cocaine self-administration reported in this investigation are not clear, but data from other investigations suggest a potential indirect interaction with dopaminergic neuronal transmission. As reviewed above, animal studies have implicated dopamine in a variety of the behavioral effects of cocaine, including its reinforcing properties. However, while dopaminergic receptor blockade can be used to treat cocaine-induced psychoses in humans, neuroleptic agents may not be useful for treating cocaine craving and subsequent drug use. These data suggest that pharmacotherapy based on modifications within a single neurotransmitter system (e.g., dopamine) may be inadequate for treating the nonmedical use of a drug with a complex neuropharmacological profile as cocaine. A dysregulation (69) or systems (48) approach to treatment which takes into account the integration of interconnected neuronal systems may prove to be more beneficial. Data obtained from a variety of sources suggest such an interplay between benzodiazepine receptors, GABAergic neurons and the dopaminergic neuronal system. GABAergic mechanisms appear to be partly involved in the complex regulation of dopaminergic neuronal activity (67). In addition, dopaminergic neuronal activity in the striatum and nucleus accumbens (terminal fields for the nigrostriatal and mesolimbic dopaminergic neuronal systems, respectively) may also influence activity of the efferent GABAergic systems which mediate various dopaminergic functions in these structures (67). High-affinity benzodiazepine receptors appear to be coupled with GABA receptor-chloride ion channel complexes in the central nervous system, and benzodiazepine receptor agonists have been demonstrated to potentiate the effects of GABA (37). Complex interactions between benzodiazepine receptors and the dopaminergic neuronal system have also been reported, and these effects may be related to the close association

between benzodiazepine and GABA receptors. For example, intraventricular injections of 6-hydroxydopamine, which decrease levels of dopamine in the central nervous system, have been demonstrated to significantly decrease the number of benzodiazepine receptors labeled with [^{3}H]flunitrazepam in the rat cerebral cortex (62) and cerebellum (18). Discrete 6-hydroxydopamine lesions in the area of the medial forebrain bundle have also been reported to reduce [^{3}H]flunitrazepam binding in the globus pallidus (49) suggesting an interrelationship between benzodiazepine receptors and dopaminergic neurons. Finally, neuroleptic drugs which block postsynaptic dopaminergic receptors and result in subsequent increased synthesis and release of dopamine through feedback mechanisms have been reported to increase benzodiazepine receptors labeled in vivo with [^{3}H]Ro 15-1788 (34,43), further suggesting direct or indirect interactions between benzodiazepine receptors and dopaminergic neuronal activity.

Recent behavioral and biochemical data suggest a potential involvement of cocaine in this integration of benzodiazepine receptors, GABA and dopaminergic neuronal activity. Chronic cocaine administration has been reported to increase the synthesis and turnover of GABA and to decrease [^{3}H]GABA binding in the rat striatum (24,25). In addition, bilateral infusions of the GABA agonist, muscimol, into the target region of the GABAergic nigrotegmental pathway in the region of the pedunculopontine nucleus completely abolish amphetamine- and cocaine-induced stereotypic sniffing and repetitive head movements while having no effect on stimulant-induced locomotor activity (3). Under the proper conditions, repeated exposure to psychomotor stimulants can result in an augmentation of the behavioral effects associated with the acute administration of the drug (41,52). Biochemical data suggest that this cocaine-induced behavioral sensitization may be related to actions at dopaminergic receptors, although results from different laboratories do not always agree regarding the nature of these effects (53). Nevertheless, daily injections of cocaine (33) or amphetamine (1) have been reported to result in a decrease in the number of dopaminergic receptors in the caudate nucleus-putamen and in an increase in the number of these binding sites in the nucleus accumbens. Preliminary data from our laboratory suggest that a similar schedule of cocaine injections results in changes in the number of benzodiazepine receptors in the terminal fields for the nigrostriatal and mesolimbic dopaminergic systems, respectively, that are opposite to those reported above for dopamine receptors (46). Finally, diazepam pretreatment has been reported to block these behavioral sensitizing effects of cocaine (53). These data suggest that at least some components of the behavioral effects of cocaine may be mediated in part through noncatecholaminergic systems. Taken together, these data suggest that some of these behavioral effects may involve interactions of the drug with dopaminergic and GABAergic neuronal activity as well as benzodiazepine receptors.

In summary, the results of this investigation demonstrate that chlordiazepoxide alters intravenous cocaine self-administration in rats. These data are consistent with clinical evidence that benzodiazepines are useful in treating cocaine-induced convulsions during acute intoxication and severe anxiety experienced during cocaine withdrawal. While the advocation of benzodiazepines to lessen the severity of cocaine withdrawal is not warranted, the results of this investigation do suggest a different noncatecholaminergic avenue for future studies to follow. Although additional research will be required to confirm these data, the results of this investigation suggest that chlordiazepoxide may alter the reinforcing efficacy of cocaine through indirect actions on dopaminergic neuronal activity potentially mediated through GABAergic mechanisms via benzodiazepine receptors.

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