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RAPID COMMUNICATION

Effects of Alprazolam on Intravenous Cocaine Self-Administration in Rats

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GOEDERS, N. E., M. A. McNULTY AND G. F. GUERIN. *Effects of alprazolam on intravenous cocaine self-administration in rats.* PHARMACOL BIOCHEM BEHAV **44**(2) 471-474, 1993. – The specificity of benzodiazepine pretreatment on the reinforcing efficacy of cocaine was investigated using a multiple schedule of cocaine and food presentation. Cocaine was available under a fixed-ratio 4 schedule of reinforcement during 1 h of the session, while food was delivered under a discrete-trial, fixed-ratio 10 schedule during the other. Following initial exposure to alprazolam, responding maintained by both cocaine and food was significantly reduced. However, tolerance quickly developed to the sedative effects of alprazolam on food-maintained responding, while no reduction in the effects of the drug on cocaine self-administration was observed. Alprazolam (0.5 to 4.0 mg/kg, IP) significantly reduced cocaine intake without affecting food-maintained responding following subsequent testing with the drug. These data suggest a potential specific effect (e.g., anxiolytic) of alprazolam in cocaine reinforcement.

Cocaine reinforcement Benzodiazepine Anxiety

INITIAL cocaine use is often reported by humans to produce profound subjective feelings of well-being and a decrease in anxiety (8). However, continued cocaine use or the administration of high doses of the drug can also induce severe anxiety (2) or panic attacks (1) in some individuals. Furthermore, some of the major symptoms observed during cocaine withdrawal in humans can often also include severe anxiety, restlessness, agitation, and depression (8). These data suggest that anxiety may be involved in the etiology of cocaine use and/or withdrawal in humans. In addition, acute and chronic cocaine administration, as well as withdrawal, have also been reported to result in anxiogenic-like behavioral responses in rats and mice (3,5,6,24). We have previously reported that pretreatment (15 min) with low doses (0.3 to 1.0 mg/kg, IP) of chlordiazepoxide produces small increases in IV cocaine self-administration with 0.5 mg/kg cocaine, while higher doses (10 mg/kg, IP) significantly decrease drug intake in rats (14). 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 reinforcing effects of cocaine. However, these decreases in drug intake may have resulted from nonspecific effects on the ability of the rats to respond with higher doses of chlordiazepoxide. The following experiments were therefore designed to extend our previous findings by using a multiple schedule of cocaine and food presentation to determine the specificity of the effects of benzodiazepines on cocaine reinforcement. The triazolobenzodiazepine, alprazolam, was investigated in these studies because this drug has been proven to be clinically effective in the treatment of anxiety and panic attacks and has been proposed to be useful in the treatment of some types of depression (4). Each of these conditions has been reported during chronic cocaine use and/or withdrawal in humans.

Six adult male Fisher strain 344 rats were implanted with chronic indwelling jugular catheters under pentobarbital anesthesia using previously reported procedures (14,17,22). After at least 4 days of recovery from surgery, the animals were trained to respond under a multiple schedule of IV cocaine presentation and food reinforcement. Cocaine was available during 1 h of the session under a fixed-ratio 4 schedule of reinforcement. Illumination of a stimulus light located above the cocaine lever indicated the availability of cocaine infusions. After completion of the response requirement, cocaine (0.5 mg/kg/200 μl) was delivered over 5.6 s through the IV catheter. A 20-s time-out period followed each infusion, dur-

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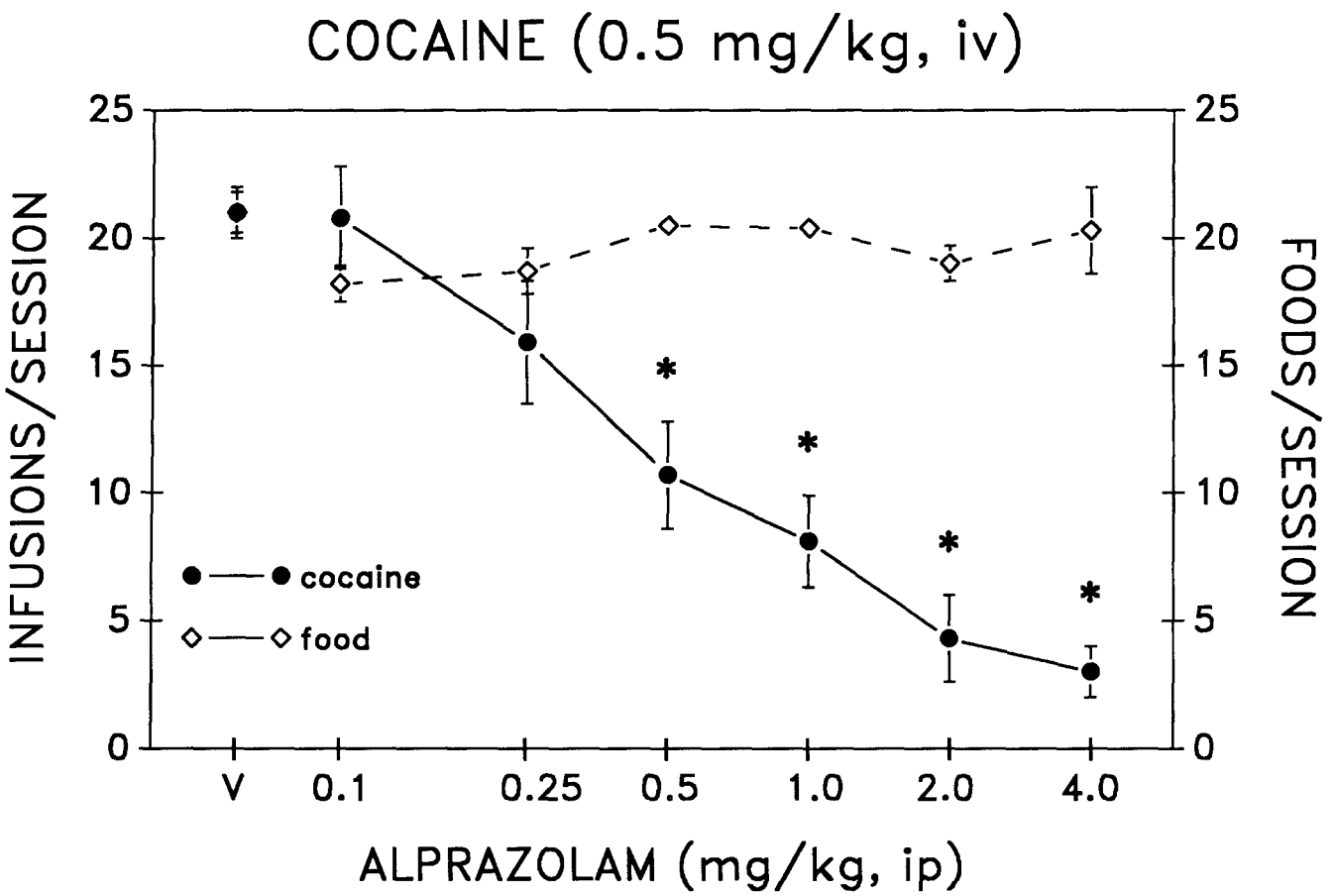

FIG. 1. Effects of alprazolam on reinforcer presentation under a multiple schedule of cocaine self-administration and food delivery. Cocaine was available under a fixed-ratio 4 schedule of reinforcement during 1 h of the session, while food was delivered under a discrete-trial, fixed-ratio 10 schedule during the other hour. Points are the mean (±SEM) for double determinations in six rats once tolerance to the sedative effects of alprazolam were obtained. Alprazolam dramatically reduced drug intake at doses that had little or no effect on food-maintained responding. Significance of the differences between the various doses of alprazolam and vehicle was determined with an analysis of variance followed by multiple *t*-tests. $*p < 0.05$.

ing which all stimulus lights were extinguished and responses on the cocaine lever were counted, but had no scheduled consequences. During the other hour of the schedule, food presentation was available under a discrete-trial fixed-ratio 10 schedule of reinforcement. Illumination of a stimulus light located above the food lever indicated the availability of food presentations. Completion of the response requirement resulted in the presentation of two 45-mg food pellets. A time-out period, during which all stimulus lights were extinguished and responses on the food lever were counted but had no scheduled consequences, followed each food presentation. This time-out period was estimated as being comparable to the average interinfusion interval generated during the cocaine component of the schedule for each rat so that similar temporal patterns of reinforcer presentation were obtained under both components of the multiple schedule. Behavioral sessions were 2 h in duration and were conducted 5 days per week. A 5-min time-out period, during which all stimulus lights were extinguished, separated the two components of the schedule. When stable baselines of responding were obtained under both components of the multiple schedule, the animals were pretreated with alprazolam (0.1, 0.25, 0.5, 1.0, 2.0, and 4.0 mg/kg, IP) or vehicle (1 ml/kg, IP) 30 min prior to the start of the behavioral session. Alprazolam was dissolved in a propylene glycol/ethanol (80 : 20) vehicle. Testing was conducted on Tuesdays and Fridays provided that responding returned to baseline levels between tests.

The effects of alprazolam on responding under the multiple schedule of cocaine self-administration and food presentation are depicted in Fig. 1. Following initial exposure to alprazolam, responding maintained by both cocaine and food was significantly reduced (data not shown). However, tolerance quickly developed to the sedative effects of alprazolam on food-maintained responding; no reduction in the effects of the drug on cocaine self-administration was observed. In other words, alprazolam reduced cocaine intake without affecting food-maintained responding following subsequent testing with the drug.

The results of these experiments demonstrate that alprazolam can influence cocaine self-administration without affecting food-maintained responding, suggesting a potential specific effect (e.g., anxiolytic) of this benzodiazepine in cocaine reinforcement. We have previously reported that cocaine differentially alters corticotropin-releasing factor (10) and benzo-

diazepine receptor (9) binding in brain regions associated with the mesocorticolimbic dopaminergic system when compared to other loci, suggesting a potential role for benzodiazepines in the neurobiological effects of the drug. We have also recently reported a differential effect of self-administered cocaine on benzodiazepine receptor binding in brain regions associated with the mesocorticolimbic dopaminergic neuronal system (13). Response-contingent cocaine (estimated by comparing changes in receptor labeling in self-administration vs. yoked-cocaine infused littermates) resulted in significant increases in benzodiazepine labeling in the medial prefrontal cortex and nucleus accumbens with decreases in the caudate nucleus, globus pallidus, and ventral tegmental area, suggesting that benzodiazepine receptors located in brain regions associated with ascending dopaminergic neurons may also be involved in cocaine reinforcement processes. In a separate experiment, rats without control over electric footshock presentation (i.e., noncontingent shock) self-administered cocaine at a higher rate and at lower doses than animals that received the same number of footshocks under different conditions (i.e., response-contingent shock) or that were never shocked (11,12). These data suggest that noncontingent electric footshock presentation increases sensitivity to cocaine, indicating that control over environmental stress influences vulnerability to self-administer the drug. Vulnerability to IV amphetamine self-administration in rats has also been reported to be associated with the animal's reactivity to a novel environment (19,20), suggesting that physiological responses to stress may be predictive of individual abuse liability. Further studies demonstrated that environmental conditions (18) or even exogenous infusions of corticosterone (21) can increase the likelihood that a rat will acquire self-administration of low doses of amphetamine, suggesting that changes in activity within the hypothalamic-pituitary-adrenal axis may be involved in the abuse liability of stimulant drugs. These reports are consistent with the behavioral data presented above demonstrating a specific decrease in cocaine self-administration following pretreatment with the benzodiazepine receptor agonist alprazolam at doses that did not affect food-maintained responding. In nonlaboratory settings, some users of cocaine are often able to control their drug intake and, therefore, do not escalate their patterns of use to levels that increase the risk of dependency and toxicity (23), suggesting that environmental factors (e.g., stress) may alter cocaine's reinforcing properties. This may help to explain why some individuals can remain casual recreational users of the drug, while others progress to compulsive drug use. In fact, a subpopulation of chronic cocaine users may actually be self-medicating to regulate painful feelings and psychiatric symptoms (e.g., anxiety, depression) via their drug use (7,15,16).

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