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Lisuride Reduces Intravenous Cocaine Self-Administration in Rats

LUIGI PULVIRENTI AND GEORGE F. KOOB[1]

Department of Neuropharmacology, The Scripps Research Institute, La Jolla, CA 92037

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PULVIRENTI, L. AND G. F. KOOB. *Lisuride reduces intravenous cocaine self-administration in rats.* PHARMACOL BIOCHEM BEHAV 47(4) 819–822, 1994.—The maintenance of intravenous (IV) cocaine self-administration appears to depend upon activation of dopamine terminals within mesocorticolimbic areas. Since the nonaddictive ergot derivative lisuride is a direct dopamine receptor agonist, the present study was designed to investigate whether administration of lisuride to rats trained to lever-press for IV self-administration of cocaine could affect the intake of cocaine. IP administration of several doses of lisuride reduced, in a dose-dependent manner, cocaine self-administration. In a control experiment, lisuride did not increase the psychomotor-activating properties of cocaine as measured by locomotor activity, suggesting that lisuride did not simply potentiate the activating effects of cocaine. The present results show that lisuride reduced IV cocaine self-administration in rats; the possibility of a new therapeutic approach to the treatment of cocaine abuse in humans using lisuride may therefore deserve clinical attention.

Lisuride Cocaine addiction Dopamine system IV self-administration

THE increase of cocaine addiction over the last few years has prompted much effort to understand the neurochemistry of cocaine abuse and to develop possible novel therapeutic approaches to cocaine abuse. Cocaine is a psychomotor stimulant, readily self-administered by animals and humans (22), and is known to block the reuptake of monoamines in the brain (14,18). With regard to its reinforcing properties, much evidence suggests that the brain dopamine system is a critical substrate. Administration of dopamine receptor antagonists at certain doses results in an increase in cocaine intake (9,24), and this has been interpreted as a compensatory mechanism to overcome reduction of the rewarding effect of cocaine by competitive antagonism at the receptor site (27). Also, destruction of dopamine terminals in the region of the nucleus accumbens and neurotoxic lesions of the ventral tegmental area result in a decrease in cocaine self-administration (25,26). These data suggest that the mesocorticolimbic dopamine system is critically involved in IV cocaine self-administration (20). Moreover, clinical studies provide some evidence that treatment of cocaine addiction with the dopamine receptor agonist bromocriptine (5,13) and the indirect dopamine agonist amantadine (31) may be an effective pharmacological treatment for cocaine addiction.

Lisuride is an ergot derivative that has been shown to interact with central dopamine transmission (15). In animals, the drug induces stereotyped movements, increases locomotor activity (2), causes contralateral turning after unilateral lesion of the nigrostriatal system (21), and stimulates mounting behavior in rats (7). Biochemical data suggests that lisuride acts as a dopamine receptor agonist at the D_2 receptor site (32). However, some of the behavioral effects of lisuride may actually be due to activation of serotonergic autoreceptors (10), resulting in a decrease of serotonergic activity, and this is supported by electrophysiological and neurochemical observations (28,29,33). Cocaine may induce similar electrophysiological changes in serotonergic neurons (4),

The purpose of the present study was to explore the effect of lisuride on intravenous cocaine self-administration in rats. To test the possible pharmacological interaction between cocaine and lisuride, the effects of lisuride on cocaine-induced locomotor activity were also studied. The present results show that lisuride reduced the intake of cocaine at doses that did not affect cocaine-induced locomotor activity.

MATERIALS AND METHODS

Male Wistar rats (Charles River, Kingston, NY), weighing 200–225 g at the start of the experiment, were housed three to

[1] Requests for reprints should be addressed to George F. Koob, Ph.D., Department of Neuropharmacology, CVN-7, The Scripps Research Institute, 10666 North Torrey Pines Road, La Jolla, CA 92037.

a cage and provided with ad lib access to food and water and maintained on a 12-h light-dark cycle (lights on 0400-1600).

All animals for self-administration studies were surgically prepared under halothane anesthesia with a chronic silastic catheter implanted into the external jugular vein. The catheter/polyethylene assembly consisted of silastic tubing attached to a guide cannula that was bent at a right angle. This junction was glued and the guide cannula was embedded into a 1-in. square of marlex mesh that was secured with silux. The catheter was passed SC from the rat's back to the jugular vein, where it was implanted. The polyethylene assembly was then mounted on the animal's back. A stylet was inserted into the guide cannula protruding from the animal's back to maintain a closed system and therefore prevented clogging of the cannula.

For self-administration testing, a cannula connector assembly that was connected to a swivel and syringe pump as described by Roberts et al. (25) was attached to the polyethylene assembly mounted on the animal's back immediately prior to the start of each session. The cannula connector was removed following the completion of a self-administration session and replaced with the guide cannula stylet.

Four days following surgery, subjects for the dose-response study were allowed 3 h access every day to a metal lever mounted on the side wall of a standard operant-conditioning cage. The cages themselves were housed inside sound-attenuating chambers. A lever press resulted in an IV injection of 0.1 ml of cocaine hydrochloride (0.75 mg/kg/injection; 2.21 μM/kg/injection) dissolved in 0.9% physiological saline and delivered over a period of 4 s. A swivel system allowed free movement of the animal in the cage. Coincident with the onset of the injection, a stimulus light was turned on for 20 s, during which time the lever became inactive. Lever presses during the period when the signal light was not lit were reinforced on a continuous reinforcement schedule.

Those animals that demonstrated stable drug intake for three days were gradually trained on a fixed-ratio schedule (FR 5) requiring a total of five responses for each reinforced response. The animals reached a stable level of drug intake (a range of less than 10% of the daily intake over three days), usually within six to eight days. This was taken as baseline and the study was begun. On a test day, the animals were pretreated immediately before the beginning of the session with lisuride. There were five different doses of the drug (0, 0.025, 0.1, 0.2, and 0.4 mg/kg; 0, 0.055, 0.22, 0.44, and 0.88 μM/kg IP) administered in a counterbalanced design: Each dose was tested only once for each animal. The drug was prepared in a vehicle solution of 0.9% physiological saline and injected in a volume of 1.0 ml/kg of body weight. At least one day of baseline self-administration separated testing days.

A total of 39 treatment observations (i.e., injection of one dose) were made on 15 individual subjects. Because of the length of time required to complete the experiment, 14 of the animals did not continue to maintain self-administration (due to cannula leaks or blockages) and were not used for the entire dose-response test regimen. As a result, statistical analysis was complicated by a confounding of independent and correlated samples.

However, the subjects were randomly assigned to drug treatment and each received a saline injection. Thus, to eliminate the possibility of unknown biases introduced by treating these as independent samples, the treatments were compared with saline data only for those animals that formed the data

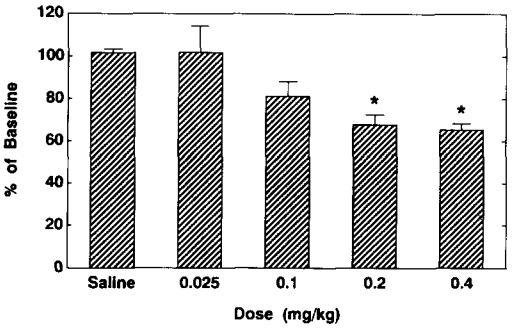

FIG. 1. Effect of lisuride pretreatment (IP) on number of reinforced responses for IV cocaine self-administration during 3 h (percentage of baseline). Values represent mean ± SEM. *$p < 0.01$, paired t test. The number of observations for each dose: saline, 8; 0.025, 8; 0.1, 7; 0.2, 8; 0.4, 8.

for a particular treatment using the paired t test. This dependent analysis reduces the degrees of freedom, but increases the power of the test. Significance was taken at $p < 0.01$, two-tailed. The 3-h session was considered appropriate because it encompassed the duration of the behavioral effects of lisuride, which are thought to last around 120 min (1,11).

For the locomotion study, naive rats were habituated to locomotor cages for 180 min one day before the test, as described previously (17). Each cage measured 36 × 25 × 20 cm with twin photocell beams across the long axis 2 cm above the cage floor. On the testing day, animals were placed in the photocell cages and received an injection of cocaine (10 mg/kg; 29.6 μM/kg IP) and one of five different doses of lisuride (0, 0.025, 0.1, 0.2, and 0.4 mg/kg IP), both immediately before test. Each group consisted of six to seven rats. To assess the effect of lisuride in naive rats, a separate group of animals was habituated as described above, and on the testing day the animals were placed in the photocell cages and received an injection of five different doses of lisuride (0, 0.025, 0.1, 0.2, and 0.4 mg/kg IP) immediately before the test. Each group consisted of nine rats. Locomotor activity was then recorded for 90 min. Total counts were compared using a one-way analysis of variance followed by a post hoc Student's t test. Stereotyped behavior was assessed by an experimenter un-

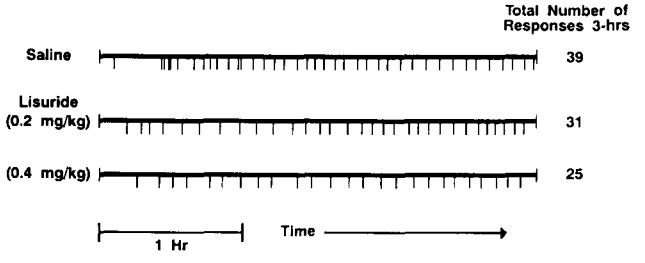

FIG. 2. Response record of a representative rat self-administering cocaine. Each record represents a separate session and each mark represents an infusion of the drug. After treatment with lisuride, the regular pattern of responding was maintained throughout the 3-h session, but with longer inter-response intervals. Total number refers to reinforced responses: The total numbers for the first, second, and third hour, respectively, were 13, 14, and 12 after saline; 8, 11 and 12 after 0.2 mg/kg lisuride; and 7, 8 and 10 after 0.4 mg/kg lisuride.

aware of treatment. Occurrences of the following signs were observed: sniffing intermittently, sniffing continuously, sniffing in one place, and head-down sniffing.

Cocaine hydrochloride was obtained by NIDA (Baltimore). Lisuride was a generous gift of Schering AG (Berlin).

RESULTS

Figure 1 shows the effect of various doses of lisuride on cocaine self-administration. Lisuride decreased responding for cocaine (expressed as percent of baseline) in a dose-dependent manner. A dose-dependent decrease was evident, with the doses of 0.2 and 0.4 mg/kg statistically significant compared to saline, $t(7) = 6.41, p < 0.01$, and $t(7) = 11.17, p < 0.01$, respectively. Baseline level of responding was 34 ± 2.6 reinforcers/3 h. Figure 2 shows the time course of the effect of lisuride throughout the 3-h session in one rat self-administering cocaine: In this figure each mark represents an infusion of the drug. Injections were self-administered at constant intervals, and as the dose of lisuride was increased, the regular pattern of responding was maintained throughout the session—but, with longer inter-response intervals. The effect of lisuride, however, appeared to be more pronounced during the first half of the session.

In the locomotor activity study, lisuride significantly increased spontaneous locomotion, $F(4, 27) = 3.028, p < 0.05$ (Fig. 3, lower panel), and the effect reached significance at the 0.4-mg/kg dose ($p < 0.01$, t test). In contrast, when rats pretreated with cocaine (10 mg/kg IP) were challenged with various doses of lisuride, locomotor activity measurement revealed that, although the lowest doses of lisuride produced a marked trend towards a decrease in cocaine-induced hyperactivity, this did not reach statistical significance, $F(4, 42) = 1.52, p = 0.213$. Also, higher doses of lisuride did not significantly affect cocaine-induced locomotor stimulation, and no overt alterations in motor behavior such as increases in stereotyped behavior were observed when the higher doses of lisuride were coadministered with cocaine (Fig. 3, upper panel).

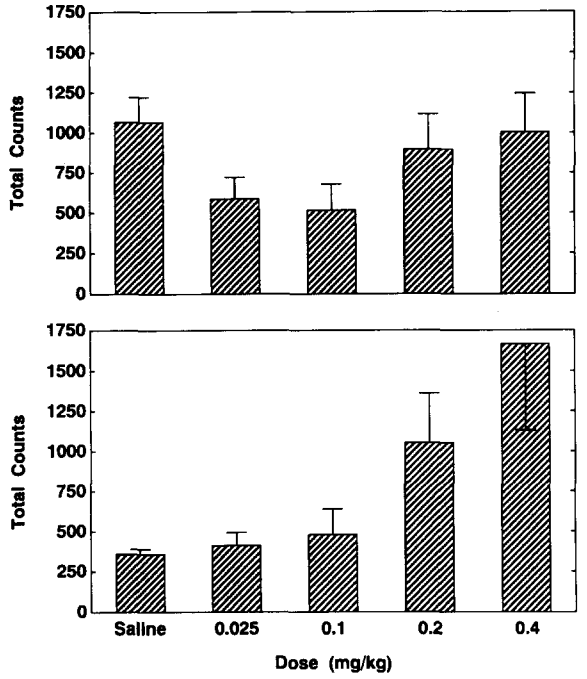

FIG. 3. Effect of various doses of lisuride (IP) on cocaine-induced (10 mg/kg IP) (upper panel) and spontaneous locomotor activity (lower panel). Lisuride induced a significant dose-dependent increase of locomotor activity in naive rats. Each group consisted of six to seven rats. In contrast, lisuride did not affect significantly cocaine-induced locomotion, although a trend towards reduction was evident with the lowest doses. Each group consisted of nine rats. Values represent mean ± SEM of total counts of horizontal activity during 90 min.

DISCUSSION

The present results show that lisuride decreased IV cocaine self-administration in rats in a dose-dependent manner. This decrease in cocaine self-administration was evident throughout the 3-h session. Also, lisuride failed to change locomotor activity produced by cocaine.

The mechanism of action of cocaine appears to depend upon blockade of monoamine reuptake (14,18), and activation of dopamine receptors appears to be critical for its reinforcing properties (9,19,20,25,26). Increases in cocaine self-administration induced by dopamine antagonists are believed to result from a reduction in the relative potency of the cocaine-induced dopamine stimulus due to receptor blockade (27). It is therefore conceivable that the reduction of cocaine intake induced by a dopamine agonist may be caused by a compensatory mechanism leading the animal to reduce its drug intake due to direct dopamine receptor stimulation (16).

Previous studies have shown that the discriminative stimulus properties of cocaine depend on dopamine receptor activation, and the cocaine cue generalizes to a number of dopamine drugs (8). Although lisuride is also thought to interact with the serotonin system (28,29,33), its discriminative stimulus properties have been suggested to depend upon activation of the dopamine system (30), with the D_2 receptor subtype specifically involved (3). Thus, results of the present study further support the hypothesis that pharmacological activation of D_2 receptors modulates cocaine self-administration, as previously suggested for bromocriptine in experimental and clinical studies (5,13,16).

The second experiment showed that the doses of lisuride effective in reducing cocaine intake do increase spontaneous locomotor activity, but do not increase cocaine-induced locomotion. Although not statistically significant, the lowest doses of lisuride produced a reduction of cocaine-induced locomotion. This may be due to an inhibitory action of low doses of lisuride on dopamine neurotransmission, probably through an interaction with dopamine autoreceptors. These results argue against a simple psychostimulant interaction between the two drugs, suggesting that lisuride did not simply potentiate cocaine's psychomotor activating properties. Also, the fact that the rats maintained a regular pattern of responding when treated with the higher doses of lisuride rules out the possibility of a motor-incapacitating effect induced by lisuride.

During cocaine addiction intense craving for the drug is experienced upon cessation of its use. This is believed to be one of the major factors leading to relapse in cocaine abuse. Moreover, a clear withdrawal from cocaine self-administration in humans has been recently shown (12), and experimental studies suggest that the neurochemical substrate for this may be, in part, dopamine depletion induced by repeated cocaine action on dopamine terminals (6). Symptoms of with-

drawal include depression of mood, fatigue, and hyperphagia, and they are suppressed by cocaine (12) as well as by bromocriptine (13). It is possible that lisuride may also show efficacy during withdrawal from psychostimulant drugs. Indeed, following withdrawal from chronic amphetamine self-administration, rats showed a state of psychomotor retardation measured as a decrease in spontaneous locomotor activity and increased catalepsy. Treatment with lisuride during the withdrawal phase prevented the occurrence of these behavioral changes (23). Clinical studies are required to validate the possibility of therapeutic use of lisuride in cocaine- or amphetamine-dependent subjects.

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