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Effects of ibogaine on responding maintained by food, cocaine and heroin reinforcement in rats

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Abstract The effects of ibogaine (40 and 80 mg/kg, IP), an indole alkaloid proposed for the treatment of drug abuse, were determined in three different groups of rats responding under an FR10 schedule of food, cocaine or heroin reinforcement. Ibogaine (80 mg/kg, IP) given 60 min before the start of the session resulted in a 97% decrease in the number of ratios completed under the food reinforcement schedule and resulted in a decrease in responding the following day. Neither 40 mg/kg ibogaine given 60 min prior to the session nor 80 mg/kg given 24 h before the session suppressed responding maintained by cocaine infusions (0.33 mg/infusion). Pretreatment with 80 mg/kg ibogaine either 60 or 90 min prior to the session suppressed cocaine self-administration on the day it was administered and the longer pretreatment continued to suppress responding for 48 h. Responding maintained by heroin (18 µg/infusion) was the most sensitive to the effects of ibogaine. Both 40 and 80 mg/kg ibogaine resulted in an almost complete suppression of responding following a 60-min pretreatment period. Responding maintained by heroin returned to control levels the day following the administration of ibogaine.

Key words Cocaine · Heroin · Ibogaine
Self-administration · Scheduled-controlled behavior
Fixed ratio

Introduction

The naturally occurring indole alkaloid, ibogaine, has been evaluated for its putative effects in the treatment of drug abuse. The drug has received US patent rights related to its reported efficacy in the treatment of narcotic, cocaine, amphetamine, nicotine and alcohol dependence (Lotsof 1985, 1986, 1989, 1991). Although ibogaine appears to alter some of the effects of opiates in a manner to suggest the drug may be useful in treating opiate abuse, reported effects of the compound have been equivocal. Ibogaine has been shown to block the increase in dopamine levels and motor activity following the administration of low doses of morphine (Maisonneuve et al. 1991, 1992b), providing support for the potential of ibogaine to antagonize some of the effects of opiates. Moreover, ibogaine has been reported to attenuate some of the effects of naloxone-precipitated withdrawal (Dzoljic et al. 1988; Glick et al. 1992) or to have no effect on withdrawal (Sharpe and Jaffe 1990; Frances et al. 1992). Additionally, the effects of ibogaine on morphine self-administration within the same study were inconsistent; decreasing self-administration only on the same day that it was administered in some rats and for a longer period of time in others (Glick et al. 1991).

Other investigations have indicated that ibogaine may augment rather than attenuate the effects of stimulants. Ibogaine has been reported to potentiate the expected increase in extracellular dopamine levels and to enhance the stimulatory motor effects of amphetamine (Maisonneuve et al. 1992a) and cocaine (Maisonneuve and Glick 1992) in rats. However, in mice ibogaine pretreatment resulted in a prolonged reduction of cocaine-stimulated motor activity (Sershen et al. 1992b) reduced amphetamine-induced locomotor activity following low doses (Sershen et al. 1992a), and did not affect increases in motor activity stimulated by high doses of amphetamine. It has recently been reported that ibogaine decreased cocaine (1.2 mg/kg) reinforced responding in rats that have an very low rate (fewer than six infusions during a 3-h session) of responding maintained by the drug

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(Cappendijk and Dzoljic 1993). Moreover, drug intake was suppressed for several days following ibogaine administration.

Since the reported effects of ibogaine on drug-induced changes in motor activity and drug self-administration are diverse, the present study was designed to determine if ibogaine would alter behavior maintained by three different reinforcers presented under slightly different conditions. Three different groups of rats were trained with food, cocaine or heroin reinforcement. The effects of two doses of ibogaine and several pretreatment times were determined.

Materials and methods

Subjects

Seventeen male Fisher 344 rats weighing 250–300 g were limited to 85% of their unrestricted body weight to minimize body weight fluctuations (Ator 1991). The rats were housed in either standard wire mesh housing cages (rats studied with food reinforcement), or wire mesh cages with a Plexiglas lid (cocaine and heroin studies). All subjects were placed on a reversed 12-h light-dark cycle (dark 0500–1700 hours) and given unrestricted access to water except during experimental sessions. Rats studied with drug reinforcement were implanted with external jugular venous catheters under anesthesia induced by pentobarbital (50 mg/kg, IP) and atropine (10 mg/kg, IP). The catheter was connected to an infusion pump (Model A, Razel Scientific Instruments, Stamford, Conn.) through a fluid swivel and a spring leash. The spring leash was attached to two nylon screws that extended above a subcutaneously implanted polypropylene plate enclosed in Teflon mesh with nylon nuts. Rats were administered penicillin G procaine (75,000 units, IM) and exterior wounds were dressed with antibiotic powder following the surgery. Rats were allowed 7–10 days to recover from surgery before training was initiated. Catheter patency was maintained by hourly infusions of saline containing heparin (1.7 units/ml) and checked periodically with methohexital (10 mg/kg, IV) for loss of consciousness within 5 s.

Apparatus

Experimental sessions with food reinforcement were conducted in sound-attenuated chambers controlled by Rockwell Aim 65 computers (using the MCS system, Micro Interfaces, Minneapolis, Minn.). The drug self-administration studies were conducted in sound-attenuated chambers connected to an IBM-compatible computer though a Med-PC system (Med Associates, St Albans, Vt.) interface. The front panel of the operant chambers (28 × 26.5 × 30 cm) used for food reinforcement studies contained a response lever located 2 cm above the floor and 3 cm from the side wall and a light (Sylvania, 1829) centered 3 cm above the lever. A food pellet chute was centered on the front wall 0.8 cm above the floor. The chamber also contained a food pellet dispenser (delivering 45 mg pellets, Noyes, Lancaster, N.H.) located behind the front wall and a tone source. The drug reinforcement studies were conducted in commercially available chambers (28.2 × 21 × 20.7 cm, model ENV-002, Med Associates, St Albans, Vt.) containing a response lever located 7 cm from the floor and 1 cm from the side wall and a light centered 6 cm above the lever. A counterbalance holding a fluid swivel for drug infusions was attached to the front and the swivel was centered above the chamber. These chambers also contained a houselight and tone source. In addition, a motor-driven syringe pump (Model A, Razel Scientific Instruments, Stamford, Conn.), which contained a 20-cc syringe was mounted on the outside of the chambers used to study cocaine and heroin reinforcement. The syringe was connected to a swivel by tubing that passed through a small port on the chamber. Drug infusions of 0.20 ml were delivered intravenously over 5.6 s.

Behavioral procedures

Five rats were trained to press a lever that resulted in presentation of a food pellet following each response during the sessions. The number of responses required for each food pellet was gradually raised to ten (fixed-ratio 10; FR10) over the first five sessions. A 6-min timeout period (TO), during which responding was recorded but had no programmed consequences, was then added to the schedule. Neither the time nor responding during the TO was used in calculating response rates. The light above the lever was illuminated when the ratio schedule was in effect and was darkened during the TO. The end of the TO was signalled by a 3-s tone in addition to illumination of the light. These sessions were 2 h in duration.

Seven rats were trained to respond on a lever resulting in cocaine presentations. The rats received a single response-independent infusion of cocaine (0.33 mg) at the start of the 3-h session, which was followed immediately by a 10-min timeout. Following this initial TO period, responding was maintained under an FR schedule of reinforcement. Completion of the ratio schedule darkened the light above the lever, illuminated the house light and activated the tone for a 20-s period during which additional responses had no programmed consequences. The ratio schedule was raised gradually from 1 to 10.

The procedure using heroin reinforcement was similar to the procedures used for cocaine reinforcement, except sessions were 4 h in duration and a 30-s TO was utilized. Infusions of heroin (18 µg/infusion) were used to maintain responding in five rats.

All sessions were conducted Monday to Friday. When the number of infusions did not vary by more than 5%, tests of ibogaine were initiated. These tests occurred twice a week providing that responding was within the range of pre-ibogaine baseline values on the preceding day.

Drugs and treatment procedures

Cocaine HCl (1.66 mg/ml) and heroin HCl (0.099 mg/ml) (National Institute on Drug Abuse) were dissolved in saline containing heparin (1.7 units/ml). Ibogaine (National Institute on Drug Abuse) was dissolved in water in a concentration of 10 mg/ml. Ibogaine was administered 60 min prior to the start of the experimental session. Pretreatment durations of 90 min and 24 h were also studied with rats receiving cocaine.

Data analysis

The number of reinforcer presentations and response rates (excluding timeouts) were determined for individual subjects and averaged. Control data were collected from the days immediately prior to administration of ibogaine or vehicle. The data were analyzed by a standard analysis of variance followed by the Bonferroni *t*-test or multiple comparison (comparison versus control) using the SigmaStat Statistical Analysis Program (Jandel, San Rafael, Calif.). Cumulative records of responding during the session were obtained from either cumulative recorders (Gerbrands, Arlington, Mass.) or the reconstruction of temporal locations of reinforcers and responses using Soft Cumulative Record software (Med Associates, St Albans, Vt.).

Results

Food reinforcement

Responding maintained by the FR10 schedule of food presentation consisted of high rates during the FR component and generated response patterns very similar to responding maintained by the drug reinforcers (see Fig. 1). The mean response rate was 41.1 responses/min (±15.7 SD) and a mean of 19 (±1 SD) pellets were delivered during control sessions. Ibogaine had a significant effect on food-maintained responding ($F = 102.062$, $P < 0.001$). Figure 2 (circles) indicates the effects of ibogaine pretreatment on the number of delivered food reinforcers. The 40 mg/kg dose of ibogaine resulted in a small decrease in food-maintained responding in two of the five rats. Figure 1 (second panel) illustrates this effect and indicates that responding was decreased in an irregular pattern across the session. The 80 mg/kg dose almost completely eliminated food-maintained responding during the session

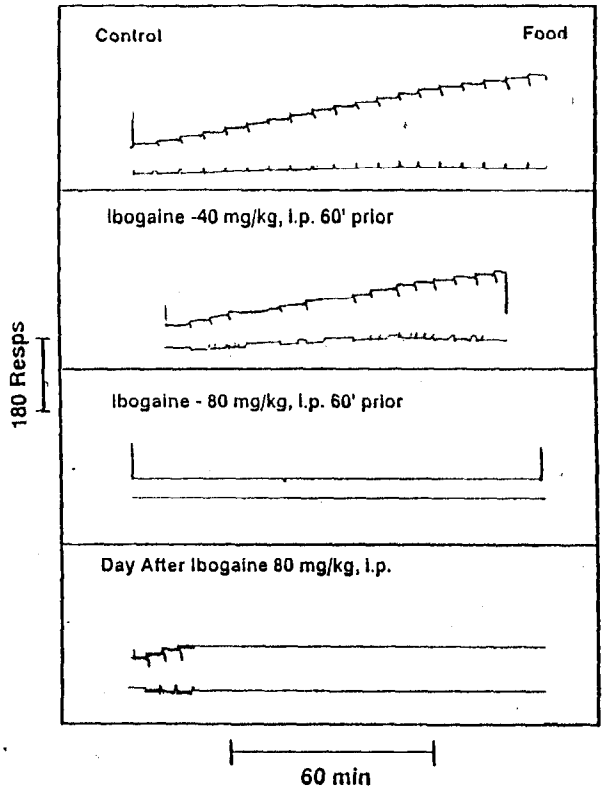

Fig. 1 Representative cumulative records of the effects of ibogaine on responding maintained by the FR10, TO 6-min schedule of food reinforcement. The *top panel* was obtained from a control session. Records displayed in the *second* and *third panels* were obtained from ibogaine test sessions. The panel contains a record from the session conducted 24 h after the 80 mg/kg ibogaine test session. The *top pen* in each panel was stepped up the page with each response and momentarily deflected with each food presentation. The *bottom pen* was down during the TO and briefly deflected upwards with each response during this period

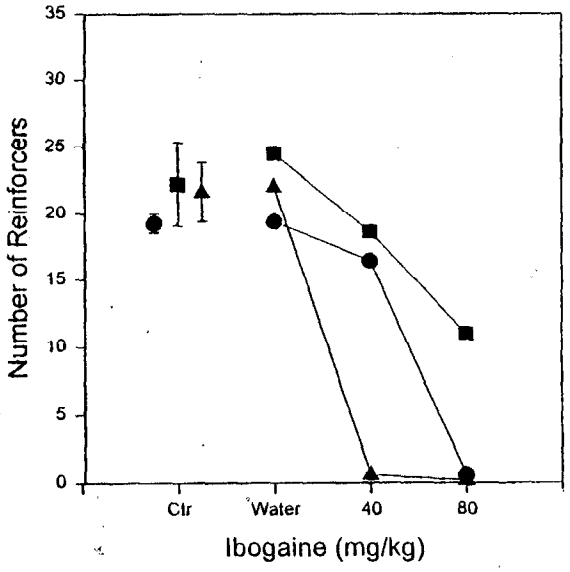

Fig. 2 Effects of ibogaine on the mean number of food, cocaine and heroin reinforcers. The data depict the control values ("Ctr") and the effects of vehicle ("Water") or ibogaine (40 mg/kg and 80 mg/kg, IP) 60 min prior to the session. *Vertical lines* above Ctr indicate ±1 SD. Data are statistically significant ($P < 0.05$) for heroin at the 40 mg/kg dose and all three reinforcers following the 80 mg/kg dose. ● food; ■ cocaine; ▲ heroin

(Fig. 1, third panel). The mean number of reinforcers delivered and response rates obtained were 1 (±1 SD) and 0.13 (±0.05 SD) responses/min, respectively. The effects of ibogaine on the number of reinforcers delivered during sessions conducted 24 h after the test sessions are presented in Table 1. The 80 mg/kg dose resulted in a significant decrease in responding 24 h later. When responding occurred patterns were similar to control performance (see Fig. 1, bottom panel). Responding returned to control values 48 h following the administration of the 80 mg/kg dose.

Cocaine reinforcement

The FR10 schedule of cocaine reinforcement maintained a consistent pattern of responding characterized by a pause after the drug infusion followed by a transition to a high rate until the next injection was delivered (see Fig. 3, left top panel). A mean response rate of 1.3 (±0.2 SD) responses/min was obtained and

Table 1 Effects of ibogaine on the number of reinforcers (mean ± SD) on the day after it was administered

	Vehicle	40 mg/kg	80 mg/kg
Food	17.7 ± 1.98	19. 8 ± 0.45	6 ± 9.54*
Cocaine	21.5 ± 1.92	20.14 ± 2.29	20 ± 4.10
Heroin	22.3 ± 2.17	21 ± 4.57	13.3 ± 11.63

*$P < 0.05$

a mean of 22 (± 3 SD) infusions were delivered over the session. Ibogaine resulted in a significant decrease in cocaine self-administration ($F = 5.046$, $P < 0.003$). Figure 2 (squares) shows that ibogaine (80 mg/kg) resulted in a significant decrease in cocaine intake following the 60-min pretreatment. This dose of ibogaine resulted in a larger decrease in the mean number of cocaine reinforcers (5 ± 7 SD) when given 90 min before the start of the session. The 40 mg/kg dose also resulted in a non-significant decrease in mean response rates (1.1 ± 0.3 SD), although three of the seven rats showed decreases of at least 50%. Cocaine self-administration was not decreased (19 ± 5) after the 24-h pretreatment time in rats not given the opportunity to self-administer cocaine the day ibogaine was given. Furthermore, responding returned to control values 24 h following the administration of the low dose and the 60-min pretreatment of the 80 mg/kg dose (see Table 1). Cocaine self-administration, however, was decreased on the second day to a mean of 6 (± 10) infusions following the 90-min pretreatment of 80 mg/kg ibogaine.

Heroin reinforcement

Responding maintained by heroin under the FR10 schedule was similar to responding maintained by the other reinforcers (see Fig. 3, top right panel). The mean response rate was 0.94 (± 0.23 SD) responses/min and a mean of 22 (± 3 SD) infusions were delivered over the 4-h session. Figure 2 (triangles) shows that both doses of ibogaine, which were given 60 min prior to the start of the session, resulted in a significant ($F = 355.4$, $P < 0.00001$) decrease in heroin self-administration. These two doses resulted in an almost complete cessation of responding through out the entire session (see Fig. 3, right panels). Heroin self-administration was decreased in two of the five rats on the day following the 80 mg/kg dose (see Table 1).

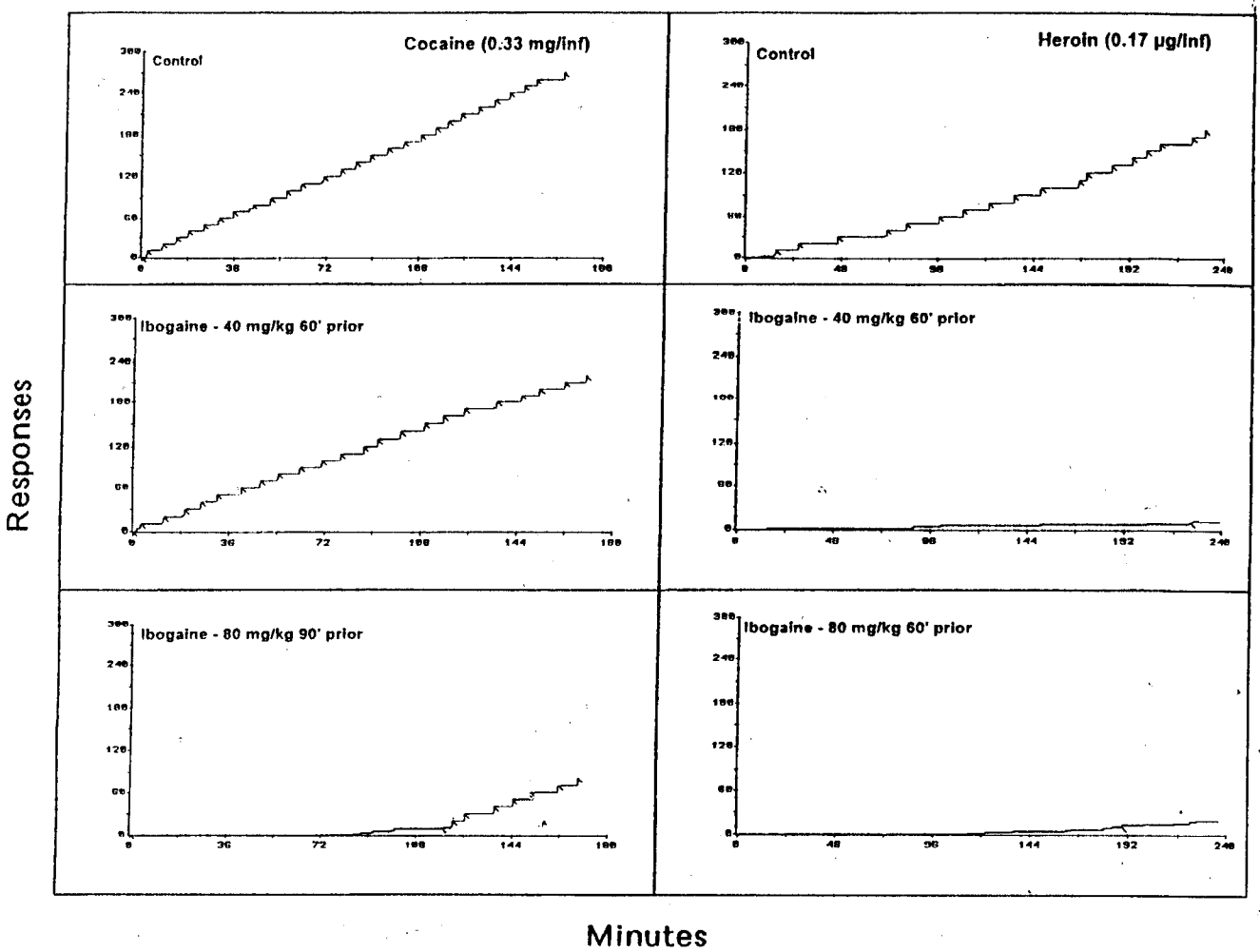

Fig. 3 Representative cumulative records depicting the effects of ibogaine on responding maintained by the FR10 schedule of cocaine (*left panels*) and heroin (*right panels*) reinforcement. The *top panels* contain a record from control sessions. The effects of the 40 mg/kg and 80 mg/kg dose following 60-min pretreatment are shown, respectively, in the *middle* and *bottom panels*. The *top pen* was stepped with each response and deflections of this pen indicate drug infusions

Discussion

Three different reinforcers were used in order to assess the potential utility of ibogaine in the treatment of drug abuse. The food schedule was 2 h in duration and included a 6-min TO, while the cocaine and heroin session was respectively, 3 and 4 h and included a brief TO period. Ibogaine resulted in an attenuation of responding maintained by food, as well as by cocaine and heroin. The effects were apparent on the day ibogaine was administered; however, responding maintained by both food and cocaine was decreased significantly 24 h after the administration of the 80 mg/kg dose.

Responding maintained by heroin was more sensitive to the rate decreasing effect of the 40 mg/kg dose of ibogaine than responding maintained by either cocaine or food reinforcement. The 80 mg/kg dose of ibogaine had a greater effect on responding maintained by food or heroin reinforcement compared with responding maintained by cocaine. The day-after effect on responding maintained by food and cocaine reinforcement was probably not related to the direct effects of ibogaine on movement which have been shown to dissipate within 19 h (Maisonneuve at al. 1992a, b).

The lack of any long-term effect of ibogaine on responding maintained by drug reinforcement is in disagreement with reports that ibogaine can result in a long-term reduction in responding maintained by morphine (Glick et al. 1991) or cocaine (Cappendijk and Dzoljic 1993). There are several methodological differences between these reports and the present study. The present study used male Fisher 344 rats trained under an FR10 schedule of reinforcement, with sessions conducted during the dark period of a reversed light/dark cycle. Glick et al. (1991) used female, Sprague-Dawley rats trained under an FR1 schedule of morphine reinforcement during the light period of a normal light/dark cycle. Cappendijk and Dzoljic (1993) used male Wistar rats and an FR1 schedule that maintained a very low rate of drug intake. Differences in gender, strain and the schedule of reinforcement used may have accounted for the discrepant effects observed between studies.

The doses of ibogaine used in the present study resulted in considerable ataxia and abnormal motor behavior that appeared to be incompatible with responding on the lever. These abnormal postures were not observed when the rats were responding. The body tremors and abnormal motor effects induced by ibogaine are suggested to be the result of activation of Purkinje cells within the cerebellum, and there is some neurotoxicity associated with this effect (O'Hearn et al. 1993).

Results from the present study suggest that while ibogaine is effective in attenuating responding maintained by both cocaine and heroin, abnormal motor behavior resulting from the administration of the compound may have contributed to the decrease in responding observed. The results also suggest that the effects of ibogaine are not limited to drug reinforcers, but can decrease responding maintained by other reinforcers as well. This effect in addition to the direct effect observed on motor activity, and the potential for neurotoxicity, suggest that the use of ibogaine in the treatment of drug abuse be viewed with some degree of caution.

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