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Ibogaine Reduces Preference for Cocaine Consumption in C57BL/6By Mice

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SERSHEN, H., A. HASHIM AND A. LAJTHA. *Ibogaine reduces preference for cocaine consumption in C57BL/6By mice.* PHARMACOL BIOCHEM BEHAV 47(1) 13–19, 1994.—After a period of forced exposure to 300 mg/l cocaine HCl in drinking water for a period of one week, followed by forced exposure to 200 mg/l cocaine for an additional week, male C57BL/6By mice developed a preference for cocaine when given a choice of drinking either water or a solution containing cocaine (200 mg/l). The mean daily intake of cocaine during the choice period was 26 ± 1 mg/kg or, when expressed as the ratio of cocaine over total fluid intake, represented a cocaine preference of 71 ± 2%. Administration of ibogaine HCl (40 mg/kg, two injections 6 h apart) two weeks after the beginning of the choice period reduced the cocaine preference for at least five days; the mean daily intake of cocaine was reduced by 38% (to 16 ± 1 mg/kg per day; $p < 0.05$) and cocaine preference was reduced to 41 ± 2% (cocaine fluid consumption/total fluid intake). An acute challenge injection of cocaine (25 mg/kg SC) produced a significant increase in cocaine-induced locomotor activity and stereotypy in mice previously exposed to cocaine in their drinking water (cocaine choice group). Five days after ibogaine administration, locomotor and stereotypy activity were significantly lower after a challenge injection of cocaine (25 mg/kg SC). Brain levels of cocaine 35 min after the challenge injection of cocaine were approximately 25% higher in ibogaine-treated mice (7.2 ± 0.5 and 9.3 ± 0.8 μg/g wet wt for water vs. mice treated with water plus ibogaine and 9.3 ± 0.2 and 11.8 ± 0.7 μg/g wet wt for cocaine drinking vs. cocaine drinking plus ibogaine treatment). Neither the reduction in cocaine preference nor attenuation in cocaine-induced ambulatory and stereotypy activity by ibogaine was accounted for by changes in brain levels of cocaine.

Drug self-administration Cocaine Ibogaine Behavior Sensitization

IBOGAINE (NIH 10567, Endabuse) is an indole alkaloid that has been suggested to have potential efficacy for interrupting dependency on opiates, cocaine, amphetamine, alcohol, and nicotine. Ibogaine has been reported to decrease morphine self-administration by Sprague-Dawley rats for several days (10). With cocaine, ibogaine has been reported to block the locomotor stimulation induced by cocaine in mice (28) or rats (3), or to increase this locomotor stimulation in rats (15). Opposite effects of ibogaine have been reported for *d*-amphetamine-induced locomotor activity: inhibition of locomotor activity in mice (27) or stimulation of activity in rats (16,27).

Whether the attenuation of cocaine effects on locomotor stimulation by ibogaine is related to alteration of cocaine-induced dopamine release is still controversial. Broderick (3) found a reduction, while Maisonneuve and Glick (15) found an increase in cocaine-induced dopamine release. Ibogaine did not alter dopamine uptake into synaptosomes (3) or alter [^{3}H]WIN binding to the dopamine binding site (28). Several explanations have been offered to account for cocaine-induced locomotor sensitization—for example, enhanced dopamine release (25,31), autoreceptor desensitization (1,14,17, 26,30), an increased sensitivity of postsynaptic receptors (11, 19,21), and conditioning effects (23), as well as genetic-based differences (13). Whether any of these mechanisms are involved in the action of ibogaine is not known. The release of dopamine from striatal slices by amphetamine in mice and rats was affected differentially by ibogaine pretreatment, suggesting an effect of ibogaine on drug-induced neurotransmitter release (27).

To further test the effect of ibogaine on cocaine-induced behavior, its effect was tested in a cocaine-preference drinking model. The present study examined the effect of ibogaine on cocaine-drinking preference in mice after a period of forced exposure to cocaine, followed by a period of choice in exposure to cocaine. In addition, the study examined whether the ibogaine-induced reduction in locomotor stimulation induced by a challenge injection of cocaine was reflected in changes in brain levels of cocaine, since cocaine levels in brains of animals receiving repeated administration of cocaine have been reported to be significantly increased over levels in animals treated acutely (12,20,22,24). Ibogaine administration was shown to have differential effects on morphine and amphetamine in the brain, increasing amphetamine but not affecting morphine levels (10).

The present data give some support to the anecdotal claims for the deterrence of cocaine use by ibogaine.

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METHODS

Animals and Drugs

Adult C57BL/6By male mice (two to four months old) were used. The animals were housed in individual cages with free access to food. Water or cocaine HCl solution (all solutions are expressed as the salt) was prepared as indicated below. Ibogaine HCl was purchased from Sigma Chemical Co. (St. Louis).

Cocaine Exposure

A cocaine choice preference drinking model was developed for mice similar to the paradigm developed for rats after a period of forced oral exposure to cocaine as described by Meert and Janssen (18). In mice, voluntary consumption was not observed. Choice preference was not observed unless the mice were shaped with a forced period of exposure to cocaine. A typical experiment consisted of two groups of 16 mice each, one group having access to water only and the other group of mice exposed to cocaine HCl in their drinking water (forced cocaine period). Mice were initially forced-exposed to a solution of cocaine (300 mg/l) for one week, followed by a period of choice-exposure for another week at 200 mg/l. This was followed by a choice drinking period, when both cocaine solution (200 mg/l) and water were available for consumption.

In the preliminary studies, mice were initially forced on 200–400 mg/l cocaine; however, at 200 mg/l cocaine fewer mice showed preference, and at 400 mg/l cocaine fluid intake was greatly reduced and there were large body weight losses.

Each cage was equipped with a 50-ml plastic tube fitted with a stopper and a 1-in. stainless steel nipple. The plastic tube was secured to reduce fluid spillage as the mice played with the tube. The shortened drinking tube also helped to reduce spillage. The bottles were weighed when full, and then every morning for calculation of daily fluid consumption. This method proved to be more accurate than measuring the volume consumed. On weekends, total consumption over the two to three day block was measured and averaged for per day intake. Daily fluid intake was expressed as ml/g body weight. Fresh drinking fluid was presented every three days. During the forced period, only one bottle was inserted into the cage, positioned in the middle. During the choice period, a bottle with cocaine solution was placed on the left side of the cage and the water bottle on the right side. For the control group, two water bottles were placed in the cage. Both bottles were positioned near the corner of the cage to minimize disturbance by the normal activity of the mice. The position of the cocaine and water bottles remained constant for the remainder of the experiment. After two weeks of choice, half of the cocaine-choice group of animals (showing a preference of approximately 70% for the cocaine solution—i.e., fluid consumption from the bottle containing cocaine over total fluid consumption × 100) and half of the water-only mice were injected twice with ibogaine HCl (40 mg/kg IP, 6 h apart; Sigma Chemical Co.). Fluid consumption was monitored for an additional five days. Five days after ibogaine, the mice were challenged with an injection of cocaine (25 mg/kg SC). Locomotor and stereotypic activity were monitored for 1 h, the animals were immediately killed, and brain tissue was prepared for measurement of cocaine.

Repeated Cocaine Administration

In a separate study, mice were injected once daily with cocaine (25 mg/kg SC; no oral cocaine) for three days, followed by two injections of ibogaine (40 mg/kg IP). The mice were challenged again 18 h later (day 4) with cocaine and behavior was monitored for 30 min, after which plasma and brain levels of cocaine were measured as described below.

Locomotor Activity

Locomotor activity and stereotypy were measured using a Columbus Instrument Auto-Track System (Columbus, OH). The system consists of a host controller, an interface box, and eight infrared beam-based activity monitors (Opto-Varimex-3 units). Animals were housed within individual transparent cages (27 × 17 × 12 cm), the same home cages used in the drinking paradigm, through which infrared beams passed in a horizontal plane. Maintaining the animals throughout the study in their home cages avoided the possible effect of acclimating to a new environment in the monitor. The home cage was placed in the center of the activity monitor. Total ambulatory counts (TACs) were calculated in 10-min segments after a cocaine challenge injection. Bursts of stereotypic movement were counted in the same time periods. TACs represent the total number of beams, on both the X and Y axes, that are interrupted by the animals in the performance of ambulatory activity. Single beams broken repeatedly by the animal in scratching, digging, or performing some other stereotypic activity were not included in this total, but recorded separately as bursts of stereotypic movement (Auto-Track program, Columbus Instruments).

TABLE 1

EFFECT OF FORCED COCAINE ON DAILY FLUID INTAKE AND COCAINE CONSUMPTION

	Cocaine Concentration (mg/l)	Cocaine (mg/kg)	Fluid Intake (ml/g)
Water		–	0.22 ± 0.01
Cocaine	200	48 ± 2	0.24 ± 0.01
	300 (initial)	38 ± 3	0.13 ± 0.01
	(final)	54 ± 3	0.18 ± 0.01
	400	49 ± 2	0.12 ± 0.01

Results are average daily fluid and cocaine consumption during a period of forced exposure to cocaine over two weeks; means ± SE; n = 48 for water animals and n = 16 for cocaine mice. The initial consumption for the first and last few days are shown for 300 mg/l.

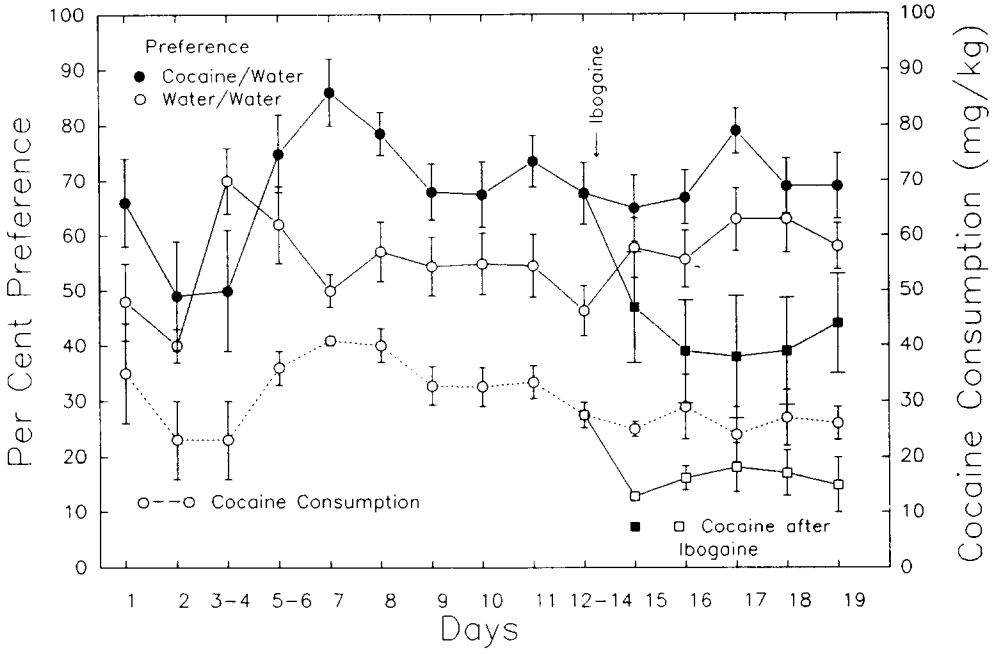

FIG. 1. Cocaine HCl consumption during the first 14 days of choice-exposure (200 mg/l) that immediately followed the forced-period of exposure to cocaine (one week at 300 mg/kg and one week at 200 mg/kg). Cocaine percent preference (cocaine fluid intake/total fluid intake × 100) (●—●) and consumption (mg/kg) (○···○) and water/water preference (left water bottle intake/total fluid intake) (○—○) are indicated. On day 14, ibogaine HCL (2 × 40 mg/kg IP) was given to half of the cocaine-choice mice, and cocaine fluid preference (■—■) and cocaine consumption (□—□) were measured for an additional five days. Results are mean ± SE; n = 8-16; cocaine consumption (○···○) vs. cocaine plus ibogaine (□—□) and cocaine preference (●—●) vs. cocaine plus ibogaine (■—■) over days 15-19 (paired t test; $p < 0.05$). Half of the water/water animals received ibogaine, but since the results were not significantly different from the water-only group the results are shown as one line (○—○).

Cocaine Determination

Brain concentrations of cocaine were measured as described by Benuck et al. (2). Blood was collected in 1.5-ml microfuge tubes containing 100 μg of heparin and 400 μg of NaF and centrifuged. After 100 μl of thr plasma was added to 300 μl of acetonitrile, it was vortexed and centrifuged. The supernatant was made basic by the addition of 100 μl of $NaHCO_3$. Cerebral cortex (200 mg) was sonicated in a microfuge tube containing 300 μl of acetonitrile and 4 mg of NaF and centrifuged, and the supernatant was collected. Lidocaine was added as an internal standard. Cocaine was extracted from the plasma and brain supernatants by addition of 700 μl of chloroform/ethanol (4 : 1). Tubes were vortexed for 30 s and centrifuged, and the upper aqueous layer was aspirated. The lower phase was dried under vacuum and the samples were redissolved in 50% methanol. Samples were analyzed by reversed-phase high-pressure liquid chromatography (HPLC) on a Versapack C-18, 10 μm column, 250 × 4.1 mm (Altech Assoc., Deerfield, IL) eluted with 0.25 M potassium phosphate buffer, pH 2.7, containing 12.5% acetonitrile at a flow rate of 1 ml/min, and UV absorbance was monitored at 235 nM.

RESULTS

Forced Cocaine Period

The average daily cocaine consumption and fluid intake during a period of forced exposure to cocaine HCL at concentrations ranging from 200–400 mg/l are shown in Table 1. At 200 mg/l cocaine HCl, fluid intake was similar to the water intake. Fluid intake at 300 mg/l cocaine was initially reduced, but after one week fluid intake was similar to that of the water-only animals. The average cocaine consumption increased from 38 ± 3 mg/kg or 0.13 ml/g to 54 ± 3 mg/kg or 0.18 ± 0.01 ml/g. At 400 mg/l cocaine HCl, fluid intake was reduced approximately 50% and the body weight of the animals dropped approximately 10% in one week. However, daily cocaine consumption was similar in the 200 and 400 mg/l groups (48 ± 2 and 49 ± 2 mg/kg) because of the 50% reduction in fluid intake at 400 mg/l cocaine HCl (0.24 ± 0.01 ml/g vs. 0.12 ± 0.01 ml/g for 200 and 400 mg/l cocaine HCl, respectively, $p < 0.001$).

In the experimental paradigm, mice were initially forced-exposed to cocaine at 300 mg/l for one week and then at 200 mg/l for another week, after which a period of choice-exposure (200 mg/l) was presented.

Choice-Cocaine Period

Percent preference (fluid consumption in left bottle [cocaine or water]/total fluid consumption × 100) and cocaine consumption (mg/kg) during days 1-14 of choice exposure are shown in Fig. 1. Within four days after choice-exposure, mice previously forced-exposed to cocaine showed a preference for cocaine with a 71 ± 2% preference (cocaine fluid intake/total fluid consumption; mean daily average during

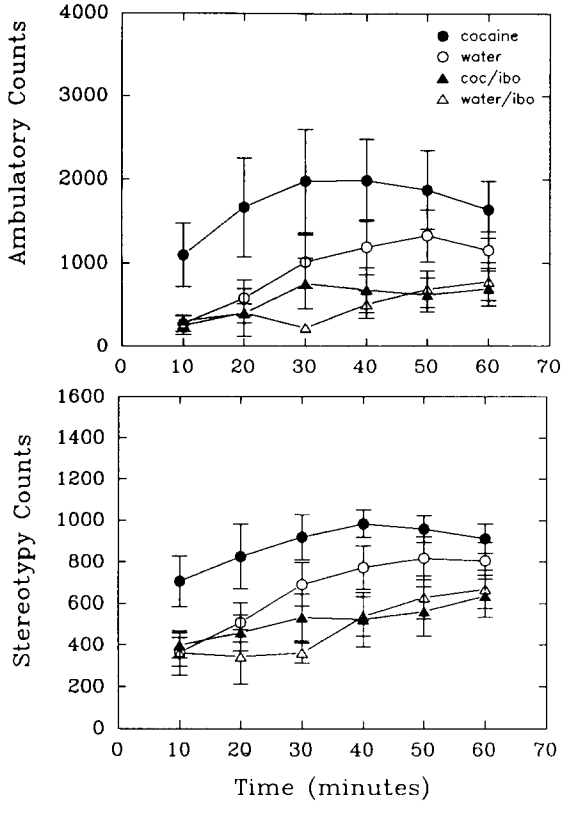

FIG. 2. The effect of ibogaine on total ambulatory counts and stereotypy counts after a cocaine challenge injection. Five days after ibogaine, all mice were challenged with cocaine (25 mg/kg SC) and activity was monitored for 1 h; mice on choice-cocaine (●—●), mice on water only (○—○); ibogaine-treated water/water mice (△—△), and ibogaine-treated choice-cocaine mice (△—△); $p < 0.01$ for cocaine vs. cocaine plus ibogaine or water plus ibogaine and $p < 0.05$ for cocaine vs. water group; paired t test; $n = 8$.

days 8–14). This preference was also observed if the positions of the cocaine and water bottles were reversed. Within one to two days, cocaine-preferring mice would relocate the cocaine-containing bottles, ruling out the possibility of an artifact as a result of a side preference. The water/water animals showed an approximately equal preference for the water bottles—for example, 57 ± 2% preference for the left water bottle/total water intake during this period (Fig. 1).

Ibogaine Treatment

After the second week of choice, half of the mice from the choice group and half from the water group were given two injections of ibogaine (40 mg/kg, IP, 6 h apart) (Fig. 1, day 14). Cocaine fluid consumption was monitored for the next five days (Fig. 1). Cocaine consumption during days 15–19 of choice averaged 26 ± 1 mg/kg, which was reduced after ibogaine to 16 ± 1 mg/kg, and cocaine preference was reduced from 71 ± 2% to 41 ± 2% (the average cocaine preference and consumption over the last five days after ibogaine; paired t test, $p < 0.05$). Since there was no significant difference in water/water preference in the water and water plus ibogaine animals, data were averaged together and shown as a single line.

Effect of Ibogaine on Locomotor Activity and Brain Cocaine Levels After a Challenge Injection of Cocaine in Cocaine-Choice Mice

Five days after ibogaine, all mice (water only; water only plus ibogaine; cocaine-choice; cocaine-choice plus ibogaine) were given a challenge injection of cocaine (25 mg/kg SC) during the daytime and activity was monitored for 1 hour (Fig. 2). Activity was increased in the cocaine-choice group versus water-only mice, indicating sensitization. Both groups of mice given ibogaine (water- or cocaine-exposed mice) showed a reduced response to the cocaine challenge compared to the nonibogaine mice (water- or cocaine-exposed mice). The average ambulatory counts over the 1-h period were 10 232 ± 2675, 5544 ± 1392, 3453 ± 869, and 2850 ± 972 for cocaine, water, cocaine plus ibogaine, and water plus ibogaine mice, respectively ($p < 0.01$ for cocaine vs. cocaine plus ibogaine or water plus ibogaine, and $p < 0.05$ for cocaine vs. water group; paired t test, $n = 8$).

In a different but similarly treated group of mice, animals were killed 35 min after the challenge injection of cocaine to measure near-peak levels of cocaine. Brain levels of cocaine after the challenge injection were significantly higher by 29% ($p < 0.05$) in mice previously exposed to cocaine in their drinking water versus the water-only mice (Table 2). Ibogaine pretreatment resulted in an approximately 25% ($p < 0.05$) increase in brain cocaine levels in both groups (water-only vs. cocaine-drinking mice).

Effect of Ibogaine on Brain Cocaine Levels After Repeated Injections of Cocaine

In a separate study, mice were given daily cocaine (25 mg/kg SC) for four days (no oral cocaine). The effect of cocaine on ambulatory activity is shown for each successive day (Fig. 3). The activity response increased and time of onset shortened with each daily injection, indicating sensitization. Ibogaine

TABLE 2

EFFECT OF IBOGAINE ON LEVELS OF COCAINE IN PLASMA AND BRAIN AFTER A CHALLENGE INJECTION OF COCAINE

Treatment	Plasma (μg/ml)	Brain (μg/g)
Cocaine Drinking		
Water	2.1 ± 0.2	7.2 ± 0.5
Water + Ibogaine	2.8 ± 0.2	9.3 ± 0.8
Cocaine	1.9 ± 0.1	9.3 ± 0.2†
Cocaine + Ibogaine	2.8 ± 0.1*	11.8 ± 0.7*
Repeated Cocaine Injections		
Cocaine	3.2 ± 0.2	11.3 ± 1.1
Cocaine + Ibogaine	3.6 ± 0.3	12.7 ± 1.6

Cocaine drinking—Mice on cocaine-choice (200 mg/l) were given 2 × 40 mg/kg ibogaine. After five days, all animals were given an acute challenge injection of cocaine (25 mg/kg) and killed 35 min later. Plasma values are μg cocaine per ml plasma, mean ± SE ($n = 4$); *$p < 0.01$ cocaine plus ibogaine versus cocaine. Brain values are μg/g wet weight, mean ± SE ($n = 4$); *$p < 0.05$ cocaine plus ibogaine versus cocaine; †$p < 0.05$ cocaine versus water.

Repeated cocaine injections—Mice were given a daily injection of cocaine (25 mg/kg SC; no oral cocaine) for four days, with one group of animals receiving 2 × 40 mg/kg IP injections of ibogaine on day 3. On day 4, animals were killed 35 min after the challenge injection of cocaine.

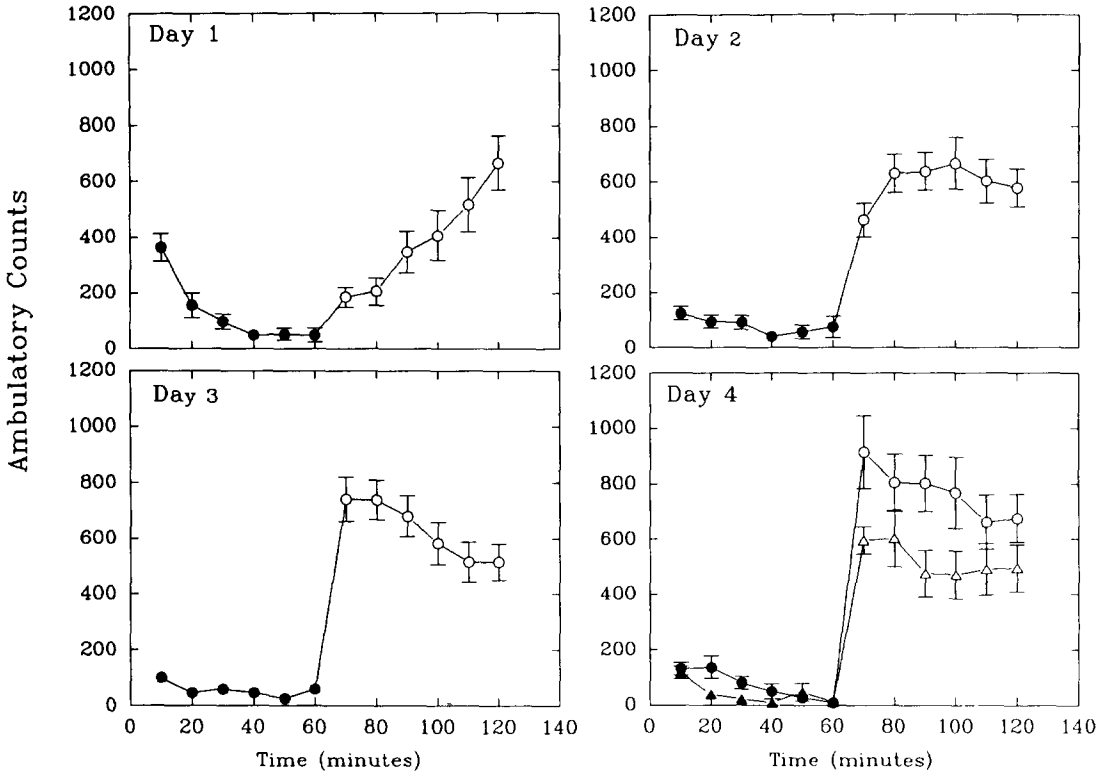

FIG. 3. Effect of daily injection of cocaine (25 mg/kg SC) on total ambulatory counts. Mice were initially injected with saline (solid symbols) and activity was monitored for 1 h, followed by an injection of cocaine, and activity was measured for an additional hour (○ – ○). On day 3, ibogaine HCl (2 × 40 mg/kg IP) was given to half of the mice at least 2 h after the cocaine injection. On day 4, 18 h after ibogaine, animals were again challenged, first with saline and then with cocaine; ibogaine-pretreated mice (△ – △) vs. nonibogaine controls (○ – ○); $p < 0.05$; n = 8–16; paired t test.

treatment on day 3, followed by a cocaine challenge 18 h later (day 4) resulted in attenuation of locomotor responses ($p < 0.05$, paired t test) (Fig. 3). In another similar group of mice, mice were killed 35 min after the challenge injection and brain cocaine was measured. No changes in brain levels of cocaine were observed between the cocaine and cocaine plus ibogaine mice (Table 2).

DISCUSSION

The present study examined whether ibogaine would reduce cocaine consumption in a mouse model of cocaine oral self-administration. A choice-preference drinking model as described for rats (9) was established in C57BL/6By mice. In the present study, to initiate preference for cocaine (200 mg/l) mice had to be previously forced on cocaine in their drinking solution prior to the choice period. Voluntary preference was not observed. This same strain of mice was shown to initiate intravenous self-administration of cocaine (4) and to show a preference for alcohol consumption (6). Cocaine can function as a positive reinforcer when delivered orally, as shown in C57BL/6J mice, for which ethanol was previously established as a reinforcer (8). Oral cocaine was also established as a positive reinforcer in drug-naive LEW rats (9). The oral route of administration of cocaine could be expected to be less potent than parenteral routes (7). With intravenous self-administration in C57BL/J6 mice, average daily drug intake approached 10 mg/kg (4), approximately threefold lower than the daily consumption seen in the present study. The daily dose of cocaine consumed in the choice drinking paradigm agrees with oral dosages used as a positive reinforcer (6–10 mg/kg cocaine per 30-min session) (8).

Optimal choice-preference was observed after a forced exposure period (one week exposure to 300 mg/l cocaine followed by one week at 200 mg/l cocaine). A higher initial level of cocaine in the drinking water (e.g., 400 mg/l) did not increase preference. After one week, body weights decreased and fluid consumption remained reduced by 50% at this concentration. At 200 mg/l, body weight changes and fluid consumption were similar to controls. Nevertheless, cocaine consumption was similar at 200 and 400 mg/l because of the reduction in fluid intake at the higher dose. This could suggest that the mice were drinking to avoid doses above a certain level. The local anesthetic effects at the high dose may also influence drinking. Attempts to increase preference were oriented towards increasing cocaine by increasing the level of cocaine during the forced-drinking period. It is possible that a greater preference rate could have been obtained after a forced period by exposing animals to a lower dose of cocaine in their drinking water during the choice period. As it was, they may have consumed more from the cocaine bottle to maintain a certain level, the same level that was achieved by consuming 70% of their fluid intake, or 26 mg/kg daily, from the 200-mg/l bottle. Nevertheless, in the present drinking paradigm

during the choice period cocaine consumption was approximately 70% of that consumed during the forced period at 200 mg/l, and at a higher preference rate than for the water bottle. Taken together with other data on oral self-administration and with the ability to relocate the cocaine bottle, the present paradigm appears to be valid for a model of self-administration.

The dependence on cocaine after long-term exposure is not clearly understood. Recent studies have suggested that dependence can develop in animals after continuous cocaine administration (5,29). An apparent preference for cocaine was observed in the present forced-choice drinking model. However, whether this preference truly demonstrates dependence cannot be ascertained without additional studies to evaluate whether a withdrawal syndrome is manifested after drug removal.

Our earlier studies have shown that ibogaine was able to reduce the locomotor stimulation induced by administration of cocaine (28) and, in addition, reduce the stimulation induced by amphetamine in mice, but potentiate the amphetamine response in rats (27). It was questioned whether this attenuation of cocaine responses reflected a blockade or a potentiation of cocaine effects. An attenuation of locomotor activity by ibogaine could reflect antagonism of the effect of cocaine, or it could occur because ibogaine enhances cocaine responses, causing the animal to go from locomotor behavior into stereotypy. This seemed unlikely because stereotypy was similarly attenuated after a challenge injection in ibogaine-treated mice (Fig. 2). In addition, the reduction of cocaine's effects that was seen the day after ibogaine treatment (28) or was shown in the present study after a challenge injection of cocaine four to five days later would suggest a long-lasting effect of ibogaine independent of any short-term acute effect of ibogaine to inhibit locomotor activity.

Sensitivity to repeated cocaine administration has been reported (11,23,24). The challenge injection of cocaine during the daytime induced an enhanced locomotor activity in the animals exposed to cocaine in their drinking water (choice group), indicating sensitization. Five days after ibogaine, this response was reduced, as was the response seen in naive mice. Behavioral sensitivity to cocaine (e.g., locomotor activation) has been shown to be positively correlated with increased concentrations of cocaine in brain (2). The apparent sensitization seen in the present study after a challenge injection of cocaine was correlated with increased brain levels of cocaine (Table 2). However, the attenuation of locomotor responses by ibogaine was not reflected by a decrease in brain levels of cocaine. In fact, in some situations ibogaine increased brain cocaine levels (Table 2). Glick et al. (10) found ibogaine to increase brain levels of amphetamine, whereas it had no effect on brain morphine levels, but attenuated morphine responses (10). It was suggested that ibogaine might irreversibly inhibit an amphetamine-metabolizing enzyme and that this action would be reflected by a potentiation of amphetamine-induced responses in the rat (10). To further complicate the situation, ibogaine-induced changes in locomotor responses and amphetamine-stimulated in vitro release of tritium from [^{3}H]dopamine-prelabeled striatum are different in rats and mice (27). The inhibition of cocaine-induced behavioral responses, in the absence of changes or a slight increase in the brain level of cocaine, must suggest an action of ibogaine on subsequent transmitter release processes, independent of drug level. The absence of metabolic effects, at least in a direction to account for decreased behavioral response to cocaine, and the absence of effects on dopamine uptake into synaptosomes (2) or the dopamine binding site (28) might also suggest genetic differences in transmitter mechanisms, which possibly extend to the effect of ibogaine on stimulant drug-induced changes in the storage and release of transmitter pools (27).

The present study shows that ibogaine reduces the preference for cocaine in a choice-preference oral drinking model using C57BL/6By mice. In our earlier studies, ibogaine was shown to block the locomotor stimulation effects of cocaine (27,28); however, it was questioned whether ibogaine would reduce cocaine self-administration. Since the previous studies were on mice and intravenous self-administration in mice is difficult, a choice-preference drinking model was established in mice as a self-administration paradigm. The data give some validity to the paradigm as a self-administration model and add additional support to the anecdotal claims for the interruption by ibogaine of cocaine use, suggesting a possible use of ibogaine in the treatment of human drug addiction and thereby warranting further study on its mechanism(s) of action.

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