

Research report

# Ibogaine effects on sweet preference and amphetamine induced locomotion: implications for drug addiction

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## Abstract

The neural basis of ibogaine's effects on drug-related behaviours is unclear. One possibility is that ibogaine interferes with the shared capacity of many addictive agents to stimulate brain dopamine activity, but reports of ibogaine effects on dopamine activity have been inconsistent. Our study suggests such inconsistencies may result from variations in prior drug exposure. If ibogaine blocks dopamine activity, then it should, like dopamine blockers, decrease preference for natural rewards such as sweet solutions. However, 40 mg/kg ibogaine i.p. did not decrease preference for a glucose + saccharin solution when it was administered to male Long Evans rats 24 h prior to test in Experiment 1. Nor did ibogaine attenuate conditioned preference for a neutral flavour previously paired with sweet taste in Experiment 2. In Experiment 3, effects of 40 mg/kg ibogaine on amphetamine-induced locomotion were investigated in drug-naïve and drug-experienced (four prior doses of 1.5 mg/kg amphetamine) rats. Locomotion was significantly lower in those ibogaine-treated rats that had previously been exposed to amphetamine than in those that had not. Thus, ibogaine may serve to decrease induced levels of dopamine activity in drug-experienced animals or humans from elevated, sensitized levels back to baseline levels. This could lead to a reduction of sensitized levels of drug craving in addiction. © 1997 Elsevier Science B.V.

*Keywords:* Rat; Ibogaine; Amphetamine; Reward; Incentive; Motivation; Sensitization; Dopamine

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## 1. Introduction

Ibogaine is an indolalkylamine that is purported to be efficacious in the treatment of addiction to stimulants, opiates, nicotine, and alcohol. Even a few doses of ibogaine have been reported to reduce withdrawal symptoms and to facilitate drug abstinence for periods of weeks or months [31–34,46,58]. This clinical claim is supported by findings from studies with rodents that ibogaine can decrease self-administration of stimulants [5,17,57] opiates [17,18], and alcohol [29,47]. The present study analyzes the actions of ibogaine within

the framework of a contemporary incentive-motivation perspective of drug self-administration and addiction.

It has been suggested that most addictive agents act directly or indirectly on a common neural circuit that naturally subserves appetitive or incentive-based behaviours [62]. The major candidate as a common neural circuit for incentive-based behaviours is the dopamine projection ascending from the ventral mesencephalon to the telencephalon, particularly the mesolimbic projection originating in the ventral tegmental area and terminating in a variety of limbic targets including the nucleus accumbens [15,26,39]. Disruption of the activity of this system, through lesions, peripheral administration of dopamine antagonists, or local injection of dopamine antagonists to the nucleus accumbens, leads to decreases in self-administration of stimulants and

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opiates [68]. However, because of its ubiquitous contribution to behaviour, disruption of mesotelencephalic dopamine activity does not merely dampen pathological drug-taking behaviour, it also disrupts aspects of feeding, sexual behaviour, avoidance, and a broad spectrum of other behaviours [4,48,54]. These deficits have been attributed to a general disruption of incentive motivation. Ibogaine could decrease intake of addictive substances by animals and humans through a disruption of incentive motivation, but in doing so it would disrupt behaviours involving natural incentives as well as drugs. Obviously, any agent indiscriminately decreasing adaptive as well as self-injurious behaviours would be of limited utility as anti-addictive agent. Thus, in Experiments 1 and 2 we explore the impact of ibogaine on incentive motivation in a setting unrelated to drug taking or reward.

Complementary to the suppression of incentive motivation mechanisms by disruption of dopamine neurotransmission is the potentiation of incentive motivation by enhancement of dopamine activity. The primary neurochemical effect of stimulant drugs such as amphetamine and cocaine appears to be an enhancement of dopaminergic neurotransmission [28,67]. This effect is shared by other drugs, including opiates, ethanol, and nicotine [2,12]. In turn, this enhanced dopamine activity increases the probability and vigour of many responses including locomotion [24]. This effect has been attributed to an enhancement in the response-eliciting capacity, or incentive value, of environmental stimuli [21,63]. The enhancement of dopamine-related behaviours by stimulants and other drugs generally increases with repeated drug administration, an effect known as reverse tolerance or sensitization [64]. Robinson and Berridge [52] have recently proposed a theory of drug addiction in which sensitization plays a key role. They propose that the incentive salience of cues related to drug-taking are related to neurotransmission in mesotelencephalic dopamine pathways and that, as the activity of those pathways is increased by repeated administration of the addictive drugs, the incentive salience of the cues is similarly sensitized. As a result, hyperresponsiveness to drug-related cues is manifested as an intense or irresistible drug craving. Thus, according to the theory of Robinson and Berridge, if ibogaine could decrease activity in sensitized dopamine pathways, it should alleviate addictive drug craving. In Experiment 3 we determine if ibogaine's effects differ as a function of amphetamine pretreatment.

## 2. Experiment 1

The intake of sweet solutions by minimally deprived rats is a prototypical example of a behaviour based on incentive motivation. In the absence of any substantial

deficit signal, rats will consume large quantities of sweet solutions, apparently for the simple reason that they taste good [60]. Consistent with the notion that inhibition of dopamine systems disrupts behaviours based on incentive motivation, intake [40,69] and sham intake [16,66] of sweet solutions is exquisitely sensitive to the effects of dopamine receptor antagonists [4,61]. If ibogaine decreases self-administration of various drugs by globally disrupting incentive motivation, then it should decrease intake of sweet solutions at those doses that have been reported to decrease drug consumption. A similar hypothesis can be derived from a neurochemical perspective: if ibogaine exerts its behavioural effects by interfering with dopaminergic neurotransmission then, like dopamine antagonists, it should decrease intake of a palatable sweet solution.

### 2.1. Methods

#### 2.1.1. Subjects

Sixteen male Long Evans rats, (280–345 g), bred in the McMaster colony, were housed in individual suspended wire cages in a room on a reversed light/dark cycle (lights off: 10:00; lights on: 22:00). Rats had free access to a standard lab diet and water except for a daily 3 h deprivation period (14:30–17:30) preceding sweet solution exposure or testing. All sweet solution exposures and testing occurred during lights out, beginning at approximately 17:30.

#### 2.1.2. Materials

A palatable sweet solution was prepared by dissolving 2.5 g D-glucose (BDH, Toronto) and 0.25 g saccharin (ICN Biomedicals, St. Laurent, Quebec) per 100 ml distilled water. Ibogaine HCl (NIDA), was dissolved in distilled water and administered intraperitoneally (i.p.) at a concentration of 10 mg/ml. A dose of 40 mg/kg was used as this dose has been found to reliably decrease self-administration of cocaine and morphine in rats [5,17,18]. Injections were i.p. as subcutaneous injections of ibogaine have been found to be ineffective in suppressing intake of alcohol by rats [29].

#### 2.1.3. Procedure

Rats were deprived of food and water daily for 3 h prior to each sweet solution exposure trial. All rats were presented with a stoppered 50 ml drinking tube containing the sweet solution and allowed to drink for 20 min after which time the drinking tube was removed. Food and water were returned 1 h following sweet solution exposure. Exposure to the sweet solution occurred on four consecutive days. One rat failed to demonstrate a preference for the sweet solution and was dropped from the experiment. Rats were injected with 40 mg/kg ibogaine ( $n = 7$ ) or distilled water vehicle ( $n = 8$ ) the day after the last pre-exposure to the sweet

solution (a pilot study had indicated that a taste aversion was conditioned if ibogaine was injected immediately following exposure to a flavour). The drug was injected a day prior to behavioural testing because: (1) doses of 40 mg/kg have been reported to decrease cocaine and opiate self-administration when injected a day prior to testing; (2) this dose of ibogaine induces transient tremors that might interfere with ingestion, but these tremors typically subside within a few hours of injection; and (3) if ibogaine is to have any utility as an anti-addictive agent the time course of its effect must extend beyond the immediate post-injection period.

After, 22 h, the ibogaine injection, 3 h after food and water deprivation, rats were simultaneously presented with two identical 50 ml drinking tubes, one containing the sweet solution, the other containing distilled water. Intake was recorded at the end of 20 min. Food and water were returned 1 h following the test. Additional preference tests were conducted 2 and 7 days after ibogaine injection.

#### 2.1.4. Data analysis

Taste preference was calculated as percentage of sweet intake relative to total intake for each of the 3 test days. Taste preferences were analyzed using a two-way (dose X day) analysis of variance (ANOVA). All analyses were conducted using STATISTICA (StatSoft) on a PC-type computer.

#### 2.2. Results and discussion

As shown in Fig. 1, ibogaine had no effect on intake of the sweet solution on any of the test days. The ANOVA indicated no main effect of drug ( $F < 1$ ), no main effect of day ( $F_{2, 34} = 2.30$ , n.s.), and no drug by

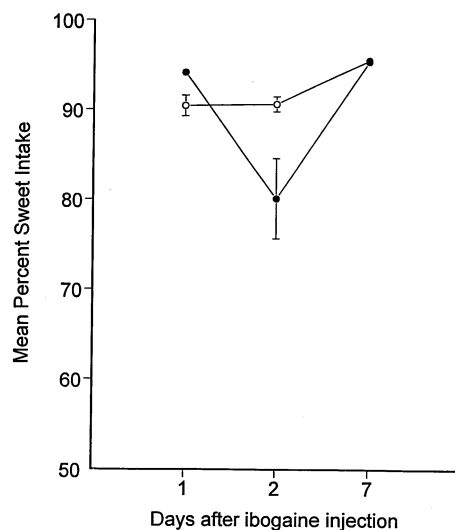


Fig. 1. Preference for the sweetened solution expressed as a percentage of total intake during the 20 min two bottle tests. ○: vehicle ( $n = 8$ ). ●: 40 mg/kg ibogaine ( $n = 7$ ).

day interaction ( $F_{4, 34} = 1.15$ , n.s.). In fact, preference for the sweet solution was 5% higher for the ibogaine treated rats on the first test day. Thus, the results of the experiment do not support the hypothesis that ibogaine indiscriminately disrupts incentive motivation. This is consistent with Sheppard's [58] report that some opiate addicts treated with ibogaine still displayed considerable interest in sexual behaviour and/or cannabis intake in the initial post-ibogaine period, despite profound decreases in their desire to take opiates.

### 3. Experiment 2

Experiment 1 demonstrated that the incentive value of a primary reinforcer is not diminished by 40 mg/kg ibogaine. However, the use of a primary reinforcer may not be entirely apt in an effort to model the effects of ibogaine on drug taking behaviour by addicts, whose behaviour is often controlled by secondary, as well as by primary, reinforcers [7,52]. Perhaps ibogaine could relieve addiction by disrupting the incentive value of secondary reinforcers, even if it does not interfere with the primary reinforcing value of stimuli such as sweet solutions. Such an effect could also be related to altered dopamine activity, as dopamine systems are activated by stimuli associated with primary reinforcers [3,30,43,45] and disruption of dopamine systems interferes with responses to those stimuli [1,3,4,14,44,49]. Thus, in Experiment 2 we examined the effect of ibogaine on responses to a stimulus (a grape or cherry flavour) that had little or no primary incentive value but which acquired secondary incentive value through pairings with a primary reinforcer (sweet taste).

#### 3.1. Methods

##### 3.1.1. Subjects

Twenty four male Long Evans rats, (250–350 g) from the McMaster colony were housed and fed as described for Experiment 1.

##### 3.1.2. Materials

As in Experiment 1, a 2.5% glucose + 0.25% solution was used as the sweet solution. The sweet solution and distilled water were then flavoured, in a counterbalanced fashion, using grape and cherry Kool-Aid (5 mg/l; Kraft General Foods Canada). Ibogaine hydrochloride (Sigma Chemical, St., Louis, MO) was dissolved in distilled water.

##### 3.1.3. Procedure

On each conditioning day, following 3 h of food and water deprivation, every rat was presented with one of the two test solutions (e.g. sweet cherry liquid or unsweetened grape liquid). Exposure to the sweetened

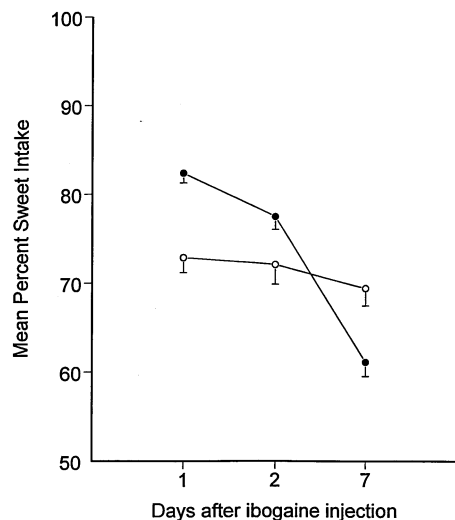


Fig. 2. Preference for the flavour previously paired with sweet expressed as a percentage of total intake during the 20 min two bottle tests. ○: vehicle ( $n = 12$ ). ●: 40 mg/kg ibogaine ( $n = 12$ ).

and unsweetened solutions varied across the 16 conditioning days in a quasi-random manner so that each rat had eight exposures to each. On the day following the final exposure to the conditioning solutions the rats were injected i.p. with 40 mg/kg ibogaine or with distilled water ( $n = 12$  in each condition). After 24 h, following 3 h of food and water deprivation, each rat was presented simultaneously with two identical drinking tubes containing grape and cherry flavoured solutions. Both solutions were sweetened on test day to ensure that there was sufficient intake to permit reliable analysis of preference. Additional preference tests occurred 2 and 7 days after ibogaine administration.

#### 3.1.4. Data analysis

Taste preference was calculated as percentage intake of the previously sweetened flavour relative to total intake for each of the 3 test days. Taste preferences were analyzed using a two-way (dose X day) ANOVA as in Experiment 1.

### 3.2. Results and discussion

Rats receiving control injections displayed a preference for the flavour that had previously been paired with sweet, with intake of the sweet-paired taste accounting for about 70% of intake on the first test day (Fig. 2). The ANOVA revealed that there was a main effect of day ( $F_{2,44} = 4.90$ ,  $P < 0.02$ ), as preference for the previously sweetened taste extinguished with repeated preference testing between the equally-sweet test solutions. Preference was not affected by ibogaine as there was no main effect of drug ( $F < 1$ ) or drug

by day interaction ( $F_{2,44} = 2.50$ , n.s.). In fact, there was a nonsignificant trend towards enhanced preference on the first test following ibogaine administration. Thus, ibogaine did not interfere with the expression of responses to secondary incentive stimuli.

### 4. Experiment 3

Based on the results of the previous experiments, it appears unlikely that ibogaine decreases drug intake by producing a general decrease in incentive motivation. It might be argued that drugs are unlike natural reinforcers, but there is little support for this hypothesis in research on the neural basis of reinforcement. An alternative explanation is that ibogaine is less effective in suppressing sweet-related behaviours than in suppressing drug intake because the brains of subjects that have been self-administering drugs have been altered by chronic exposure to the drugs. Stimulants [27,51] and other drugs [8,9,25,59] produce behavioural sensitization; these behavioural effects must involve substantial long-term changes in synaptic efficiency. Further, it has been proposed that these changes lie at the very core of drug addiction [52]. Any agent that could negate or reverse the effects of sensitization would, by this theory, have the capacity to alleviate drug addiction.

The effects of ibogaine on drug-induced locomotion and dopamine activity have been examined with inconsistent results, perhaps because of differences in pretest drug exposure. Studies which have examined the effect of injecting ibogaine the day prior to test in naive rodents have generally found increases in stimulant-induced locomotion or dopamine activity [19,35,37,56] but decreased cocaine-induced locomotion was reported in a study with mice that had received several preinjections of cocaine [55]. Similarly, ibogaine induced decreases in morphine-induced locomotion [36,38] are larger in animals chronically pretreated with morphine [23,42]. It is also worth noting that the consistent ability of ibogaine to reduce rodent self-administration of stimulants, alcohol, and opiates has necessarily been demonstrated exclusively in drug-experienced animals. The present experiment examines the effect of prior ibogaine-administration on amphetamine-induced locomotion in both amphetamine-naive and amphetamine-pretreated rats.

#### 4.1. Methods

##### 4.1.1. Subjects

Thirty two male Long Evans rats, (250–300 g) from the McMaster colony were housed as described for Experiment 1. Food was available ad lib at all times except during testing.

#### 4.1.2. Materials

Amphetamine (Sigma Chemicals, St. Louis, MO) was dissolved in 0.9% saline at a concentration of 1.5 mg/ml and a volume of 1.0 ml/kg was injected i.p. Ibogaine HCl (Research Biochemicals, Natick, MA) and was dissolved in distilled water to a concentration of 8 mg/ml and injected at a volume of 5 ml/kg. A 1.0 m<sup>2</sup> open field constructed of plywood was painted black and sectioned into 10 cm<sup>2</sup> squares with white dividing lines. Locomotion sessions were recorded on videotape using a Panasonic WV BL200 video camera.

#### 4.1.3. Procedure

Rats were randomly assigned to four groups ( $n = 8$  per group). Rats of two of these groups received injections of amphetamine (1.5 mg/kg) every other day for a total of four injections; rats of the other two groups received injections of saline vehicle. Rats were transported to the test room for all injections. They were injected with amphetamine and returned to their home cages; after 1 h they were returned to the colony. On each of two noninjection days the rats were placed in the open field for 15 min in order to reduce novelty effects. The injection regimen was followed by a 5-day withdrawal period as the expression of behavioural sensitization is more robust if time is allowed after the final injection [51]. On the 6th day, rats of one amphetamine-pretreated group and one saline-pretreated group were injected with 40 mg/kg ibogaine, while rats of the other two groups were injected with an equivalent volume of distilled water. On the test day, 22 h after injection of ibogaine, all rats were transported to the experimental room and given a challenge injection of amphetamine (1.5 mg/kg) i.p. 10 min prior to being placed in the open field. Locomotor activity was videotaped for 30 min. Videotaped locomotion was subsequently scored by determining the number of times both front paws crossed a line on the grid in the activity box by an observer unaware of the drug treatment (ibogaine or saline) of the rats.

#### 4.1.4. Statistical analysis

Rats' locomotor activity was analyzed using a two-way (amphetamine pretreatment X ibogaine treatment) ANOVA. A least significant differences (LSD) test was used for post-hoc analyses. All statistical tests were conducted using STATISTICA.

#### 4.2. Results and discussion

Ibogaine (40 mg/kg) differentially affected amphetamine-induced locomotor behaviour in amphetamine-pretreated and amphetamine-naïve rats. The ANOVA revealed a significant interaction of amphetamine pretreatment and ibogaine treatment ( $F_{1,28} = 6.04$ ,  $P < 0.02$ ). No significant main effects of

amphetamine pretreatment or ibogaine treatment were observed ( $F < 1$ ). The LSD post-hoc test indicated a significant difference between the two ibogaine groups ( $P < 0.05$ ). That is, the amount of amphetamine-induced locomotion observed following ibogaine administration was lower in those rats pretreated with amphetamine than in those rats not exposed to amphetamine prior to the locomotion test (Fig. 3).

The results of this study are consistent with previous studies that have demonstrated that ibogaine administration (40 mg/kg) decreases drug-induced horizontal locomotor activity when administered following repeated drug pretreatment [23,42,55,56]. However, it is not possible to conclude that the differential effects of ibogaine were due to a reversal of amphetamine sensitization as there was no statistical evidence of sensitization following amphetamine pretreatment in this study.

The dose of ibogaine that was used in this experiment was the same as that used in the previous two experiments; in each case the ibogaine was injected approximately 1 day prior to behavioural testing. Other time intervals or doses might have had effects in Experiments 1 or 2. The half-life of ibogaine in rodents is 1 h [11,70], however its effects on drug self-administration can be observed for days following administration of a single dose, presumably due to the formation of an active metabolite [10,36], possibly noribogaine [41]. Given that the dosing regime selected for this study has previously been found consistently to decrease drug self-administration by rodents, this study establishes that there is a dissociation between the effects on amphetamine-induced locomotion in drug experienced

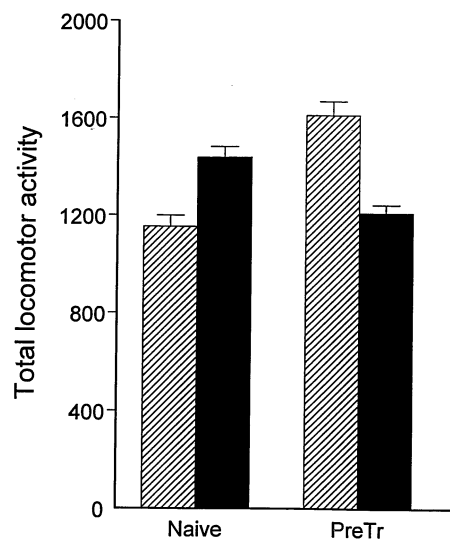


Fig. 3. Total locomotion during the open field test. Cross hatched bars: vehicle. Filled bars: 40 mg/kg ibogaine. Naive: No exposure to amphetamine before test day. PreTr: Pretreated with amphetamine. ( $n = 8$  per group). The ibogaine group that received amphetamine pretreatment locomoted significantly less than the ibogaine group that received no amphetamine pretreatment.

rats and its effects on primary and secondary taste rewards.

## 5. General discussion

Ibogaine has been reported to reduce drug craving in humans [31–34,58] and drug self-administration in both humans [31–34] and laboratory animals [5,17,18,29,47]. The purpose of this study was to investigate the actions of ibogaine within the framework of a contemporary incentive-motivation perspective on drug self-administration and addiction. Using prototypical examples of behaviours based on incentive motivation, it was demonstrated that ibogaine did not attenuate an unconditioned preference for a sweet solution nor did it block a conditioned preference for a neutral flavour previously paired with this sweet solution (Experiments 1 and 2). Additionally, ibogaine was effective at reducing hyperlocomotion induced by amphetamine injection in drug-experienced, but not in drug naive rats (Experiment 3). Thus, it appears unlikely that ibogaine's putative anti-addiction property results from a general disruption of the neural circuitry that naturally subserves appetitive or incentive-based behaviours. Rather, these results are consistent with the suggestion that one potential mechanism to account for this drug's effect may be an ability to reverse the neurochemical alterations produced by chronic drug administration.

Although this study is the first to examine the effects of ibogaine on incentive motivation in a non-drug related setting, the results are consistent with clinical observations that ibogaine does not disturb the desire to engage in other non-drug incentive-based behaviours such as sex [58]. In addition, this study supports other observations [23,42,55,57] that ibogaine's efficacy at reducing drug-induced behaviour is a function of previous drug experience. These considerations are critical in evaluating the clinical potential of this drug.

Several lines of evidence suggest that ibogaine's effects are mediated by its effects on dopaminergic systems [17,19,20,35–38]. This is important, as the mesencephalic dopamine system may act a common neural circuit for incentive-based behaviours [4,15,26,39,48,54] and drug-induced enhancement of dopaminergic activity mediates the hyperlocomotion observed during stimulant and opiate administration [6,13,24,27,50,51,53]. The repeated administration of such drugs results in sensitization of both the dopaminergic response and the behavioural response to subsequent drug administration [22,64,65]. Robinson and Berridge [52] proposed that the sensitization of mesolencephalic dopamine by chronic drug administration sensitizes addicts to the incentive salience of drug-related cues. According to this theory, the addict becomes hyperresponsive to these cues and this is manifested as

intense drug craving. According to this theory, ibogaine's efficacy as an anti-addiction agent may vary with the degree of dopaminergic sensitization. Significant behavioural sensitization was not observed in this study, which may have been the consequence of a short testing period. Nonetheless, these results, and those of other studies [23,42,55,57] are consistent with the idea that ibogaine could mediate its anti-addiction effects through the negation or reversal of drug-induced enhancements of mesencephalic dopaminergic activity.

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