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Ibogaine fails to interrupt the expression of a previously established morphine place preference

Tracey Lyn Luxton
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Ibogaine fails to interrupt the expression of a previously established morphine place preference.

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Abstract

Ibogaine, a proposed anti-addictive agent, has been found to interfere with the acquisition of a weak morphine-induced place preference. The purpose of the present experiments was to determine if ibogaine given at various times prior to a test for morphine place conditioning would interfere with the expression of a morphine (5 mg/kg) conditioned place preference. A single injection of 40 mg/kg ibogaine 24 h, 12 h or 4 h prior to the test did not interfere with the expression of a previously established morphine conditioned place preference (CPP). Two injections of 40 mg/kg ibogaine 48 h and 24 h or 24 h and 4 h prior to the test also did not interfere with the expression of a morphine place preference. Finally, a single injection of 80 mg/kg ibogaine was also ineffective in attenuating the expression of a morphine CPP. Ibogaine appears to be incapable of attenuating the expression of a previously established morphine CPP.

Acknowledgements

I would like to thank Dr. Linda Parker for her guidance, tireless devotion and support throughout this experiment. My gratitude is expressed to Dr. Angelo Santi, Dr. William Hockley, Suzanne Erb and Marion Corrick for their valued assistance. Special thanks go to Dr. Shepard Siegel for taking time out of his ever busy schedule to assist throughout this project. To all, I am sincerely grateful.

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Introduction

Undoubtedly, addiction to drugs is a major problem in society. The use of nicotine, alcohol and illicit drugs is widespread. All drugs, whether they are licit or illicit, can create detrimental financial, societal, and in the least, medical consequences. As a result, The National Institute on Drug Abuse (NIDA) has targeted the development of medication that blocks craving for addictive drugs as a high priority research area (Touchette, 1993). Although a number of substances have been isolated that selectively block the rewarding effects of specific agents (eg Wise, 1989), recently a drug has been identified that is purported to attenuate craving for a broad spectrum of addictive agents (Touchette, 1993). Anecdotal evidence suggests that the hallucinogenic ibogaine effectively blocks craving for a wide variety of drugs (Lotsof, 1985, 1986, 1989, 1991).

Ibogaine is an extract of *Tabernanthe iboga*, a shrub native of the West African nation, Gabon. Folklore (Siegel, 1984) suggests that the psychoactive properties of ibogaine were discovered by natives witnessing boars digging up the roots of the plant. After eating the roots, the boars went into a wild frenzy, possibly escaping from a frightening hallucination (Siegel, 1984). Natives in Gabon use small quantities of ibogaine as a stimulant enabling hunters to stalk prey, and large quantities in hallucinogenic rituals where it is believed that chewing the root enabled people to

speak with the dead (Jetter, 1994).

More intriguing are the purported effects of ibogaine on craving for psychoactive agents. In the initial reports, Howard Lotsof, a former heroin addict, took ibogaine to obtain a new "high." After recovering from a prolonged (3 day) hallucinogenic episode, he reported the absence of craving for heroin or other psychoactive agents. This experience prompted Lotsof to propose a new treatment for heroin addiction that was based on repeated treatments with ibogaine. Although ibogaine is a controlled agent in the United States, it is not a controlled drug in Holland; therefore, Lotsof became involved in treating heroin addicts willing to travel to Holland for ibogaine treatments. Lotsof reported that 1-2 treatments with ibogaine reduced craving for heroin for weeks to months (Sisko, 1994). The treatment procedure appeared promising enough to be awarded U.S. patents proposing treatment with ibogaine for opiate (patent # 4 499 096, 1985), alcohol (patent # 4 857 523, 1989), cocaine and amphetamine (patent # 4 587 243, 1986) and nicotine (patent # 5 026 697, 1991) addiction.

NIDA is currently initiating clinical trials to assess the ability of ibogaine to interrupt addiction (Doblin, 1994). However, there has been relatively little basic experimental investigation of the ability of ibogaine to modify drug reward. A purpose of the present investigation was to provide additional information on the ability of

ibogaine to modify morphine reward.

Ibogaine Interferes with Drug Self-Administration

Although there has been little experimental investigation of the ability of ibogaine to interfere with drug reward, a few investigations using the self-administration paradigm show promising results (Glick, Rossman, Steindorf, Maisonneuve, & Carlson, 1991; Sershen, Hashim, & Lajtha, 1994).

A standard laboratory measure of the rewarding properties of drugs is the drug self-administration paradigm, either intravenous or oral self-administration. In the intravenous self-administration paradigm, animals are trained to press a lever in order to receive an intravenous injection of a drug. If the drug is rewarding, it establishes and/or maintains lever pressing. In the oral self-administration paradigm, rats are trained to drink a solution containing the drug. Ibogaine has been shown to interfere with intravenous self-administration of morphine (Glick et al., 1991) and intravenous and oral self-administration of cocaine (Sershen et al., 1994; Cappendijk & Dzolijic, 1993).

Glick, et al. (1991) found that rats trained to self-administer morphine reduced their responses to obtain morphine after an intraperitoneal (IP) injection of ibogaine. Female, Sprague-Dawley rats were shaped to bar press for infusions of morphine. Daily 1 hour sessions

continued for about 2 weeks until self-administration rates stabilized. Doses ranging from 0-80 mg/kg of ibogaine were then administered 15 minutes prior to a morphine self-administration session. It was found that doses of 10 mg/kg or higher significantly reduced morphine self-administration, with doses of 40 mg/kg or higher having the greatest effect.

Ibogaine interfered with responding maintained by morphine, but it was not clear whether the effect was on motoric responding or was specific to the rewarding properties of morphine. Therefore, in a second experiment, Glick et al. (1991) assessed the aftereffects of a single treatment of ibogaine (40 mg/kg). Ibogaine was given either as a pre-treatment 15 minutes prior to or as a post-treatment 5 minutes after the first morphine self-administration session. The rate of responding was measured in one hour daily sessions for seven days. A significant reduction in responding for morphine occurred in the ibogaine pretreated group; this decrease in responding was most probably due to the motoric effects caused by ibogaine. More importantly, it was found that 24 hours after the ibogaine treatment, both the groups given ibogaine, before or after the first session displayed a reduction in responding for morphine. On the other hand, ibogaine did not attenuate the rate of responding for water when administered 24 hr prior to an operant session. Therefore,

the delayed effect of ibogaine on self-administration of morphine was not due to a prolonged motoric deficit produced by ibogaine. The reduction in responding for morphine must have occurred due to a change in the reinforcing efficacy of morphine. However, as noted by Glick et al. (1991), the direction of the change in reinforcing efficacy is not clear; a decrease in responding for morphine would result: 1) if ibogaine reduced the rewarding properties of morphine rendering each infusion less potent, or 2) ibogaine enhanced the rewarding properties of morphine rendering each infusion more potent.

Ibogaine has also been reported to interfere with both oral (Cappendijk & Dzolijic, 1993) and intravenous (Sershen, Hashim, and Lajtha, 1994) self-administration of cocaine. Sershen et al. (1994) reported that ibogaine reduced oral cocaine self-administration in mice. Mice were initially trained to drink cocaine until they showed a preference for the cocaine solution relative to water in a two choice test. The mice were then given two injections of ibogaine (40 mg/kg), 6 hours apart, and their cocaine consumption was monitored for 5 days following the injections. The results showed that the preference for the cocaine solution was significantly reduced for the five days following the injections. Ibogaine also interfered with intravenous cocaine self-administration in rats (Cappendijk & Dzolijic, 1993). Once the animals had been trained to self-administer

cocaine, they were assigned to one of three ibogaine pretreatment groups: 1) a single administration of ibogaine (10-40 mg/kg i.p.), 2) three consecutive administrations of ibogaine (40 mg/kg, once per day) or 3) ibogaine once at the beginning of each of three consecutive weeks. Although each group displayed suppressed cocaine self-administration for a 24 hour period, the group given weekly injections of ibogaine displayed the greatest suppression of cocaine self-administration; the duration of the suppression increased as the number of injections increased. These results suggest that ibogaine changes the reinforcing efficacy of cocaine as well as morphine, however, as discussed above, the direction of the change is ambiguous.

Although the self-administration method is an effective tool for assessing the abuse potential of drugs, one disadvantage is that, since the test is not drug free, motoric effects of the drug may interfere with responding. For example, amphetamine causes an increase in activity level. Animals self-administering amphetamine may show a high rate of responding that is not due only to the rewarding properties of the drug, but may be due to the drug's motoric effects. Thus, it is not always clear that the effects of the drug on responding are due to motivational changes rather than motor changes.

A second disadvantage of the self-administration paradigm as a measure of the rewarding properties of a drug

is that a change in response rate cannot be interpreted unambiguously. A decrease in response rate could occur if the rewarding property of each infusion is reduced or if the rewarding property of each infusion is enhanced rendering each infusion more potent. In order to overcome this problem, progressive ratio schedules of reinforcement have been developed to measure the cost of a drug injection over a session of responding (e.g. Hodos, 1961). Once the animal has acquired a stable pattern of self-administration on a fixed ratio schedule, the response requirement for each drug injection is increased until the subject fails to receive an infusion in a given period of time. The largest ratio completed in that session is called the breaking point. The breaking point unambiguously increases as the rewarding efficacy of the drug increases and decreases as the rewarding efficacy of the drug decreases. To date, however, there have been no reports of the ability of ibogaine to modify the breaking point of a progressive ratio schedule for infusions of morphine or cocaine.

Ibogaine Interferes with the Establishment of a Morphine Place Preference

Another paradigm that has been purported to assess the rewarding properties of drugs is the conditioned place preference paradigm. Generally in this paradigm, animals experience two unique chambers, one is paired with the drug and the other is paired with saline. At a later time, the

animals are given the opportunity to explore both chambers. If they spend more time in the drug-paired chamber than in the saline paired chamber, then the drug is considered rewarding, but if they spend less time in the drug-paired chamber than the saline-paired chamber, then the drug is considered aversive. The major advantage of place conditioning is that testing is conducted drug-free, thereby preventing the potential confound of drug-induced motoric effects that are inevitable in the self-administration paradigm. Furthermore, the results of place conditioning provide unambiguous evidence of the direction of a change in the rewarding efficacy of morphine. When morphine is employed in place conditioning, there is a positive linear relationship between the morphine dose and the strength of the preference; at doses lethal to half of the rats, the remaining rats still have conditioned place preferences (van der Kooy, 1987). Therefore, if a pretreatment interferes with the establishment of morphine place preferences, it cannot be interpreted as potentiating the effects of morphine rendering it aversive.

Ibogaine not only interferes with morphine self-administration (Glick et al., 1991), but it also interferes with the establishment of a morphine-induced place preference (Parker, Siegel & Luxton, submitted). Ibogaine (40 mg/kg) was administered 24 hours or immediately prior to 5 mg/kg morphine conditioning and the effect of pretreatment

on the establishment of a morphine-induced conditioned place preference was assessed. After one conditioning trial, ibogaine blocked the acquisition of the place preference whether it was given 24 hours or immediately prior to a morphine place conditioning trial. However, after 4 conditioning trials, ibogaine no longer interfered with the morphine-induced place preference conditioning; that is, ibogaine pretreated rats displayed place preferences of a similar magnitude as saline pretreated rats.

It is conceivable that the interference with morphine place conditioning was the result of a summation of aversive properties of ibogaine and rewarding properties of morphine during conditioning trials. If ibogaine is aversive, then it would be expected to attenuate the morphine place preference without necessarily modulating the rewarding effect of morphine. To exclude this possible explanation for these results, Parker et al. (submitted) determined whether ibogaine (40 mg/kg) alone would independently produce a conditioned place preference or avoidance if given either immediately prior to conditioning (Immediate groups) or 24 hours prior to conditioning (Delayed groups). Ibogaine produced neither a place preference nor a place aversion after 1 or 4 conditioning trials in either the Immediate or Delayed groups.

Finally, Parker et al. (submitted) determined whether ibogaine's ability to interfere with morphine place

preference conditioning was the result of interference with learning in general or interference with morphine reward. If ibogaine interferes with learning, it should not only interfere with place preference learning, but it should also interfere with place aversion learning. Parker et al. (submitted) found that ibogaine (40 mg/kg), given 24 hours or 15 minutes prior to naloxone (1 mg/kg or 2 mg/kg) or lithium chloride (75 mg/kg) did not attenuate place aversion learning. The interference with morphine-induced place preference learning, therefore, suggested that ibogaine interferes with the rewarding properties of morphine rather than interfering with learning in general. Ibogaine, however, does not interfere with learning about aversive stimuli.

Ibogaine, therefore, interfered with one-trial morphine place-preference learning. However, the ability of ibogaine to modify the demonstration of a place preference once it has been established has not been tested. It is assumed that rats approach a place previously paired with morphine because it has become conditionally rewarding (van der Kooy, 1987). The purpose of the present series of experiments was to determine whether ibogaine would interfere with the conditioned rewarding properties of the place cues by testing its ability to interfere with expression of morphine place preference learning.

EXPERIMENT 1

In Experiment 1, the ability of a single injection of 40 mg/kg ibogaine to attenuate the expression of a previously established morphine place preference was assessed. A dose of 40 mg/kg ibogaine is sufficient to interfere with the establishment of a morphine-induced place preference (Parker et al., submitted). Since ibogaine attenuates both morphine self-administration and the establishment of a morphine place preference for up to a 24 hour period, the ibogaine pretreatment intervals were 24 h, 12 h and 4 h prior to place preference testing.

Method

Subjects

The subjects were 64 male Sprague-Dawley rats weighing between 200-224 grams upon arrival in the laboratory. They were fed Purina rat chow and water ad-libitum and housed in individual stainless steel cages in a room maintained on a 12:12-hr light-dark cycle. The rats were conditioned and tested during the light phase of the cycle.

Drugs

Ibogaine Hydrochloride (40 mg/kg) was prepared at a concentration of 10 mg/ml of distilled water. Morphine (5 mg/kg) was prepared at a concentration of 2.5 mg/ml of distilled water. All injections were given intraperatoneally (IP).

Apparatus

The place conditioning apparatus consisted of four wooden shuttleboxes (66 by 25 by 30 cm each). The shuttleboxes were each separated into two chambers by removable dividers and covered with wire mesh lids. Both chambers were painted black but differed in floor texture, one with a wire grid floor (.625 cm/grid), and the other floor with 5 cm wide sandpaper strips (grit 60) separated by 5 cm of wooden floor.

A video camera that was attached to the ceiling transmitted the signal corresponding to the widest section of the rat's body to the videotracking apparatus (Videomex, V, Columbus Instruments) which sent the signal to a computer for analysis. For purposes of activity measure, each chamber was divided into 8 sectors and crossings between sectors served as a measure of activity.

Procedure

The rats received a single place conditioning cycle consisting of a saline conditioning trial (Monday) and a morphine conditioning trial (Tuesday). On each trial, the rats were injected with saline solution (at a volume of 2 ml/kg) or morphine solution (5 mg/kg) and 5 min later were placed in the appropriate chamber (Grid or Sandpaper) for 30 minutes. Immediately after each rat's trial, the apparatus was cleaned with soapy water.

The place preference test occurred on Friday, 72 hours after the morphine conditioning trials. As depicted in Figure 1, all rats received 3 injections 24 hr, 12 hr and 4 hr prior to the test. The solution injected was either saline or ibogaine (at a volume of 4 ml/kg). The groups differed on the basis of the time of the ibogaine injection: 24 hr (n=16), 12 hr (n=16), 4 hr(n=16) and no ibogaine (n=16).

Preference tests occurred 4 hr after the final pretest injection. During testing, the dividers separating the two chambers were removed. The rats were given 15 minutes free access to both chambers, and the amount of time spent in each chamber as well as the number of sector crossings in each chamber were recorded.

The amount of time spent in each chamber for each rat was transformed into grid preference ratios: Time spent in the grid chamber/time spent in grid chamber + time spent in

Figure 1. Design of Experiment 1.

Experiment 1

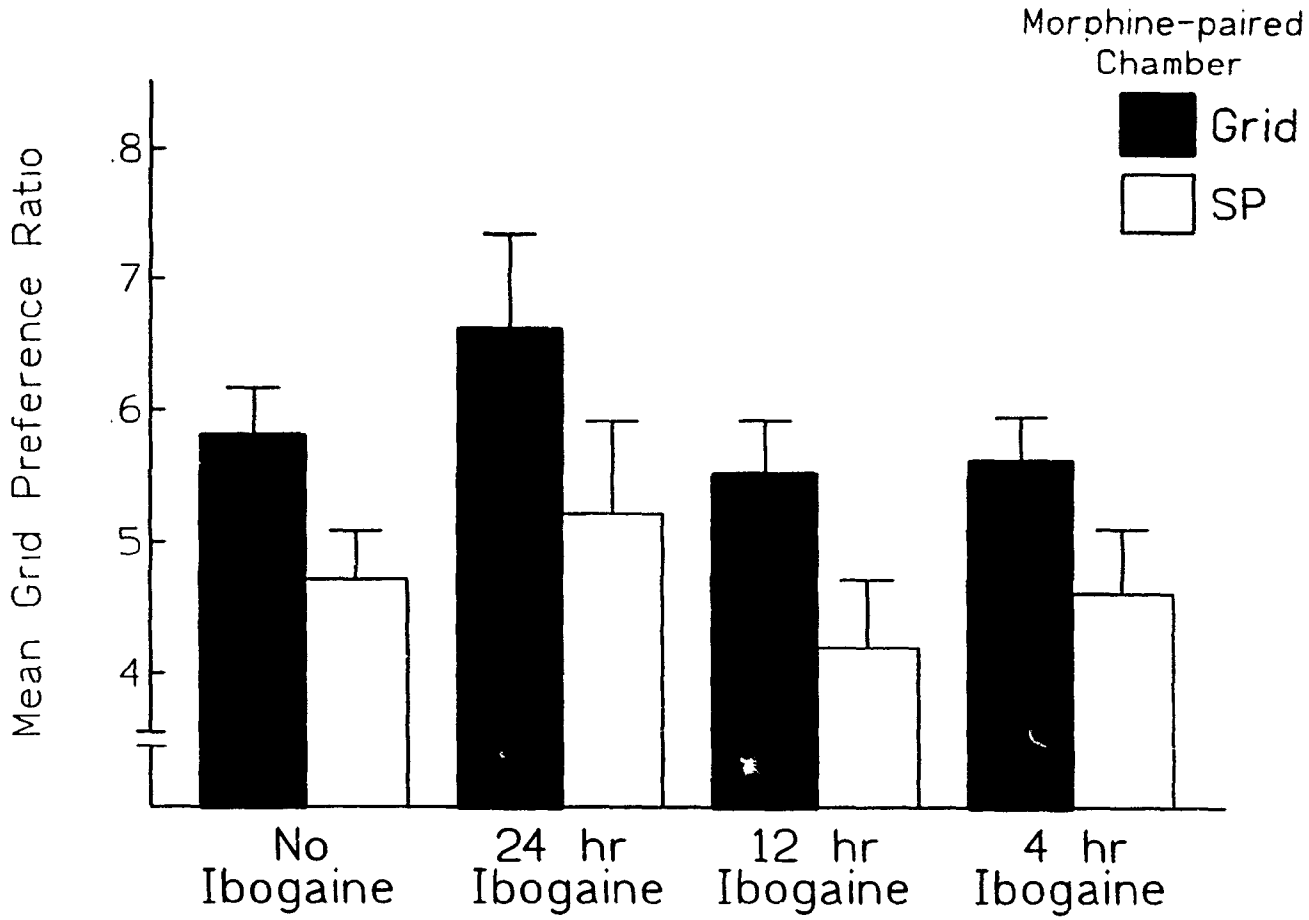
Treatment Group	24 Hours Prior to Test	12 Hours Prior to Test	4 Hours Prior to Test
No Ibogaine	Saline	Saline	Saline
24 hr Ibogaine	Ibogaine	Saline	Saline
12 hr Ibogaine	Saline	Ibogaine	Saline
4 hr Ibogaine	Saline	Saline	Ibogaine

sandpaper chamber. The grid preference ratios were compared between the rats that had morphine paired with the grid chamber and those that had morphine paired with the sandpaper chamber. A conditioned place preference would be evident as a greater grid preference ratio for the group that had morphine paired with the grid chamber than the group that had morphine paired with the sandpaper chamber (Reicher and Holman, 1977; Parker & Gillies, in press).

Results and Discussion

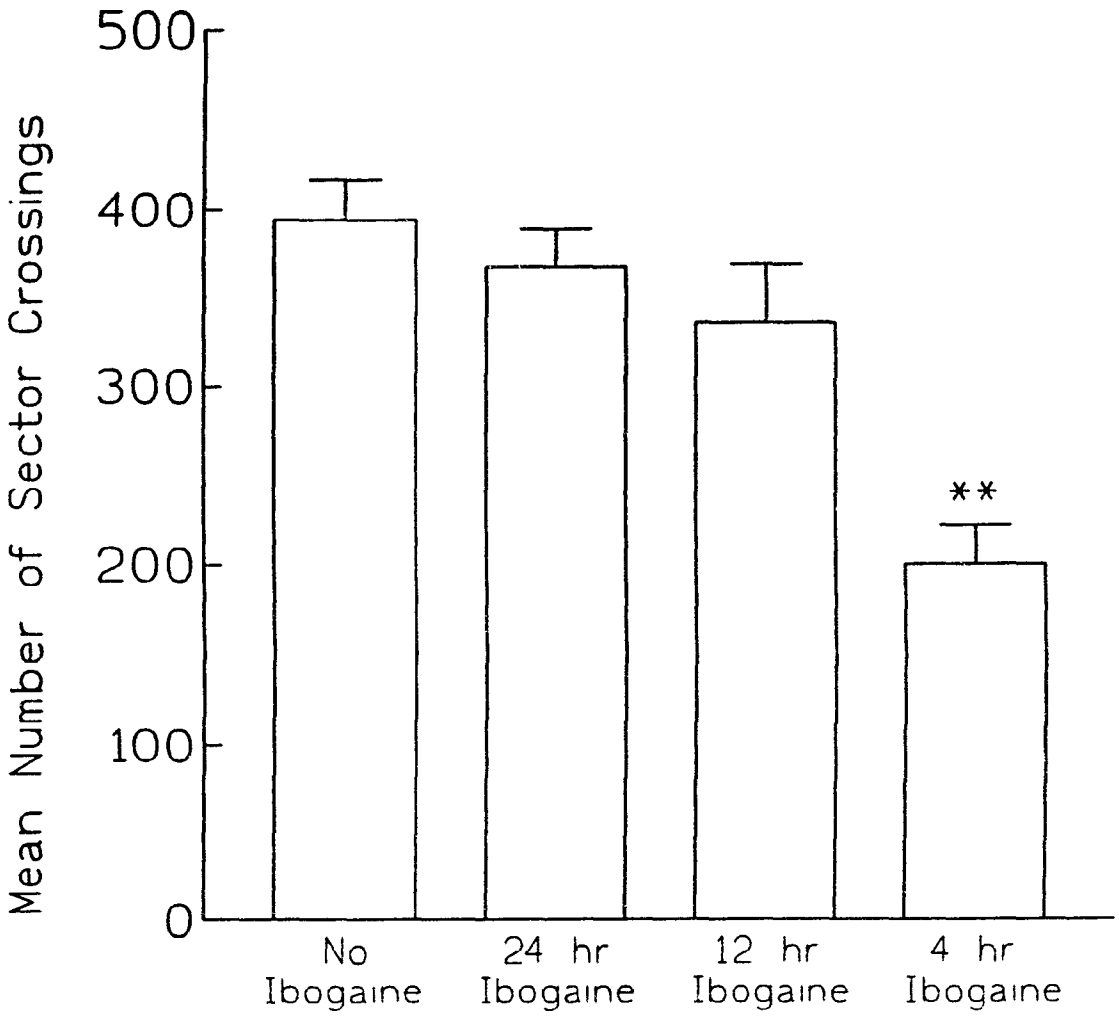
The mean preference for the grid chamber is presented in Figure 2. As is apparent in the figure, ibogaine did not attenuate the display of a morphine-induced place preference. Each ibogaine group displayed a preference for the morphine paired chamber. The 4 X 2 Between Groups Analysis of Variance (ANOVA) with the factors of Treatment Groups (24 hr ibogaine, 12 hr ibogaine, 4 hr ibogaine, no ibogaine) and morphine-paired chamber (grid, sandpaper), revealed only a significant effect of morphine-paired chamber, F (1, 56) = 11.0, $p<.01$. The treatment group by morphine-paired chamber interaction was not significant. A single injection of ibogaine did not interfere with the expression of a morphine-induced place preference.

Figure 2. Mean grid preference ratio (+SEM) for the various pretesting groups that had morphine paired with the grid and with the sandpaper chambers in Experiment 1.


Morphine-paired Chamber
Grid
SP
Mean Grid Preference Ratio
.8
7
6
5
4
No Ibogaine
24 hr Ibogaine
12 hr Ibogaine
4 hr Ibogaine

To assess the effect of ibogaine on activity during testing, the total mean number of sector crossings in both chambers for each group during the test are presented in Figure 3. A one way ANOVA for treatment group revealed a significant effect of treatment group $F(3,60)=12.11$, $p<.001$. Subsequent Neuman-Keuls tests revealed that the group given ibogaine 4 hours prior to the test had significantly lower levels of activity than the other three groups ($p<.05$). The other groups did not significantly differ from each other. Therefore, ibogaine had a behavioral effect, but it did not interfere with the expression of the preference for the morphine paired chamber.

Figure 3. Mean number of sector crossings (+SEM) in the entire apparatus during preference testing in Experiment 1.


Mean Number of Sector Crossings
500
400
300
200
100
0
**
No Ibogaine
24 hr Ibogaine
12 hr Ibogaine
4 hr Ibogaine

EXPERIMENT 2

Regardless of the pretreatment interval, a single injection of ibogaine did not interfere with the display of a previously established morphine-induced place preference. However, in the human treatment of addiction the treatment regime often includes more than one ibogaine treatment (Touchette, 1993). Additionally, Cappendijk and Dzoljic (1993) demonstrated that multiple ibogaine injections are more effective than a single injection in attenuating cocaine self-administration. Therefore, in Experiment 2, two injections of 40 mg/kg of ibogaine were administered prior to a test of a previously established morphine-induced place preference.

Method

The subjects were 84 male Sprague-Dawley rats weighing between 250-350 grams. The procedures were identical to those of Experiment 1 except for pretest injection time and the number of ibogaine injections. As depicted in Figure 4, all rats received a pretesting injection 48 hr, 24 hr and 4 hr prior to testing. The solution injected was either saline or 40 mg/kg ibogaine (at a volume of 4 ml/kg). The groups differed on the basis of the time of the ibogaine injections. Group 48-24 (n=28) received ibogaine injections

Figure 4. Design of Experiment 2.

Experiment 2

Treatment Group	48 Hours Prior to Test	24 Hours Prior to Test	4 Hours Prior to Test
No Ibogaine	Saline	Saline	Saline
48-24 hr Ibogaine	Ibogaine	Ibogaine	Saline
24-4 hr Ibogaine	Saline	Ibogaine	Ibogaine

48 hr and 24 hr and a saline injection 4 hr prior to testing. Group 24-4 (n=28) received ibogaine injections 24 and 4 hr and a saline injection 48 hr before testing. Group No Ibogaine (n=28) received saline injections 48 hr, 24 hr and 4 hr prior to testing. The n was increased in this experiment in an attempt to increase the power of the statistical analysis. Preference tests were as described in Experiment 1 and again occurred 4 hours after the final pretest injection.

Results and Discussion

As apparent in Figure 5, even 2 injections of 40 mg/kg ibogaine did not modify the display of a morphine place preference. A 3 X 2 ANOVA with the factors of Treatment Groups (24-48 hr ibogaine, 24-4 hr ibogaine, no ibogaine) and morphine-paired chamber (grid, sandpaper) revealed only a significant effect of morphine-paired chamber, $F(1,78) = 16.6$, $p < .001$. Even though Figure 5 suggests that ibogaine may have enhanced the display of a morphine-induced place preference, the interaction between treatment group and morphine paired chamber was not significant.

Figure 6 presents the mean number of sector crossings in the entire apparatus for the various groups during testing. A significant treatment group effect was again found, $F(2,81)=62.96$, $p<.001$. Subsequent Neuman-Keuls

Figure 5. Mean grid preference ratio (+SEM) for the various pretesting groups that had morphine paired with the grid and with the sandpaper chambers in Experiment 2.

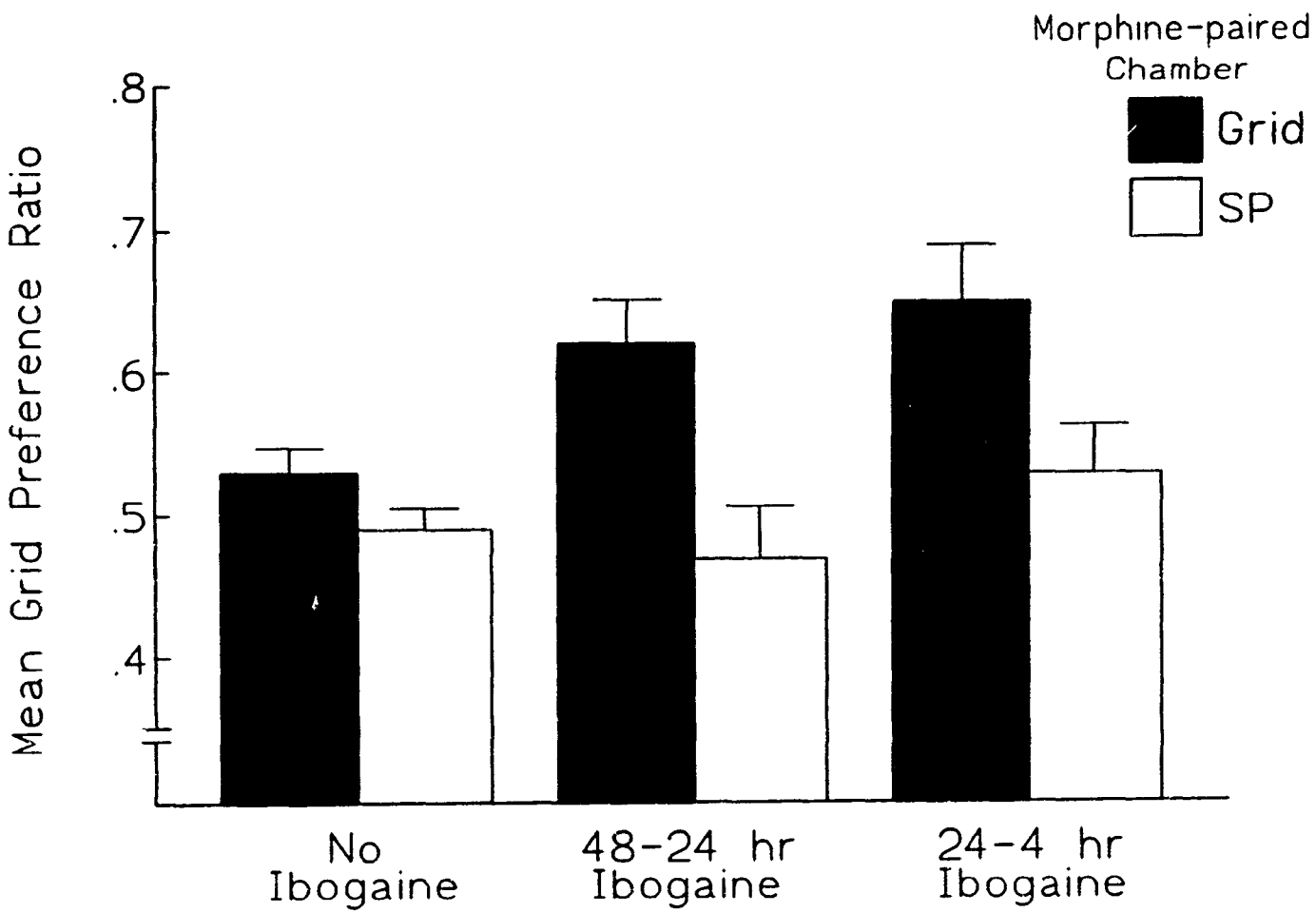
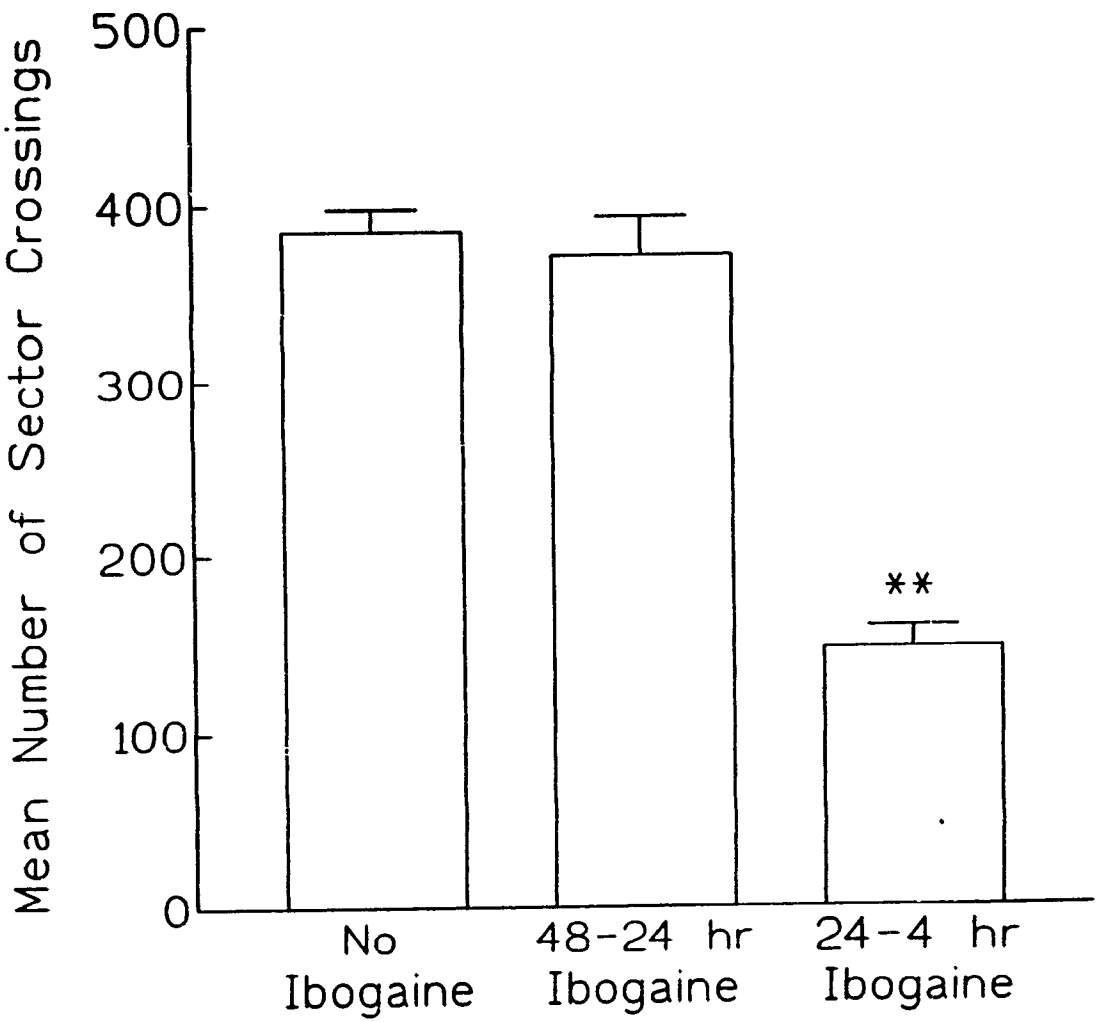

Morphine-paired Chamber
Grid
SP
Mean Grid Preference Ratio
.8
.7
.6
.5
.4
No Ibogaine
48-24 hr Ibogaine
24-4 hr Ibogaine

Figure 6. Mean number of sector crossings (+SEM) in the entire apparatus during preference testing in Experiment 2.


Mean Number of Sector Crossings
500
400
300
200
100
0
**
No Ibogaine
48-24 hr Ibogaine
24-4 hr Ibogaine

tests revealed that the group given ibogaine 24-4 hours prior to the test displayed fewer sector crossings during testing than the other two groups ($p<.05$).

EXPERIMENT 3

In Experiments 1 and 2, a dose of 40 mg/kg of ibogaine administered on one or two occasions prior to a test did not interfere with the display of a morphine place preference. Perhaps this dose of ibogaine was insufficient for producing the effect. A single dose of 80 mg/kg has been reported to be near threshold in producing damage to the Purkinje cells of the cerebellum (O'Hearn & Molliver, 1994). Therefore, Experiment 3 determined whether a single administration of a dose of 80 mg/kg (at a volume of 8 ml/kg) of ibogaine 24 hr prior to a test would interfere with the expression of a morphine place preference.

Method

The subjects were 31 male Sprague-Dawley rats weighing between 200-224 grams upon arrival in the laboratory. The procedures were identical to those of Experiment 1 and 2 except for pretest injection time and the dose of ibogaine. All rats received a single pretest injection 24 hr prior to testing; the solution injected was either saline (n=16) or 80 mg/kg of ibogaine (n=15).

Results and Discussion

Figure 7 presents the mean grid preference ratio for the groups in Experiment 3. Even a single dose of 80 mg/kg ibogaine did not interfere with the expression of a morphine place preference. A 2 x 2 Between Groups ANOVA with the factors of Treatment Group and morphine paired chamber revealed only a significant effect of morphine paired chamber, $F(1,27) = 6.20$, $p < .05$.

Figure 8 presents the mean number of sector crossings in the entire apparatus for the ibogaine and no ibogaine groups. Group Ibogaine displayed a lower level of activity than group No Ibogaine, $t(29) = 1.85$, $p < .05$, one tailed. Consistent with the results of Experiments 1 and 2 with 40 mg/kg of ibogaine given 4 hrs and 24-4 hrs prior to testing, in the present experiment, a single injection of 80 mg/kg of ibogaine suppressed activity over a 24 hour period. However, in none of the experiments did ibogaine interfere with the expression of a previously established morphine induced place preference.

Figure 7. Mean grid preference ratio (+SEM) for the various pretesting groups that had morphine paired with the grid and with the sandpaper chambers in Experiment 3.

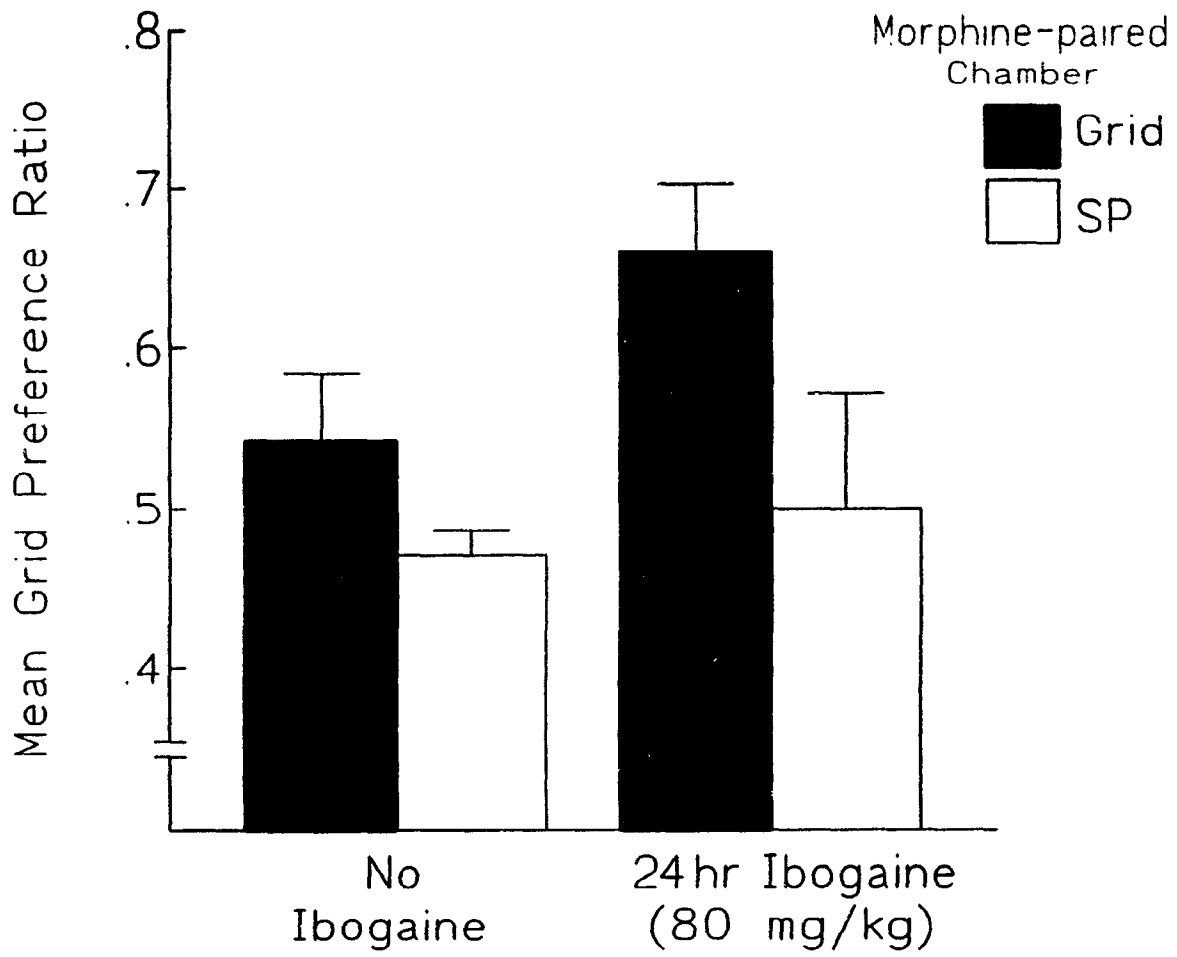
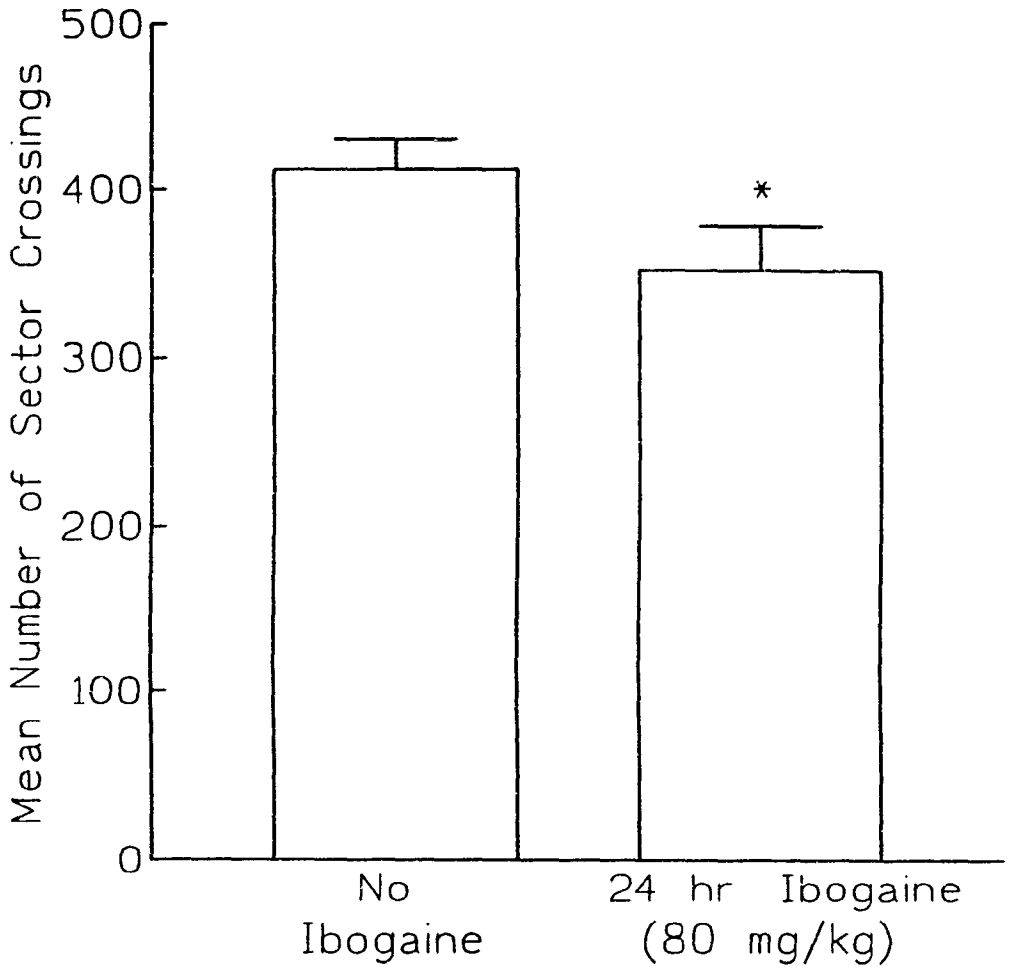

Mean Grid Preference Ratio
.8
.7
.6
.5
.4
Morphine-paired Chamber
Grid
SP
No Ibogaine
24 hr Ibogaine (80 mg/kg)

Figure 8. Mean number of sector crossings (+SEM) in the entire apparatus during preference testing in Experiment 3.


Mean Number of Sector Crossings
500
400
300
200
100
0
*
No Ibogaine
24 hr Ibogaine (80 mg/kg)

GENERAL DISCUSSION

The results consistently suggest that ibogaine does not interfere with the expression of an established preference for a morphine-paired chamber. At a dose of 40 mg/kg, neither a single ibogaine injection 24, 12 or 4 hrs prior to the preference test (Experiment 1) nor two ibogaine injections 48-24 or 24-4 hrs prior to the preference test (Experiment 2) reduced the strength of the preference for a morphine-paired chamber. Furthermore, even a dose of 80 mg/kg of ibogaine administered 24 hr prior to preference testing (Experiment 3) did not modify the strength of a morphine-induced place preference.

Ibogaine did, however, modify general activity during the place preference test. In Experiments 1 and 2, when 40 mg/kg of ibogaine was administered 4 hr prior to testing, rats displayed a reduction in overall activity; however, this reduction in activity was not apparent 12-24 hr following the injection. In Experiment 3, when the dose of ibogaine was increased to 80 mg/kg, rats displayed suppressed activity 24 hr after the injection. Therefore, the failure of ibogaine to attenuate the expression of a previously established morphine-induced place preference cannot be attributed to physiological inactivity of ibogaine at the doses employed.

Although ibogaine does not interfere with the

expression of a previously learned morphine place preference, it has been shown to attenuate the establishment of a 1 trial morphine place preference (Parker, Siegel & Luxton, submitted). It is of interest that other treatments have been shown to selectively interfere with the acquisition, but not the expression of drug-induced place preference conditioning. These treatments include anatomical and pharmacological manipulations.

Lesions of specific neural structures have been shown to interfere selectively with acquisition of drug-induced place preference learning. The ventral pallidum (VP) has been implicated in the acquisition, but not in the expression, of an amphetamine-induced place preference (Hiroi & White, 1993). Pre-conditioning lesions of the VP, but not post-conditioning lesions, have been found to attenuate an amphetamine conditioned place preference. Similarly, another area receiving output from the nucleus accumbens (the primary reward site), the tegmental pedunculopontine nucleus (TPP), has been found necessary for the acquisition of a morphine-induced place preference, but not for the expression of a morphine place preference (Bechara & van der Kooy, 1989). Lesions of the TPP prior to morphine place conditioning eliminate the place preference while lesions after conditioning have no effect on the expression of the place preference. Thus, anatomical investigations demonstrate that the structures involved in

the acquisition of a place preference are not necessarily involved in the expression of the preference.

Pharmacological manipulation also has demonstrated the independence of systems involved in the acquisition and expression of drug-induced conditioned behaviours. Dopamine blockade by pimozide attenuates the establishment of amphetamine-induced conditioned activity, but not its expression (Beninger & Hahn, 1983). Similarly, opiate blockade by naloxone attenuates the establishment but not the expression of a heroin-induced place preferences (Hand, Stinus & Moal, 1989). Again, the systems that mediate acquisition and expression may be independent. On the other hand, both the acquisition and expression of amphetamine-induced place preferences have been shown to be mediated be dopaminergic activity in the ventral striatum (Everitt, Morris, O'Brien & Robbins, 1991; Hiroi & White, 1990; Hiroi & White, 1991).

Recently, it has been reported that ibogaine inhibits binding of MK-801 to NMDA (N-methyl-D-aspartate) receptors (Popik, Layer and Skolnick, 1994) that are thought to be involved in learning (Morris, Anderson, Lynch & Baudry, 1986; Shapiro & Carmanos, 1990). It is interesting to note that pretreatment with MK-801, a known NMDA receptor antagonist, has been shown to interfere with the acquisition of spatial learning (Shapiro & Carmanos, 1990), olfactory learning (Staubli, Thibault, DiLorenzo & Lynch, 1989),

context dependent tolerance (Trujillo & Akil, 1991) and context dependent sensitization (Stewart & Druhan, 1993), but does not interfere with the expression of any of these learned behaviours. This pattern is similar to the effect of ibogaine on the acquisition and expression of morphine-induced conditioned place preference learning. Although highly speculative at this time, it is plausible that the ability of ibogaine to interfere with the establishment of a morphine place preference is mediated by its effects on the NMDA glutamate receptor.

In each of the experiments that examined the ability of ibogaine to modify the establishment or the expression of a morphine-induced place preference, the rats were morphine naive prior to conditioning. Bechara, Harington, Nader and van der Kooy (1992) demonstrated that the neural substrate mediating morphine-induced place conditioning differs in naive and morphine dependent rats. In morphine naive rats, but not morphine dependent rats, lesions of the TPP interfere with the establishment of morphine place preference (Bechara & van der Kooy, 1991). In morphine dependent, but not naive rats, pretreatment with the dopamine blocker, a-flupentixol, interferes with the acquisition of a morphine place preference. It is conceivable that ibogaine would more effectively interfere with the acquisition and/or expression of morphine place conditioning in dependent rats than in non-dependent rats.

Research has shown that ibogaine reduces the rise in dopamine which normally occurs from morphine treatment (Maisonneuve, Keller & Glick, 1991). If dopamine blocking agents selectively interfere with the establishment of a conditioned place preference in morphine dependent, but not morphine naive rats, it is conceivable that ibogaine will more effectively block morphine-induced conditioned place preferences in dependent rats than naive rats and possibly more effectively block the expression of these place preferences. This is especially interesting when the application of the treatment is considered. That is, ibogaine treatment of addiction has been proposed as a pharmacological treatment in dependent human drug abusers. Future research will address this issue.

Appendix A.

Ibogaine: Behavioral and Neurochemical Effects.

It has recently been suggested that ibogaine, an indole alkaloid found in the African shrub *Tabernanthe iboga*, may reduce craving for narcotics (patent # 4 499 096, 1985), alcohol (patent # 4 857 523, 1989), cocaine and amphetamine (patent # 4 587 243 1986) and nicotine (patent # 5 026 697, 1991). However, there is little animal research investigating the central mechanisms of ibogaine and how it affects rewarding drugs. Of the investigations completed, the interaction between ibogaine and addicting drugs on locomotor activity, central neurotransmitter measures, drug discrimination tasks, and opiate withdrawal have all been assessed revealing some insight, but also discrepancies.

Locomotor Activity: Interactions of Ibogaine and Drugs of Abuse

To assess the interaction of ibogaine and other rewarding drugs, locomotor activity induced by cocaine or amphetamine in mice and rats after ibogaine treatment has been examined (Sershen, Hashim, Harsing & Lajtha, 1992; Maisonneuve, Rossman, Keller and Glick, 1992). Sershen et al. (1992) gave mice an injection of ibogaine (40 mg/kg) or saline followed 2 and 24 hours later by cocaine injections (25 mg/kg s.c.). The results showed that, at both intervals, ibogaine reduced the cocaine-induced locomotor activity in the mice. Furthermore, even when tested 5 days later, cocaine-induced locomotor activity remained suppressed.

Sershen et al. (1992) further investigated the effect of ibogaine on amphetamine-induced motor stimulation in both rats and mice. In mice, ibogaine (20 and 40 mg/kg) was given either 2 or 18 hours prior to treatment with various doses of d-amphetamine (1, 5 and 10 mg/kg). At 40 mg/kg, but not 20 mg/kg, ibogaine reduced amphetamine-induced locomotor activity when given at both pretreatment intervals. The results found with rats are not consistent with these findings. Female Sprague-Dawley rats were pretreated with ibogaine (40 mg/kg i.p.) 18 hours prior to d-amphetamine (1.25 mg/kg i.p.) treatment. It was found that ibogaine did not reduce locomotor activity as it had in mice, but, in fact, potentiated amphetamine-induced locomotor activity in rats. Maisonneuve, Keller and Glick (1992) similarly reported that ibogaine potentiates amphetamine-induced locomotor activity in rats. The reasons for the discrepancy between the effects of ibogaine on amphetamine-induced activity in rats and mice is unclear, although it is possible that ibogaine may have a time and dose-dependent effect that differs in the two species. The effect of ibogaine on dopamine release and metabolism may also differ between the two species.

The effect of ibogaine on morphine-induced locomotor activity in rats (Maisonneuve, Rossman, Keller & Glick, 1992) has also been examined. Morphine affects locomotion in a time/dose dependent fashion. Low doses produce an

increase in locomotor activity, while high doses initially inhibit and then stimulate activity. Similar to previous studies using amphetamine, ibogaine (40 mg/kg i.p.) was given 19 hours prior to morphine treatment (.5, 1.25, 5, 10, 20, or 30 mg/kg i.p.). Also, rats were administered ibogaine (40 mg/kg i.p.) 1 week or 1 month prior to morphine (5 mg/kg). Ibogaine pretreatment 19 hours prior to morphine resulted in significant decreases in locomotor activity produced by all doses of morphine except 30 mg/kg, which may have produced floor effects in locomotion. One week after ibogaine treatment, there was still a decrease in morphine-induced locomotor activity. One month after ibogaine treatment, there was no effect on activity. The ibogaine-induced decrease in morphine locomotor behaviour may represent either an attenuation or a potentiation of the effects of morphine because at doses greater than 5 mg/kg morphine alone produced motor suppression rather than motor activation.

Mechanism of Action of Ibogaine

The mechanism of action of ibogaine is unknown. Strangely, the effects of ibogaine appear to persist well beyond the time in which it should be cleared from the body (Dhahir, 1971). Despite the short half life in rodents, approximately 1 hour, the effects of ibogaine on morphine and cocaine self-administration have been reported to

persist for days after the initial administration. Glick, Rossman, Wang, Dong and Keller (1993) state three possible explanations for ibogaine's long lasting effects: ibogaine may produce neuronal structural change, persist in low levels in the system, or it may have a metabolite with a long half-life. Although it is still uncertain precisely what is occurring, many researchers have attempted to investigate the mechanism of action of ibogaine.

Ibogaine alone. Maisonneuve et al. (1992) examined the effects of ibogaine on postmortem tissue content of dopamine and its metabolites, Homovanillic acid (HVA) and dihyroxyphenylacetic acid (DOPAC), in the prefrontal cortex, nucleus accumbens and the striatum. Typically, an increase in the turnover or catabolism of dopamine results in an increase in metabolite levels. One hour after ibogaine treatment, levels of dopamine were decreased while HVA levels were increased in all three brain areas. A decrease in DOPAC was found in the nucleus accumbens only. Nineteen hours after ibogaine treatment the levels of dopamine and HVA returned to normal, while the levels of DOPAC were decreased in the nucleus accumbens and striatum. One week after ibogaine treatment, only a marginal decrease in striatal DOPAC still existed. One month later, no significant changes were noted. Changes in striatal dopamine and its metabolites within 24 hours of an ibogaine injection were also found by Sershen et al. (1992).

Dopamine levels steadily decreased for 2 hours following the ibogaine injection, returning to normal 24 hours later. DOPAC levels increased shortly after the injection also returning to normal 24 hours later. HVA levels similarly showed an acute increase, but fell below control levels at the 24 hour interval. The authors suggest that the increase in the ratio of metabolites of dopamine to dopamine may be caused by ibogaine transiently enhancing dopamine catabolism. Although it is uncertain why striatal DOPAC levels differ between Maisonneuve et al. (1991) and Sershen et al. (1992) one hour after ibogaine administration, the discrepancy may be due to species and/or sex differences. As mentioned, Maisonneuve et al. (1991) used female Sprague-Dawley rats while Sershen et al. (1992) used male mice.

More specifically, ibogaine appears also to act at kappa-opiate receptors (Deecher, Teitler, Soderlund, Bornmann, Kuehne & Glick, 1992). Deecher et al. (1992) evaluated the affinity of ibogaine at many neuroreceptor sites. The results showed that ibogaine had a significant affinity for kappa-opiate receptors, yet strangely not for dopaminergic, serotonergic or GABA receptor sites. The finding that ibogaine did not appear to have a specific affinity for dopaminergic receptors, yet still has an effect on dopamine and its metabolites (Maisonneuve et al., 1991; Sershen et al., 1992) suggests it may indirectly modify dopamine release. It is conceivable that ibogaine may

produce its anti-addictive properties through interactions with kappa-opiate receptor sites.

Interactions of ibogaine and drugs of abuse. Undoubtedly, ibogaine in isolation altered the levels of dopamine and its metabolites. As mentioned, ibogaine reduced morphine-induced locomotor activity, possibly by affecting the dopamine levels in the striatum, which is involved in morphine-induced rigidity (Maisonneuve et al., 1992). Maisonneuve, Keller and Glick (1991) also investigated the effect of ibogaine on morphine-induced changes in the dopamine system. Ibogaine (40 mg/kg i.p.) was injected 19 hours prior to the morphine (5 mg/kg i.p.) injection. Dopaminergic increases in response to the morphine injection normally seen in the striatum, nucleus accumbens and prefrontal cortex were blocked by the ibogaine pretreatment. Normal prefrontal increase in DOPAC and HVA found after morphine treatment were also blocked. This finding is somewhat difficult to reconcile with previous findings suggesting ibogaine, in isolation, causes an increase in the metabolites of dopamine (Sershen et al., 1992). Maisonneuve et al. (1992) suggest that the inhibitory effect of ibogaine on dopamine transmission in the nucleus accumbens that usually follows morphine administration may decrease the reinforcing efficacy of morphine.

Maisonneuve et al. (1992) measured brain levels of dopamine and its metabolites after ibogaine and amphetamine

treatment. Rats were given injections of either saline or ibogaine (40 mg/kg) 19 hours prior to d-amphetamine or saline treatment. In the nucleus accumbens, DA levels increased significantly more in the ibogaine pretreated rats shortly after the amphetamine injection than in the rats pretreated with saline. This elevation in DA was maintained for 100 minutes after the amphetamine injection. DOPAC and HVA levels in both areas were significantly decreased in comparison to baseline levels for 20-180 minutes after the amphetamine injection. The decreases were greater in the striatum. These increases in dopamine in the nucleus accumbens and striatum correlate with the enhancement of amphetamine-induced locomotor activity caused by ibogaine, suggesting that ibogaine potentiates the effects of amphetamine on striatal DA release. The authors further suggest that ibogaine either intensifies the actions of d-amphetamine which enhance dopamine release, or it inhibits enzymes involved in the metabolism of amphetamine.

Effect of Ibogaine on Central Morphine and Amphetamine Levels. Because of Maisonneuve et al.'s (1992) suggestion that ibogaine inhibits the behavioral effects of morphine, yet potentiates the effects of amphetamine, Glick, Gallagher, Hough, Rossman and Maisonneuve (1992) assessed the effects of ibogaine on the brain levels of morphine and amphetamine. Ibogaine (40 mg/kg i.p.) was injected in rats 19 hours prior to an injection of morphine (10 mg/kg i.p.).

Ibogaine had no effect on the brain levels of morphine when measured either 30 minutes or 2 hours after morphine treatment. In contrast, ibogaine given 19 hours prior to amphetamine treatment (1.25 mg/kg i.p.) resulted in a small, but significant, increase in amphetamine levels measured 30 minutes after treatment, and a fourfold increase in amphetamine levels 2 hours after amphetamine treatment. Glick et al. (1992) again suggest that ibogaine may inhibit an amphetamine-metabolizing enzyme explaining why a 19 hour pretreatment and a 30 minute pretreatment show almost identical brain levels of amphetamine.

Drug Discrimination with Ibogaine.

Drug discrimination paradigms have also been used to assess the mechanism of action of ibogaine (Palumbo & Winter, 1992; Schechter & Gordon, 1993) with conflicting results. In this paradigm, interoceptive cueing effects of psychoactive drugs serve as a discriminative stimuli for operant responding for reward. Animals are given a specific drug and are then given the opportunity to respond in a specific manner to receive reward. For example, in a two lever operant chamber, responses on the left lever produce reinforcement under a certain drug stimulus state, while responses on the right lever are reinforced under a saline stimulus state. Since drugs that have a similar mechanism of action often produce similar interoceptive cues, the

injection of a similar substance produces responses on the lever associated with the original substance.

Palumbo and Winter (1992) attempted to characterize the effects of ibogaine by comparing it with dimethoxy-4-methylamphetamine (DOM), a hallucinogenic with a selective affinity for 5-hydroxytryptamine^2 (5-HT^2) receptors, yohimbine, an indolealkylamine with central stimulatory effects which acts at the 5-HT^1 receptors, and lysergic acid diethylamide (LSD), a hallucinogenic which has an affinity for 5-HT^{1A}, 5-HT^{1B}, and 5-HT^2 receptors. DOM, yohimbine and LSD all serve as effective discriminative stimuli. Male Fischer rats were trained to depress levers in a two-lever operant chamber for liquid reward. Three groups were trained with yohimbine, DOM and LSD respectively with one lever being the drug appropriate lever and the other being appropriate if no drug was given with a criteria of 83% correct responding. During subsequent test sessions, ibogaine (1 mg/kg - 20 mg/kg) or ibogaine with the 5-HT^1, 5-HT^2 antagonist pizotyline (10 mg/kg) was given to determine if responding appropriate to one of the three drugs occurred. Since pizotyline blocks a 5-HT^1 and 5-HT^2 receptors, it also blocks the stimulus properties of DOM and LSD which both activate these receptors. Therefore, if the stimulus properties of ibogaine are produced by a similar mechanism as are those of DOM and LSD, ibogaine and pizotyline should produce fewer DOM or LSD appropriate

responses than ibogaine alone. Indeed, ibogaine (15 mg/kg) resulted in DOM and LSD appropriate responding, and this responding was completely blocked by pizotyline treatment. Ibogaine, however, did not generalize to yohimbine. Since ibogaine generalized to DOM and LSD which both have an affinity for 5-HT^2 receptors, but not with yohimbine which has an affinity for 5-HT^1 receptors, 5-HT^2 receptors appear to be involved in producing the stimulus properties of ibogaine.

A similar discrimination study completed by Schechter and Gordon (1993), however, failed to confirm the ability of ibogaine to generalize with other hallucinogenic drugs. In animals trained to discriminate between ibogaine (10 mg/kg) and saline, the stimulus properties of ibogaine failed to generalize with CGS 10476B (a dopamine antagonist), and serotonergically active drugs, fenfluramine, TFMPP, DOI, MDMA, quipazine and LSD. However, the conflicting results may exist due to the different doses of ibogaine employed. Palumbo and Winter (1992) required doses of 15 mg/kg or higher of ibogaine to show stimulus generalization with .1 mg/kg LSD, while Schechter and Gordon used only a dose of 10 mg/kg with a dose of .12 mg/kg LSD. Additionally, Schechter and Gordon (1993) reported that the number of animals tested with LSD was low due to low quantities of LSD available for testing.

Overall, ibogaine affects dopamine and its metabolites,

has an affinity for kappa-opiate receptors, as well as having stimulus properties which may involve serotonergic receptors.

Ibogaine and Morphine Withdrawal

Ibogaine has also been found to affect the withdrawal symptoms produced by morphine (Glick, Rossman, Rao, Maisonneuve and Carlson, 1992; Dzoljic, Kaplan & Dzoljic, 1988). Glick et al., (1992) induced the withdrawal symptoms of wet dog shakes, grooming, teeth chattering, diarrhea, weight loss, burying and flinching by giving naltrexone injections to morphine dependent rats. Thirty minutes prior to the naltrexone treatment (1 mg/kg, IP), the experimental rats were pretreated with ibogaine (40 and 80 mg/kg, IP) and then observed for two hours. A reduction was found in wet dog shakes, grooming, teeth chattering and diarrhea, but not in weight loss, burying and flinching. A problem with this experiment is that the animals were experiencing tremors due to the ibogaine at the same time the withdrawal symptoms were being noted. Since these tremors, which last 2-3 hours, may have interfered with the expression of the symptoms, a second experiment introduced naltrexone 4 hours after ibogaine treatment (a time at which tremors were no longer apparent). The results showed that the same withdrawal symptoms were reduced. Since ibogaine has been purported to reduce craving for morphine (Lotsof, 4 499 096, 1985) the ability of ibogaine to attenuate morphine

withdrawal effects is important for theorists (i.e. Siegel, 1989) who argue that craving for a drug is the result of the elicitation of conditional responses by drug associated cues.

Dzoljic et al. (1988) also found ibogaine reduced naloxone-precipitated withdrawal in morphine-dependent rats. Chronic morphine-dependence was induced by 85 mg morphine pellets implanted subcutaneously. Opiate withdrawal was precipitated by a IP dose of naloxone (5 mg/kg) 72 hours after the pellet implantation. Ibogaine was administered intracerebroventricularly (icv) at a dose range of 4-16 mg 15 minutes prior to naloxone injection. Observations made for 45 minutes from the time of ibogaine treatment revealed a reduction in rearing, digging, head hiding, chewing, teeth chattering, writhing, jumping and salivation. Other withdrawal signs were not significantly affected.

Conflicting results were found by Sharpe and Jaffe (1990). Morphine-dependence was induced in rats by subcutaneous 75 mg morphine pellets given 3 days prior to naloxone (0.5 mg/kg s.c.). Ibogaine (5, 10, 20 and 40 mg/kg, s.c.) administered 15 minutes prior to naloxone did not significantly reduce signs of naloxone-precipitated withdrawal except grooming. These differences could be due to several factors: 1) different routes of administration were used in the studies, 2) different doses of naloxone employed, or different strain of animal. Glick et al.

(1992) administered all substances IP, Dzoljic et al. (1988) administered icv while Sharpe and Jaffe (1990) administered s.c. making it difficult to compare effective doses. Also, Glick et al. (1992) and Dzoljic et al. (1988) used a higher dose of naloxone (1 and 5 mg/kg respectively). It could be that higher doses of naloxone act on other opioid receptors with which ibogaine is acting. Finally, Glick et al. (1992) and Dzoljic et al. (1988) used Sprague-Dawley rats, while Sharpe and Jaffe (1990) used Wistar rats.

Conclusion

Though the mechanism of action of ibogaine is still relatively unknown, it does modify the central effects of addictive drugs. Research to date, though confusing and apparently conflicting, suggests ibogaine has widespread action on many central systems. For example, ibogaine may alter the effects of addictive substances by its action on the dopamine system. In isolation, ibogaine appears to reduce dopamine levels suggesting support for its anti-addictive properties. Ibogaine shows discriminative properties which involves 5-HT2 receptors suggesting the involvement of serotonin receptors in ibogaine's effects. The involvement of NMDA receptors has also been suggested. More research is necessary to isolate the mechanism of action of ibogaine and how its putative anti-addictive properties are produced.

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