Chapter 11

MODULATION OF THE EFFECTS OF REWARDING DRUGS BY IBOGAINE

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I. Introduction

Ibogaine (NIH 10567, Endabuse™) is an alkaloid obtained from the root of *Tabernanthe iboga*, a shrub indigenous to equatorial Africa. There are anecdotal reports that ibogaine is effective in the treatment of a variety of addictive disorders (1,2). Indeed, Howard Lotsof (NDA International) has patented ibogaine treatments for dependencies on heroin (U.S. Patent 4,499,091), amphetamine (U.S. Patent 4,587,243), cocaine (U.S. Patent 4,587,243), alcohol (U.S. Patent 4,857,523), and nicotine (U.S. Patent 5,026,697). Results of research with ibogaine indicate that the alkaloid may modulate the rewarding properties of drugs (e.g. 3,4) and interfere with withdrawal reactions (5-7) in animals. This chapter reviews some of the evidence that ibogaine modulates drug effects in animals.

II. Ibogaine-Morphine Interactions

A. Ibogaine Potentiates Morphine Analgesia

If ibogaine is to be used as a treatment for opiate addiction, it is important to understand the interaction between ibogaine and opiate drugs. Although Matwyshyn and Bhargava (8) reported that ibogaine does not modulate some effects of morphine (analgesia and hypothermia) in mice, others have reported that the alkaloid augments the effects of morphine in rats (9). An early report by Schneider and McArthur (10) reported that ibogaine (at doses ranging from 50-100 mg/kg) potentiated the lethal effect of morphine and (at doses ranging from 3-24 mg/kg) enhanced the analgesic effect of morphine in rats. Such potentiation of morphine’s effects by ibogaine has profound implications for the manner in which ibogaine is used clinically in treating opiate dependence. All efforts must be made to ensure that the opiates are not available to the patient during treatment.

B. Ibogaine Interferes with Morphine Tolerance

Ibogaine has been reported to modulate the development of morphine tolerance (11). Rats were injected with morphine (5 mg/kg) at 48-hour intervals, and, 30 minutes after each injection, analgesia was assessed with the “hot-plate” procedure and the latency to respond (paw lick or jump) was measured. The effect of ibogaine injected prior to morphine on the development of analgesic...
tolerance was evaluated. Various doses of ibogaine (10-40 mg/kg), and intervals between ibogaine and morphine administration (30 min-24 hr), were assessed. The results indicated that although ibogaine (at all doses) by itself had no effect on hot-plate response latency, 20 mg/kg ibogaine administered 30 minutes prior to morphine clearly retarded the development of morphine analgesic tolerance. A lower dose of ibogaine, or longer pretreatment intervals (e.g., 40 mg/kg ibogaine injected 24 hours prior to each morphine injection), did not affect the development of tolerance.

III. Ibogaine and Morphine Reward

A. Animal Models of Drug Reward

There are two commonly used methods for evaluating drug reward in animals: Drug self-administration and place preference conditioning. In drug self-administration, an animal must make some response, such as a lever press, which is followed by a presentation of the drug reward. This approach evaluates the ability of a drug to directly reinforce behavior. In essence, this method determines whether the animal will “work for” or “seek” the drug. In fact, rats will “work for” most drugs that humans tend to abuse (see ref. 12), suggesting that these drugs are also rewarding for rats.

The place-conditioning paradigm is an alternative measure of drug reward (for review, see ref. 13). With this procedure, during a training period, rats are confined to one distinctive compartment following injection of a drug and an alternative compartment following injection of an inert substance. Their preference for one or the other compartment is subsequently evaluated during a test in which they are undrugged, and have access to both compartments. It is inferred that the drug is rewarding if the rat displays a preference for the drug-associated compartment (and aversive if the rat displays a preference for the alternative compartment). Rats form a preference for a place paired with the same drugs that they tend to self-administer (13).

B. Ibogaine and Morphine Self-Administration

The results of several experiments, using rats and mice, suggest that ibogaine reduces the self-administration of drugs of abuse (see ref. 14). Glick et al. (3) reported that ibogaine (in doses ranging from 2.5 to 40 mg/kg) decreased intravenous self-administration of morphine in a dose-dependent manner. The 40 mg/kg dose of ibogaine, administered 5 minutes prior to a self-administration
session, interfered with water-reinforced responding (as well as morphine-reinforced responding), and this acute action may be attributable to the motoric effects of ibogaine. However, the alkaloid continued to suppress responding for morphine reinforcement, but not water reinforcement, long after the tremorogenic effect of ibogaine was no longer apparent. Glick et al. (3) reported that a single 40 mg/kg ibogaine dose attenuated morphine self-administration for a period of several days (see also ref. 15).

In contrast with findings suggesting that ibogaine has a long-lasting effect on drug reinforcement is a report that the alkaloid has a short-term effect, but not a persistent (24-hour) effect, on responding for heroin (16). The reasons for the discrepant findings are not clear. However, as discussed by Glick et al. (15), there are many procedural differences between the experiments that have reported various effects of ibogaine on drug self-administration.

C. IBOGAINE AND MORPHONE-INDUCED PLACE PREFERENCE

I. IBOGAINE ATTENUATES THE ESTABLISHMENT OF A MORPHONE-INDUCED PLACE PREFERENCE

Although self-administration of drugs provides an intuitively appealing measure of drug reward, the effect of pharmacological pretreatment on operant responding for drug reinforcement cannot be interpreted unambiguously. As discussed by Glick et al. (3), there are several reasons why a pretreatment may decrease drug self-administration: (1) the pretreatment agent reduces drug reward, (2) the pretreatment agent interferes with responding for reward, or (3) the pretreatment agent increases the rewarding properties of the drug, rendering each infusion more potent. The place preference paradigm provides an unambiguous measure of the rewarding properties of morphine, because the strength of a place preference is proportional to the dose of morphine (13,17,18). Therefore, if ibogaine attenuates the rewarding effect of morphine, it should attenuate a morphine-induced place preference.

Using the place preference paradigm, Parker, Moroz, and Siegel (4) found that ibogaine reduces the ability of a single injection of morphine to produce a preference in rats. This attenuation of morphine’s rewarding properties is seen if ibogaine (40 mg/kg) is administered either immediately (i.e., 10 min) or 24 hours before the opiate. Ibogaine-induced interference with morphine place preference does not appear to be the result of the summation of the independent hedonic properties of ibogaine and morphine, because ibogaine alone produced neither a place preference nor place aversion. Although the effect of ibogaine was apparent with a one-trial, morphine-induced place preference, it was not maintained after four training trials. That is, rats receiving ibogaine pretreatment prior to each of four place preference trials responded with a preference for the morphine side.
that was similar in strength to that of rats not pretreated with ibogaine. These results suggest that: (1) ibogaine may only modulate a weak (i.e., one-trial) place preference, but not a strong (i.e., four-trial) place preference, or (2) repeated exposure to ibogaine reduces its efficacy in attenuating the rewarding effect of morphine. Moroz, Parker, and Siegel (19) later found evidence that supports the latter alternative, as discussed subsequently.

Additional experiments by Parker et al. (4) were designed to determine if ibogaine attenuated morphine-induced place preference because it interfered with morphine reward or because it generally interfered with drug-place associations. If ibogaine generally affected drug-place associations, it should not only interfere with place preference learning, but it should also interfere with place-aversion learning. Ibogaine, administered either 10 minutes or 24 hours prior to several doses of drugs known to induce place aversion (naloxone and lithium chloride) did not affect the magnitude of the place aversions. Ibogaine selectively modulated the rewarding properties of morphine, rather than generally interfering with place conditioning.

2. Ibogaine and the Expression of Morphine-Induced Place Preference Learning

The finding that ibogaine interferes with morphine place preference learning (4) is consistent with suggestions that ibogaine is an N-methyl-D-aspartate (NMDA) antagonist (14), inasmuch as other NMDA antagonists also interfere with this type of learning (20-22). However, NMDA antagonists are known to interfere selectively with the acquisition, but not with the expression, of a variety of previously learned tasks (e.g., 23,24). Thus, it might be expected that ibogaine would not interfere with a previously established morphine place preference. We recently have reported such a finding (25). A one-trial morphine place preference was induced (using procedures similar to those of Parker et al. [4]). A single injection of 40 mg/kg ibogaine, either 24 hours, 12 hours, or 4 hours prior to a preference test did not interfere with the expression of the morphine place preference. A variety of other ibogaine pretreatment regimens (involving higher doses or multiple injections of ibogaine and various intervals between ibogaine administration and place preference testing) were similarly ineffective. In summary, the results of Luxton et al. (25), together with the previous results of Parker et al. (4), indicate that ibogaine, like other NMDA antagonists, interferes with the establishment, but not the expression, of a morphine place preference.

D. Ibogaine and Morphine Withdrawal Symptoms

Advocates for the use of ibogaine as a treatment for addiction emphasize its efficacy in reducing opiate withdrawal symptoms (26,27). Indeed, laboratory
experiments with animals have demonstrated that ibogaine interferes with somatic symptoms of naloxone-precipitated withdrawal (5-7,14), although there are some conflicting results (28,29).

In morphine-dependent animals, administration of an opioid antagonist drug such as naloxone or naltrexone, produces somatic signs of withdrawal that include rearing, grooming, jumping, wet-dog shakes, teeth chattering, salivation, and diarrhea. Glick et al. (7) reported that ibogaine (40 mg/kg, i.p.) attenuated some signs of withdrawal (wet-dog shakes, grooming, teeth chattering, and diarrhea) when administered either 4 hours or 30 minutes prior to naltrexone (1 mg/kg, i.p.) in rats that had received 5 days of exposure to slow-release morphine pellets. Therefore, ibogaine may reverse somatic signs of opiate withdrawal.

Opiate dependence is typically thought to occur only after prolonged opiate exposure. However, human and animal research has shown that naloxone-precipitated withdrawal can be observed even when naloxone is administered up to several hours after a single administration of morphine (30-34). This phenomenon has been termed “acute opiate dependence” and may represent the early developmental states of the dependence process. In nondependent opiate users, June et al. (33) examined opioid agonist effects, morphine plasma levels, and withdrawal effects precipitated by naloxone (10 mg/70 kg, administered intramuscularly) at 1, 3, 6, 12, 18, 24, 30, 36, and 42 hours after a single dose of morphine (18 mg/70 kg, administered intramuscularly). The intensity of subjectively reported precipitated withdrawal effects was greatest when testing was conducted at 6 hours after morphine administration and persisted for up to 24 hours after morphine administration, whereas, peak intensity of agonist effects (pupil constriction and subjective ratings) and highest plasma morphine concentrations were observed at the shortest test interval (1 hour) after morphine. Therefore, acute opiate dependence produced by a single dose of morphine peaks later and persists over a longer duration after morphine administration than do other agonist effects. The discrepancy between peak agonist effects and peak withdrawal effects suggests that neural adaptations underlying acute morphine dependence develop over a 6-hour time period and gradually decay over time. The discrepancy also suggests that the agonist effect of acute morphine administration is mediated by a different mechanism than the effect of naloxone-precipitated morphine withdrawal (33).

In the rat, acute opiate dependence can be demonstrated when naloxone is administered between 30 min and 48 hr (30,31) after a single morphine exposure. Acute dependence is evidenced as specific somatic withdrawal reactions (e.g., wet dog shakes) or as aversive stimulus properties which modify behavior. For instance, Gellert and Sparber (31) reported that administration of a low dose of naloxone 48 hours after a single morphine exposure significantly decreased operant responding for food, whereas it was without effect in opiate naïve rats. The aversive properties of withdrawal apparently suppressed responding. The
aversive properties of withdrawal have also been evaluated using the place-
conditioning paradigm (35-39); rats learn to avoid a place previously paired with
naloxone-precipitated withdrawal (37). In fact, a naloxone-precipitated,
withdrawal-induced place aversion can be produced 24 to 48 hours after a single
injection of morphine (34).

Ibogaine interferes with acute opioid dependence. Parker and collaborators
(40) recently reported that ibogaine interferes with naloxone-precipitated
withdrawal in rats treated with morphine 24 hours prior to the conditioning trial.
On each of two conditioning trial cycles, rats were administered morphine (20
mg/kg, s.c.) or saline 24 hours prior to an injection of naloxone (1 mg/kg, s.c.)
and placement in a chamber. Half of the rats were injected with ibogaine (40
mg/kg, i.p.) and half were injected with saline 4 hours before the naloxone
injection. Ninety-six hours later, the rats received a drug-free place preference
test.

Ibogaine attenuated naloxone-precipitated morphine withdrawal. Figure 1
presents the mean number of seconds that the rats spent on the naloxone-paired
minus the saline-paired floor during the place preference test. The groups
displayed on the abscissa include those injected with morphine 24 hours prior to

![Figure 1](image)

**Figure 1.** Mean (±sem) seconds spent on the naloxone-paired minus the saline-paired floor during the place conditioning test by groups MN and SN pretreated with ibogaine or saline during conditioning.
naloxone (MN) and those injected with saline 24 hours prior to naloxone (SN). Among each conditioning group, the black bars represent the rats pretreated with ibogaine 4 hours prior to naloxone and the white bars represent the rats pretreated with saline 4 hours prior to naloxone. Ibogaine pretreatment interfered with the naloxone-induced place aversion displayed by Group MN, without modulating the weaker aversion displayed by Group SN. This latter finding is consistent with those of Parker, Luxton, and Siegel (4) who reported that ibogaine did not interfere with the establishment of a naloxone-induced place aversion, but did interfere with the establishment of a morphine-induced place preference.

In a second experiment, Parker et al. (40) evaluated the potential of ibogaine to interfere with the expression of naloxone-precipitated somatic withdrawal symptoms. As in the previously described place-conditioning experiment, on each of two conditioning trial cycles, rats were administered morphine (20 mg/kg, s.c.) or saline 24 hours prior to an injection of naloxone (1 mg/kg, s.c.) and placement in a chamber. Half of the rats in each group were injected with ibogaine (40 mg/kg, i.p.) and the other half of the rats were injected with saline, 4 hours before the naloxone injection. The rats were then placed in the observation chamber for 1 hour. During the second repetition of the cycle, all subjects were videotaped for a period of 10 minutes following the naloxone injection. Videotapes were later scored for instances of wet dog shakes, mouth movements, teeth chattering, and genital licks. The frequency of each withdrawal behavior displayed by each rat was scored by two observers (one who was aware of testing conditions, and one who was unaware of testing conditions).

![Figure 2](image_url)

**Figure 2.** Mean (±sem) frequency of somatic withdrawal reactions (mouth movements + wet-dog shakes + teeth chattering + genital licking) by groups MN and SN pretreated with ibogaine or saline solution.
Ibogaine attenuated naloxone-precipitated morphine withdrawal behavior as it had attenuated the withdrawal-induced place aversion. Figure 2 presents the mean frequency of withdrawal behaviors (the summed frequencies of wet dog shakes, teeth chattering, mouth movements, and genital licks) for the various groups. Rats in Group MN displayed fewer somatic withdrawal behaviors when pretreated with ibogaine than they did when pretreated with saline. Consistent with the effect of ibogaine on the motivational effects of withdrawal, ibogaine did not modulate somatic withdrawal behaviors in Group SN.

Ibogaine, therefore, not only interferes with withdrawal from chronically administered morphine (e.g. 5-7,14), but it also interferes with withdrawal from acutely administered morphine. It interferes with both the aversive motivational properties of withdrawal, as revealed by the place conditioning paradigm, and the somatic properties of withdrawal, as revealed by direct observation of somatic withdrawal symptoms.

IV. Ibogaine and Other Drugs of Abuse

A. Ibogaine and Self-Administration of Other Drugs of Abuse

Anecdotal reports indicate ibogaine decreases dependence on a wide variety of drugs of abuse, including alcohol, amphetamine, cocaine, nicotine, and opiates (27). Indeed, there is evidence that ibogaine interferes with self-administration of drugs other than morphine. For example, Rezvani, Overstreet, and Lee (41) reported that ibogaine reduced ethanol consumption in several strains of ethanol-preferring rats. There are also reports that ibogaine has a long-lasting suppressive effect on intravenous (42) and oral self-administration (43) of cocaine.

B. Ibogaine and Amphetamine-Induced Place preference Learning

Ibogaine also interferes with the establishment of amphetamine-induced place preference learning (19). Since ibogaine produces prolonged (24-hour) interference with the establishment of a morphine-induced place preference (4), rats were injected with ibogaine or saline solution 24 hours prior to an amphetamine injection that preceded placement in a conditioning chamber. Rats were tested drug-free following one, and again following four, conditioning trials. The preference test results revealed that ibogaine interfered with the establishment of an amphetamine-induced place preference following one, but
not following four, conditioning trials. This effect paralleled that found with morphine place preference learning (4).

In order to determine whether the reduced effectiveness after four trials was the result of tolerance to ibogaine, rats were given weekly injections of ibogaine (group ibogaine-experienced) or saline (group ibogaine-naïve) in their home cage over four weeks prior to place conditioning trials. On place-conditioning trials, rats in groups ibogaine-experienced and ibogaine-naïve were injected with ibogaine 24 hours before amphetamine conditioning trials on each of two weekly cycles. In a subsequent place preference test, ibogaine blocked an amphetamine place preference only in the group ibogaine-naïve—that is, prior experience with ibogaine eliminated its ability to interfere with amphetamine place preference learning. Therefore, ibogaine’s reduced effectiveness across multiple conditioning trials may be the result of the development of tolerance to ibogaine.

V. Ibogaine and Craving: Future Directions

A. The Reinstatement Paradigm

Anecdotal reports by abstinent individuals suggest that re-exposure to a formerly self-administered substance induces a strong motivational state or “craving” for the drug, and is a frequent precursor to relapse (e.g., 44). Several investigators have developed animal models of relapse to account for this phenomenon. One of these models is “reinstatement.”

In the reinstatement model, rats are first trained to self-administer a rewarding drug by pressing a lever. Following such training, the response is extinguished—that is, an inert substance is substituted for the drug, resulting in a decrease in responding. Then, to “whet the rat’s appetite,” the drug is administered and the rat is provided the opportunity to lever press. In the reinstatement paradigm, a single administration of the reinforcing drug can reinstate previously extinguished self-administration behavior (e.g., 45,46). In fact, following extinction training, a priming injection of morphine can also reinstate a conditioned place preference (47). Future experiments might examine the ability of ibogaine administered 24 hours prior to a priming injection of morphine to interfere with the reinstatement of a conditioned place preference. Such a finding would provide evidence that ibogaine, indeed, can interfere with drug craving in animals.

Most research evaluating the motivational effects of drugs has used either self-administration or place preference procedures. Ettenberg and colleagues (e.g., 48-50) have demonstrated the utility of the runway procedure in investigations of
drug reward. Rats are trained to traverse an alley for intravenous drug administration. With some rewarding drugs, the well-trained rat exhibits both “approach” and “retreat” behavior. That is, it quickly runs toward the goal, then reverses direction and runs away from the goal, then again runs toward the goal. There may be several cycles of this retreat behavior each trial, apparently indicating conflict: “retreat behavior might be reflective of a conflict resulting from concurrent positive and negative associations with the goal box” (51).

There is considerable evidence that some commonly abused drugs have, simultaneously, both rewarding and aversive effects (52-55). One possible mechanism by which ibogaine may attenuate drug reward is by increasing the aversive effect of drugs (rather than by decreasing the reinforcing effect of drugs). As suggested by Ettenberg and Geist (48), the spatiotemporal record of behavior in the straight alley permits evaluation of the aversive effect of the drug (e.g., number of retreats), as well as the rewarding effect of the drug. If ibogaine augments the aversive effects of drugs, this should be manifest as an increase in retreat behavior by ibogaine pretreated rats.

Ettenberg, MacConell, and Geist (56) described evaluation of reinstatement in the straight alley. Rats were first trained to run down the alley for heroin reinforcement. When the response was established, it was extinguished—rats received an IV infusion of saline, rather than heroin, in the goal box. When rats reached an extinction criterion, the effect of a single priming infusion of heroin was evaluated. Rats received a single “treatment trial”—they received a single i.v. infusion of either heroin or saline in the goal box. The effect of the prime was evaluated 24 hours later, on the “test day”. Rats were undrugged on this test day. Rats primed with heroin on the post-extinction treatment trial ran significantly faster on the test day than did rats primed with saline, demonstrating the reinstatement effect. It would be of interest to determine if ibogaine would interfere with this reinstatement effect in the runway situation.

B. Ibogaine and Morphine Reward in Dependent Rats

Although our previously described studies employed nondependent rats, the anecdotal reports of ibogaine’s effectiveness in humans are based on reports from drug-dependent humans (e.g., 26,27). Furthermore, some current animal models of craving (57-59) emphasize the role of drug experience in establishing the motivational state necessary for craving.

If ibogaine interferes with craving, then one might expect that it would more effectively interfere with the establishment or the expression of morphine place preference learning and runway behavior in drug-dependent than in drug-naïve rats. In fact, Pearl, Johnson, and Glick (60) reported that ibogaine modified morphine-induced motoric effects and morphine-induced dopamine release in morphine-experienced rats more effectively than in morphine-inexperienced rats.
Future studies will evaluate the efficacy of ibogaine to interfere with morphine reward in rats that are maintained on morphine over a period of one month and rats that are morphine naïve. It is conceivable that ibogaine may more effectively modulate drug reward in drug-experienced rats than in naïve rats.

C. IBOGAINE AND NONPHARMACOLOGICAL REWARD

Interest in the effects of ibogaine have focused on the alkaloid’s potential in attenuating drug reward, but it is possible that ibogaine generally affects reward processes. There are few studies evaluating the effects of ibogaine on nonpharmacological reinforcement, and the available data are inconsistent. Glick et al. (3) reported that ibogaine does not have a long-lasting effect on operant responding for water reinforcement, but Dworkin et al. (16) reported that ibogaine has a long-lasting effect on responding for food.

Rats show a conditioned preference for a chamber in which they were previously given access to food (e.g., 61), even when they are sated. Furthermore, both sucrose (62) and saccharin solution (63) have been reported to produce a place preference in sated rats. In pilot experiments, we have also found that nondeprived rats will readily learn to traverse a runway for highly palatable sweet solution (a mixture of 0.16% saccharin and 3% glucose in water). As discussed by others (e.g., 12) such instrumental responding for a palatable solution by non-deprived subjects would seem to approximate the motivational properties of responding for a drug reward. It would be of interest to examine the effects of ibogaine on non-pharmacological reward using the place conditioning and runway paradigms.

D. FUTURE STUDIES: SUMMARY

These proposed directions for research should provide greater insight into the mechanism by which ibogaine modulates the rewarding properties of drugs as well as withdrawal effects. Considerable evidence is accruing that future research on the putative antiaddictive properties of ibogaine would be fruitful.

V. Conclusions

Considerable evidence indicates that ibogaine modulates a variety of opiate effects in rats. Ibogaine potentiates opiate-induced analgesia and lethality (10) and interferes with morphine tolerance (11). It also interferes with the rewarding properties of morphine when assessed in self-administration (3) and in place
preference learning (4). Finally, ibogaine also interferes with the aversive properties of opiate withdrawal (7,40).

Advocates for ibogaine as an antiaddictive medication argue that ibogaine modulates a variety of addictive disorders, not only opiate addiction. Animal evidence reported above also indicates that ibogaine modulates the rewarding properties of stimulants when evaluated in the self-administration paradigm (42) or in the place preference paradigm (19).

The encouraging results of animal work with ibogaine suggest that further work with this agent is warranted to evaluate its potential antiaddictive properties. Yet any enthusiasm for ibogaine as an antiaddictive drug must be tempered by a report that, at high doses, it may produce cerebellar damage in rats (64). However, there are reports that ibogaine does not produce such damage at doses that effectively modulate drug reward in animals (65,66).

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References

11. MODULATION OF THE EFFECTS OF REWARDING DRUGS
