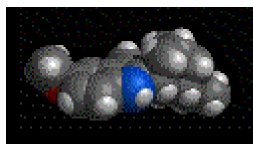
The Ibogaine Dossier



NYU Conference on Ibogaine Nov 5-6, 1999

T. iboga roots

Ibogaine is extracted from the bark of the root

Pharmacology of Ibogaine and Ibogaine-Related Alkaloids

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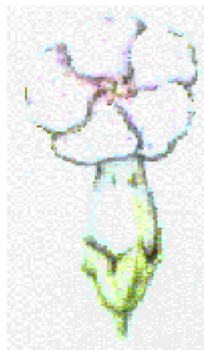

T. iboga flower

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I. INTRODUCTION

Ibogaine (12-methoxyibogamine, NIH 10567, Endabuse) is one of the psychoactive indole alkaloids found in the West African shrub, *Tabernanthe iboga*. For over a century, both extracts of *T. Iboga* and its constituent alkaloids, including ibogaine, have been used as medicinals (*1*). What makes this alkaloid of particular interest to contemporary pharmacology are anecdotal observations indicating that ibogaine possesses "anti-addictive" properties. Thus, ibogaine (6-25 mg/kg, in humans) has been claimed to attenuate both dependence and withdrawal symptoms to a variety of abused drugs including opiates, alcohol, nicotine and psychostimulants (*2-9*). Preclinical studies demonstrating that ibogaine reduces self-administration of both cocaine and morphine, and attenuates the symptoms of morphine-withdrawal, are consistent with these claims [reviewed in (Popik and Glick (*10*))]. This chapter reviews the pharmacological properties of ibogaine and related alkaloids. Since our last comprehensive review (*11*), more than one hundred new reports on the pharmacological actions of ibogaine and ibogaine-like alkaloids have appeared. The chemistry of ibogaine has been reviewed by Taylor in this series (*12,13*).

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II. HISTORICAL OVERVIEW.

Ibogaine is derived from *Tabernanthe iboga*, a shrub indigenous to Central-West Africa. The iboga shrub, a member of the family Apocynaceae (order Contortae), is typically found in the undergrowth of tropical forests (*14*). The roots of *Tabernanthe iboga* were used in tribal initiation rites (*15,16*). Although the details of such ceremonies vary, it was believed that iboga root enabled initiates to make contact with ancestors in the spirit world. Ibogaine has also been found in *Tabernanthe crassa* (*17*). Nineteenth century reports from French and Belgian explorers first described the stimulant and aphrodisiac effects of eating iboga root (*1,16*). The first botanical description of the plant, was made by Baillon in 1889 (*18*).

Dybovsky and Landrin (*19*), as well as Haller and Heckel (*20*), were the first to isolate a crystalline alkaloid from iboga root, which they called "ibogaine" or "ibogine". In 1901 French pharmacologists found ibogaine to have an unusual type of excitatory effect in animals (*21-23*). Phisalix (*23*) suggested that ibogaine could produce hallucinations based on observations of unusual behavior in dogs. The alkaloid was subsequently tested in Western clinical settings, and was recommended as a stimulant for the treatment of convalescence and neurasthenia (*24*). Despite such recommendations, ibogaine never enjoyed wide clinical use and was neglected by researchers for almost 30 years. In the 1940's Raymond-Hamet and coworkers

published a series of papers describing the pharmacological properties of ibogaine on isolated tissues and the cardiovascular system (*25-32*).

Lambarene, an extract of the roots of the iboga relative *Tabernanthe manii*, was sold in France during the 1930's. It contained about 8 mg of ibogaine, and was described as a stimulant. Iperton, another ibogaine extract, was also used as a tonic or stimulant (*33*). Ibogaine has been used by athletes as a performance enhancing drug (*34*). In many countries, including the United States, ibogaine use is prohibited, perhaps because of its purported hallucinogenic effects (widely publicized in the late 1960's) and its appearance on the illicit drug market. In 1970, the United States Food and Drug Administration classified ibogaine as a Schedule I substance (all non-research use forbidden).

Beginning in 1985, a series of patents was issued for the use of ibogaine as a rapid means of interrupting addiction to narcotics (morphine and heroin) (3), cocaine and amphetamine (4), alcohol (5), nicotine (6) and poly-drug dependency syndrome (*35*). These patents claim that an oral or rectal dose of ibogaine (4-25 mg/kg) interrupts the dependence syndrome, allowing patients to maintain a drug-free lifestyle for at least 6 months.

Based on open clinical studies, it has been claimed (*36*) that ibogaine therapy resulted in 25% of patients remaining drug-free without craving for 6 months. This group included those who were both highly motivated to quit and had relatively stable home environments. Another 40-50% of patients had their addictions interrupted successfully, and required psychotherapy. Twenty to 30% of patients had returned to drug use within a month following treatment. Somewhat lower success rates (10-15%) are cited by Touchette (*37*).

In the absence of appropriately controlled clinical studies, the efficacy of ibogaine as an anti-addictive agent cannot be rigorously assessed at the present time. Nonetheless, interest in ibogaine as a treatment for addiction has increased. In 1985 NDA International, Inc. (Staten Island, NY, USA) began a campaign to persuade the U.S. government to initiate controlled clinical trials with ibogaine (*38*). At the same time, the use of ibogaine for treating opioid dependence has increased in Europe (*39*). At present, clinical trials to evaluate the safety of ibogaine are underway at the University of Miami and are planned in New York. Clinical trials to test the anti-addictive efficacy of ibogaine are underway in The Netherlands and Panama (*38,40-44*). According to Ali *et al*., (*45*), the U.S. Food and Drug Administration and the National Institute for Drug Abuse has approved the use of ibogaine on a limited basis to treat cocaine addiction.
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III. CHEMICAL STRUCTURE AND PROPERTIES.

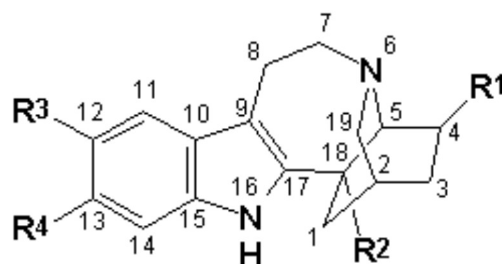

Figure 1.

Compound	R1	R2	R3	R4
Ibogaine	CH_2CH_3	H	OCH_3	H
O-Desmethylibogaine	CH_2CH_3	H	OH	H
(±)-Ibogamine	CH_2CH_3	H	H	H
(±)-Coronaridine	CH_2CH_3	CO_2CH_3	H	H
Tabernanthine	CH_2CH_3	H	H	OCH_3
O-t-Butyl-O-Desmethylibogaine	CH_2CH_3	H	$OC(CH_3)_3$	H

Although ibogaine was first isolated and identified in 1901, (*19-21,46*), the structure of this and related alkaloids (Fig. 1) were first established by Taylor in 1957 (*47*) [see also Taylor (*12,13*)]. Total synthesis from nicotinamide was reported using a 13- (*48*) or 14-step (*49*) sequence. The ^{13}C NMR spectra of several iboga alkaloids were published in 1976 (*50*). The synthesis of tritiated ibogaine was recently reported (*51,52*).

Ibogaine (mol. wt. 310.44) has a melting point of 153° at 0.01 mm Hg and a pK_a of 8.1 in 80% methylcellosolve. The absorption maxima in methanol are 226 (log e 4.39) and 296 (log e 3.93) nm. Ibogaine crystallizes from alcoholic solutions into small, reddish prismatic needles; it is levorotatory $[a]_D$ -53° (in 95% ethanol) and is soluble in ethanol, methanol, chloroform and acetone, but insoluble in water. Ibogaine hydrochloride (freezing point 299°C, $[a]_D$ -63° (ethanol), $[a]_D$ -49° (H_2O)) is soluble in water, ethanol and methanol, is slightly soluble in acetone and chloroform, and is practically insoluble in ether (*53*). Ibogaine is heat- and light-sensitive (*54*) and can spontaneously oxidize in solution, giving iboluteine and ibochine (*16,34*). Alkaloids structurally related to ibogaine include tabernanthine, ibogamine, iboxigaine, gabonine, iboquine, kisantine and ibolutenine. Structural similarities between ibogaine and other indole alkaloid hallucinogens have also been reported (*55*). The synthesis of several ibogaine derivatives has recently been published by Repke and coworkers (*56*).
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IV. PHARMACOKINETICS.

After parenteral administration, ibogaine has been identified in various biological materials, including blood and urine (humans) and in the liver, kidney and brain of laboratory animals (*54,57-59*). One hour after intraperitoneal administration, high concentrations of ibogaine were present in rat liver and kidneys (*60*). After intravenous injection of 10 mg/kg to mice, maximal brain concentrations (48 µg/g of wet weight [~133 µM]) were achieved in 10 sec (*61*).

Recently, Gallagher *et al*., (*62*) have developed a highly sensitive and specific method to quantify ibogaine in plasma and tissues. This method uses organic extraction, derivatization with trifluroacetic anhydride, and detection by gas chromatography-mass spectrometry (GC/MS). Similar methods were developed by Hearn *et al*., (*63*), Alburges *et al*., (*64*) and Ley *et al*., (*65*). Using a GC/MS method, Pearl and colleagues (*66*) reported that 1, 5 and 19 hours after intraperitoneal administration of 40 mg/kg of ibogaine, the whole brain levels of ibogaine were 10, 1 and 0.7 µM in female rats and 6,

0.9 and 0.2 μM in male rats, respectively. Hough *et al*., (*67*) studied the tissue distribution of ibogaine after i.p. and s.c. administration in rats. One hour after i.p. dosing (40 mg/kg), drug levels ranged from 106 ng/ml (~ 0.3 μM) in plasma to 11,308 ng/g (~ 36 μM) in fat, with significantly higher values after s.c. administration of the same dose. Drug levels were 10-20 fold lower 12 hours later. These data indicate that ibogaine is subject to a significant "first pass" effect after i.p. dosing, and that there is a marked propensity for ibogaine to be deposited in adipose tissue, reflecting its lipophilicity. Consistent with its lipophilicity, ibogaine levels in adipose tissue were very high for at least 12 hours after administration. Based on these data, it was suggested that a single dose of ibogaine may provide a long-acting, depot-like time course of action (*67*).

The reported long-term effects of ibogaine (e.g. (*68-70*)), have led to the hypothesis that this alkaloid may be metabolized to an active principle with a long half life (*71*). At present, there is no *direct* evidence to support this hypothesis. Ibogaine was reported to disappear from the rat at a rate of ~4% of the administered dose per hour with ~ 5% of the injected dose eliminated unchanged in urine. Elimination kinetics from brain yielded a half-life of 60 min in rodents (*60,61*) and suggest a one-compartment model. After administration of ibogaine (10 mg/kg, p.o.) to rabbits, urine concentrations reached a maximum 4-5 hours later, then decreased rapidly and disappeared after 6 hours (*54,60*). Taken together, these data suggest that ibogaine is extensively metabolized. Inspection of ibogaine's structure (Fig. 1) led us to hypothesize that a likely degradation pathway is *O*-demethylation at C12. Based on this hypothesis, *O*-desmethylibogaine (also known as noribogaine or 12-hydroxyibogamine), was synthesized by Dr. C. Bertha at the National Institutes of Health in 1994. At the same time, *O*-*tert*-butyl-*O*-desmethylibogaine was synthesized in an attempt to make an ibogaine derivative resistant to *O*-demethylation (Fig. 1). Thus, the first compound was synthesized to investigate the potential pharmacological actions of a likely ibogaine metabolite. The second compound permitted examination of the pharmacological effects of an ibogaine derivative that would not be degraded by *O*-demethylation. The synthesis of these compounds was described by Layer *et al*., (*72*).

Recent studies have indeed demonstrated that ibogaine is metabolized, and that *O*-desmethylibogaine can be detected in human plasma (*73*) as well as in the plasma and brains of ibogaine-treated rats (*66*). Behavioral and neurochemical studies in rodents have established that *O*-desmethylibogaine is pharmacologically active (discussed later).

Following an i.p. dose of ibogaine (40 mg/kg), Pearl *et al*., (*66*) reported brain *O*-desmethylibogaine concentrations of 20, 10 and 0.8 μM in female rats and 13, 7 and 0.1 μM in male rats, respectively, at 1, 5, and 19 hours after administration. These data suggest that gender differences in pharmacological responses to ibogaine may be attributed to pharmacokinetic, rather than pharmacodynamic, factors. While a report of one human subject (*73*) indicated that *O*-desmethylibogaine persisted in plasma at high levels for at least 24 hours after oral ibogaine administration, it is not clear if this pattern will be representative.

There is evidence indicating that the various pharmacological effects of ibogaine may be attributable, at least in part, to its metabolite(s). For example, the tremorigenic effects of ibogaine dissipate much more rapidly than its ability to attenuate the morphine withdrawal syndrome in rats (*74*). This finding suggests that an active principle(s) responsible for one action may be more rapidly metabolized than compound(s) involved in other actions. Alternatively, the various pharmacological effects of ibogaine may involve different neurotransmitter pathways (discussed later).

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V. GENERAL PHARMACOLOGICAL ACTIONS.

A. Animal Studies

1. Locomotor activity.

Ibogaine produces complex effects on locomotor activity in rodents. A dose of 20 mg/kg (i.p.) slightly increased locomotor activity in mice (*75*) while Sershen *et al.,* (*76*) reported that 40 mg/kg (i.p.) decreased locomotor activity in male mice at 1, but not 24, hours after injection. The same dose inhibited locomotion in female rats during the first hour after injection, whereas one week later locomotor activity was increased (*69*).

Recently, Pearl and colleagues (*66*) noted gender differences in the effects of ibogaine on locomotor activity (40 mg/kg, i.p., 5 or 19 hours before test). In control males and females the locomotor activity decreased during the second hour of observation. Ibogaine treatment in females prevented this decrease in locomotor activity. In females, but not males, ibogaine decreased locomotor activity when given 19 hours before the test (*66*). Another study revealed that in male rats, a single dose of 40 mg/kg inhibited locomotor activity 4 hours after injection; a dose of 80 mg/kg decreased motor activity 24 hours after injection (*77*).

Rats injected with doses of 20-60 mg/kg of ibogaine displayed slower response times on sensory and sensory-motor tests and were also impaired in performing specific motor reflexes at doses of 40-60 mg/kg. Furthermore, these rats exhibited a marked reduction in locomotor activity as well as in emotionality at doses ranging from 10- 40 mg/kg. At higher doses (40 mg/kg), rats appeared virtually inactive (*78*). In other studies, at doses above 25 mg/kg, ibogaine produced ataxia, splayed hind limbs, outstretched forelimbs, Straub tail and hyperexcitability (*79*).

One hour after *O*-desmethylibogaine or 18-methoxy-coronaridine injection (40 mg/kg), locomotor activity was increased during the second hour of observation (*66,80*). In our studies, high doses (120 mg/kg) of *O*-desmethylibogaine and *O*-*t*-butyl-*O*-desmethylibogaine produced profound ataxia and convulsions (*72*). Ibogaine, *O*-desmethylibogaine, and *O*-*t*-butyl-*O*-desmethylibogaine, (80 mg/kg) did not significantly influence rotorod performance in mice (*72*).
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a. Effects on locomotor activity induced by other drugs

Ibogaine has been found to affect the motor stimulant properties of amphetamine, cocaine, and morphine in rodents (hyperlocomotion induced by these drugs is believed to reflect their "psychotomimetic" qualities in man). Although the results of these studies are not uniform, in general, it has been found that in *female* rats this alkaloid *potentiates* the locomotor response to amphetamine and cocaine, whereas opposite effects were reported in *male* rats and mice.

Sershen *et al.,* (*81*) found that ibogaine (40 mg/ kg i.p., 2 or 18 hours before amphetamine) enhanced amphetamine (1 mg/kg) - induced hypermotility in female rats. In other studies, an amphetamine-induced increase in locomotor activity was potentiated in female rats pretreated with ibogaine (40 mg/kg, i.p.) 19 hours earlier (*82*). Cocaine-induced hypermotility in female rats was also potentiated by ibogaine (*83,84*). Broderick *et al.*, (*85,86*) reported that ibogaine (20-40 mg/kg, i.p.) administration to male rats for four days reduced cocaine (20 mg/kg) - induced hypermotility. Ibogaine (40 mg/kg, i.p.) administration also reduced cocaine- (25 mg/kg, s.c.) induced hypermotility in male mice (*76*), a finding in agreement with the amphetamine (1 mg/kg) - ibogaine interaction (*81*) in this gender and species. Recent data demonstrate

that the effects of ibogaine on cocaine (20 mg/kg) -induced hyperactivity in female rats are time dependent. Thus, given 1 h before cocaine, ibogaine and *O*-desmethylibogaine (40 mg/kg) inhibited cocaine-induced hyperactivity, but when given 19 h before cocaine they produced the opposite effect (*80*).

Ibogaine pretreatment (40 mg/kg, i.p. 19 hours before measurement) decreased or blocked the locomotor stimulation induced by morphine (0.5-20 mg/kg) in rats (*69,71*). Ibogaine administered one week (but not one month) before morphine (5 mg/kg) reduced the motor stimulant effects of this opiate (*69*). Pearl *et al.*, (*87*) found that ibogaine (5-60 mg/kg) is more potent in inhibiting morphine-induced hyperlocomotion in rats pretreated with morphine for several (1-4) days compared to non-pretreated rats. Doses of ibogaine (5-10 mg/kg) that alone were inactive in drug-naive animals attenuated morphine-induced hyperactivity in the morphine pretreated rats. The inhibitory effects of ibogaine on morphine-induced hyperlocomotion appear gender related, because ibogaine is more potent in female rats (*66*). Ibogaine-induced inhibition of morphine - induced hyperlocomotion can be reversed by coadministration of a kappa antagonist (norbinaltorphine, 10 mg/kg) and an NMDA agonist (NMDA, 20 mg/kg). However, neither norbinaltorphine nor NMDA alone blocked this action of ibogaine (*88*).

O-Desmethylibogaine (10-40 mg/kg) also inhibited morphine-induced hyperlocomotion in female rats. However in male rats, the dose of 10 mg/kg potentiated and 40 mg/kg inhibited morphine-induced hyperlocomotion (*66,89*).

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2. Tremor.

Like the somewhat structurally related alkaloid harmaline, ibogaine produces tremors. In mice, ibogaine is tremorigenic both when given intracerebrally (ED_{50} 127 nmol/g brain, ~ 46 μ g/g with a latency to tremor of about 1 minute) (*90*), and systemically (ED_{50} 12 mg/kg, s.c.) (*61*). In rats, ibogaine produced fine tremors, flattening of body posture, and flaccid hind limbs up to 2 hours after administration of 40 mg/kg (i.p.) (*91*). Low-amplitude whole body tremors appearing within 10 min after administration of as little as 10 mg/kg of ibogaine have also been reported (*92*). O'Hearn *et al*., (*93*) reported that a high dose of ibogaine (100 mg/kg) produced ataxia and high-frequency tremor of the head and trunk in rats. Ibogaine-induced tremor preferentially involves the head and upper extremity in rats and mice (*94*). Ibogaine (20 mg/kg) - induced tremors in mice were blocked more potently by CCK-8 and ceruletide compared to other reference compounds, including prolyl-leucylglycine amide (MIF), atropine, haloperidol, biperiden, ethopropazine, trihexyphenidyl, methixene and clonazepam (*95*).

Zetler *et al.,* (*61*) established the tremorigenic structure-activity relationship of several ibogaine-like compounds in descending order of potency: tabernanthine > ibogaline > ibogaine > iboxygaine > *O*-desmethylibogaine. Glick *et al.,* (*96*) found that at behaviorally effective doses (2-80 mg/kg) ibogaine, desethylcoronaridine, harmaline and tabernanthine produced tremors for at least 2-3 hours. Both the *R* and *S* enantioners of ibogamine and coronaridine were devoid of this action. The ibogaine-like alkaloids, 18-methoxycoronaridine and *O*-desmethylibogaine were also found to lack tremorigenic effects (*89,97*).

The tremorigenic properties of ibogaine and related compounds have been attributed to an action on GABAergic pathways (*98-100*) and to the blockade of voltage-dependent sodium channels.

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3. Anxiety and fear.

Schneider and Sigg (*101*) described the behavioral effects of ibogaine in cats. The authors concluded that after intravenous administration of 2-10 mg/kg, ibogaine produced fear-like reactions that persisted for 10-20 minutes with a normal appearance observed 1-2 hours after injection. The electroencephalographic pattern obtained after ibogaine administration (2-5 mg/kg) showed a typical arousal syndrome, resembling that observed after direct stimulation of the reticular formation. This arousal syndrome was inhibited by atropine (2 mg/kg) (*101*). Gershon and Lang (*102*) described the effects of ibogaine in dogs, which become more tense and alert, interpreted as the appearance of anxiety. Moreover, they observed that the dogs exhibited a lack of recognition of both their regular handlers and environment.

Recently, Benwell *et al*., (*103*) reported reductions in open arm entries in the elevated plus-maze test when rats were tested 22 hours after pretreatment with ibogaine (40 mg/kg, i.p.). In mice, ibogaine (2.5 mg/kg) exhibited anxiogenic actions, whereas a dose of 1 mg/kg had anxiolytic effects (*104*). These are perhaps the most compelling preclinical data that ibogaine may influence anxiety levels because anxiolytic agents (e.g. benzodiazepines) increase open arm entries in this test.

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4. Effects on self-administration of other drugs.

Ibogaine (40 mg/kg, i.p.) inhibits the self-administration of cocaine in rodents. Cappendijk and Dzoljic (*105*) trained male Wistar rats to intravenously self-administer cocaine; a single dose of ibogaine (40 mg/kg) decreased cocaine intake by 40-60% for several days, and repeated treatment with ibogaine at one-week intervals decreased cocaine self-administration by 60-80%. This decrease was maintained for several weeks. Similar effects were found in mice that developed a preference for cocaine in the drinking water. Thus, ibogaine administration (two weeks after the beginning of a choice period, 2 doses of 40 mg/kg, 6 hours apart) diminished cocaine preference for five days (70). According to Vocci and London (*106*), some investigators have failed to replicate ibogaine's effect on cocaine self-administration in the rat (*107*) and rhesus monkey (*108*). Also Dworkin *et al*., (*109*) reported that neither 40 mg/kg of ibogaine given 60 min prior to the session, nor 80 mg/kg given 24 hour before the session, suppressed responding maintained by intravenous cocaine infusions. In this study, cocaine self-administration was inhibited by pretreatment with ibogaine (80 mg/kg) either 60 or 90 min prior to the session (*109*). However, because this dose of ibogaine reduced scheduled food intake, these latter effects of ibogaine on cocaine self-administration appear to be unspecific.

Glick *et al.,* (*96*) demonstrated that ibogaine and several *iboga* alkaloids (tabernanthine, *R*- and *S*-coronaridine, *R*- and *S*- ibogamine, desethylcoronaridine, and harmaline) reduced cocaine self-administration in rats in a dose-related fashion (2.5-80 mg/kg). For some alkaloids, these effects were seen the day after injection. *O*-Desmethylibogaine (40 mg/kg) (*89*) and 18-methoxycoronaridine (*97*) were also reported to inhibit cocaine self-administration.

Ibogaine dose dependently (2.5-40 mg/kg) reduced intravenous morphine self-administration in female Sprague-Dawley rats immediately after injection as well as on the next day (*68*). In some animals, a reduced morphine intake was observed for several days; other rats required several doses of ibogaine to achieve a prolonged reduction. Similar effects were demonstrated for other ibogaine-like alkaloids including *O*-desmethylibogaine (*89*), tabernanthine, *R*- and *S*-coronaridine, *R*- and *S*- ibogamine, desethylcoronaridine, harmaline (*96*) and 18-methoxycoronaridine (*97*). However, data from another study revealed somewhat different results. Thus, Dworkin *et al*., (*109*)

found that ibogaine (40 or 80 mg/kg) diminished heroin self-administration in male Fisher rats only on the day it was administered. Moreover, the same study revealed that ibogaine treatment resulted in a 97% decrease in responding for a food reinforcement schedule, suggesting that its effects on heroin self-administration were unspecific.

Ibogaine-induced inhibition of morphine self-administration has been found to be reversed by sequential administration of a kappa antagonist (norbinaltorphine, 10 mg/kg) and an NMDA agonist (NMDA, 20 mg/kg). Neither norbinaltorphine nor NMDA alone were effective in this respect (88).

Ibogaine (10-60 mg/kg) reduced alcohol intake in alcohol-preferring Fawn Hooded rats, without affecting either blood alcohol concentrations or food intake (*110,111*). The authors concluded that a metabolite could be involved, because ibogaine was effective in this measure when administered intraperitoneally and intragastrically, but not subcutaneously (*112*). A recent study demonstrated an attenuation of alcohol consumption by the ibogaine congener, 18-methoxycoronaridine in rats (113).

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5. Effects on drug dependence.

Repeated administration of ibogaine (10 or 40 mg/kg) did not produce dependence in rats as measured using the Primary Physical Dependence test (*114*).

In morphine-dependent rats, the opioid antagonist naloxone induces a withdrawal syndrome, characterized (in rats) by increased rearing, digging, jumping, salivation and "wet-dog" head shaking. Ibogaine dose-dependently reduced the frequency of some of these withdrawal symptoms (jumping, rearing, digging, head hiding, chewing, teeth chattering, writhing, penile licking) after both intracerebroventricular (4-16 µg) (*115*) and i.p. administration (40 and 80 mg/kg) (*74,116*). However, these effects could not be replicated in other studies in either rats (*39,117*) or mice (*118*). At least the second failure to replicate can be attributed to the fact that in the Frances *et al*., (*118*) study, ibogaine was administered to animals that developed a full withdrawal syndrome. In morphine-dependent monkeys, ibogaine (2 and 8 mg/kg, s.c.) partially suppressed the total number of withdrawal signs (*114*). Our studies (*72,119*) demonstrate that ibogaine inhibits the morphine withdrawal syndrome in mice in a dose-related fashion. This effect was reversed by combining ibogaine treatment with glycine. Structure-activity studies revealed that among various ibogaine-like compounds (including *O*-desmethylibogaine and *O*-*t*-butyl-*O*-desmethylibogaine), only ibogaine inhibited the intensity of morphine withdrawal (*72*). Both the ability of glycine to inhibit this effect of ibogaine and the failure of other ibogaine derivatives to potently inhibit the binding of noncompetitive NMDA antagonists (e.g., [^{3}H]–N-[1-(2-thienyl)cyclo-hexyl]-3,4-pipenoline (TCP) and [^{3}H]–MK-801) suggests that the NMDA antagonist actions of ibogaine are responsible for its anti-withdrawal effects. This hypothesis is supported by the observation that while *O*-desmethylibogaine and *O*-*t*-butyl-*O*-desmethylibogaine had much higher affinities for kappa opioid receptors than ibogaine did, only ibogaine exhibited a significant affinity for NMDA receptors.

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6. Pain and analgesia.

Ibogaine did not mimic the analgesic action of morphine in either the tail flick (1-40 mg/kg, i.p.) or hot plate (up to 20 mg/kg, i.p.) tests, although it exhibited analgesic activity in the phenylquinone writhing test (ED_{50} 9.7 mg/kg) (*114,120,121*). Ibogaine did not exhibit antinociceptive activity when given twice a day for 4 days (*122*). Ibogaine either increased (*120,123*) or did not affect (*114,121*) morphine analgesia in

the tail flick test. Similarly, it did not influence analgesia produced by either a kappa opioid agonist (U-50,488H) or a delta opioid agonist [D-Pen^2,D-Pen^5]enkephalin (DPDPE) (*121*). Ibogaine has been reported to decrease analgesia in rats when given 19 hours prior to morphine (*123*), but another report indicates ibogaine is not effective when given 4-24 hours prior to morphine administration in mice (*121*). In addition, Cao and Bhargava (*122*) demonstrated that ibogaine (40-80 mg/kg) inhibited the development of analgesia to mu, but not kappa or delta, agonists in mice.

O-Desmethylibogaine (40 mg/kg) potentiated morphine-induced analgesia in rats (*123*) and mice (*121*). This effect was no longer apparent 19 hours after its administration (*123*). The potentiation of morphine-induced analgesia may be attributed to the relatively high affinity of *O*-desmethylibogaine at opioid mu (K_i 2.66 ± 0.62 µM) and kappa (K_i 0.96 ± 0.08 µ M) receptors (*124*). However, this interpretation appears unlikely because *O*-desmethylibogaine pretreatment did not influence either kappa - or delta - opioid agonist - induced antinociception (*121*).

Ibogaine (10-40 mg/kg) completely blocked the antinociceptive effect of (–)-epibatidine in rodents, but was ineffective when given at a dose of 40 mg/kg 24 h before epibatidine. These data suggest that this was an effect of ibogaine and not that of its putative, long-lasting metabolite (*125*). This blockade of the antinociceptive effect of epibatidine is not surprising, because epibatidine-induced analgesia is mediated by a mechanism fundamentally different from that of the opioids.

TOP

7. Aggression.

Compared to other psychoactive compounds (e.g. psilocybin, JB-336, and bufotenine), ibogaine (10 mg/kg) had a negligible effect on the aggressiveness of isolated mice and muricidal behavior in rats (*126*).

TOP

8. Interoceptive properties.

Animals can be trained to "recognize" similarities among drugs. Such discriminative (interoceptive) properties may suggest a similar mechanism of action not necessarily related to the structure of a compound.

No generalization between ibogaine and serotonergic ligands (e.g. fenfluramine, *N*-(3-trifluoromethylphenyl)piperazine [TFMPP], 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane [DOI], methyl-enedioxymethamphetamine [MDMA], quipazine or LSD) was found in drug-discrimination paradigms (*127,128*). However, Palumbo and Winter (*129*) did observe a generalization between ibogaine (15-20 mg/kg) and dimethoxymethylamphetamine [DOM] (0.6 mg/kg), as well as between ibogaine and LSD (0.1 mg/kg) in a two-lever discrimination task. Because pizotyline (BC-105) blocked DOM-appropriate and LSD-appropriate responses, an involvement of 5-HT_2 or 5-HT_1 receptors in the stimulus properties of ibogaine was suggested. Similarly, no generalization between ibogaine and CGS 10476B (a dopamine release-inhibiting agent) was found in a drug-discrimination paradigm (*127*).

In contrast, ibogaine substituted as an interoceptive cue in mice trained to recognize MK-801 (dizocilpine) (*119*), but not to [(+)-HA-966] (a low efficacy partial agonist of the glycine site at the NMDA receptor) (*130*) in a T-maze drug discrimination paradigm.

Helsley and colleagues (*131*) studied the interoceptive cue produced by ibogaine in male Fisher rats. The time course of the ibogaine (10 mg/kg) cue revealed that a maximum of ibogaine-appropriate responses were observed at a 60 min pretreatment time, and, that at the pretreatment time of 8 hours, no ibogaine-like responses were

observed. These findings, together with observation that *O*-desmethylibogaine substituted only partially to the ibogaine cue, suggest that the subjective effects of ibogaine are not due to this putative metabolite. The same study however, revealed that harmaline completely substituted as an ibogaine cue (*131*). This later finding indicates that animals may recognize the tremorigenic effects of ibogaine.

TOP

9. Reinforcing effects.

Ibogaine does not appear to possess rewarding or aversive effects as measured in the conditioned place preference/aversion test (*132*), a preclinical procedure that can predict abuse potential in humans. Nonetheless, the same authors reported that ibogaine (40 mg/kg) may attenuate the acquisition, but not expression of morphine and amphetamine place-preference in male rats (*77,132,133*). This dose of ibogaine did not interfere with the acquisition of conditioned place aversion induced by either naloxone or lithium chloride (*132*). Ibogaine (40 mg/kg, 22 hours before the test) attenuated the establishment of lithium- and morphine-induced conditioned taste aversion (*134*). These results suggest a specific action of ibogaine on the neurochemical and behavioral (both reinforcing and aversive) actions of morphine rather than on opioid system(s), because the reinforcing effects of naloxone were unaffected. In support to these findings, it has been reported that ibogaine (20 or 40 mg/kg, 24 h before the test) neither decreased the preference for a sweet solution nor attenuated conditioned preference for a flavor previously associated with sweet taste (*135*).

TOP

10. Effects on learning and memory.

At a dose used in the majority of contemporary behavioral studies in rodents (40 mg/kg), ibogaine has been found to attenuate the acquisition of spatial memory, perhaps due to reductions in locomotor activity and in detection of sensory information (*78*). However, at much lower doses (0.25 - 2.5 mg/kg), ibogaine as well as *O*-desmethylibogaine (but not *O*-*t*-butyl-*O*-desmethylibogaine) facilitated spatial memory retrieval (*136*). Using a spatial memory task, Helsley *et al*., (*92*) found that: 1) two doses of ibogaine (50 mg/kg, spaced by 8 hours) decreased the response rate, but did not affect acquisition rate; 2) ibogaine, even at the highest doses of 30 and 46 mg/kg given 20 min before the learning trial did not affect task acquisition; 3) 30 mg/kg of ibogaine administered just after the learning trial facilitated the consolidation of memory trace.

TOP

11. Cardiovascular actions.

Gershon and Lang (*102*) found that ibogaine produced a rise in blood pressure and increased heart rate in conscious dogs. These effects were blocked by atropine (*137*). However, in anesthetized dogs, ibogaine produced a fall in blood pressure and reduced heart rate reduction, leading the authors to propose an interaction between anaesthesia and the cardiovascular effects of ibogaine (*102*). Schneider and Rinehart (*137*) postulated a centrally mediated stimulatory effect of ibogaine. Ibogaine also potentiated the pressor response to both adrenaline and noradrenaline. More recently, Hajo-Tello *et al.,* (*138*) found that tabernanthine (an alkaloid closely related to ibogaine) induced a negative inotropic effect in electrically stimulated myocardial tissue and a negative chronotropic effect in the perfused rat heart. Tabernanthine also produced bradycardia and hypotension in anesthetized rats and dogs (*139*). Binienda *et al*. (*140*) reported that ibogaine (50 mg/kg) reduced heart rate in rats immediately after injection; this reduction

persisted up to 90 minutes after injection.
TOP

B. Human Studies.

Numerous psychotropic actions of ibogaine have been reported. These actions seem to depend on both dose and setting. In addition, the psychoactive effects of iboga extracts (which are likely to contain additional alkaloids and are usually taken in a ritualistic setting) may be different from those of ibogaine. Thus, users of the crude extract of *Tabernanthe iboga* taken in sufficiently high doses have reported fantastic visions, feelings of excitement, drunkenness, mental confusion and hallucinations when (*101*). The total extract of iboga shrub is certainly a central stimulant, and in higher doses may lead to convulsions, paralysis and finally respiratory arrest. The psychotropic actions of the plant extract include visual sensations; objects are seen to be surrounded by specters or rainbows. In high doses it may produce auditory, olfactory and taste synesthesias. The state of mind has been reported to vary from profound fear to frank euphoria (*141*).

When given orally, both ibogaine and the total iboga extract elicits subjective reactions that last for approximately 6 hours. Fifty percent of subjects are reported to experience dizziness, incoordination, nausea, and vomiting (*7,33,142*). Typically, the drug produced a state of drowsiness in which subjects did not want to move, open their eyes, or attend to the environment. Many subjects were light-sensitive, and covered their eyes or asked that the lights be turned off. Sounds or noises were disturbing. Ibogalin (0.1-1.2 mg/kg, p.o.), an alkaloid closely related to ibogaine and a constituent of the total iboga extract, did not produce psychotomimetic effects in humans (*143*). Ibogalin also differs from ibogaine in pharmacokinetics and tremorigenic activity (*90*).

The psychoactive properties of ibogaine and related compounds were studied by Naranjo (*33,142*) who reported that patients described the psychic state produced by ibogaine (~ 300 mg) as similar to a dream state *without* loss of consciousness. Ibogaine-induced fantasies [often described as a "*movie run at high speed*" or "*slide show*" (*7*)] were reported as rich in archetypal contents, involving animals and/or the subject with or without other individuals. These fantasies were easy to manipulate by both the subjects and the psychotherapist (*33,142*). At higher doses, ibogaine appears to produce visual and other hallucinations associated with severe anxiety and apprehension (*101,144,145*).
TOP

VI. LETHALITY AND NEUROTOXIC EFFECTS.

The LD_{50} of ibogaine has been determined in guinea pig (82 mg/kg, i.p.) and rat (327 mg/kg, intragastrically and 145 mg/kg, i.p.) (*60,146*).

No significant pathological changes in rat liver, kidney, heart and brain following chronic ibogaine treatment (10 mg/kg, for 30 days or 40 mg/kg, for 12 days, i.p.) were reported (*60*). Sanchez-Ramos and Mash (*42*) found no evidence of gross pathology in African green monkeys given ibogaine in doses of 5-25 mg/kg, p.o. for 4 consecutive days.

However, O'Hearn *et al*., (*147,148*) and O'Hearn and Molliver, (*93*) reported that repeated administration of ibogaine (100 mg/kg, i.p.) to rats caused the degeneration of a subset of Purkinje cells in the cerebellar vermis. This degeneration was accompanied by a loss of microtubule-associated protein 2 (MAP-2) and calbindin. Argyrophilic degeneration, astrocytosis and microgliosis were also observed. The damage seemed to be dependent on the presence of an intact inferior olivary nucleus (*149*). Ibogaine-

induced cerebellar toxicity seem to be independent on its action at NMDA receptors, because neither MK-801 nor phencyclidine produce the same pattern of degeneration (*150*). The neurotoxic effects of high doses of ibogaine were confirmed in rats, but not mice, by Scallet *et al*., (*151,152*) and Molinari *et al*., (*153*), who, in addition found that the "typical" dose of 40 mg/kg did not produce significant damage to female rat cerebellum. The lack of neurotoxicity after lower, behaviorally active doses of ibogaine was also demonstrated by showing that chronic administration (60 days) of 10 mg/kg of ibogaine produced no change in the number of Purkinje cerebellar cells (*154*).

In spite of these findings, examination of cellular markers that are more sensitive toneurotoxic agents than gross histology indicates that ibogaine administration may produce significant change in many other brain structures. Thus, O'Callaghan *et al*., (*155,156*) examined the effects of acute and chronic administration of ibogaine on glial fibrillary acidic protein (GFAP) levels. Acutely, ibogaine increased GFAP in both sexes; whereas chronic administration (14 days) produced increases only in females. Ibogaine - induced changes in GFAP were dose-related, and, contrary to other studies, observed in other brain structures including hippocampus, olfactory bulb, brain stem and striatum. In addition, these authors reported that in females treated chronically with ibogaine, severe hippocampal damage was present as measured by increases in the cytoskeletal proteins neurofilament 68 (NF-68) and beta-tubulin. These latter markers indicate a damage-induced sprouting response (*156*). Ibogaine administration also produced an increase in c-fos immunostaining in several brain regions of mice and rats; the effects in rats were observed in all cortical layers while in mice the response was limited to cortical layer 2 (*152*). Human SK-N-SH neuroblastoma cells cultured in the presence of 3-30 μ M ibogaine (but not *O*-desmethylibogaine or 18-methoxycoronaridine) demonstrated concentration- and time-dependent morphological changes characterized by the loss of processes, cell rounding, detachment and ultimately cell death (*157*). Similar results were observed with primary cultures of rat cerebellar granulae cells. Because in this study only alkaloids that had marked affinity at $sigma_2$ sites were neurotoxic, Vilner *et al*., (*157*) proposed that $sigma_2$ sites may be implicated in the neurotoxicity of ibogaine. The neurotoxic effects of ibogaine have been recently reviewed by Vocci and London (*106*).

Acute treatment with the ibogaine-like alkaloid, 18-methoxycoronaridine (100 mg/kg) did not produce gross pathological changes in the cerebellum (*97*). In contrast, another indole alkaloid, harmaline, produced ibogaine-like degeneration of Purkinje cells in the cerebellar vermis (*93*).

It has been reported that multiple doses of a non-NMDA antagonist (GYKI 52466) resulted in a substantially greater loss of Purkinje cells and microglial activation compared to ibogaine (50-100 mg/kg) alone (*158*). On the other hand, the noncompetitive NMDA antagonist MK-801 (1 mg/kg) markedly attenuated the degree of Purkinje cell loss caused by ibogaine (*158*). This later finding strongly supports the notion that the loss of cerebellar Purkinje cells produced by ibogaine is unrelated to its NMDA antagonist properties (*159*). In fact, ibogaine can also exhibit neuroprotective properties, reducing glutamate-induced neurotoxicity in primary cultures of cerebellar granule cell neurons with an EC_{50} of 4-5 μM (*119*). These neuroprotective effects of ibogaine have recently been patented by Olney (*160*). Consistent with its properties as an NMDA antagonist, ibogaine inhibited NMDA - induced lethality in mice in a dose-dependent manner (*161*), and also protected mice from maximal electroshock seizures (ED_{50} ~ 31 mg/kg) (*162*).

Phase I toxicity studies in drug-addicted individuals are in progress at the University of Miami (*42,163*).

TOP

VII. EFFECTS ON SPECIFIC NEUROTRANSMITTER SYSTEMS

A. Ibogaine Effects on Dopaminergic Systems.

Ibogaine (at concentrations £ 100 µM) does not affect radioligand binding to dopamine receptors (D_1, D_2, D_3, D_4) (*164-166*). The affinity of ibogaine for dopamine transporters as measured by inhibition of [^{3}H]WIN 35,248, [^{125}I]RTI-121 or [^{125}I]RTI-55 binding was ~ 1.5 - 4 µ M (*73,76,166,167*). However, in another study, ibogaine did not affect binding of [^{3}H]GBR-12935, a ligand that also appears to label dopamine transporters (*85*). Ibogaine inhibited [^{3}H]dopamine uptake in porcine kidney cells transfected with dopamine transporter with a K_i ~86 µM (*168*).

The *in vivo* and *ex vivo* effects of ibogaine on dopamine metabolism in mesolimbic areas of the rodent brain (striatum, nucleus accumbens) are controversial and highly inconsistent. In an attempt to reconcile several contradictory findings, one may note the following.

Dopamine concentrations are reduced and dopamine metabolites dihydroxyphenyl-acetic acid (DOPAC) and homovanilic acid (HVA) are increased by ibogaine under certain experimental conditions. For example, when either measurements are taken shortly (within 2 h) after ibogaine administration or when relatively high concentrations (£ 100 µM) are used (*69,71,76,81,169-173*). Reductions in extracellular dopamine concentrations were also observed after administration of a number of ibogaine derivatives, including *O*-desmethylibogaine (*89*) and 18-methoxycoronaridine (*97*).

When dopamine is measured at longer periods after ibogaine administration (e.g., up to a week) or low concentrations (e.g., 10 µM) are applied, brain concentrations appear unchanged and metabolite concentrations are decreased (*69,71,76,81,82,169,170,172*).

The increased levels of extracellular dopamine metabolites together with decreased or unchanged levels of dopamine suggests that ibogaine increases dopamine turnover shortly after administration. This may be followed by a decrease in turnover that may persist for some time after ibogaine administration. French *et al*., (*91*) demonstrated that doses of ibogaine (~ 1.5 mg/kg, i.v.), much lower than a "typical" dose of 40-80 mg/kg, markedly excited dopaminergic neurons in the ventral tegmental area of the rat.

TOP

1. Dopaminergic effects: Pharmacological Specificity.

Administration of a kappa antagonist (norbinaltorphimine, 10 mg/kg) and NMDA (10 mg/kg) (either jointly or individually) reversed ibogaine (40 mg/kg) induced decreases in striatal dopamine and increases in dopamine metabolites (*88*). Similarly, Reid *et al*., (*172*) observed that the decrease in dopamine levels produced by ibogaine (100 µ M) was reversed by either naloxone (1 µM) or norbinaltorphimine (1-10 µM). However, functionally opposite effects were observed by Sershen *et al*., (*174,175*) who reported that the ability of the kappa opioid agonist (U-62066) to inhibit electrical- or cocaine-induced [^{3}H]dopamine release from mouse striatum was attenuated by pretreatment of mice with ibogaine (40 mg/kg, i.p., 2 hours prior; or 2 x 40 mg/kg, 6 hours apart, killed 18 hours later) (*174,175*).

Ibogaine-induced dopamine release from the isolated mouse striatum has been studied by Harsing *et al.,* (*176*). Ibogaine increased basal tritium outflow ([^{3}H]dopamine (DA) and [^{3}H]DOPAC), but was without effect on electrically stimulated tritium overflow. This dopamine releasing effect was: a) reduced by the dopamine uptake inhibitors cocaine and nomifensine, b) unaltered by omission of Ca^{++} from the

perfusion buffer, c) tetrodotoxin insensitive, d) unaffected by an agonist (quinpirole) or an antagonist (sulpiride) of the D_2 dopamine receptor, and e) unaffected by pretreatment with reserpine. In this study, ibogaine did not affect dopamine uptake, whereas Reid *et al*., (*172*) found that both ibogaine and harmaline (10 µM-1 mM) inhibited it. As mentioned above, ibogaine has been reported to inhibit radioligand binding to the dopamine transporter with relatively high affinity.

Sershen *et al*., (*177*) reported an involvement of serotonin receptors in the regulation of dopamine release by ibogaine. Thus, administration of ibogaine blocked the ability of a $5HT_{1B}$ agonist (CGS-12066A [10 µM]) to increase [^{3}H]dopamine increase in striatal slices. In other studies, a concentration of ibogaine (1 µM) that was without effect on dopamine efflux inhibited both NMDA (25 µ M) and (±)pentazocine (100 nM) - induced dopamine release in striatal slices (*178*).

There are few reports of the effects of ibogaine-like alkaloids on dopamine metabolism. Like ibogaine, *O*-desmethylibogaine acutely decreases dopamine release in the rat nucleus accumbens and striatum (*89*). Administration of the *R*- entantiomers of coronaridine and ibogamine decreased dopamine levels in both nucleus accumbens and striatum, whereas the *S*-enantiomers produced no significant changes in dopamine levels in either region (*96*).

In an attempt to reconcile several conflicting findings, Staley *et al*., (*167*) proposed that ibogaine might promote redistribution of intraneuronal dopamine from vesicular to cytoplasmic pools. Ibogaine displays micromolar affinity for vesicular monoamine transporters labeled with [^{125}I]-tetrabenazine (*167*); these sites are crucial for the translocation of dopamine into synaptic vesicles. The inhibitory effect of ibogaine on vesicular monoamine transporters could result in redistribution of dopamine in the cytoplasm. Under such conditions, rapid metabolism of dopamine by monoamine oxidase would account for the decrease in tissue dopamine content and the parallel increase in its metabolites.

Multiple transmitter systems have been shown to modulate dopaminergic function in the central nervous system. Because ibogaine can interact with many of these systems, including kappa opioid receptors, NMDA receptors, serotonin receptors, and dopamine transporters, it is not surprising that this alkaloid can produce complex (and sometimes apparently opposite) effects on dopaminergic function. Thus, the effects of ibogaine on dopaminergic function described in this section likely reflect the dose (or concentration) of alkaloid, preparation employed (e.g., slice versus intact animal), and brain region studied.

TOP

2. Ibogaine alters the effects of abused drugs on dopaminergic systems.

In general, ibogaine attenuates the increases in mesolimbic dopamine produced by drugs (e.g, nicotine, morphine) that appear to act preferentially at dopaminergic cell bodies. In the case of drugs that act at terminal regions (e.g., cocaine and amphetamine), a gender difference has been observed. In female rats, ibogaine enhances stimulant-induced increases in dopamine concentrations, whereas it decreases the effects of these stimulants in male rats and mice.

Neurochemical studies were performed in male mice given two doses of ibogaine (40 mg/kg, i.p., 18 hours apart) followed by amphetamine (5 mg/kg) administered 2 hours after the second dose of ibogaine (*81*). Striatal levels of dopamine and dopamine metabolites [DOPAC, HVA and 3-methoxytyramine (3-MT)] measured 1 hour after amphetamine were decreased in mice that received ibogaine relative to saline-pretreated, amphetamine-treated controls. Compared to controls, levels of DOPAC and

HVA were decreased in the amphetamine and ibogaine groups, and further decreased in the group that received ibogaine and amphetamine. However, in female rats, amphetamine-induced increases in extracellular dopamine concentrations in both the striatum and the nucleus accumbens were further potentiated by ibogaine (40 mg/kg, i.p., 19 hours preceding amphetamine) (*82*). Similarly, Glick *et al.,* (*169*) found that ibogaine potentiated amphetamine-induced increases in extracellular dopamine concentrations in female rat nucleus accumbens and striatum. In this study, however, no effect of ibogaine was seen on amphetamine-induced decreases in extracellular concentrations of dopamine metabolites. Similarly, ibogaine potentiated cocaine-induced increases in extracellular dopamine levels in striatum and nucleus accumbens of female rats (*84*). However, quite opposite data were obtained by Broderick *et al.,* (*85,86*) who examined dopamine release in male rats using semiderivative *in vivo* voltametry. In these experiments, ibogaine (40 mg/kg i.p. given for four days) reduced the increase in dopamine release from nucleus accumbens induced by cocaine (20-40 mg/kg, s.c.). A presynaptic mechanism for these actions was suggested. An inhibitory effect of ibogaine on amphetamine metabolism has been proposed (*179*), because amphetamine levels were higher after ibogaine administration in female rats. However, ibogaine administration had no effect on brain cocaine levels (*169*).

Ibogaine (40 mg/kg, i.p. in rats) given 19 hours before morphine (5 mg/kg) prevented the increase in extracellular dopamine concentration in the striatum, prefrontal cortex and nucleus accumbens typically observed in rats (*71,83*). However, in the ibogaine plus morphine group, the levels of dopamine *metabolites* were increased (as was observed in the morphine group), suggesting that ibogaine did not prevent morphine from activating dopamine neurons. The authors suggest that ibogaine treatment may change the properties of dopaminergic neurons in such a way that dopamine release is unaffected under normal conditions, but altered when stimulated (in this case, by morphine). Nineteen hours after placebo or ibogaine (10 mg/kg, i.p.), female rats responded similarly with increased dopamine release in nucleus accumbens following a morphine challenge (*180*). However, in rats that received two doses of morphine during two days preceding the experiment, ibogaine pretreatment had inhibitory effects on dopamine response to a morphine challenge. A pharmacokinetic explanation for the effects of ibogaine on morphine-induced actions is unlikely, because ibogaine (40 mg/kg, i.p. 19 hours before measurement) did not modify brain levels of morphine (10 mg/kg) in rats (*71*).

Benwell *et al*., (*103*) reported that ibogaine (given 22 hours before nicotine) attenuated the increase in dopamine overflow in the nucleus accumbens evoked by nicotine administration. Similar effects were demonstrated, when ibogaine was administered 19 hours prior to nicotine infusion (*181*).

TOP

B. Opioid Systems

At concentrations of up to 100 µM, ibogaine was reported not to affect [^{3}H]carfentanil or [^{3}H]enkephalin binding indicating that this alkaloid does not affect mu or delta opioid receptors (*124,165*). In contrast, Pearl *et al*., (*124*) and Sweetnam *et al*., (*166*) demonstrated that ibogaine inhibited radioligand binding to mu opioid receptors with K_i values ~ 11-20 µM. *Ex vivo* studies demonstrated that ibogaine and *O*-desmethylibogaine enhanced the inhibition of adenylyl cyclase activity by a maximally effective concentration of morphine in the rat frontal cortex, midbrain and striartum (*182*). This later effect is not likely mediated via a direct action at opioid receptors because it was observed at maximally effective concentration of morphine.

Ibogaine inhibits (K_i ~2-4 μM) [^{3}H]U-69593 binding to kappa opioid receptors (*56,72,124,165*). This binding is reversible, suggesting that the long-term effects of ibogaine cannot be attributed to an irreversible effect at this site. Recently, Codd (*183*) demonstrated that ibogaine inhibits binding to sites labeled by [^{3}H]naloxone characterized by a two-site model, with K_i values of 130 nM and 4 μM.

O-Desmethylibogaine had a higher affinity than ibogaine for all of the opioid receptors studied: kappa K_i ~ 1 μM, mu K_i ~ 2.7 μM and delta K_i ~ 24.7 μM (124) (a recent study showed much higher affinity of *O*-desmethylibogaine at the mu receptor; K_i ~ 160 nM (*184*)). Our work (*72*) demonstrated that *O*-desmethylibogaine had a 10- to 100-fold higher affinity for kappa receptors compared to ibogaine. The magnitude of this potency difference was species-specific (e.g., in rats: IC_{50} ~ 0.3 μM for *O*-desmethylibogaine and IC_{50} ~30 μM for ibogaine). The same study demonstrated a moderate affinity of *O*-*t*-butyl-*O*-desmethylibogaine for kappa receptors (IC_{50} ~17 μM in rat forebrain) suggesting that if any of ibogaine's *in vivo* actions are produced at kappa receptors, then *O*-*t*-butyl-*O*-desmethylibogaine would be active. In this respect, *O*-*t*-butyl-*O*-desmethylibogaine did not influence the morphine withdrawal syndrome (*72*) at doses comparable to ibogaine.
TOP

C. Serotonergic Systems.

Ibogaine (at concentrations up to 1 μM) had no effect on [^{3}H]serotonin binding (*185*) and concentrations of up to 3.5 μM had no effect on [^{3}H]LSD binding (*186*). More recent studies using serotonin subtype selective ligands are discrepant. Deecher *et al*., (*165*) reported that ibogaine did not displace ligands acting at 5-HT_{1a}, 5-HT_{1b}, 5-HT_{1c}, 5-HT_{1d}, 5-HT_2, or 5-HT_3 receptors. However, Repke *et al*., (*56*) reported that ibogaine inhibited binding of 5-HT_{1a}, 5-HT_{2a}, or 5-HT_3 ligands with low affinity (K_i values: >100, 12.5 and >100 μM, respectively) and Sweetnam *et al*., (*166*) reported IC_{50} values of ~ 4 μM to inhibit radioligand binding to both 5-HT_2, and 5-HT_3 receptors.

Despite these discrepancies, both *ex vivo* and *in vivo* studies suggest that ibogaine can affect serotonergic transmission. *Ex vivo* studies indicate that ibogaine and *O*-desmethylibogaine enhance the inhibitory effects of serotonin on adenylyl cyclase activity in rat hippocampus (*182*). Broderick *et al.,* (*86*) reported that ibogaine (40 mg/kg, i.p. for 4 days) increased 5-HT concentrations in rat nucleus accumbens. Consistent with this finding, Ali *et al*., (*171*) demonstrated that ibogaine increased 5-HT levels in striatum. Sershen *et al*., (*76*) reported that ibogaine (40-50 mg/kg) decreased levels of the serotonin metabolite 5-hydroxy-indoleacetic acid [5-HIAA] in mouse frontal cortex, hippocampus and olfactory tubercle 2 and 24 hours after injection. Ibogaine also decreased 5-HIAA levels in rat nucleus accumbens and striatum (*103,171*), but increased 5-HIAA and decreased 5-HT (lasting at least 7 days) in medial prefrontal cortex (*103*). Long and Lerrin (*187*) demonstrated that ibogaine is a reversible inhibitor of the active transport of serotonin into blood platelets, a finding supported by a recent observation that ibogaine inhibited serotonin transporters (in a porcine kidney cell line) with a K_i ~ 10 μM (168).

Sershen *et al.,* (*177*) demonstrated that ibogaine inhibited the ability of a 5-HT_{1b} agonist (CGS-12066A) to increase stimulation-evoked [^{3}H]dopamine release from both rat and mouse striatal slices. Additionally, ibogaine increased the ability of a 5-HT_3 agonist (phenylbiguanide) to enhance stimulation-evoked [^{3}H]dopamine release from the mouse striatal slice (*174*). In these studies, ibogaine (40 mg/kg, i.p.) was

administered 2 hours prior to slice preparation. In other studies, ibogaine (20 mg/kg) enhanced cocaine-induced reductions in serotonin concentration in the nucleus accumbens (rat), an action attributed to a presynaptic release mechanism (*85,86*). However, Sershen *et al*., (*175*) reported that cocaine increased [^{3}H]serotonin efflux in striatal slices and this efflux was absent in mice pretreated with either ibogaine or a 5-HT_{1b} agonist. These later findings led Sershen to suggest an action of ibogaine at the HT_{1b} receptor that is likely unrelated to the ability of cocaine to inhibit serotonin reuptake blockade (*188*). The inhibitory effect of the kappa-opioid agonist U-62066 (1µM) on [^{3}H]serotonin release in striatal slices could be blocked by *in vivo* ibogaine administration (*175*).

TOP

D. Calcium Regulation.

Ibogaine (80 µM) non-competitively antagonized calcium-induced contraction of rat aorta and mesenteric artery (*138*), which was interpreted as an action on intracellular calcium metabolism. Tabernanthine, an alkaloid related to ibogaine, inhibited depolarization-stimulated ^{45}Ca influx and contractions in the rat aorta (*189*). Ibogaine inhibited the binding of [^{3}H]isradipine (an L-type calcium channel blocker) in the mouse cerebral cortex with an IC_{50} of ~28 µM (*11*).

TOP

E. Cholinergic Systems.

Ibogaine (at concentrations of up to 100 µM) was reported not to inhibit the binding of ligands acting at nicotinic or muscarinic receptors (*165*). However, subsequent studies demonstrated that ibogaine inhibited the binding of muscarinic M_1, M_2 and M_3 ligands at concentrations of ~ 31, 50 and 12.5 µM, respectively (*56*). Sweetnam *et al*., (*166*) showed that ibogaine inhibited radioligand binding to M_1, and M_2 receptors with IC_{50} values of 5-7 µM. These authors also reported that ibogaine did not inhibit the binding of [^{3}H]NMCI, a nonselective ligand at nicotinic receptors. *Ex vivo* studies have shown that neither ibogaine nor *O*-desmethylibogaine affect the inhibitory action of the muscarinic acetylcholine agonist, carbachol on adenylyl cyclase activity in the rat (*182*).

In a recent study, Badio *et al*., (*125*) demonstrated that ibogaine potently (IC_{50} ~ 20 nM) blocked ^{22}NaCl influx through nicotinic receptor channels in rat pheochromocytoma cells. This effect was seen in the cells expressing ganglionic, but not neuromuscular, nicotinic receptor subtypes. This inhibition was noncompetitive because it was not overcome by increasing concentrations of agonist. Moreover, the blockade was not completely reversible, suggesting that ibogaine may have a long-lasting effect. *O*-Desmethylibogaine and *O*-*t*-butyl-*O*-desmethylibogaine were 75- and 20-fold less potent, respectively, than ibogaine in blocking nicotinic receptor-mediated responses. The same study demonstrated that ibogaine, as expected for a noncompetitive blocker, had a relatively low affinity (K_i ~ 4 µM) as an inhibitor of the binding of an agonist [^{3}H]nicotine. In support to these findings, Schneider *et al*., (*190*) reported recently that ibogaine (£ 10 µ M) had an inhibitory action on nicotinic receptor-mediated catecholamine release in bovine adrenal chromaffin cells. Consistent with the Badio *et al*., (*125*) study, these inhibitory effects appeared to be long-lasting.

TOP

F. Gamma-Aminobutyric Acidergic [GABAergic] Systems.

Two independent studies (*165,166*) did not find any effect of ibogaine (at concentrations of up to 100 μM) on radioreceptor binding to $GABA_A$ receptors. In addition, ibogaine did not influence $^{36}Cl^-$ uptake through GABA-gated channels (*165*) or GABA-evoked currents in rat cultured hippocampal neurons (*162*).

TOP

G. Voltage-Dependent Sodium Channels.

Ibogaine inhibited (K_i ~ 8.1 μM) [^{3}H]batrachotoxin A 20-a-benzoate binding to voltage-dependent sodium channels in depolarized mouse neuronal preparations (*165*). Ibogaine analogs, including ibogamine, tabernanthine and coronaridine, exhibited potencies similar to ibogaine in this assay.

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H. Glutamatergic Systems.

Our studies (*159*) indicate that ibogaine is a competitive inhibitor of [^{3}H]MK-801 binding (K_i ~1 μM) to NMDA receptor-coupled ion channels. In contrast, ibogaine did not affect [^{3}H](±)- a -amino-3-hydroxy-5-methylisoxazole-4-propionic acid ([^{3}H]AMPA), [^{3}H]kainate or [^{3}H]glutamate to either the NMDA or metabotropic receptor sites, binding. These findings are consistent with a specificity of ibogaine for NMDA receptor-coupled cation channels (*159,162,166*). The potency of ibogaine to inhibit [^{3}H]MK-801 binding was also examined in 8 distinct brain regions of Sprague-Dawley male rats and compared with the dissociation constants for [^{3}H]MK-801 estimated using saturation analyses. A high correlation (r=0.976, p=0.0004) was obtained between the K_i of ibogaine and K_d of [^{3}H]MK-801 in these brain regions (*119*), consistent with the notion that these compounds share a common binding site. The ability of ibogaine to act as a non-competitive NMDA antagonist can also be demonstrated using [^{3}H]1-[1-(2-thienyl)cyclohexyl]piperidine ([^{3}H]TCP), a thienyl derivative of phencyclidine, resulting in a K_i ~1.5 μM in rat forebrain (*119*).

Structure-activity studies were performed using a series of ibogaine analogs, including the putative ibogaine metabolite *O*-desmethylibogaine, its metabolism resistant analog *O*-*t*-butyl-*O*-desmethylibogaine, the iboga alkaloids [(±)-ibogamine, (±)-coronaridine, tabernanthine], harmaline, and indolotropanes. Ibogaine was the most potent inhibitor of [^{3}H]MK-801 binding (K_i ~ 1.2 μM); the compounds with the greatest structural similarity to ibogaine, *O*-desmethylibogaine and *O*-*t*-butyl-*O*-desmethylibogaine were much less potent (K_i ~ 5.5 and 179.0 μ M respectively) (*72*). A ~ 5 fold lower affinity of *O*-desmethylibogaine compared to ibogaine at [^{3}H]MK-801 binding sites was also reported by Mash *et al*., (*191*).

Consistent with these neurochemical studies, ibogaine produced a voltage-dependent block of NMDA-evoked currents in hippocampal cultures (*119,162*). In addition, ibogaine (100 μ M) and *O*-desmethylibogaine (1 mM) blocked the ability of NMDA (100 μ M, 5 sec) to depolarize frog motoneurons in a non-competitive and use-dependent manner (*192*).

TOP

I. Sigma Receptors.

In our studies (11), ibogaine inhibited [^{3}H]pentazocine (a $sigma_1$ receptor ligand) binding, to high (IC_{50} ~86 nM) and low (IC_{50} ~5.6 μM) affinity sites in mouse

cerebellum. Bowen *et al*., (*193*) demonstrated that ibogaine had high affinity for $sigma_2$ sites (K_i ~ 200 nM) and low affinity for $sigma_1$ sites (K_i ~ 8.5 μM), a ~ 43- fold selectivity for $sigma_2$ sites. The affinities of tabernanthine (13-methoxyibogamine) and (±)-ibogamine for $sigma_2$ sites were similar to that of ibogaine. *O*-Desmethylibogaine, had a markedly reduced affinity for $sigma_2$ sites (K_i ~ 5 μM) and also lacked affinity for $sigma_1$ sites. The related alkaloids, (±)-coronaridine [(±)-18-carbomethoxyibogamine] and harmaline lacked affinity for both sigma receptor subtypes. *O*-t-Butyl-*O*-desmethylibogaine inhibited radioligand binding to $sigma_1$ sites with a K_i ~ 3.5 μM and $sigma_2$ sites with a K_i ~ 346 nM [c.f. Bowen *et al*, (*72*)]. The much higher affinity of ibogaine for $sigma_2$ sites compared to $sigma_1$ sites was also reported by Mach *et al*., (*194*). Bowen *et al*., (*195*) examined the ability of ibogaine and related compounds to modulate calcium release from intracellular stores in indo-1 loaded human SK-N-SH neuroblastoma cells. Consistent with its affinity at $sigma_2$ sites, ibogaine produced a concentration-dependent increase (13-45%) in intracellular calcium levels. *O*-Desmethylibogaine, was ineffective in this measure at concentrations up to 100 μ M. These data suggest that the shared *in vivo* effects of ibogaine and *O*-desmethylibogaine are probably not mediated by sigma sites.
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J. Miscellaneous Actions of Ibogaine.

Deecher *et al.,* (*165*) reported that ibogaine (up to 100 μM) did not inhibit radioligand binding to cannabinoid receptors. Ibogaine and *O*-desmethylibogaine had no influence on basal or forskolin-stimulated adenylyl cyclase in the rat frontal cortex, midbrain or striatum (*182*). *O*-Desmethylibogaine, but not ibogaine, produced concentration - dependent increases in the generation of [^{3}H]inositol phosphates that were not altered by inclusion of tetrodotoxin, cadmium or omega-conotoxin (*196*). These results suggest that the effect of *O*-desmethylibogaine on phosphoinositide hydrolysis was not secondary to the release of one or more neurotransmitters. Ali *et al*., (*45*) reported that ibogaine (0.5-250 μ M) reduced nitric oxide synthase activity in mouse brain; similar effects were noted in the striatum, hippocampus and cerebellum of mice treated parenterally with ibogaine (50 mg/kg). In radioligand binding studies, no effect of ibogaine has been found on $alpha_1$, $alpha_2$ or $beta_1$ adrenergic receptors (*165*). Moreover, ibogaine (20 mg/kg) did not modify cerebral noradrenaline levels in rats (*197*). Binienda *et al*., (*140,198*) reported that although ibogaine (50 mg/kg) challenge in rats was associated with a decrease in delta, theta, alpha and beta power spectra of cortical EEG during the first 30 min, and subsequent recovery of all except delta bands in the next 15 min, MK-801 (1 mg/kg) treatment was followed by a decrease in power of all four frequency bands for the entire time of recording. The selective power decrease in delta EEG frequency band of the cortical EEG may suggest the activation of dopamine receptors.

In the anesthetized rat, ibogaine produced a slight hypoglycemia (*60*). After administration of 50 mg/kg of ibogaine, elevations of corticosterone levels were noted 15 - 120 min, but not 24 hours later (*170,171,173*). The same dose of ibogaine rapidly and transiently increased plasma prolactin levels (171,173). Bunag and Walaszek (*199*) reported that ibogaine antagonized the contractile responses produced in guinea pig ileum by substance P and angiotensin. Alburges and Hanson (*200*) reported that ibogaine administration produced increases of neurotensin-like immunoreactivity in striatum, nucleus accumbens and substantia nigra and substance P -like immunoreactivity in striatum and substantia nigra. Ibogaine or harmaline suppressed

several (T-cell regulatory and effector, B-cell, and natural killer cell) immune functions *in vitro* (*201*). Van Beek *et al*., (*17*) reported that ibogaine showed activity against the gram-positive *Bacillus subtilis*. Ibogaine did not alter colonic temperature in mice, nor did it affect morphine- or kappa [U-50,488H]–opioid induced hypothermia (*121*).
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VIII. CONCLUSIONS.

The renewed interest in ibogaine during the past decade stems from anecdotal clinical observations that ibogaine offers a novel means of treating drug addictions. Preclinical studies are, in general, consistent with these claims. Thus, ibogaine reduces self-administration of cocaine and morphine, attenuates morphine withdrawal, and blocks conditioned place preference produced by morphine and amphetamine. Preclinical studies also suggest there is no abuse liability associated with ibogaine. At doses that interfere with tolerance and dependence phenomena, brain concentrations of ibogaine are at levels that can affect a variety of neurotransmitter systems. Many of these effects (e.g., use dependent block of NMDA receptor-coupled cation channels, interactions with dopamine transporters and kappa opioid receptors) have previously been implicated in drug seeking phenomena. However, at the present time, the only mechanism that can be invoked to explain ibogaine's effects on drug seeking phenomena with some certainty is its ability to inhibit naloxone-precipitated jumping through blockade of NMDA receptors. Nonetheless, it is still uncertain whether the anti-addictive properties of ibogaine result from a single mechanism or are produced at multiple loci.

The involvement of dopaminergic pathways in drug seeking phenomena can be considered dogma, and ibogaine undoubtedly affects these pathways. Nonetheless, based on available data no clear picture has emerged about how this interaction contributes to the anti-addictive properties of ibogaine, or any other anti-addictive medications. Additional systematic studies are obviously needed. Anecdotal reports claim long term effects of ibogaine on drug seeking following a single administration or short course of therapy. This claim has been borne out, at least in part, by preclinical studies. Based on these observations, it is unlikely that ibogaine serves simply as substitution therapy. It has been hypothesized that a long-lived metabolite is responsible for ibogaine's putative anti-addictive properties, but additional studies are required in this area.

One of the central issues regarding the molecular mechanisms responsible for the anti-addictive actions of ibogaine is whether its NMDA antagonist action is sufficient to explain these effects. Thus, there is an established body of preclinical data (and an emerging body of clinical data) demonstrating that NMDA antagonists interrupt drug seeking phenomena to a variety of addictive substances. Although it is now well established that ibogaine is a noncompetitive NMDA antagonist (albeit 1000-fold less potent than the prototype compound, dizocilpine), with the exception of its ability to block naloxone precipitated jumping in morphine-dependent mice, it is uncertain if these effects can be attributed to other mechanisms.

Recent structure activity studies demonstrate that *O*-desmethylibogaine, which is less potent than ibogaine at NMDA receptors, appears as active as ibogaine in acutely blocking morphine and cocaine self-administration. This observation strongly suggests that other mechanisms may be operative. A similar argument can be made for harmaline, which is somewhat structurally related to ibogaine and shares some of its pharmacological actions (e.g., tremor and neurotoxic effects, reductions in cocaine and morphine self-administration), but is not an NMDA antagonist. Although inhibition of

drug self-administration by harmaline may be due to unspecific effects (e.g., general malaise), these findings nonetheless raise the possibility that ibogaine's anti-addictive properties may be produced through multiple mechanisms. The involvement of sigma sites in these phenomena appears to be even more obscure because in contrast to ibogaine, harmaline has no appreciable affinity at sigma sites whereas *O*-desmethylibogaine lacks affinity at a sigma$_2$ site, yet all three block cocaine and morphine self-administration.

Ibogaine can affect several aspects of serotonergic transmission at concentrations that are readily achieved in the brain following pharmacologically relevant doses [reviewed by Sershen *et al*., (*188*)]. Because multiple serotonin receptor subtypes, as well as serotonin reuptake, are modulated by ibogaine, it is not surprising that the effects of this alkaloid on steady state levels of serotonin and its metabolites (whether measured *in situ* or *ex vivo*) are complex. Clearly, additional clinical studies are necessary to examine the efficacy of ibogaine as an anti-addictive agent. Similarly, additional preclinical studies will be required to elucidate the molecular mechanism(s) responsible for these pharmacological actions.

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TOP

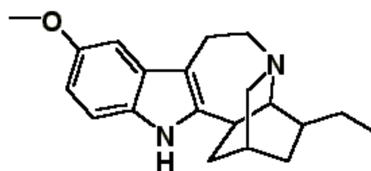
XI. Table 1. Interactions of ibogaine with neurotransmitter systems: radioligand binding studies.

Receptor system	Ligand	K_i or IC_{50}† [μM]	Reference
Alpha-adrenergic$_1$	prazosin	7.2 ± 3.0†	*166*
Dopamine transporter	WIN 35,248	1.5†	*76*
Dopamine transporter	WIN 35,248	3.5 ± 0.6†	*166*
Dopamine transporter	RTI-121	2.0	*73*
Dopamine transporter	RTI-55	4.11 ± 0.45†	*167*
Monoamine transporter (vesicular)	tetrabenazine	2.23 ± 0.22†	*167*
Muscarinic M_1	pirenzepine	7.6 ± 0.7†	*166*
Muscarinic M_2	AF-DX384	5.9 ± 1.4†	*166*
Nicotinic	nicotine	4.0 ± 0.6	*125*
Nicotinic noncompetitive	carbamylcholine-induced $^{22}NaCl$ influx	0.02 ± 0.007†	*125*
NMDA ion channel	MK-801	1.0 ± 0.1	*159*
NMDA ion channel	MK-801	1.1 ± 0.03	*72*

NMDA ion channel	MK-801	5.6 ± 0.8†	*166*
NMDA ion channel	MK-801	4-10	*191*
NMDA ion channel	MK-801 or TCP	0.01-0.05 and 2-4	*202*
NMDA ion channel	TCP	1.5 ± 0.3	*119*
Opioid	naloxone	0.13 ± 0.03	*183*
Opioid (kappa)	U69,593	2.1 ± 0.2	*165*
Opioid (kappa)	U69,593	29.8 ± 8.3† (rat) 13.8 ± 0.6† (mouse) 21.0 ± 1.1† (giunea-pig)	*72*
Opioid (kappa)	U69,593	5.5	*56*
Opioid (kappa)	U69,593	3.77 ± 0.81	*124*
$Serotonin_2$	ketanserin	4.8 ± 1.4†	*166*
$Serotonin_3$	GR-75558	3.9 ± 1.1†	*166*
Serotonin transporter	RTI-55	0.55 ± 0.03	*73*
Serotonin transporter	RTI-55	10	*168*
Serotonin transporter	RTI-55	0.59 ± 0.09†	*167*
Serotonin transporter	paroxetine	9.30 ± 1.70†	*167*
Sigma	haloperidol	0.003†	*164*
Sigma	pentazocine	0.086†	*11*
$Sigma_1$	pentazocine	9.3 ± 0.63	*194*

$Sigma_1$	pentazocine	8.6 ± 1.1	*193*
$Sigma_1$	pentazocine	1.5-3	*202*
$Sigma_2$	DTG	0.0904 ± 0.0101	*194*
$Sigma_2$	DTG	0.201 ± 0.023	*193*
$Sigma_2$	DTG	1.5-3	*202*
Voltage-dependent sodium channels	batrachotoxin A 20-a-benzoate	8.1 ± 1.3	*165*

LEGEND TO TABLE 1. Presented are K_i or IC_{50} (†) values for various neurotransmitter systems affected by ibogaine with affinities higher than 10 μ M. The affinities of *O*-desmethylibogaine for the corresponding receptors are presented in footnotes.



ibogaine