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Ibogaine and Noribogaine: Comparing Parent Compound to Metabolite

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ABSTRACT

Ibogaine is one of the psychoactive alkaloids found in the West African shrub *Tabernanthe iboga*. Since the 1980s, a series of US patents have claimed efficacy for ibogaine in the treatment of drug addiction. Since then, more than 60 scientific publications on ibogaine and drug addiction have been published. Ibogaine has an acute and a prolonged effect on neurochemistry and behavior. Its metabolite, noribogaine (12-hydroxyibogamine), is produced through metabolic demethylation soon after oral ibogaine administration. Although, they share similar chemical structures, ibogaine and noribogaine display different binding profiles. In rodents both, ibogaine and noribogaine, decreased morphine and cocaine intake and modulated dopaminergic transmission. In rats trained to discriminate ibogaine from saline, complete generalization to noribogaine was obtained. Attempts to correlate brain levels of both, the parent compound and the metabolite indicate that noribogaine is primarily responsible for ibogaine discriminative stimulus. Ibogaine-induced neurotoxicity tends to occur at doses much higher than the proposed dose for humans, but caution is important when extrapolating data from ibogaine's effects observed in rodents. Although a definitive clinical validation of purported ibogaine effects is still unavailable, ibogaine has opened new perspectives in the investigation of pharmacotherapies for drug addiction.

INTRODUCTION

Ibogaine is one of the naturally occurring psychoactive alkaloids found in the West African shrub *Tabernanthe iboga*. Extracts of iboga are used for religious purposes in Af-

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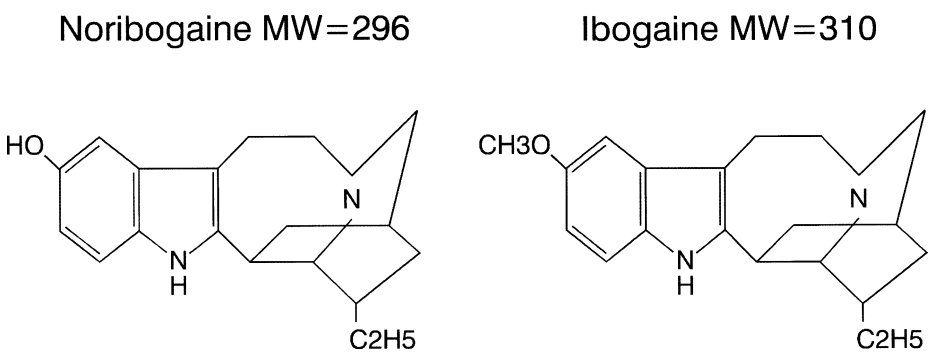

Fig. 1. The structures of noribogaine and ibogaine.

rican cults. The earliest Western reference to this plant dates from 1864, when the surgeon Griffon du Bellay described the plant as "*an aphrodisiac and a stimulant of the nervous system*." This plant was named *Tabernanthe iboga* in 1889, when the first botanical description of it was completed. In 1901, the crystalline alkaloid from the *iboga* root was isolated and named ibogaine (83).

Ibogaine became publicly available during the 1930s, when a tablet containing about 8 mg of ibogaine named Lambarene was marketed in France. Its use became popular among athletes as a performance-enhancing drug. Ibogaine was finally banned in many countries after reports of its hallucinogenic properties. In 1970, the United States Food and Drug Administration (FDA) classified ibogaine as a Schedule I substance, which means that all nonresearch use is forbidden (83).

Since the 1980s, United States patents, Nos. 4,499,096 (49), 4,587,243 (50), 4,857,523 (51), 5,026,697 (52), and 5,152,994 (53), have claimed efficacy for ibogaine in the treatment of opiate, stimulant, alcohol, nicotine, and polydrug addiction, respectively. These claims have caught the attention of scientists, and since then more than 60 scientific publications addressing several issues related to ibogaine and drug addiction have been released.

In rats, ibogaine and ibogaine-related alkaloids dose-dependently decreased morphine and cocaine intake, which was not due to motor impairment produced by the alkaloids (32). Ibogaine had either an acute or prolonged effect on morphine self-administration (28). Also, the consumption of other addictive substances, such as alcohol (88) and cocaine (97), was attenuated by ibogaine in alcohol-preferring rats and C57BL/6BY mice, respectively.

Ibogaine produced a significant reduction of certain signs of naloxone-precipitated withdrawal in morphine-dependent rats independently of the motor-impairing effects of ibogaine (30). However, other studies reported failure of ibogaine to reduce naloxone-precipitated withdrawal in morphine-dependent rats (102) or to interrupt the expression of a previously established morphine-place preference (54).

Reports indicating that ibogaine might produce toxic neurological reactions has hindered comprehensive research with humans subjects. It has been reported that doses of ibogaine (100 mg/kg) produced intense glial activation in the cerebellum of male Sprague–Dawley rats (71). This finding is highly suggestive of a potential for ibogaine to induce injury to cerebellar neurons. These neurotoxic reactions were further characterized

to be of the excitotoxic degeneration type, possibly occurring via activation of the inferior olivary nucleus (70).

Since the levels of ibogaine in plasma could not explain its protracted actions, an ibogaine metabolite, which lasts in human plasma for a longer period than the parent compound, has been considered as a tentative explanation for the prolonged effects. The long-term effects of ibogaine have proved to last at least 19 h in certain behavioral and neurochemical investigations (59).

The research on ibogaine has pioneered new courses in the development of pharmacological tools to treat drug addiction. Since pharmacotherapies for drug addiction have focused on single modes of action, ibogaine with its multiple action has been considered a prototype of a new class of potentially useful antiaddicitive agents (36). In the so called interference therapy, agents would be expected to modulate or interfere with the mode of action of the abused drug (36). Although ibogaine research is not yet conclusive, it has expanded its scope to the assessment of ibogaine metabolite and congeners, which might help to define a therapeutic opportunity for *iboga* alkaloids in the future. Also, through ibogaine investigation, a further clarification of addiction-related phenomena may be achieved. This review on ibogaine and noribogaine research aims to put together several pieces of this challenging and interesting scientific puzzle.

PHARMACOKINETIC AND PHARMACODYNAMIC ISSUES

Uncontrolled assessments with human subjects have reported a long-term promotion of drug abstinence in humans after ibogaine administration (103). These anecdotal reports were coincident with the demonstrated long-term effects of ibogaine on cocaine and morphine self-administration in rats (17,28). These questions have led to the hypotheses that ibogaine would remain in the body for long periods or that active metabolites could be responsible for the protracted effects.

Animal Studies

The half-life of ibogaine in rodents was previously observed to be about 1 h (22). In male NMRI-mice, after intravenous injection of ibogaine (10 mg/kg), maximal brain concentrations were achieved in 10 s (110). Ibogaine achieves widespread distribution throughout the body of rats at 1 h after i.p. and at 12 h after s.c. administration, but particularly high concentrations of the alkaloid were found in the brain and fatty tissue (44). Higher ibogaine levels were found in most tissues of female Sprague–Dawley rats after s.c. administration when compared to the administration by the i.p. route (44).

The significant correlation between the distribution coefficient and maximal brain concentration of certain *iboga* alkaloids, including ibogaine and noribogaine, indicates that lipid solubility is an important factor for the initial concentration of the alkaloids in the brain (110). The 100-fold concentration of the drug in fatty tissue is consistent with the highly lipophilic nature of ibogaine (44). Ibogaine is lipophilic and concentrated in fat, and might be converted to noribogaine after slow release from fatty tissue (44). Adipose

tissue may serve as a reservoir of ibogaine, generating the release and metabolism over longer periods (44).

Both the parent compound and metabolite have high buffer partition coefficients indicating an ability to penetrate the blood-brain barrier (110), which is consistent with the rapid entry of ibogaine into the brain as shown elsewhere (104). It was hypothesized that sequestration of ibogaine into lipophilic compartments in the brain may result in lower drug concentrations in the extracellular fluid and that noribogaine may achieve higher extracellular fluid concentration than the parent compound due to the more polar nature of the metabolite (104). Slow elimination of noribogaine could result from *O*-demethylation of central nervous system (CNS)-stored ibogaine, which could contribute to some of the reported aftereffects of single dose of ibogaine (104).

One hour after the administration of ibogaine its levels in whole brain and in plasma were higher in female than in male rats (79), suggesting that the amount of ibogaine reaching the plasma and brain compartments is gender related. Nevertheless, there is no definitive explanation to account for the greater bioavailability of ibogaine in females compared with males.

Pharmacokinetic studies demonstrate that both ibogaine and noribogaine are found in rat brains following oral administration (50 mg/kg) at levels ranging from 1 to 17 μM (104). Plasmatic, cortical, and cerebellar concentrations of both ibogaine and noribogaine in male hooded rats increased according to the dose of ibogaine administered systemically, producing concentrations of noribogaine greater than those of ibogaine in the plasma and in the cerebral cortex but not in the cerebellum (111). In mouse brain, maximal concentrations of ibogaine and noribogaine after 10 mg/kg i.v. injection of each alkaloid were 47.6 (μg/g wet weight) and 14.7 (μg/g wet weight), respectively (110).

The pharmacological relevance of micromolar brain concentrations of ibogaine and noribogaine is supported by a series of studies which demonstrated that doses of ibogaine within the 30–80 mg/kg range are active in behavioral studies designed to assess reinforcing effects, tolerance, and withdrawal symptoms associated with psychomotor stimulants and opiates as well as control of discriminative stimulus (9,17,28, 30,111).

Human Studies

Using quantitative gas chromatography/mass spectrometry, it was possible to detect the ibogaine metabolite 12-hydroxyibogamine (noribogaine) in brain and biological fluids (38,63). Pharmacokinetic analysis of the clearance rates for the parent compound and metabolite suggest that noribogaine has a relatively long half-life in blood of drug dependent patients (63). While the majority of absorbed ibogaine is eliminated within 24 h postdose (>90%), the concentration of the metabolite was still quite appreciable (63). In individuals given 5 mg of ibogaine-HCl, the alkaloid could not be detected in urine after 4 h using thin-layer chromatography (48).

Noribogaine is produced by metabolic demethylation of ibogaine soon after oral ibogaine is given, indicating first-pass metabolism. Cytochrome P4502D6 catalyzes the *O*-demethylation of ibogaine to noribogaine (68). The most probable site for metabolic demethylation of ibogaine is the methoxy group (68). Both ibogaine and noribogaine are stable in a human plasma matrix at room temperature for a period of at least 1 week (2).

Uncontrolled observations in humans indicate that ibogaine is capable, in some individuals, of reducing withdrawal symptoms and of suppressing drug taking behavior (103). Ibogaine had been administered to opiate and cocaine addicts in Europe and Central America through an informal self-help network (100). A phase I pharmacokinetic and safety trial on cocaine-dependent volunteers was initiated at the University of Miami with the approval of the Drug Advisory Committee of the FDA to evaluate any possible therapeutic and/or toxic effect in humans. In the trial, 1 and 2 mg/kg of ibogaine were administered to volunteers ($n = 9$) with recent histories of cocaine abuse. No significant posturographic abnormalities or clinical evidence of permanent ataxia were found in the subjects. In open-label studies conducted elsewhere, 30 (23 male, 7 female) drug-dependent subjects were assigned to one of three fixed-dose treatments under open-label conditions: 500, 600, and 800 mg of ibogaine. Preliminary results demonstrated that single oral doses of ibogaine were well tolerated in drug-dependent subjects and that there were no significant safety problems within this dose range. The most frequent side effects observed were nausea and mild tremor (65).

RECEPTOR SITES INVOLVEMENT

Ibogaine and noribogaine have different affinities for several molecular targets (104,105). Although sharing similar chemical structures, noribogaine and ibogaine display different binding profiles. Noribogaine binds to the serotonin (5-HT) transporter in the mid-nanomolar range with a 10-fold higher potency than ibogaine and elevates 5-HT levels in the same range compared to ibogaine (63). Noribogaine was 50-fold more potent at displacing radioligand binding at the 5-HT transporter than at the dopamine (DA) transporter (63).

Noribogaine inhibited the binding of the cocaine congener [^{125}I]RTI-55 to the 5-HT transporter with very high potency ($IC_{50} = 0.04 \pm 0.01$ μM; $K_i = 40.7 \pm 11.6$ nM) (63,104); however, ibogaine and noribogaine exhibited 15- to 20-fold lower potency for inhibition of paroxetine binding to the 5-HT transporter, which might be due to the non-identity of binding sites associated with the 5-HT transporter. It has been suggested that ibogaine displays different DA transporter binding affinities depending upon the radioligand used to label these sites, possibly because ibogaine recognizes different domains on the DA transporter protein (7).

Conflicting results have been found regarding ibogaine and noribogaine affinities for the 5-HT_{1A} and 5-HT_2 receptors. Studies have shown the absence of significant potency in both the parent compound and the metabolite for binding to the 5-HT_{1A} and 5-HT_2 receptors (104) or a lack of affinity of ibogaine for serotonin receptors (types 1_A, 1_B, 1_C, 1_D, 2, and 3) (20). Another study demonstrated, however, potencies in the low micromolar range for ibogaine binding to the 5-HT_2 ([^{3}H]ketanserin, $K_i = 4.8 \pm 1.4$ μM) and 5-HT_3 ([^{3}H]GR-65630, $IC_{50} = 3.9 \pm 1.1$ μM) receptor subtype (105). Ibogaine did not inhibit binding at the $5HT_1$ receptor in concentrations of up to 1 mM (105).

In radioligand binding assays, ibogaine and noribogaine were equipotent at the DA transporter (63). Although both compounds failed to significantly elevate DA levels, higher doses produced a trend towards increased synaptic DA concentrations (63). In fact,

it was observed that ibogaine can produce variable effects on DA extracellular levels depending on dose selection (86). Local perfusion with ibogaine produced a biphasic dose-dependent effect on DA levels: lower concentrations ($10^{-6} – 10^{-4}$ M) of ibogaine decreased whereas higher concentrations ($5 \times 10^{-4} – 10^{-3}$ M) strongly stimulated DA levels (86). The former effect, decreasing DA levels, is consistent with previous microdialysis studies on local ibogaine effects, which demonstrated a significant decrease in DA levels (31). The former effect, enhancing DA levels, is consistent with previous studies on mouse striatal slices, which demonstrated a significant augmentation of preloaded [^{3}H]DA efflux after 10^{-5} M ibogaine administration (37).

Ibogaine and noribogaine may interact with the DA transporter in a similar manner to cocaine, but with a lower potency, or they may function as cocaine partial agonists at the DA transporter, blocking the access of cocaine and decreasing the rapid elevation of DA which mediates the rewarding effects of cocaine (104). At the nerve terminal level, ibogaine releases DA, and the primary source for this release is probably the cytoplasmic pool (37). Ibogaine displays moderate affinity for the vesicular monoamine transporter and may regulate the distribution of DA between vesicular and cytoplasmic pools (104). It was suggested that stimulation of DA release is mediated by ibogaine interaction with the DA transporter in an amphetamine-like manner (86). Ibogaine would stimulate DA levels by inhibiting the dopamine transporter.

Reuptake studies have shown that ibogaine at 100 μM does not significantly inhibit [^{3}H]GBR-12935 binding to the DA transporter protein (15). Ibogaine did not affect either the binding of [^{3}H]WIN 35,248 to the cocaine binding site in striatal tissue measured *in vitro* (98), or SCH 23390 or *N*-methyl spiperone binding to D_1 and D_2 receptors, respectively (20). Ibogaine did not inhibit binding at D_1, D_2, D_3, and D_4 dopaminergic receptors subtypes (105).

Ibogaine has been described to competitively inhibit the binding of PCP-like radioligands such as [^{3}H]MK-801 (81) and [^{3}H]TCP (105) to the *N*-methyl-D-aspartate (NMDA) receptor–coupled ion channels. Ibogaine is 4–6-fold more potent than noribogaine in inhibiting [^{3}H]MK-801 binding, but both drugs are 50–1000-fold less potent than dizocilpine with regard to binding to the NMDA receptor complex (64). Both ibogaine and noribogaine competitively displace specific [^{3}H]MK-801 binding to caudate and cerebellar membranes from postmorten human brain with submicromolar and micromolar affinities (64). It has been observed that modification of the ibogaine molecule can alter its affinity for NMDA receptors (47). Ibogaine interacts with PCP binding sites located in the ionophore of the NMDA receptor complex and with σ binding sites (45). Ibogaine displays significant affinity for the σ_2 sites and lower affinity for the σ_1 sites, whereas noribogaine had lower affinity than the parent compound to any of these receptor sites (13,55,104).

Noribogaine is more active than ibogaine at both μ- and κ-opioid receptors and, unlike ibogaine, is active at the δ receptor (75,78,104). Ibogaine selectively inhibits the development of tolerance to morphine, a μ-opioid receptor agonist, but not to U-50,488 or DPDPE, κ- and δ-opioid receptor agonists, respectively (16). Ibogaine interacts significantly with κ- (87) and μ-opioid (19) receptors, expressing at the latter a two-site binding model. Noribogaine acts as a full agonist at the μ-opioid receptor with a level of intrinsic activity comparable to the full agonists DAMGO and morphine (75). Evidence for roles of κ-opioid and NMDA receptors in the mechanism of the action of ibogaine have been presented elsewhere (36).

Ibogaine has been regarded as a noncompetitive blocker of nicotinic receptors, since it has blocked $^{22}NaCl$ influx through the ganglionic-type nicotinic receptor channels of rat pheochromocytoma PC12 cells (5). Low concentration of ibogaine had a potent inhibitory action on nicotinic acetylcholine receptor-mediated catecholamine release as observed in cultured chromaffin cells (96). Ibogaine inhibits human muscle-type and ganglionic nicotinic acetylcholine receptors with IC_{50} values of 22.3 and 1.06 μM, respectively (27).

MOTIVATIONAL EFFECTS

Self-Administration

In female Sprague–Dawley rats, ibogaine dose-dependently decreased morphine intake in the hour after ibogaine treatment and, to a lesser extent, 1 day later (28). Although the acute effect could be attributed to motor impairment, a protracted effect was observed, which occurred when there were no signs of ibogaine-induced impairment. Ibogaine has also an inhibitory effect on cocaine self-administration in male Wistar rats (17). A single injection of ibogaine 40 mg/kg produced a significant decrease of cocaine intake, which remained unaltered for more than 48 h (17).

It has been proposed that the effects of ibogaine on morphine self-administration might be at least partially mediated by a combination of κ-opioid agonist and NMDA antagonist actions (36). A combination of a κ-opioid antagonist (nor-binaltorphimine; norBNI) and an NMDA agonist (NMDA) significantly antagonized the decrease of morphine self-administration produced by ibogaine in female Sprague–Dawley rats, while neither norBNI nor NMDA alone had significant effect (36).

Ibogaine produced an attenuation of three different schedules of reinforcement, food, cocaine or heroin, in three groups of rats under a FR 10 schedule in male Fischer 344 rats (24). However, no long-term effect of ibogaine on responding maintained by drug reinforcement was observed in this study, which contrasts with previous reports of long-term reductions of morphine (28) and cocaine (17) self-administration produced by ibogaine. Differences in animal gender, strain, and schedule of reinforcement were postulated to account for the different findings (24).

It has been observed in female Sprague–Dawley that the 'anti-addictive' and tremorigenic effects of the *iboga* alkaloids are dissociated (32). Harmaline, which compared to ibogaine produces tremors, did not present any protracted effect on drug self-administration. However, the *R*-enantiomers of both ibogamine and coronaridine had significant prolonged effect on self-administration. Neither the *R*- nor the *S*-enantiomers of these agents produced any significant tremorigenic activity. Actually, *R*-ibogamine and *R*-coronaridine significantly decreased accumbal and striatal dopamine levels, whereas *S*-ibogamine and *S*-coronaridine had no significant effects. Thus, the effects of these alkaloids on drug self-administration appear to be related to an initial decrease of dopaminergic activity (32).

Noribogaine (40 mg/kg) decreased morphine and cocaine self-administration, reduced the locomotor stimulant effect of morphine, and decreased extracellular levels of dopamine in the nucleus accumbens and striatum of female Sprague–Dawley rats. These ef-

fects were similar to previously observed effects of ibogaine (40 mg/kg), although noribogaine did not induce any ibogaine-like tremors (34).

It has been shown that 18-methoxycoronaridine, an *iboga* alkaloid congener which presented no apparent tremorigenic effect and no evidence of cerebellar toxicity after a high dose (100 mg/kg), decreased morphine and cocaine self-administration and the extracellular levels of dopamine in the nucleus of female Sprague–Dawley rats (33). Indeed, in morphine self-administration experiments, 18-methoxycoronaridine produced a downward shift in the entire morphine dose–response curve (58).

Precipitated Withdrawal

It has been reported that ibogaine administered intracerebroventricularly (4–16 μg) attenuated naloxone-precipitaded withdrawal signs in morphine-dependent Wistar rats (25). Other studies supported the idea that ibogaine is capable of soothing morphine withdrawal. Ibogaine (40 and 80 mg/kg, i.p.) administered to morphine-dependent Sprague–Dawley rats 30 minutes prior to a naltrexone challenge significantly reduced the occurrence of four withdrawal signs (30). In order to avoid the interference of ibogaine-induced tremors in the expression of the opioid-induced withdrawal, ibogaine 40 mg/kg was administered 4 h prior to naltrexone, and a significant reduction of the same four withdrawal signs was observed (30).

Not only ibogaine (40 mg/kg, i.p.) but also norharman (20 mg/kg, i.p.), a physiological substance structurally related to ibogaine and found in elevated levels in the plasma of alcoholics and heroin addicts, inhibited morphine withdrawal syndromes in male Wistar rats (18). The ibogaine congener 18-methoxycoronaridine also attenuated some of the morphine withdrawal signs in rats (90).

Other reports, however, indicated that ibogaine failed to reduce these signs in the morphine-dependent mice (26) and rats (102). Although ibogaine-pretreated male Sprague–Dawley rats presented decreased grooming compared with vehicle controls, any other opiate withdrawal sign precipitated by naloxone was reduced in either nontremorigenic (5 and 10 mg/kg, s.c.) or behaviorally toxic (20 and 40 mg/kg, s.c.) doses (102). In morphine-dependent mice, ibogaine did not reduce withdrawal signs but significantly increased the number of vertical jumps induced by naloxone within different epochs of chronic morphine treatment (26). In morphine-dependent monkeys, ibogaine reduced the total number of withdrawal signs but did not substitute completely for morphine, although signs of toxicity were evident particularly at the highest dose (8 mg/kg, s.c.) (1).

The discrepancies between the positive and negative findings may reflect different research protocols adopted in these studies, including rat strains, route of administration, and dose of naloxone. It is noteworthy that s.c. injections of ibogaine failed to block opiate withdrawal in animal as well as to reduce alcohol intake in alcohol-preferring rats (see below), whereas the i.p. route administration produced positive results in both circumstances. As mentioned previously, considerably higher ibogaine levels were detected in most tissues, particularly in fat, after s.c. administration (44). Factors, such as formation of local depots, poor absorption of ibogaine into the circulation, and lack of metabolic activation by the liver after s.c. administration, were cited as possible causes for ineffectiveness (88).

In the plus-maze test, acutely increasing doses of ibogaine given to mice produced a reduced aversion to the open arms. After abrupt cessation of cocaine administration, ibogaine significantly enhanced the time spent in the open arms, reversing the aversive state (74).

Two-Bottle Choice Procedure

It has been shown that, when injected i.p. or i.g. but not s.c., ibogaine can significantly reduce alcohol intake without an effect on blood alcohol concentration or food intake in three strains of alcohol-preferring rats in a two-bottle choice procedure (88). The failure of s.c. administration of ibogaine to reduce alcohol intake may be due to the poor absorption of ibogaine into the circulation, which includes the formation of depots (88). Ibogaine itself may be ineffective in reducing alcohol intake, possibly due to reduced first-pass metabolism and hence to lower levels of noribogaine.

A single injection of 18-methoxycoronaridine (i.p.) significantly attenuated alcohol-preferring rats' preference for alcohol and alcohol consumption in a two-bottle choice procedure (89). Ibogaine reduced preference of C57BL/6By mice for cocaine consumption, which was developed after a period of forced exposure to either cocaine HCl or water (97).

Place Preference

In male Sprague–Dawley rats, ibogaine failed to interrupt the expression of a previously established morphine place preference (54). Nevertheless, ibogaine interfered with the establishment of place preference induced by morphine (77) or amphetamine (67).

OTHER BEHAVIORAL EFFECTS

Drug Discrimination

It has been shown that rats can be trained to discriminate the interoceptive stimuli elicited by ibogaine (10 mg/kg) which produced, at best, intermediate ibogaine-appropriate responding to drugs acting on 5-HT and/or with hallucinatory properties (95). Similarly, male Fischer-344 rats trained on the serotonergic compounds, lysergic acid diethylamide (LSD), a nonspecific 5-HT agonist, and 2,5-dimethoxy-4-methylamphetamine (DOM), a selective 5-HT_2 agonist, did not generalize fully to the ibogaine stimuli (76). Rats trained on fenfluramine did not generalize the fenfluramine discriminative stimulus to different doses of ibogaine (94). In ibogaine trained male Fischer-344 rats, a series of monoamine reuptake inhibitors caused significant increase in ibogaine-appropriate responding (108). Although the 5-HT_{2C} antagonist properties of metergoline blocked ibogaine generalization to the 5-HT_{2C} agonists, MK-212 and mCPP, metergoline was ineffective in blocking ibogaine discrimination, suggesting that, although ibogaine may act as an agonist at 5-HT_{2C} receptors, this interaction is not essential to its discriminative cue (43).

In mice trained on dizocilpine (0.17 mg/kg) in a T-shaped maze drug discrimination procedure, ibogaine produced a dose-dependent increase in the percentage of mice choosing the arm of the T-maze associated with the training dose of dizocilpine (82). Although activity at a common site labelled by PCP-like radioligands such as [^{3}H]MK-801 and by [^{3}H]TCP is considered to be predictive of PCP-like discriminative stimulus effects (107), neither phencyclidine (PCP) nor dizocilpine, both noncompetitive NMDA-antagonist drugs, substituted for the ibogaine stimulus in rats trained on ibogaine (10 mg/kg, i.p., 60-min pretreatment time) (46). Ibogaine also failed to produce PCP-like discriminative stimulus effects in monkeys and rats trained to discriminate PCP (0.1 mg/kg) from sham injection (46). In mice trained in a T-maze to discriminate the low-efficacy partial agonist of the glycine site (+)-HA-966 (170 mg/kg, i.p.) from saline, ibogaine did not substitute for the training drug (109).

Intermediate levels of generalization were observed with the subtype nonselective σ ligands; 3-(3-hydroxyphenyl)-*N*-(1-propyl)-piperidine [(+)-3-PPP] and 1,3-di(2-tolyl)guanidine (DTG) but not with the σ_1-selective agents (+)-*N*-allyl-normetazocine [(+)-SKF 10,047] and (+)-pentazocine (41). Although neither morphine, the prototypic μ-agonist, nor κ-selective agonists, bremazocine and U-50,488, substituted for ibogaine, intermediate levels of generalization were observed with the mixed action opiates (–)-SKF 10,047, (±)-pentazocine, nalorphine, diprenorphine, and the opiate antagonist naltrexone but not with naloxone or the selective κ-antagonist norBNI (41). Naloxone produced complete antagonism of the ibogaine-appropriate responding produced by both (–)-SKF 10,047 and nalorphine (41). These findings indicate that σ_2 and opiate receptors may be involved in the mediation of ibogaine effects.

In male Fischer-344 rats trained with ibogaine (10 mg/kg, 60-min pretreatment time, i.p. injection), 6-methoxyharmalan completely substituted (86.3%) for the ibogaine stimulus; partial substitution was observed with harmine, harmane, harmalol, and tetrahydro-β-carboline (THBC) (42). These findings provide evidence for an ibogaine-like effect of certain β-carbolines. Ibogaine did not affect cocaine discrimination in male Sprague–Dawley rats trained to discriminate cocaine from its vehicle (93).

Fischer-344 rats trained to discriminate ibogaine (10 mg/kg, i.p., 60-min pretreatment time) from water achieved intermediate generalization to the ibogaine metabolite noribogaine (12-hydroxyibogamine), whereas complete generalization was obtained to the chemically related compound harmaline (40). Recent investigations indicate that noribogaine is the major factor responsible for the ibogaine discriminative stimulus (111). Male hooded rats trained to discriminate ibogaine (10 mg/kg) from saline presented complete generalization to noribogaine at doses of 3.2, 10, and 20 mg/kg, and the ED_{50} for noribogaine was 1.98 mg/kg compared with 4.51 mg/kg for ibogaine, indicating the greater potency of the metabolite (111).

Locomotor Activity

When administered 1 h prior to cocaine, ibogaine as well as noribogaine decreased hyperactivity induced by cocaine. In contrast, when administered 19 h prior to cocaine, both substances potentiated the locomotor activity induced by cocaine in female Sprague–Dawley rats (57). These findings could not be explained by motor impairment since

neither ibogaine nor noribogaine produced a deficit in motor activity following saline administation.

It has been previously observed that ibogaine reduced cocaine-induced locomotor stimulation in C57BL/6 mice when given 2 h prior to a cocaine injection (98). However, when administered 19 h prior to cocaine injection in Sprague–Dawley rats, ibogaine stimulated the motor activity induced by cocaine (57). Similarly, ibogaine has reduced amphetamine-induced locomotor stimulation in C57BL/6By mice, but stimulated it in rats (99). Ibogaine pretreatment given 19 h earlier enhanced the stimulatory motor effects induced by a wide range of D-amphetamine doses (60) but decreased the stimulatory motor effects induced by a wide range of morphine doses (62).

Locomotion was significantly lower in ibogaine-treated male Long Evans rats that had previously been exposed to amphetamine than in rats that had not (12). It was suggested that ibogaine might help to decrease induced levels of DA activity in drug-experienced animals or humans from elevated, sensitized levels back to baseline levels (12). Similarly, doses of ibogaine (5 and 10 mg/kg) which alone were inactive, inhibited morphine-induced locomotor activity in rats preatreated with morphine (80). It was suggested that variable histories of opioid exposure might account for individual differences in the efficacy of ibogaine to inhibit opioid addiction (80).

Ibogaine administered 22 h earlier did not attenuate the hyperlocomotion evoked by nicotine in rats (8). In male hooded rats, coadministration of ibogaine with nicotine had no effect either on the degree of sensitization developed after chronic nicotine or on the expression of the sensitized response to 0.4 mg/kg of nicotine (112). In the elevated plus-maze test, when rats were pretreated (22 hours) with ibogaine (40 mg/kg), both saline- and nicotine-treated rats displayed significant reductions in the open arms entries, indicating an ibogaine-induced anxiogenic effect (8). These results are not in agreement with data observed in mice elsewhere (74).

Antagonism of morphine-induced increase of locomotor activity was observed in female but not in male rats (79). Either at 19 h after ibogaine (10–60 mg/kg, i.p.) administration, or at 1 h after noribogaine (5–40 mg/kg, i.p.) antagonism of morphine was significantly greater in female than in male rats (79). In this study, route of administration played a significant role in determining the efficacy of ibogaine antagonism of morphine-induced locomotor activity, with s.c. administration of ibogaine producing greater antagonism of morphine-induced activity than with a comparable i.p. dose (79). Nevertheless, although locomotor activity following saline injection did not differ between sexes, either parent compound or metabolite produced significant effects on basal locomotor activity, which could possibly influence the interaction among ibogaine, noribogaine and morphine.

Antinociception

Ibogaine and noribogaine increased morphine antinociception in morphine-tolerant mice (101). When co-administered with morphine, ibogaine increased both the degree and duration of morphine antinociception. However, when ibogaine was given 19 h earlier, there was a reduction of morphine antinociception (6). Noribogaine, when co-administered with morphine, simulated the results produced by ibogaine–morphine co-admmistration, although noribogaine produced a more pronounced antinociception than the compa-

rable ibogaine treatment. Noribogaine did not present a significant effect after the 19 h pretreatment infusion (6).

It was later reported that several doses of ibogaine, when given 10 min before assessment, did not modify the antinociceptive effects of morphine, U50, 488H, and [D-Pen2,D-Pen5]enkephalin (DPDPE), respectively μ-, κ-, and δ-opioid receptor agonists (10). Noribogaine (40 mg/kg) produced an increase of morphine (5 mg/kg)-induced antinociception, but it had no effect on the U50,488H, or DPDPE effects, providing evidence for a possible interaction between noribogaine and μ-opioid receptors (10).

Noribogaine significantly attenuated the development of tolerance to the antinociceptive action of morphine in mice (9), indicating that the ibogaine metabolite may be mediating the inhibitory effect of ibogaine on morphine tolerance *in vivo*.

NEUROCHEMISTRY

Several neurotransmitters exert their cellular effects through a modulation of adenylyl cyclase activity. It has been demonstrated that although neither ibogaine nor noribogaine alone regulated adenylyl cyclase activity, both compounds potentiated the receptor-mediated inhibition of enzyme activity by opioid and 5-HT receptors but not by muscarinic acetylcholine receptors (84).

Strong ibogaine induction of *c-fos* in cortex, hippocampus, and paraventricular hypothalamus indicated these areas as possible neuroanatomical/neurochemical substrates for the psychopharmacological properties of ibogaine, since the localization of the nuclear early/immediate gene product *c-fos* can act as a biomarker for the ibogaine effect on cells in various brain regions (91).

Noribogaine but not ibogaine produced an increase in [^{3}H]inositol phosphate (IP_3) in either striatal or hippocampal slices. Since the addition of tetrodoxin cadmium chloride, or Na^+ and Ca^{2+} channel blockers did not alter noribogaine-induced IP_3 production, noribogaine appears to produce a direct effect on phosphoinositide turnover (85). It is proposed that IP_3 augmentation might be associated with protein kinase activation, which in turn might be involved in the production of long term neurochemical effects (85).

Ibogaine increases corticosterone secretion, elevates prolactin plasma levels, and produces acute reduction of DA levels and elevation of levels of DA metabolites, homovanilic acid (HVA), and 3,4-dihydroxyphenylacetic acid (DOPAC), in striatum and frontal cortex (4). Ibogaine either decreased 5-HT and its metabolite 5-hydroxyindole acetic acid (4) or had no appreciable effect on 5-HT levels (7). Preliminary data suggest that, while noribogaine may be more effective than ibogaine in inhibiting 5-HT reuptake, ibogaine may cause the release of 5-HT (36).

Ibogaine at low concentrations (<10 μM) was found to inhibit nicotinic receptor-mediated catecholamine release selectively, providing *in vitro* evidence for an ibogaine mechanism of action at nicotinic ACh receptors (56). In [^{3}H]DA uptake evaluation, ibogaine significantly inhibited [^{3}H]DA uptake from striatal synaptosomes, suggesting that ibogaine affects DA levels by inhibiting the DA transporter. In a way similar to the effect of amphetamines, pretreatment with the tyrosine hydroxylase inhibitor, α-MPT, significantly reduced the effect of ibogaine on striatal DA levels (86). Neurotensin systems may

be involved in ibogaine effects since ibogaine treatment affected neurotensin systems by increasing striatal, nigral, cortical, and accumbal neurotensin-like immunoreactivity (3).

Microdialysis

It has been observed that acute administration of most addictive drugs, including cocaine, amphetamine, and nicotine, increase the levels of DA release (23). In the mesocortical and mesolimbic pathways, the neuronal bodies are located in the ventral tegmental area (VTA) projecting to the prefrontal cortex (PFC) and nucleus accumbens (NAC). Since DA transmission appears to be so intimately involved with the central effects of drugs of abuse, several studies on microdialysis were conducted to assess the putative therapeutic effects of ibogaine (32,59,61).

The effect of a single ibogaine (40 mg/kg) dose on the extracellular levels of DA and its metabolites HVA and DOPAC has been investigated at various times after ibogaine administration (62). One hour after ibogaine (40 mg/kg) infusion, a 50% decrease of the extracellular levels of DA was observed as well as an increase of 37–100% of HVA levels in the STR, NAC, and PFC. After 19 h and still after 1 week, DOPAC striatal levels were decreased, which indicates not only an acute but also a protracted effect of ibogaine on DA and DA metabolite levels in discrete regions of SNC (62).

Acutely, ibogaine (40 mg/kg, i.p.) decreased DA extracellular levels in the STR, increased DA levels in the PFC, and had no significant effect on DA levels in the NAC. Nineteen hours after ibogaine injection, DA levels were still decreased in the striatum and HVA and DOPAC levels were decreased in the regions investigated. When injected 19 h prior to a morphine challenge (5 mg/kg, i.p.), ibogaine (40 mg/kg) prevented the morphine-induced rise of DA levels in the STR, NAC, and PFC (59). Ibogaine downregulated the cocaine-induced increase in DA release and potentiated the cocaine-induced decrease of 5-HT release in the NAC (14).

Ibogaine infusion (40 mg/kg, i.p.) was associated with a significant reduction of 5-hydroxyindoleacetic acid (5-HIAA) levels in the NAC and STR, with an increase in the level of this metabolite in the medial prefrontal cortex (mPFC), while 5-HT levels in the mPFC were reduced (8). However, in another investigation (40 mg/kg, i.p. for all drugs), ibogaine administration elicited large increases of extracellular 5-HT levels, up to 25-fold in the NAC and 10-fold in the STR; noribogaine produced moderate increases, up to 8-fold in the NAC and up to 5-fold in STR. 18-Methoxycoronaridine had no effect on extracellular 5-HT levels, suggesting that stimulation of the ascending serotonergic system may not be an essential factor in the purported antiaddictive actions of these drugs (106). Methodological features, such as dilution of ibogaine in ethanol or 5-HT release from a vascular source, may account for the different findings.

Ibogaine (40 mg/kg, i.p.) potentiated the increase in extracellular DA levels in the STR and NAC when administered 19 h prior to a cocaine (20 mg/kg) challenge (57) or a D-amphetamine(1.25 mg/kg, i.p.) challenge (60). It was proposed that, since high doses of D-amphetamine and cocaine can be aversive and anxiogenic, ibogaine potentiation of the effects of both stimulants might lead to a decrease in the reinforcing effect of D-amphetamine.

Since it had been shown that ibogaine pretreatment prevented the rise of DA levels after a morphine injection (59) and yet augmented it after (+)-amphetamine administration (60), the brain levels of both morphine and (+)-amphetamine were measured after ibogaine pretreatment by gas chromatography/mass spectometry (19 h) (29). Ibogaine (40 mg/kg) pretreatment had no effect on the cerebral levels of morphine but significantly increased brain amphetamine levels either at 30 min or at 2 h after the infusion of the respective substances (29). These findings suggest that ibogaine might interact with amphetamine through metabolic or pharmacokinetic mechanisms, without affecting morphine levels.

The local administration of ibogaine in the STR and NAC produced effects that mimicked both the acute and persistent effects of ibogaine systemic administration. Local perfusion of high doses of ibogaine (200–400 μM) reproduced acute ibogaine effects (decreased extracellular levels of DA and increased extracellular levels of DA metabolites), whereas the perfusion of low concentrations of ibogaine (10 μM) reproduced ibogaine long-lasting effects (decreased extracellular levels of DOPAC); these data indicate that ibogaine might act directly in brain regions containing dopaminergic inervation (31). It was also observed that the local administration of ibogaine (10 μM) increased the effects of systemically administered amphetamine (1.25 mg/kg) on the extracellular levels of DA, whereas the systemic administration of ibogaine (40 mg/kg) increased the effects of local administration of D-amphetamine (1–10 μM), indicating the involvement of a pharmacodynamic mechanism in the interaction of D-amphetamine and ibogaine (31).

Local perfusion of ibogaine through microdialysis probes in the NAC and STR of rats produced a biphasic dose-response effect on extracellular dopamine levels (86). Lower doses ($10^{-6} – 10^{-4}$ M) produced a decrease while higher doses ($5 \times 10^{-4} – 10^{-3}$ M) produced an increase in DA levels. Norbinaltorphimine ($10^{-6} – 10^{-5}$ M), a κ-opiate receptor selective antagonist, and naloxone, a nonselective opiate receptor antagonist, did not affect DA levels, but when co-administered with ibogaine (10^{-4} M) these drugs blocked the decrease in DA levels produced by ibogaine. These findings suggest the involvement of κ-opiate receptors in the mediation of ibogaine inhibitory effects on DA release (86).

Although a lower dose of ibogaine (10 mg/kg) had no effect on morphine-induced DA release, morphine pretreatment combined with ibogaine (10 mg/kg) completely blocked morphine-induced elevation of DA, but not of DA metabolites. The authors proposed that prior morphine exposure enhances the opioid antagonist effect of ibogaine on the dopaminergic system (80). Preatreatment with ibogaine (40 mg/kg, i.p.) 19 h prior to the first nicotine infusion (0.32 mg/kg) significantly attenuated the increase in extracellular DA levels induced by nicotine infusions suggesting that ibogaine may decrease the rewarding effect of nicotine (8,61).

The effect of some *iboga* alkaloids, the *R* and *S* enantiomers of ibogamine and coronaridine, on the extracellular dopamine levels in NAC and STR was correlated with the effect of these alkaloids on self-administration of addictive drugs. Although the *R* enantiomers of ibogamine and coronaridine had a siginificant prolonged effect on cocaine and morphine self-administration, only (*R*)-ibogamine and (*R*)-coronaridine significantly decreased accumbal and striatal DA, whereas (*S*)-ibogamine and (*S*)-coronaridine had no significant effects. These observations of the effects of these alkaloids on drug self-administration, are related to an initial decrease in dopaminergic activity (32).

TOXICITY ISSUES

Tremorigenic Activity

Ibogaine-induced cerebellar damage has been most closely linked to its tremorigenic activity (70,72). Ibogaline, an *iboga* alkaloid closely related to ibogaine, causes tremor and olivocerebellar activation (21). As with ibogaine, harmaline also produces activation of the olivocerebellar pathway and degeneration of cerebellar Purkinje cells, suggesting that these related plant alkaloids have a similar mechanisms of action (70). Olive ablation prevents ibogaine-induced tremor, supporting the proposal that ibogaine acts on the inferior olive (72).

The s.c. tremor-producing ED_{50} for ibogaine and noribogaine is 34.8 (31.4–38.9) μmol/kg and 176 (130–238.3) μmol/kg, respectively (110). It was observed that intracerebral potency does not depend on lipid solubility and, unlike ibogaine, a dose of 10 mg/kg of noribogaine i.v. did not produce any tremor in male NMRI-mice (110). The tremor-producing potency of *iboga* alkaloids depends more on chemical structure than on lipid solubility (110). In terms of the influence of chemical structure on pharmacological properties, it is reported that the methoxy (OCH_3) group enhances tremorigenic potency, whereas a hydroxy group has the opposite effect (68). Ibogaine has a OCH_3 group at C-12, whereas noribogaine, which is generated after the *O*-demethylation of ibogaine, has a hydroxy (OH) group at the same position (47).

It has been shown that the putative "anti-addictive" and the tremorigenic effects of the *iboga* alkaloids can be dissociated (32). Alkaloid-induced tremors disappeared within 4 h after administration whereas several alkaloids produced a significant reduction of morphine and cocaine self-administration for 1 or more days. Moreover, the efficacy of alkaloids to induce tremors was unrelated to their efficacy to induce decreasing effects on drug self-administration (32).

In an attempt to obtain safer ibogaine-like agents, 18-methoxycoronaridine (MC), a novel synthetic *iboga* alkaloid congener that mimics ibogaine's effects on drug self-administration was developed (33). MC had no apparent tremorigenic effect, and there was no evidence of cerebellar toxicity after a high dose (100 mg/kg) of the drug.

Neurotoxicity and Lethality

It has been demonstrated that ibogaine-induced degeneration of Purkinje cells is mediated through the olivocerebellar projection (72). In rats, when ibogaine, 100 mg/kg, was administered after the pharmacological ablation of the inferior olive by a neurotoxic drug regimen, little or no Purkinje cell degeneration or glial activation was observed, which indicates that ibogaine is not directly toxic to Purkinje cells (72). Ibogaine-induced toxicity might be rather indirect and dependent on the integrity of the olivocerebellar projection (72).

When the level of gliosis was determined by quantification of glial fibrillary acidic protein (GFAP), it was observed that after acute administration of ibogaine, rats of both sexes showed dose-related increases in GFAP that were not confined to the cerebellar vermis, indicating that areas outside the cerebellum might be susceptible to ibogaine in-

duced neurotoxicity (69). The effect of ibogaine on cells of various brain regions was also assessed through the localization of the nuclear early/immediate gene product *c-fos*.

In a study in which an equal dose of ibogaine (100 mg/kg, i.p.) was given to mice and rats, with the exception of the cortex, similar levels of *c-fos* protein expression were observed in other brain areas, which indicates that pharmacodynamic effects of ibogaine on the cortex may differ between the two species (91). In rats, cells synthesized *c-fos* protein in response to ibogaine in all the cortical layers, whereas in mice the reaction was mostly limited to layer 2 (91).

The *c-fos* results indicate considerable differences in the response in the cortex of rat and mice. Both mice and rats had elevated *c-fos* expression, but only rats had a global cortical response to ibogaine. It was observed that ibogaine can yield *c-fos* protein both with and without an intact inferior olivary nucleus, independent of cerebellar neurotoxicity (73).

When a re-evaluation was carried out to ascertain whether lower doses of ibogaine would also produce neurotoxic reactions, it was observed that rats given the smaller ibogaine dose (40 mg/kg) displayed no degeneration above the levels observed in saline-treated rats (66). Neurotoxic reactions occurred at a high dose (100 mg/kg), which is four times greater than the proposed human dose of approximately 25 mg/kg. Ibogaine (10 mg/kg) administered every other day for 60 days to a group of 6 male Fischer-344 rats produced no significant differences in the number of Purkinje cells compared with control group that received saline in the same regimen (39).

Ibogaine produced neurodegeneration in the rat but not in the mouse cerebellum, even at the same high dose shown elsewhere to be neurotoxic to rats. This suggests caution when extrapolating from ibogaine's effects observed in rodents (92). Studies conducted in African green monkeys with routine histopathological evaluation failed to demonstrate any neuropathological damage caused by ibogaine following 5 days of repeated dosing at either 25 mg/kg, p.o. or 100 mg/kg, s.c. (65).

Since drug metabolism and sensitivity may differ among species, a systematic dose-response analysis is needed to assess the dose-relatedness of ibogaine neurotoxic effects (65). No evidence of any significant cytopathology or neurodegeneration in any brain area was observed in a female subject who had received 4 doses of ibogaine ranging from 10 to 30 mg/kg over a period of 15 months and who died from natural causes (65). Besides interspecies differences, it was also observed that long-term exposure to ibogaine (14 days) might produce significantly different toxic responses in male and female rats (69). In female rats, ibogaine produced dose-dependent increases in GFAP in hippocampus, brain stem striatum, and olfactory bulbs, whereas no significant increase of the concentration of GFAP was observed in any brain region of male rats with this drug regimen (69).

The LD_{50} of ibogaine has been determined in guinea pig (82 mg/kg, i.p.) and rat (145 mg/kg i.p.) (83). Ibogaine (40 and 80 mg/kg) produced 80 and 100% mortality, respectively, in mice implanted with morphine pellets, although mortality was not observed in mice given the same doses of noribogaine (9).

CONCLUSION

Although the half-life of ibogaine in rodents is about 1 h, the alkaloid achieves widespread distribution throughout the body. Due to its highly lipophilic nature, ibogaine is

TABLE 1. The effect of ibogaine, noribogaine and related alkaloids on intravenous self-administration of addictive substances

Self-administration	Gender	Strain	Effect	Schedule of administration	Reference
Cocaine	Male	Wistar	Decrease	Ibogaine 40 mg/kg, i.p.	17
Morphine	Female	Sprague–Dawley	Persistent decrease (aftereffect)	Ibogaine 40–80 mg/kg, i.p.	28
Cocaine and heroin	Male	Fischer 344	Decrease (no aftereffect)	Ibogaine 80 mg/kg, i.p.	24
Cocaine and morphine	Female	Sprague–Dawley	Decrease	Ibogaine 40 mg/kg, i.p.	36
Cocaine and morphine	Female	Sprague–Dawley	Persistent decrease (aftereffect)	Ibogaine (and related alkaloids) 40 mg/kg, i.p.	32
Cocaine and morphine	Female	Sprague–Dawley	Decrease	Noribogaine 40 mg/kg, i.p.	34
Cocaine and morphine	Female	Sprague–Dawley	Persistent decrease (aftereffect)	Methoxycoronaridine 40 mg/kg, i.p.	33
Morphine	Female	Sprague–Dawley	Decrease	Methoxycoronaridine 40 mg/kg, i.p.	58

concentrated in the brain and fatty tissue, where it is converted to noribogaine after slow release. Noribogaine is produced through ibogaine metabolic demethylation. Ibogaine levels tend to be higher in females and this difference might be related to sex hormones and their interactions with the enzymes involved in ibogaine metabolism. Cortex, hippocampus, and paraventricular hypothalamus are putative neuroanatomical/neurochemical substrates for the psychopharmacological properties of ibogaine, since the alkaloid induces formation of the nuclear early gene product *c-fos* in these areas. Although ibogaine is responsible for the actions in the brain, other effects, including the prolonged ones, are attributed to the metabolite noribogaine.

Noribogaine acts with significant agonistic activity at μ-opioid receptors. Noribogaine is also more active than ibogaine at κ-opioid receptors. When co-administered with morphine, ibogaine and mainly noribogaine increase both the degree and duration of morphine antinociception, providing evidence for a possible interaction between noribogaine and μ-opioid receptors. Intermediate levels of generalization of ibogaine discriminative stimulus to the mixed action opiates indicate that opioid receptors may be involved in the ibogaine effects.

Ibogaine infusion decreased morphine and cocaine intake, even when there were no signs of ibogaine-induced motor impairment. The 'anti-addictive' and tremorigenic effects of the *iboga* alkaloids are dissociated. The effects of these alkaloids on drug self-administration are related to the modification of DA transmission. The tremor-producing effect of *iboga* alkaloids depends mainly on the chemical structure. The OCH_3 group enhances tremorigenic potency whereas a OH group has the opposite effect.

Ibogaine interferes with the establishment of place preference induced by morphine. Ibogaine produces an acute and a protracted effect on DA and DA metabolite levels in certain SNC areas. Ibogaine potentiation of cocaine or D-amphetamine central effects might lead to a decrease in the reinforcing effect of these stimulants. The *ibo-*

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Cocaine and morphine	Female	Sprague–Dawley	Decrease	Noribogaine 40 mg/kg, i.p.	34
Cocaine and morphine	Female	Sprague–Dawley	Persistent decrease (aftereffect)	Methoxycoronaridine 40 mg/kg, i.p.	33
Morphine	Female	Sprague–Dawley	Decrease	Methoxycoronaridine 40 mg/kg, i.p.	58

ga alkaloid congener 18-methoxycoronaridine, which is devoid of tremorigenic effect and cerebellar toxicity, decreases morphine and cocaine self-administration, with an associated effect on DA transmission in the nucleus accumbens.

Noribogaine binds to the 5-HT transporter with a higher potency than ibogaine. Preliminary data suggest that while noribogaine may be more effective than ibogaine in inhibiting reuptake of 5-HT, ibogaine may cause the release of 5-HT. However, rats trained on a nonspecific 5-HT agonist (LSD) and a 5-HT_2 agonist (DOM) did not generalize fully to the ibogaine stimuli. Noribogaine is the major factor responsible for ibogaine discriminative stimulus. Complete generalization of ibogaine (10 mg/kg) discriminative stimulus to noribogaine at doses of 3.2, 10, and 20 mg/kg was achieved, indicating the greater potency of the metabolite. Since β-carbolines and serotonergic compounds acting at 5-HT_2 receptors are known to produce anxiety and hallucination, respectively, in humans, it is understood that ibogaine might share some pharmacological characteristics with these classes of compounds.

Both ibogaine and noribogaine are less potent than dizocilpine regarding binding to the NMDA receptor complex. Noncompetitive NMDA-antagonist drugs, phencyclidine (PCP) and dizocilpine, do not generalize to the ibogaine stimulus. Hence, an antagonistic effect at the NMDA receptor complex is unlikely to explain the putative anti-addictive properties of ibogaine.

Ibogaine-induced degeneration of Purkinje cells is mediated through the olivocerebellar projection; however, areas outside the cerebellum might be susceptible to ibogaine neurotoxic effects. Nevertheless, neurotoxic reactions occur at doses much higher than the proposed dose for humans. Certain ibogaine dose regimens did not produce any significant difference from saline-treated control groups regarding the number of Purkinje cells. Drug metabolism and sensitivity may differ among species and between sexes, suggesting caution when extrapolating data from ibogaine's effects observed in rodents.

The investigation of ibogaine's complex pharmacology has propelled a new impetus in the quest for pharmacological tools to treat drug addiction. Although a definitive clinical validation of purported ibogaine effects is still unavailable, ibogaine has opened new perspectives for more effective and less toxic compounds.

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