

**A CHRONOLOGY OF
SELECTED ABSTRACTS**

IBOGAINE:

Rapid Method for the Interruption of the
Narcotic Addiction Syndrome*

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A Chronology of Selected Abstracts

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2. Leal, M.B., Michelin, K., Souza, D.O., Elisabetsky, E. (2003) Ibogaine attenuation of morphine withdrawal in mice: Role of glutamate N-methyl-D-aspartate receptors. *Prog. Neuropsychopharmacol. Biol. Psychiatry*. **27**(5):781-785.
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Differential effects of ibogaine on local cerebral glucose utilization in drug-naive and morphine-dependent rats.

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Ibogaine, a hallucinogenic indole alkaloid, has been proposed as a treatment for addiction to opioids and other drugs of abuse. The mechanism for its putative anti-addictive effects is unknown. In this study, the effects of ibogaine on local cerebral glucose utilization (LCGU) were determined in freely moving, drug-naive, or morphine-dependent adult, male, Sprague-Dawley rats using the [(14)C]2-deoxyglucose (2-DG) method. Morphine-dependent rats were treated with increasing doses of morphine (5-25 mg/kg, s.c., b.i.d.) and then maintained at 25 mg/kg (b.i.d.) for 4-7 days. For the 2-DG procedure, rats were injected with saline or ibogaine (40 mg/kg, i.p.). 2-DG was administered 1 h after administration of ibogaine. The rate of LCGU was determined by quantitative autoradiography in 46 brain regions. In drug-naive animals, ibogaine produced significant increases in LCGU in the parietal, cingulate, and occipital cortices and cerebellum compared to controls consistent with its activity as a hallucinogen and a tremorogen. Morphine-dependent rats had only minor alterations in LCGU at the time assessed in this experiment. However, in morphine-dependent animals, ibogaine produced a global decrease in LCGU that was greatest in brain regions such as the lateral and medial preoptic areas, nucleus of the diagonal band, nucleus accumbens shell, inferior colliculus, locus coeruleus, and flocculus compared to morphine-dependent animals treated with saline. These findings indicate that ibogaine produces distinctly different effects on LCGU in drug-naive and morphine-dependent rats. This suggests that different mechanisms may underlie ibogaine's hallucinogenic and anti-addictive effects.

Ibogaine attenuation of morphine withdrawal in mice: role of glutamate N-methyl-D-aspartate receptors.

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Ibogaine (IBO) is an alkaloid with putative antiaddictive properties, alleviating opiates dependence and withdrawal. The glutamate N-methyl-D-aspartate (NMDA) receptors have been implicated in the physiological basis of drug addiction; accordingly, IBO acts as a noncompetitive NMDA antagonist. The purpose of this study was to evaluate the effects of IBO on naloxone-induced withdrawal syndrome in morphine-dependent mice, focusing on the role of NMDA receptors. Jumping, a major behavioral expression of such withdrawal, was significantly ($P < .01$) inhibited by IBO (40 and 80 mg/kg, 64.2% and 96.9% inhibition, respectively) and MK-801 (0.15 and 0.30 mg/kg, 67.3% and 97.7%, respectively) given prior to naloxone. Coadministration of the lower doses of IBO (40 mg/kg) and MK-801 (0.15 mg/kg) results in 94.7% inhibition of jumping, comparable to the effects of higher doses of either IBO or MK-801. IBO and MK-801 also significantly inhibited NMDA-induced (99.0% and 71.0%, respectively) jumping when given 30 min (but not 24 h) prior to NMDA in nonaddictive mice. There were no significant differences in [3 H]MK-801 binding to cortical membranes from naive animals, morphine-dependent animals, or morphine-dependent animals treated with IBO or MK-801. This study provides further evidence that IBO does have an inhibitory effect on opiate withdrawal symptoms and suggests that the complex process resulting in morphine withdrawal includes an IBO-sensitive functional and transitory alteration of NMDA receptor.

Ibogaine interferes with motivational and somatic effects of naloxone-precipitated withdrawal from acutely administered morphine.

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It has been reported that ibogaine interferes with somatic withdrawal reactions in rats chronically treated with morphine. The present experiments demonstrated that ibogaine also interferes with motivational withdrawal reactions and somatic withdrawal reactions in rats treated with morphine on only two occasions. On each of two conditioning trials, naloxone was administered 24 h following an injection of morphine. Four hours prior to each naloxone administration, rats were injected with either ibogaine or saline. In two experiments, ibogaine interfered with naloxone-precipitated withdrawal. In Experiment 1, ibogaine-treated rats displayed a weaker aversion to the withdrawal-paired chamber, and in Experiment 2, ibogaine-treated rats displayed fewer somatic withdrawal reactions than did saline treated rats.

Ibogaine in the treatment of heroin withdrawal.

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Ibogaine is a naturally occurring psychoactive indole alkaloid derived from the roots of the rain forest shrub *Tabernanthe iboga*. It has been suggested that the alkaloid reduces craving for opiates and other illicit drugs, and has ameliorative effects in acute opiod withdrawal . However, objective investigations of ibogaine's effects on drug craving, and the signs and symptoms of opiate withdrawal, have not been done in either research or conventional treatment settings. We have had the opportunity to describe the clinical experience of a series of patients undergoing opiate detoxification with ibogaine. The study was conducted in a 12 bed freestanding facility in St. Kitts, West Indies. The treatment program had a planned duration of 12 to 14 days and stated goals of: (1) safe physical detoxification from opiates, (2) motivational counseling, and (3) referral to aftercare programs and community support groups (12 step programs). Physical dependence on opiates is characterized by a distinctive pattern of signs and symptoms that make up the naturalistic withdrawal syndrome. Objective signs of opiate withdrawal were rarely seem and none were exacerbated at later time points. The results suggest that ibogaine provided a safe and effective treatment for withdrawal from heroin and methadone. These preliminary results demonstrate that single doses of ibogaine were well tolerated in drug-dependent subjects. Our observations of the safety of ibogaine have not been limited to opiate-dependent subjects. To date, we have evaluated ibogaine's safety in more than 150 drug-dependent subjects that were assigned to one of three fixed-dose treatments under open label conditions; 8, 10, 12, mg/kg ibogaine. To date, no significant adverse events were seen under these study conditions.

(Abstract supplied ARI)

In vivo neurobiological effects of ibogaine and its O-desmethyl metabolite, 12-hydroxyibogamine (noribogaine), in rats.

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Ibogaine is a naturally occurring compound with purported antiaddictive properties. When administered to primates, ibogaine is rapidly o-demethylated to form the metabolite 12-hydroxyibogamine (noribogaine). Peak blood levels of noribogaine exceed those of ibogaine, and noribogaine persists in the bloodstream for at least 1 day. Very few studies have systematically evaluated the neurobiological effects of noribogaine *in vivo*. In the present series of experiments, we compared the effects of *i.v.* administration of ibogaine and noribogaine (1 and 10 mg/kg) on motor behaviors, stress hormones, and extracellular levels of dopamine (DA) and serotonin (5-HT) in the nucleus accumbens of male rats. Ibogaine caused dose-related increases in tremors, whereas noribogaine did not. Both ibogaine and noribogaine produced significant elevations in plasma corticosterone and prolactin, but ibogaine was a more potent stimulator of corticosterone secretion. Neither drug altered extracellular DA levels in the nucleus accumbens. However, both drugs increased extracellular 5-HT levels, and noribogaine was more potent in this respect. Results from *in vitro* experiments indicated that ibogaine and noribogaine interact with 5-HT transporters to inhibit 5-HT uptake. The present findings demonstrate that noribogaine is biologically active and undoubtedly contributes to the *in vivo* pharmacological profile of ibogaine in rats. Noribogaine is approximately 10 times more potent than ibogaine as an indirect 5-HT agonist. More importantly, noribogaine appears less apt to produce the adverse effects associated with ibogaine, indicating the metabolite may be a safer alternative for medication development.

Ibogaine: complex pharmacokinetics, concerns for safety, and preliminary efficacy measures

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Ibogaine is an indole alkaloid found in the roots of *Tabernanthe Iboga* (Apocynaceae family), a rain forest shrub that is native to western Africa. Ibogaine is used by indigenous peoples in low doses to combat fatigue, hunger and thirst, and in higher doses as a sacrament in religious rituals. Members of American and European addict self-help groups have claimed that ibogaine promotes long-term drug abstinence from addictive substances, including psychostimulants and opiates. Anecdotal reports attest that a single dose of ibogaine eliminates opiate withdrawal symptoms and reduces drug craving for extended periods of time. The purported efficacy of ibogaine for the treatment of drug dependence may be due in part to an active metabolite. The majority of ibogaine biotransformation proceeds via CYP2D6, including the O-demethylation of ibogaine to 12-hydroxyibogamine (noribogaine). Blood concentration-time effect profiles of ibogaine and noribogaine obtained for individual subjects after single oral dose administrations demonstrate complex pharmacokinetic profiles. Ibogaine has shown preliminary efficacy for opiate detoxification and for short-term stabilization of drug-dependent persons as they prepare to enter substance abuse treatment. We report here that ibogaine significantly decreased craving for cocaine and heroin during inpatient detoxification. Self-reports of depressive symptoms were also significantly lower after ibogaine treatment and at 30 days after program discharge. Because ibogaine is cleared rapidly from the blood, the beneficial aftereffects of the drug on craving and depressed mood may be related to the effects of noribogaine on the central nervous system.

Long-lasting ibogaine protection against NMDA-induced convulsions in mice.

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Ibogaine, a putative antiaddictive drug, is remarkable in its apparent ability to downgrade withdrawal symptoms and drug craving for extended periods of time after a single dose. Ibogaine acts as a non-competitive NMDA receptor antagonist, while NMDA has been implicated in long lasting changes in neuronal function and in the physiological basis of drug addiction. The purpose of this study was to verify if persistent changes in NMDA receptors could be shown in vivo and in vitro after a single administration of ibogaine. The time course of ibogaine effects were examined on NMDA-induced seizures and [3H] MK-801 binding to cortical membranes in mice 30 min, 24, 48, and 72 h post treatment. Ibogaine (80 mg/kg, ip) was effective in inhibiting convulsions induced by NMDA at 24 and 72 hours post administration. Likewise, [3H] MK-801 binding was significantly decreased at 24 and 72 h post ibogaine. No significant differences from controls were found at 30 min or 48 h post ibogaine. This long lasting and complex pattern of modulation of NMDA receptors prompted by a single dose of ibogaine may be associated to its antiaddictive properties.

A dose-response study of ibogaine-induced neuropathology in the rat cerebellum.

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Ibogaine (IBO) is an indole alkaloid from the West African shrub, *Tabernanthe iboga*. It is structurally related to harmaline, and both these compounds are rigid analogs of melatonin. IBO has both psychoactive and stimulant properties. In single-blind trials with humans, it ameliorated withdrawal symptoms and interrupted the addiction process. However, IBO also produced neurodegeneration of Purkinje cells and gliosis of Bergmann astrocytes in the cerebella of rats given even a single dose (100 mg/kg, ip). Here, we treated rats ($n = 6$ per group) with either a single ip injection of saline or with 25 mg/kg, 50 mg/kg, 75 mg/kg, or 100 mg/kg of IBO. As biomarkers of cerebellar neurotoxicity, we specifically labeled degenerating neurons and axons with silver, astrocytes with antisera to glial fibrillary acidic protein (GFAP), and Purkinje neurons with antisera to calbindin. All rats of the 100-mg/kg group showed the same pattern of cerebellar damage previously described: multiple bands of degenerating Purkinje neurons. All rats of the 75-mg/kg group had neurodegeneration similar to the 100-mg/kg group, but the bands appeared to be narrower. Only 2 of 6 rats that received 50 mg/kg were affected; despite few degenerating neuronal perikarya, cerebella from these rats did contain patches of astrocytosis similar to those observed with 75 or 100 mg/kg IBO. These observations affirm the usefulness of GFAP immunohistochemistry as a sensitive biomarker of neurotoxicity. None of the sections from the 25-mg/kg rats, however stained, were distinguishable from saline controls, indicating that this dose level may be considered as a no-observable-adverse-effect level (NOAEL).

Pharmacokinetic characterization of the indole alkaloid ibogaine in rats.

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To investigate the pharmacokinetic properties of ibogaine, a putatively anti-addictive alkaloid, levels of this drug were quantified in plasma and tissues for up to 3 h following i.v. infusion in rats. Immediately following a 31-35 min infusion (20 mg/kg), mean plasma ibogaine levels were 373 ng/ml; these values declined rapidly thereafter in a biexponential manner. The plasma time course in 5 of 7 animals demonstrated an excellent fit to a two-compartment pharmacokinetic model, with alpha and beta half-lives of 7.3 min and 3.3 h, respectively. Drug clearance was estimated to be 5.9 l/h (n = 7). Ibogaine levels in brain, liver and kidney 3 h after the end of drug infusion were 143-170 ng/g, close to simulated values for the peripheral pharmacokinetic compartment. However, 3-h drug levels in adipose tissue were much higher (3,328 ng/g), implying the need for a more complex pharmacokinetic model. Mechanisms for the initial, rapid disappearance of plasma ibogaine are thought to include metabolic demethylation as well as redistribution to body stores. The sequestration of ibogaine by adipose tissue probably contributes to a protracted persistence of drug in the body. This persistence may be underestimated by the beta half-life reported in the present study.

Treatment of acute opioid withdrawal with ibogaine.

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Ibogaine is an alkaloid with putative effect in acute opioid withdrawal. Thirty-three cases of treatments for the indication of opioid detoxification performed in non-medical settings under open label conditions are summarized involving an average daily use of heroin of .64 +/- .50 grams, primarily by the intravenous route. Resolution of the signs of opioid withdrawal without further drug seeking behavior was observed within 24 hours in 25 patients and was sustained throughout the 72-hour period of posttreatment observation. Other outcomes included drug seeking behavior without withdrawal signs (4 patients), drug abstinence with attenuated withdrawal signs (2 patients), drug seeking behavior with continued withdrawal signs (1 patient), and one fatality possibly involving surreptitious heroin use. The reported effectiveness of ibogaine in this series suggests the need for systematic investigation in a conventional clinical research setting.

The effects of ibogaine on dopamine and serotonin transport in rat brain synaptosomes.

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Ibogaine has been shown to affect biogenic amine levels in selected brain regions. Because of the involvement of these neurotransmitters in drug addiction, the effects of ibogaine on biogenic amine transport may contribute to the potential anti-addictive properties of ibogaine *in vivo*. With rat brain synaptosomes as our experimental system, we measured the effects of ibogaine on the uptake and release of dopamine (DA) and serotonin (5-HT). Ibogaine competitively blocked both DA and 5-HT uptake with IC₅₀ values of 20 microM at 75 nM 3H-DA and 2.6 microM at 10 nM 3H-5-HT. Ibogaine had no effect on K⁺-induced release of 3H-DA from preloaded synaptosomes, but 20 microM and 50 microM ibogaine inhibited roughly 40% and 60%, respectively, of the K⁽⁺⁾-induced release of 3H-5-HT from preloaded synaptosomes. In the absence of a depolarizing stimulus, ibogaine evoked a small release of 3H-DA but not 3H-5-HT. These relatively low-potency effects of ibogaine on DA and 5-HT uptake in synaptosomes are consistent with the low binding affinity of ibogaine that has been previously reported for DA and 5-HT transporters. Our results show that if ibogaine modulates DA and 5-HT levels in the brain by directly blocking their uptake, then a concentration of ibogaine in the micromolar range is required. Furthermore, if the anti-addictive effects of ibogaine require this concentration, then ibogaine likely exerts these effects through a combination of neurotransmitter pathways, because binding affinities and functional potencies of ibogaine in the micromolar range have been reported for a variety of neuronal receptors and transporters.

Enhancement of morphine antinociception by ibogaine and noribogaine in morphine-tolerant mice.

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The effects of ibogaine, an alkaloid isolated from the bark of the African shrub, *Tabernaemontana iboga*, and noribogaine, a metabolite of ibogaine, on morphine antinociception were determined in male Swiss-Webster mice. Mice were rendered tolerant to morphine by implanting them with a pellet containing 25 mg of morphine base for 3 days. Placebo pellet-implanted mice served as controls. The antinociception of morphine (10 mg/kg, s.c.) was determined alone or in combination with an appropriate dose of ibogaine or noribogaine. Tolerance to morphine developed as a result of morphine pellet implantation as evidenced by decreased antinociceptive response to morphine. Both ibogaine and noribogaine dose-dependently enhanced morphine antinociception in morphine-tolerant but not in morphine-naive mice. It is concluded that ibogaine and noribogaine enhance morphine antinociception in morphine-tolerant mice.

Cytochrome P450D6 catalyzes the O-demethylation of the psychoactive alkaloid ibogaine to 12-hydroxyibogamine.

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Ibogaine is a psychoactive alkaloid that possesses potential as an agent to treat opiate and cocaine addiction. The primary metabolite arises via O-demethylation at the 12-position to yield 12-hydroxyibogamine. In this report, evidence is presented that the O-demethylation of ibogaine observed in human hepatic microsomes is catalyzed primarily by the polymorphically expressed cytochrome P-450D6 (CYP2D6). An enzyme kinetic examination of ibogaine O-demethylase activity in pooled human liver microsomes suggested that two (or more) enzymes are involved in this reaction: one with a low K_{Mapp} (1.1 μM) and the other with a high K_{Mapp} ($>200 \mu\text{M}$). The low K_{Mapp} activity comprised $>95\%$ of total intrinsic clearance. Human liver microsomes from three individual donors demonstrated similar enzyme kinetic parameters (mean $K_{Mapp} = 0.55 \pm 0.09 \mu\text{M}$ and $310 \pm 10 \mu\text{M}$ for low and high K_M activities, respectively). However, a fourth human microsome sample that appeared to be a phenotypic CYP2D6 poor metabolizer possessed only the high K_{Mapp} activity. In hepatic microsomes from a panel of human donors, the low K_{Mapp} ibogaine O-demethylase activity correlated with CYP2D6-catalyzed bufuralol 1'-hydroxylase activity but not with other P450 isoform-specific activities. Quinidine, a CYP2D6-specific inhibitor, inhibited ibogaine O-demethylase ($IC_{50} = 0.2 \mu\text{M}$), whereas other P450 isoform-specific inhibitors did not inhibit this activity. Also, of a battery of recombinant heterologously expressed human P450 isoforms, only rCYP2D6 possessed significant ibogaine O-demethylase activity. Thus, it is concluded that ibogaine O-demethylase is catalyzed by CYP2D6 and that this isoform is the predominant enzyme of ibogaine O-demethylation in humans. The potential pharmacological implications of these findings are discussed.

Medication development of ibogaine as a pharmacotherapy for drug dependence.

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The potential for deriving new psychotherapeutic medications from natural sources has led to renewal interest in rain forest plants as a source of lead compounds for the development of antiaddiction medications. Ibogaine is an indole alkaloid found in the roots of *Tabernanthe iboga* (Apocynaceae family), a rain forest shrub that is native to equatorial Africa. Ibogaine is used by indigenous peoples in low doses to combat fatigue, hunger and in higher doses as a sacrament in religious rituals. Members of American and European addict self-help groups have claimed that ibogaine promotes long-term drug abstinence from addictive substances, including psychostimulants and cocaine. Anecdotal reports attest that a single dose of ibogaine eliminates withdrawal symptoms and reduces drug cravings for extended periods of time. The purported antiaddictive properties of ibogaine require rigorous validation in humans. We have initiated a rising tolerance study using single administration to assess the safety of ibogaine for treatment of cocaine dependency. The primary objectives of the study are to determine safety, pharmacokinetics and dose effects, and to identify relevant parameters of efficacy in cocaine-dependent patients. Pharmacokinetic and pharmacodynamic characteristics of ibogaine in humans are assessed by analyzing the concentration-time data of ibogaine and its desmethyl metabolite (noribogaine) from the Phase I trial, and by conducting *in vitro* experiments to elucidate the specific disposition processes involved in the metabolism of both parent drug and metabolite. The development of clinical safety studies of ibogaine in humans will help to determine whether there is a rationale for conducting efficacy trials in the future.

Mechanisms of antiaddictive actions of ibogaine.

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Ibogaine, an alkaloid extracted from *Tabernanthe iboga*, is being studied as a potential long-acting treatment for opioid and stimulant abuse as well as for alcoholism and smoking. Studies in this laboratory have used animal models to characterize ibogaine's interactions with drugs of abuse, and to investigate the mechanisms responsible. Ibogaine, as well as its metabolite, noribogaine, can decrease both morphine and cocaine self-administration for several days in some rats; shorter-lasting effects appear to occur on ethanol and nicotine intake. Acutely, both ibogaine and noribogaine decrease extracellular levels of dopamine in the nucleus accumbens of rat brain. Ibogaine pretreatment (19 hours beforehand) blocks morphine-induced dopamine release and morphine-induced locomotor hyperactivity while, in contrast, it enhances similar effects of stimulants (cocaine and amphetamine). Ibogaine pretreatment also blocks nicotine-induced dopamine release. Both ibogaine and noribogaine bind to kappa opioid and N-methyl-D-aspartate (NMDA) receptors and to serotonin uptake sites; ibogaine also binds to sigma-2 and nicotinic receptors. The relative contributions of these actions are being assessed. Our ongoing studies in rats suggest that kappa agonist and NMDA antagonist actions contribute to ibogaine's effects on opioid and stimulant self-administration, while the serotonergic actions may be more important for ibogaine-induced decreases in alcohol intake. A nicotinic antagonist action may mediate ibogaine-induced reduction of nicotine preferences in rats. A sigma-2 action of ibogaine appears to mediate its neurotoxicity. Some effects of ibogaine (e.g., on morphine and cocaine self-administration, morphine-induced hyperactivity, cocaine-induced increases in nucleus accumbens dopamine) are mimicked by kappa agonist (U50,488) and/or a NMDA antagonist (MK-801). Moreover, a combination of a kappa antagonist and a NMDA agonist will partially reverse several of ibogaine's effects. Ibogaine's long-term effects may be mediated by slow release from fat tissue (where ibogaine is sequestered) and conversion to noribogaine. Different receptors, or combinations of receptors, may mediate interactions of ibogaine with different drugs of abuse.

Observations on Treatment With Ibogaine

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I was given the opportunity to be present while three addicted patients were administered ibogaine hydrochloride. This agent is a hallucinogenic indole alkaloid reported to be effective in the treatment of addiction to multiple drugs of abuse, including opiates, stimulants, and alcohol. I would like to relate my observations as a neurologist concerning clinical and EEG examinations performed during and after treatment. All three were addicted to cocaine (intranasal, intravenous [IV], or crack: 0.5-8 gm/day), one to heroin (1 gm/day IV), and two to alcohol. Screening medical and psychiatric examinations were performed, as well as laboratory exams, including ECG, EEG, and MRI. Ibogaine hydrochloride was administered in capsule form (20-25 mg/kg). General medical monitoring was continuous, and neurologic/EEG studies were performed intermittently over 24 hours. Patients were kept in a quiet, darkened room and generally remained lying in bed. Regarding neurological signs: all patients developed transient cerebellar dysfunction within 2 hours, which was variably expressed as nystagmus, intention tremor without dysmetria, and gait ataxia. Signs were present but improved at 8 hours. Visual hallucinosis with eyes closed was seen in only one patient. Reality-testing remained normal in all, and there were no signs or symptoms of anxiety or thought disorder. Routine EEG studies were normal in all cases, during and after treatment. No general medical or ECG abnormalities were seen. At 24 hours after treatment, all neurologic examinations were normal, and patients did not have subjective or objective signs of withdrawal or craving. My observations suggest that ibogaine causes transient vestibulocerebellar dysfunction, not unlike other soporifics, and is generally well tolerated.

(Abstract provided by ARI)

The effects of sigma, PCP, and opiate receptor ligands in rats trained with ibogaine as a discriminative stimulus.

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Although the mechanism of action of ibogaine, a hallucinogen that may be useful in the treatment of addiction, remains unknown, receptor binding studies suggest that ibogaine produces its effects via interactions with multiple receptor types. In addition to serotonergic receptors, which have been studied previously with respect to ibogaine, likely candidates include opiate, sigma (sigma), and phencyclidine (PCP) binding sites. In an attempt to determine which of these receptor interactions are involved in the *in vivo* effects of ibogaine, ligands for sigma, PCP, and opiate receptors were assessed for their ability to substitute for or to antagonize the ibogaine-induced discriminative stimulus (10 mg/kg I.P., 60 min pre-session) in Fischer-344 rats. Intermediate levels of generalization were observed with the subtype nonselective sigma ligands 3-(3-hydroxyphenyl)-N-(1-propyl)-piperidine [(+)-3-PPP] (69.0%) and 1,3-di(2-tolyl)guanidine (DTG) (73.5%) but not with the sigma1-selective agents (+)-N-allylnormetazocine [(+)-SKF 10,047] and (+)-pentazocine. These findings, along with observations that ibogaine has appreciable affinity for sigma2 receptors, suggest that these receptors may be involved in the ibogaine discriminative stimulus. With regard to opiate receptors, neither morphine, the prototypic mu agonist, nor kappa selective agonists (bremazocine, and U-50488) substituted for ibogaine. However, intermediate levels of generalization were observed with the mixed action opiates (-)-SKF 10,047 (78.9%), (+/-)-pentazocine (73.9%), nalorphine (70.4%), and diprenorphine (75.0%) indicating a potential role for opiate receptors in the ibogaine stimulus. Partial substitution was also observed with naltrexone (55.6%) but not with naloxone or the selective kappa antagonist nor-binaltorphimine (nor-BNI). These agents were largely ineffective as antagonists of the ibogaine cue, although naloxone produced a moderate but statistically significant antagonism (69.8%). In addition, naloxone produced complete antagonism of the ibogaine-appropriate responding elicited by both (-)-SKF 10,047 (19.7%) and nalorphine (25.8%), whereas the ibogaine-appropriate responding produced by diprenorphine was only partially antagonized (44.4%). The latter observations taken together with the finding that both nalorphine (>100 microM) and diprenorphine (30 microM) have extremely low affinity for sigma2 receptors, suggest that the ibogaine-appropriate responding produced by these agents is not mediated by sigma2 receptors. These findings imply that opiate effects may be involved in the ibogaine stimulus. In contrast to sigma2 and opiate receptors, ibogaine's reported interactions with NMDA receptors do not appear to be involved in its discriminative stimulus, as neither PCP nor MK-801 produced a significant level of ibogaine-appropriate responding. Thus, the present study offers evidence that unlike NMDA receptors, both sigma2 and opiate receptors may be involved in the ibogaine discriminative stimulus.

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

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

Effects of ibogaine on performance in the 8-arm radial maze.

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The effects of ibogaine were studied in 12 rats trained to perform in an 8-arm radial maze. In Phase I, the mean number of sessions to criterion and cumulative errors to criterion, as well as mean response rate, were determined for two groups of six animals in a task where only four arms were baited. Group 1 received a potentially neurotoxic dose of ibogaine (50 mg/kg IP administered twice, with approximately 8 h between injections), and group 2 received vehicle. Both groups had similar levels of performance, but ibogaine-treated subjects had a significantly lower rate of responding in the maze. During Phase II, subjects were given a range of doses of ibogaine 20 min prior to working in the maze. Ibogaine produced a dose-dependent decrease in response rate, but efficiency (% arms correct) was not affected. In Phase III, subjects were divided into the same groups as they had been in Phase I. Ibogaine (30 mg/kg, IP) or vehicle was administered immediately following daily sessions in the maze. Ibogaine-treated rats committed significantly fewer errors than those in the vehicle treated group. Thus, in the present study, ibogaine failed to produce any deleterious effects on either acquisition of a novel task or efficiency in a previously learned task.

Effects of ibogaine on the development of tolerance to antinociceptive action of mu-, delta- and kappa-opioid receptor agonists in mice.

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The effects of ibogaine, an alkaloid isolated from the bark of the African shrub, *Tabernanthe iboga*, on the development of tolerance to the antinociception action of morphine, U-50,488H and [D-Pen²,D-Pen⁵]enkephalin (DPDPE), which are mu-, kappa- and delta-opioid receptor agonists, respectively, were determined in male Swiss-Webster mice. Mice were rendered tolerant to opioid receptor agonists by injecting morphine (20 mg/kg, s.c.), U-50,488H (25 mg/kg, i.p.) or DPDPE (20 microg/mouse, i.c.v.) twice a day for 4 days. Ibogaine (20, 40 or 80 mg/kg, i.p.) given twice a day for 4 days did not alter the tail-flick latency. Ibogaine (40 or 80 mg/kg, i.p.) injected 10 min before each injection of morphine inhibited the development of tolerance to the antinociceptive action of morphine, however, the lower dose of ibogaine (20 mg/kg, i.p.) was ineffective. Ibogaine (20, 40 or 80 mg/kg, i.p.) given prior to the injection of U-50,488H or DPDPE did not modify the development of tolerance to their antinociceptive action. It is concluded that ibogaine inhibits selectively the development of tolerance to the antinociceptive action of mu- but not kappa- or delta-opioid receptor agonists in mice.

Evidence for roles of kappa-opioid and NMDA receptors in the mechanism of action of ibogaine.

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Ibogaine, a putatively anti-addictive alkaloid, binds to kappa-opioid and NMDA receptors. In the present study we investigated the roles of kappa-opioid and NMDA actions in mediating ibogaine's (40 mg/kg, i.p.) behavioral and neurochemical effects in rats. A combination of a kappa-opioid antagonist (norbinaltorphimine, 10 mg/kg, s.c.) and a NMDA agonist (NMDA, 20 mg/kg, i.p.) partially prevented ibogaine-induced inhibition of intravenous morphine self-administration and ibogaine-induced antagonism of morphine-induced locomotor stimulation. The combination, as well as norbinaltorphimine and NMDA alone, blocked the acute effects of ibogaine on dopamine release and metabolism in the striatum. The data suggest that both kappa-opioid agonist and NMDA antagonist actions of ibogaine contribute to its putative anti-addictive effects.

Modulation of morphine-induced antinociception by ibogaine and noribogaine.

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The potential modulation of morphine antinociception by the putative anti-addictive agent ibogaine and its active metabolite (noribogaine) was investigated in rats with the radiant heat tail-flick test. Ibogaine pretreatment (40 mg/kg, i.p., 19 h) significantly decreased morphine (4 mg/kg, s.c.) antinociception, with no effects in the absence of morphine. However, co-administration of ibogaine (1-40 mg/kg, i.p.) and morphine (4 mg/kg, s.c.) exhibited a dose-dependent enhancement of morphine antinociception. Co-administration of noribogaine (40 mg/kg, i.p.) and morphine also resulted in an increase in morphine antinociception, while noribogaine pretreatment (19 h) had no effect on morphine antinociception. The results show that ibogaine acutely potentiates morphine antinociception and that noribogaine could be the active metabolite responsible for this effect. However, the inhibitory effects of a 19 h ibogaine pretreatment, which resemble ibogaine-induced inhibition of morphine's stimulant properties, cannot be accounted for by noribogaine.

Ibogaine neurotoxicity: a re-evaluation.

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Ibogaine is claimed to be an effective treatment for opiate and stimulant addiction. O'Hearn and Molliver, however, showed that ibogaine causes degeneration of cerebellar Purkinje cells in rats. The present study re-examined cerebellar responses to the high doses of ibogaine used by O'Hearn and Molliver (100 mg/kg or 3 x 100 mg/kg) and sought to determine whether a lower dose (40 mg/kg), one effective in reducing morphine and cocaine self-administration, produced similar responses. Purkinje cell degeneration was evaluated with a Fink-Heimer II stain, and enhanced glial cell activity with an antibody to glial fibrillary acidic protein. Every rat treated with the high dose of ibogaine displayed clear evidence of Purkinje cell degeneration. The degeneration consistently occurred in the intermediate and lateral cerebellum, as well as the vermis. Purkinje cells in lobules 5 and 6 were particularly susceptible. Given the response properties of cells in these lobules, this finding suggests any long-term motor deficits produced by ibogaine-induced degeneration should preferentially affect the head and upper extremity. In marked contrast, rats given the smaller dose of ibogaine displayed no degeneration above the level seen in saline-treated animals. When combined with information on other compounds, these data suggest that the degenerative and "anti-addictive" properties of ibogaine reflect different actions of the drug.

The effect of ibogaine on Sigma- and NMDA-receptor-mediated release of [3H]dopamine.

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The indole alkaloid ibogaine has been suggested to have potential for inhibiting dependency on stimulant drugs. Radioligand binding studies have suggested possible multisite actions of ibogaine: affinity at the kappa-opioid, NMDA, and sigma receptors, with effects on dopamine (DA) release. To further investigate the multiplicity of sites of action of ibogaine and the presynaptic regulation of the DA release, the effect of ibogaine on NMDA- and sigma-receptor-mediated efflux of [3H]DA was measured in striatal tissue from C57BL/6By mice. Striatal tissue was incubated in vitro with [3H]DA and the effect on DA release was measured. Both NMDA (25 microM) alone increased the efflux of DA. (+/-)-Pentazocine (100 nM) did not inhibit the NMDA-evoked release. MK-801 (5 microM) completely inhibited the NMDA-evoked release and inhibited the (+/-)-pentazocine-evoked release by 49%. Ibogaine (10 microM) itself increased the efflux of DA; at 1 microM it was without effect. Ibogaine (1 microM) inhibited the NMDA-evoked release of DA by 31% and inhibited the (+/-)-pentazocine-evoked release by 48%. In addition, the level of basal release of DA obtained after the NMDA- or (+/-)-pentazocine-evoked-release remained higher in the tissue exposed to ibogaine throughout. The results suggest that sigma receptors can regulate the release of DA, along with an action at the NMDA receptor. We previously reported action of ibogaine at the kappa-opioid site. The elevated basal release of DA in the presence of ibogaine after NMDA- or (+/-)-pentazocine-evoked release may reflect the ibogaine-induced removal of the tonically active kappa-opioid system that acts presynaptically to reduce dopamine release. The kappa-opioid system also appears to be inhibitory on both the NMDA and sigma receptors.

Tissue distribution of ibogaine after intraperitoneal and subcutaneous administration.

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The distribution of the putative anti-addictive substance ibogaine was measured in plasma, brain, kidney, liver and fat after ip and sc administration in rats. One hr after ip dosing (40 mg/kg), drug levels ranged from 106 ng/ml (plasma) to 11,308 ng/g (fat), with significantly higher values after sc administration of the same dose. Drug levels were 10-20 fold lower 12 hr after the same dose. These results suggest that: 1) ibogaine is subject to a substantial "first pass" effect after ip dosing, demonstrated by higher drug levels following the sc route, 2) ibogaine shows a large accumulation in adipose tissue, consistent with its lipophilic nature, and 3) persistence of the drug in fat may contribute to a long duration of action.

NMDA antagonist properties of the putative antiaddictive drug, ibogaine.

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Both anecdotal reports in humans and preclinical studies indicate that ibogaine interrupts addiction to a variety of abused substances including alcohol, opiates, nicotine and stimulants. Based on the similarity of these therapeutic claims to recent preclinical studies demonstrating that N-methyl-D-aspartate (NMDA) antagonists attenuate addiction-related phenomena, we examined the NMDA antagonist properties of ibogaine. Pharmacologically relevant concentrations of ibogaine produce a voltage-dependent block of NMDA receptors in hippocampal cultures (K_i , 2.3 μM at -60 mV). Consistent with this observation, ibogaine competitively inhibits [^3H]1-[1-(2-thienyl)-cyclohexyl]piperidine binding to rat forebrain homogenates (K_i , 1.5 μM) and blocks glutamate-induced cell death in neuronal cultures (IC_{50} , 4.5 μM). Moreover, at doses previously reported to interfere with drug-seeking behaviors, ibogaine substitutes as a discriminative stimulus (ED_{50} , 64.9 mg/kg) in mice trained to discriminate the prototypic voltage-dependent NMDA antagonist, dizocilpine (0.17 mg/kg), from saline. Consistent with previous reports, ibogaine reduced naloxone-precipitated jumping in morphine-dependent mice (ED_{50} , 72 mg/kg). Although pretreatment with glycine did not affect naloxone-precipitated jumping in morphine-dependent mice, it abolished the ability of ibogaine to block naloxone-precipitated jumping. Taken together, these findings link the NMDA antagonist actions of ibogaine to a putative "antiaddictive" property of this alkaloid, its ability to reduce the expression of morphine dependence.

Prior morphine exposure enhances ibogaine antagonism of morphine-induced locomotor stimulation.

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Ibogaine is currently being investigated for its potential use as an anti-addictive agent. In the present study we sought to determine whether prior morphine exposure influences the ability of ibogaine to inhibit morphine-induced locomotor stimulation. Female Sprague-Dawley rats were pretreated once a day for 1-4 days with morphine (5, 10, 20 or 30 mg/kg, i.p.) or saline and then received ibogaine (40 mg/kg, i.p.) 5 h after the last morphine pretreatment dose. Compared to rats pretreated with saline, rats pretreated with morphine (10, 20 or 30 mg/kg, i.p.) before ibogaine (40 mg/kg, i.p.) showed a significant reduction in morphine-induced (5 mg/kg, i.p.) locomotor stimulation when tested 29 h after ibogaine administration. Furthermore, this effect was apparent over a range of ibogaine (5-60 mg/kg, i.p.) and morphine test (2.5-5 mg/kg, i.p.) dosages. Doses of ibogaine (5 and 10 mg/kg, i.p.) which alone were inactive inhibited morphine-induced locomotor activity when rats had been pretreated with morphine. These results, showing that morphine pre-exposure affects ibogaine activity, suggest that variable histories of opioid exposure might account for individual differences in the efficacy of ibogaine to inhibit opioid addiction.

Receptor binding profile suggests multiple mechanisms of action are responsible for ibogaine's putative anti-addictive activity.

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The indole alkaloid ibogaine (NIH 10567, Endabuse) is currently being examined for its potential utility in the treatment of cocaine and opioid addiction. However, a clearly defined molecular mechanism of action for ibogaine's putative anti-addictive properties has not been delineated. Radioligand binding assays targeting over 50 distinct neurotransmitter receptors, ion channels, and select second messenger systems were employed to establish a broad in vitro pharmacological profile for ibogaine. These studies revealed that ibogaine interacted with a wide variety of receptors at concentrations of 1-100 microM. These included the mu, delta, kappa, opiate, 5HT₂, 5HT₃, and muscarinic₁ and ₂ receptors, and the dopamine, norepinephrine, and serotonin uptake sites. In addition, ibogaine interacted with N-methyl-D-aspartic acid (NMDA) associated ion and sodium ion channels as determined by the inhibition of [³H]MK-801 and [³H]bactrachotoxin A 20-alpha-benzoate binding (BTX-B), respectively. This broad spectrum of activity may in part be responsible for ibogaine's putative anti-addictive activity.

Effect of ibogaine on serotonergic and dopaminergic interactions in striatum from mice and rats.

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The effect of ibogaine (Endabuse, NIH 10567) on serotonin uptake and release, and on serotonergic modulation of dopamine release, was measured in striatal tissue from rats and mice. Two hours after treatment in vivo with ibogaine (40 mg/kg i.p.) the uptake of labeled [3H]serotonin and [3H]dopamine uptake in striatal tissue was similar in the ibogaine-treated animal to that in the control. The 5HT1B agonist CGS-12066A (10^{-5} M) had no effect on stimulation-evoked tritium release from mouse or rat striatal tissue preloaded with [3H]serotonin; however, it elevated tritium efflux from striatal tissue preloaded with [3H]dopamine. This increase was not seen in mice treated with ibogaine 2 or 18 hours previously, or in rats treated 2 hours before. Dopamine autoreceptor responses were not affected by ibogaine pretreatment in either mouse or rat striatal tissue; sulpiride increased stimulation-evoked release of tritium from tissue preloaded with [3H]dopamine. The long-lasting effect of ibogaine on serotonergic functioning, in particular, its blocking of the 5HT1B agonist-mediated increase in dopamine efflux, may have significance in the mediation of its anti-addictive properties.

Effects of iboga alkaloids on morphine and cocaine self-administration in rats: relationship to tremorigenic effects and to effects on dopamine release in nucleus accumbens and striatum.

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Ibogaine, a naturally occurring alkaloid, has been claimed to be effective in treating addiction to opioid and stimulant drugs and has been reported to decrease morphine and cocaine self-administration in rats. The present study sought to determine if other iboga alkaloids, as well as the chemically related harmala alkaloid harmaline, would also reduce the intravenous self-administration of morphine and cocaine in rats. Because both ibogaine and harmaline induce tremors, an effect that may be causally related to neurotoxicity in the cerebellar vermis, the tremorigenic activities of the other iboga alkaloids were assessed. Lastly, in view of the involvement of the dopaminergic mesolimbic system in the actions of drugs of abuse, the effects of some of the iboga alkaloids on extracellular levels of dopamine and its metabolites in the nucleus accumbens and striatum were determined. All of the tested alkaloids (i.e., ibogaine, tabernanthine, R- and S-coronaridine, R- and S-ibogamine, desethylcoronaridine, and harmaline) dose-dependently (2.5-80 mg/kg) decreased morphine and cocaine intake in the hour after treatment; decreases in morphine and cocaine intake were also apparent the day after administration of some but not all of these alkaloids (i.e., ibogaine, tabernanthine, desethylcoronaridine, and the R-isomers of coronaridine and ibogamine). In some rats, there were persistent decreases in morphine or cocaine intake for several days after a single injection or after two or three weekly injections of one or another of these alkaloids; R-ibogamine produced such effects more consistently than any of the other alkaloids

A preliminary investigation of ibogaine: case reports and recommendations for further study.

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A naturally occurring substance, ibogaine, was taken by seven individuals who were addicted to opiates. Ibogaine, an alkaloid with psychotropic effects at doses of 200-300 mg and above, was taken in single doses of 700-1800 mg by the subjects in the study. At the end of the 24-38-hr psychoactive period induced by the drug at these doses, none of the subjects displayed significant opiate withdrawal symptoms. At the lowest dose of 700 mg, one subject recontinued his drug abuse after 2 days; of the remaining six individuals who took 1,000 mg or above, two relapsed after a number of weeks, one reverted to intermittent heroin use, and three appear to have remained drug-free 14 weeks or more after undergoing this experimental treatment. Ibogaine may be of value in the present and could serve as a model for the development of improved agents for the treatment of substance abuse in the future.

The putative anti-addictive drug ibogaine is a competitive inhibitor of [3H]MK-801 binding to the NMDA receptor complex.

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Ibogaine is a putative anti-addictive drug with potential efficacy for the treatment of opiate, stimulant, and alcohol abuse. We now report ibogaine is a competitive inhibitor (K_i , 1.01 +/- 0.1 microM) of [3H]MK-801 binding to N-methyl-D-aspartate (NMDA) receptor coupled cation channels. Since MK-801 can attenuate the development of tolerance to morphine and alcohol as well as sensitization to stimulants in preclinical studies, the reported ability of ibogaine to modify drug-seeking behavior in man may be attributable to a blockade of NMDA receptor coupled cation channels.

Effects of ibogaine on acute signs of morphine withdrawal in rats: independence from tremor.

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Because of the claim that ibogaine suppresses the symptoms of "narcotic withdrawal" in humans, the effect of ibogaine on naltrexone-precipitated withdrawal signs in morphine-dependent rats was assessed. Morphine was administered subcutaneously through implanted silicone reservoirs for 5 days. Ibogaine (20, 40 or 80 mg/kg, i.p.) or saline was administered 30 min prior to challenge with naltrexone (1 mg/kg, i.p.) and withdrawal signs were counted for the following 2 hr. Ibogaine (40 and 80 mg/kg) significantly reduced the occurrence of four signs (wet-dog shakes, grooming, teeth chattering and diarrhea) during naltrexone-precipitated withdrawal; three other signs (weight loss, burying and flinching) were unaffected. Ibogaine induces head and body tremors lasting for 2-3 hr and the tremors might have interfered with the expression of opioid withdrawal. To examine this issue, another experiment was conducted in which ibogaine (40 mg/kg) or saline was administered 4 hr prior to challenge with naltrexone. Although there was a complete absence of tremors, ibogaine still significantly reduced the occurrence of the same four signs of withdrawal.

Acute and prolonged effects of ibogaine on brain dopamine metabolism and morphine-induced locomotor activity in rats.

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Ibogaine, an indolalkylamine, proposed for use in treating opiate and stimulant addiction, has been shown to modulate the dopaminergic system acutely and one day later. In the present study we sought to systematically determine the effects of ibogaine on the levels of dopamine (DA) and the dopamine metabolites 3,4 dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) in tissue at several time points, between 1 h and 1 month post-injection. One hour after ibogaine-administration (40 mg/kg i.p.) a 50% decrease in DA along with a 37-100% increase in HVA were observed in all 3 brain regions studied: striatum, nucleus accumbens and prefrontal cortex. Nineteen hours after ibogaine-administration a decrease in DOPAC was seen in the nucleus accumbens and in the striatum. A week after administration of ibogaine striatal DOPAC levels were still reduced. A month after ibogaine injection there were no significant neurochemical changes in any region. We also investigated the effects of ibogaine pretreatment on morphine-induced locomotor activity, which is thought to depend on DA release. Using photocell activity cages we found that ibogaine pretreatment decreased the stimulatory motor effects induced by a wide range of morphine doses (0.5-20 mg/kg, i.p.) administered 19 h later; a similar effect was observed when morphine (5 mg/kg) was administered a week after ibogaine pretreatment. No significant changes in morphine-induced locomotion were seen a month after ibogaine pretreatment. The present findings indicate that ibogaine produces both acute and delayed effects on the tissue content of DA and its metabolites, and these changes coincide with a sustained depression of morphine-induced locomotor activity.

Effects and aftereffects of ibogaine on morphine self-administration in rats.

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Ibogaine, a naturally occurring alkaloid, has been claimed to be effective in treating addiction to opiate and stimulant drugs. As a preclinical test of this claim, the present study sought to determine if ibogaine would reduce the intravenous self-administration of morphine in rats. Ibogaine dose dependently (2.5-80 mg/kg) decreased morphine intake in the hour after ibogaine treatment (acute effect) and, to a lesser extent, a day later (aftereffect); while the acute effect could be attributed to abnormal motor behavior (whole body tremors), the aftereffect occurred at a time when ibogaine should have been entirely eliminated from the body and when there was no obvious indication of ibogaine exposure. In some rats, there was a persistent decrease in morphine intake for several days or weeks after a single injection of ibogaine; other rats began to show such persistent changes only after two or three weekly injections whereas a few rats were apparently resistant to prolonged aftereffects. Aftereffects could not be attributed to a conditioned aversion. Although ibogaine also depressed responding acutely in rats trained to bar-press for water, there was no evidence of any aftereffect a day or more later; the interaction between ibogaine and morphine reinforcement was therefore somewhat specific. Further studies are needed to characterize the nature of the ibogaine-morphine interaction as well as to determine if ibogaine also affects the self-administration of other drugs.

Effect of ibogaine on naloxone-precipitated withdrawal syndrome in chronic morphine-dependent rats.

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Ibogaine, an indole alkaloid, administered intracerebroventricularly 4-16 micrograms, attenuated a naloxone-precipitated withdrawal syndrome in chronic morphine-dependent rats. It appears that ibogaine has a more consistent effect on certain selective withdrawal signs related to the locomotion. This might explain an attenuating effect of ibogaine on some withdrawal signs. However, due to complex interaction of ibogaine with serotonin and other neurotransmitter systems, the mechanism of ibogaine antiwithdrawal effect remains unknown and requires further elucidation.

NOTES