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100 Years of Ibogaine: Neurochemical and Pharmacological Actions of a Putative Anti-addictive Drug

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I. Introduction

Ibogaine (NIH 10567, Endabuse™) is one of the psychoactive indole alkaloids found in the West African shrub, *Tabernanthe iboga*. Since its introduction to Western medicine more than a century ago, ibogaine has had a variety of uses ranging from a trypanocide to an adjunct for psychotherapy (Naranjo, 1969, 1973). However, during the past decade, anecdotal observations have led to the hypothesis that ibogaine possesses "anti-addictive" properties (Lotsof, 1985, 1986, 1989, 1991, 1995; Kaplan et al., 1993; Sisko, 1993; Touchette, 1993). Preclinical studies demonstrating that ibogaine reduces self-administration of both cocaine and morphine and attenuates the symptoms of morphine withdrawal support this hypothesis. Unresolved, however, is the mechanism(s) responsible for these putative "anti-addictive" and other psychopharmacological effects of ibogaine. This manuscript reviews the ibogaine literature, from the initial botanical description of *Tabernanthe iboga* over 100 years ago to potential molecular mechanisms for its "anti-addictive" properties.

In this article, the term drug addiction refers to "*a behavioral pattern of drug use, characterized by overwhelming involvement with the use of a drug (compulsive use), the securing of its supply, and a high tendency to relapse after withdrawal*" (Jaffe, 1985). Traditional theories concerning drug addiction involve the development of drug dependence, including both physical and psychological dependence. Physical dependence refers to "*an adaptive state that manifests itself by intense phys-*

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Abbreviations: NMDA, N-methyl-D-aspartate; i.p., intraperitoneal; ED_{50}, median effective dose; DA, dopamine; DOPA, dihydroxyphenylalanine (methyldopa); DOPAC, dihydrophenylacetic acid; HVA, homovanillic acid; c.f., confer; LSD, lysergic acid diethylamide; HT, hydroxytryptamine.

ical disturbances when the administration of the drug is suspended," whereas psychological dependence is *"a condition in which a drug produces a feeling of satisfaction and a psychic drive that requires periodic or continuous administration of the drug to produce pleasure or avoid discomfort"* (Eddy et al., 1965). The Diagnostic and Statistical Manual of Mental Disorders III (American Psychiatric Association, 1987) defines drug dependence as *"a cluster of cognitive, behavioral, and physiologic symptoms that indicate that the person has impaired control of psychoactive substance use and continues use of the substance despite adverse consequences."* In animals, drug dependence is often demonstrated by the appearance of measurable behavioral phenomena after discontinuing the administration of the drug or after administration of an appropriate antagonist. For example, the appearance of a naloxone-precipitated withdrawal syndrome (including diarrhea, vocalization, wet dog shakes, and teeth chattering) in morphine-treated rats is taken as *prima facie* evidence of dependence. Such behavioral phenomena are characteristic for each class of abused compound.

Despite many years of intensive research, a safe, reliable and cost-effective treatment for addiction has not been developed (for review see Jaffe, 1985, 1987). Despite the apparent similarities among the psychological symptoms (drug dependence and compulsive craving) produced by many, if not all, substances of abuse, existing pharmacological treatments have traditionally been targeted to specific receptor systems at which the abused drugs are presumably acting. Hence, opioid antagonists (Cochin and Mushlin, 1976; Resnick et al., 1980; Jaffe, 1987; Buie, 1994), the acylating μ-opioid receptor ligand β-funaltrexamine (DeLander et al., 1984), and particularly the mixed μ receptor agonist/κ receptor antagonist buprenorphine (Forsyth et al., 1993; Torrens et al., 1993; Frischer, 1992; Buie, 1994) have been proposed as treatments for opiate dependence. However, their efficacy is questionable, and, as indicated in clinical trials, buphrenorphine has been abused (Frischer, 1992). Traditional methadone therapy, although effective while the treatment is maintained, has a relapse rate exceeding 80% when the drug is discontinued (Ball and Ross, 1991). Similarly, compounds acting at dopamine re-uptake sites have been proposed for the treatment of stimulant (e.g., cocaine) abuse (Berger et al., 1989; Preston et al., 1993; Buie, 1994), and benzodiazepine receptor ligands have been suggested as substitution treatment for benzodiazepine abuse (Jaffe, 1985). There are a few exceptions to this receptor-targeting strategy including clonidine (an α_2-adrenoceptor agonist) and vasopressin derivatives. Similarly, L-type calcium channel blockers have been proposed for the treatment of opiate addiction, although they do not exert direct pharmacological actions on opioid systems (see Vetulani and Bednarczyk, 1977; Gold et al., 1978 for clonidine, Van Beek-Verbeek et al., 1993 for vasopressin, and Contreras et al., 1988; Zharkovsky et al., 1993 for L-type calcium channel antagonists, respectively). The use of NMDA antagonists offers a new paradigm for the treatment of addiction, because preclinical data suggest that these compounds are effective in attenuating the development of tolerance and in decreasing the symptoms of dependence of all abused substances examined to date (see VII., Conclusions). The recent demonstration that ibogaine is an NMDA antagonist (Popik et al., 1994; in review) is consistent with the notion that this class of compounds may offer a general approach to the treatment of addiction.

II. Historical Overview

Ibogaine is derived from *Tabernanthe iboga*, a shrub indigenous to Central-West Africa. The *iboga* shrub, a member of the family *Apocynaceae* in the order *Contortae*, is typically found in the undergrowth of tropical forests and reaches a height of 6 feet (Evans-Schultes and Hofmann, 1980). In Gabon, the roots of *Tabernanthe iboga* are used in the initiation rites of a number of secret societies, including the Bwiti cult (Fernandez, 1982). Although the details of such ceremonies vary, in general, cult members or initiates believe that *iboga* root enables them to make contact with ancestors in the spirit world. According to Pope (1969), humans may have learned of the properties of the *iboga* plant by observing animal behavior. Thus, several accounts report that the local inhabitants observed boars, porcupines, and gorillas digging up and eating the roots of *Tabernanthe iboga*, after which the animals would enter into a wild frenzy.

Nineteenth century reports from French and Belgian explorers first described the stimulant and aphrodisiac effects of eating *iboga* root. They further reported that eating the root greatly increased the endurance and strength of warriors. The earliest known Western reference to the plant is attributed to Griffon du Bellay, a surgeon, who made his observations in 1864 near Cape Lopez, Gabon. The effects of eating *iboga* root are described: *"In small quantities it is an aphrodisiac and a stimulant of the nervous system; warriors and hunters use it constantly to keep themselves awake during night watches . . . "* (Lecomte, 1864; Pope, 1969). Professor Henri Baillon (Baillon, 1889), in the 1889 session of the Linnaen Society in Paris, described samples obtained from Gabon and French Congo and offered the first botanical description of the plant, naming it *Tabernanthe iboga*. The genus name *Tabernanthe* derives from Tabernae-anthos (similar to Tabernaemontana flowers), whereas the species name *iboga* is derived from the native Nipongive dialect.

Dybovsky and Landrin (1901) as well as Haller and Heckel (1901) were the first to isolate a crystalline alkaloid from *iboga* root, which they called "ibogaine" or "ibogine." In 1901, French pharmacologists found ibogaine to have an unusual type of excitatory effect in ani-

mals (Lambert and Heckel, 1901; Lambert, 1902; Phisalix, 1901). Based on observations of unusual behavior in dogs, Phisalix (1901) suggested that ibogaine could produce hallucinations. The alkaloid was subsequently tested in Western clinical settings and recommended as a stimulant for treatment of convalescence and neurasthenia, as well as trypanosomiasis (cf Pope, 1969). In spite of such recommendations, ibogaine was never widely used in the clinic and was neglected by researchers for almost 30 years. In the 1940s, Raymond-Hamet and coworkers (Rothlin and Raymond-Hamet, 1938; Raymond-Hamet and Rothlin, 1939; Raymond-Hamet, 1940a, 1940b, 1940c, 1941a, 1941b; Raymond-Hamet and Vincent, 1960) published a series of papers about the pharmacological properties of ibogaine on isolated tissues and the cardiovascular system.

Lambarene, an extract of the roots of the *iboga* relative *Tabernanthe manii*, was marketed in France during the 1930s. A tablet of Lambarene contained about 8 mg of ibogaine and was described in the package information as "*a neuromuscular stimulant, promoting cell combustions and getting rid of fatigue, indicated in cases of depression, asthenia, in convalescence, infectious diseases.*" Later, another *iboga* extract, Iperton, was used as a tonic or stimulant (Naranjo, 1969). Iperton contained 40 mg of the total extract of *Tabernanthe iboga* and 10 mg of *belladonna* extract per capsule. More recently, ibogaine has been used by athletes as a performance-enhancing drug (De Sio, 1970). In many countries, including the United States, ibogaine use is prohibited, perhaps because of its purported hallucinogenic effects (widely publicized in the late 1960s) and its appearance on the illicit drug market. In 1970, the United States Food and Drug Administration classified ibogaine as a Schedule I substance (all nonresearch use forbidden).

Beginning in 1985, a series of five patents was issued for the use of ibogaine as a rapid and easy means of interrupting addiction to narcotics (morphine and heroin) (Lotsof, 1985), cocaine and amphetamine (Lotsof, 1986), alcohol (Lotsof, 1989), nicotine (Lotsof, 1991), and polydrug dependency syndrome (Lotsof, 1992). These patents claim that an oral or rectal dose of ibogaine (4 to 25 mg/kg) interrupts the dependence syndrome, allowing patients to maintain a drug-free lifestyle for at least 6 months. According to Regan (1992), ibogaine induced: (*a*) the release of repressed memories; (*b*) intellectual re-evaluation of memories; and (*c*) integration of new insights into the personality of the patient. Based on open, nonblinded studies, it has been claimed (Regan, 1992) that ibogaine therapy resulted in 25% of patients remaining drug-free without craving for 6 months. This group included those who were both highly motivated to quit and had relatively stable home environments. Another 40 to 50% of patients had their addictions interrupted successfully but required psychotherapy. Twenty to 30% of patients had returned to drug use within a month following treatment. Although the efficacy of the drug cannot be rigorously assessed in the absence of appropriately controlled clinical studies, interest in ibogaine as a treatment for addiction has increased. In 1985, NDA International, Inc. (Staten Island, NY) began a campaign to persuade both the United States Congress and executive branch agencies to invest resources to study ibogaine (Food and Drug Administration Advisory Committee, 1993). At the same time, the use of ibogaine for treating opioid dependence has gained a degree of popularity among people with drug addiction in Europe (Sharpe and Jaffe, 1990). At present, clinical trials to test the safety of ibogaine are underway at the University of Miami and planned in New York; clinical trials to test the efficacy of ibogaine as a treatment for addiction are planned in The Netherlands (Food and Drug Administration Advisory Committee, 1993; Touchette, 1993; Buie, 1994; Sanchez-Ramos and Mash, 1994).

III. Chemical Structure and Properties

Whereas ibogaine was first isolated and identified in 1901 (Dybovsky and Landrin, 1901; Haller and Heckel, 1901; Lambert and Heckel, 1901; Landrin, 1905), the structure of this and related alkaloids (fig. 1) was first established by Taylor in 1957 (see also Taylor, 1965, 1968). Total synthesis from nicotinamide was reported using a 13- (Buchi et al., 1966) or 14-step (Rosenmund et al., 1975) sequence. The ^{13}C-nuclear magnetic resonance spectra of several *iboga* alkaloids was published in 1976 (Wenkert et al., 1976). The synthesis of tritiated [^{3}H]-ibogaine was recently reported (Seltzman et al., 1992, 1994).

Ibogaine has a melting point of 153°C at 0.01 mm Hg and pK_a = 8.1 in 80% methylcellosolve. The absorption maxima in methanol are 226 and 296 nM (log ϵ_{226} = 4.39; log ϵ_{298} = 3.93). Ibogaine crystallizes from alcoholic solutions into small, reddish prismatic needles; it is levorotatory $[\alpha]_D$ = –53° (in 95% ethanol) and is soluble in ethanol, methanol, chloroform, and acetone but insoluble in water. Ibogaine hydrochloride (freezing point 299°C, $[\alpha]_D$ = –63° (ethanol), $[\alpha]_D$ = –49° (H_2O)) is soluble in water, ethanol, and methanol, is slightly soluble in acetone and chloroform, and is practically insoluble in ether (Stecher et al., 1968). Ibogaine is heat- and light-sensitive (Cartoni and Giarusso, 1972) and can spontaneously oxidize in solution, giving iboluteine and ibochine (Pope, 1969; De Sio, 1970). Alkaloids that are structurally similar to ibogaine include harmaline, tab-

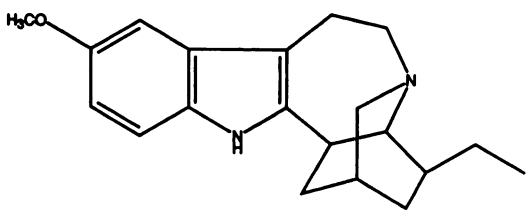

FIG. 1. The structure of ibogaine.

ernanthine, ibogamine, iboxigaine, gabonine, iboquine, kisantine, and ibolutenine. Structural similarities between ibogaine and other indole alkaloid hallucinogens have also been reported (Kelley and Adamson, 1973). The synthesis of several ibogaine derivatives has recently been reported (Repke et al., 1994).

IV. Pharmacokinetics

One hour after i.p. injection to rats, ibogaine was found in high concentrations in the liver and kidneys (Dhahir, 1971). After intravenous injection of 10 mg/kg in mice, maximal brain concentrations (48 μg/g of wet weight [~133 μM]) were achieved in 10 sec (Zetler et al., 1972). Elimination kinetics from brain yielded a half-life of 60 min in rodents (Dhahir, 1971; Zetler et al., 1972) and suggest a one-compartment model. Ibogaine disappeared from the rat body at a rate of about 4% of the administered dose per hour and was undetectable after 12 hr. About 5% of the injected dose was eliminated unchanged in urine. After administration of ibogaine (10 mg/kg per os) to the rabbit, the drug concentration in urine reached a maximum 4 to 5 hr later, then decreased rapidly and disappeared after 6 hr (Cartoni and Giarusso, 1972). However, the various pharmacological actions of ibogaine differ with respect to time-course; for example, the tremorigenic effects dissipate much more rapidly than the attenuation of a morphine withdrawal syndrome in rats (Glick et al., 1992b). The reported long-term effects of ibogaine (observed up to 1 week after administration both in humans and animals) have led to the hypothesis that this alkaloid may be metabolized to an active principle with a long half-life (Maisonneuve et al., 1991a). At present, there is no direct evidence to support this hypothesis.

After parenteral administration, ibogaine has been identified in various biological materials including blood and urine (humans) and in the liver, kidney, and brain of laboratory animals (Dhahir et al., 1971; Cartoni and Giarusso, 1972; Dhahir et al., 1972; Bertol et al., 1976).

V. General Pharmacological Actions

A. Animal Studies

Ibogaine has dose-dependent effects on locomotor activity in rodents. A dose of 20 mg/kg (i.p.) slightly increased locomotor activity in mice without producing the piloerection and salivation seen after lysergic acid diethylamide (3 mg/kg) administration (Chen and Bohner, 1958). Sershen et al. (1992b) reported that ibogaine (40 mg/kg i.p.) decreased locomotor activity in male mice at 1 hr but not at 24 hr after injection. The same dose inhibited locomotion in rats during the first hour after injection (but not later), whereas 1 week later, locomotor activity was increased (Maisonneuve et al., 1992b). In another study (O'Hearn and Molliver, 1993), a high dose of ibogaine (100 mg/kg) produced ataxia and high-frequency tremor of the head and trunk in rats. Some rats had strong extensor limb movements that propelled them off the floor of the cage. Hypotonia of the trunk and flaccid limbs were observed later in the first hour, with animals lying motionless on the cage floor with eyes open, although responding to tactile stimuli. Tremor and ataxia gradually resolved over 6 to 8 hr, and spontaneous activity increased. Locomotion appeared normal the next day.

Like the structurally related harmaline, ibogaine produces tremors. In mice, ibogaine is tremorigenic, both when given intracerebrally (ED_{50} 127 nmol/g brain, ~46 μg/g with a latency to tremor of about 1 min) (Singbarth et al., 1973) and systemically (ED_{50} 12 mg/kg subcutaneous) (Zetler et al., 1972). Zetler et al. (1972) also established the tremorigenic structure-activity relationship of several ibogaine-like compounds, with the descending order of potency: tabernanthine > ibogaline > ibogaine > iboxygaine > noribogaine. Recently, Glick et al. (1994) found that, whereas ibogaine and tabernanthine produced tremors, ibogamine and coronaridine were devoid of such an effect.

Schneider and Sigg (1957) described the behavioral effects of ibogaine in cats. After intravenous administration of 2–10 mg/kg, ibogaine exerted effects that were almost immediate and included excitation, pupil dilation, salivation, partial piloerection, and tremor. These symptoms gradually developed into a rage state. Animals remained in place, slightly shivering, tail outstretched, while making hissing sounds as if trying to threaten an imaginary object. Often, a cat would try to cover its head and hide in a corner of the cage or try to climb the walls. These symptoms were accompanied by mewing and a peculiar type of clonic extension of the hind and front limbs. Rapid respiration and ataxia were noted. Salivation, but no urination or defecation, occurred during the phase of rage. These behaviors were observed during a period of 10 to 20 min following intravenous injection; after 1 to 2 hr, the cats appeared to behave normally. The electroencephalographic pattern obtained after ibogaine administration (2 to 5 mg/kg) showed a typical arousal syndrome, resembling that observed after direct stimulation of the reticular formation.

Gershon and Lang (1962) described the effects of ibogaine in dogs. Animals become more tense and alert, interpreted by these authors as the appearance of anxiety. Moreover, they observed that the dogs exhibited a lack of recognition of both their regular handlers and environment. Body tremor and shaking were also noted. Dogs developed a peculiar stance with legs apart and back arched. The same authors recorded various physiological responses produced by ibogaine. The alkaloid produced a rise in blood pressure and increased heart rate in conscious dogs; changes in electrocardiogram indicated accentuation of sinus arrhythmia by potentiating vagus effects. However, in anesthetized dogs, the blood pressure fell and the heart rate was reduced, lead-

ing the authors to propose an interaction between anesthesia and the cardiovascular effects of ibogaine. Schneider and Rinehart (1957) postulated a centrally mediated stimulatory effect for ibogaine action. Ibogaine also potentiated the pressor response to both adrenaline and noradrenaline. More recently, Hajo-Tello et al. (1985) found that tabernanthine (an alkaloid closely related to ibogaine) induced a negative inotropic effect in electrically stimulated myocardial tissue and a negative chronotropic effect in the perfused rat heart. Tabernanthine produced also bradycardia and hypotension in anesthetized rats and dogs (Hajo et al., 1981).

B. Human Studies

Numerous psychotropic actions of ibogaine have been reported. These actions seem to depend on both the dose and setting. In addition, the psychoactive effects of *iboga* extracts (which are likely to contain additional alkaloids and are usually taken in a ritualistic setting) may be different from those of ibogaine. Thus, users of the crude extract of *Tabernanthe iboga* among (e.g.,) the secret societies in Africa have reported fantastic visions, feelings of excitement, drunkenness, mental confusion, and hallucinations when taken in sufficiently high doses (Schneider and Sigg, 1957). These indigenous people use the drug as a ritual, ordeal, or initiation potion (Raponda-Walker, 1961, c.f. [Evans-Schultes and Hofmann, 1980]). Typically, high doses are used that often result in lethargic states lasting up to 4 or 5 days and are sometimes fatal. The total extract of *iboga* shrub is certainly a central stimulant and in higher doses may lead to convulsions, paralysis, and finally, respiratory arrest. The psychotropic actions of the plant extract include visual sensations; objects are seen to be surrounded by specters or rainbows. In high doses, it may produce auditory, olfactory, and taste synesthesia; the state of mind can vary from profound fear to frank euphoria (Mandrile et al., 1985). As mentioned earlier in this review (see II., Historical Overview), in smaller quantities, ibogaine has been widely used by native Africans to combat fatigue (Schneider and Sigg, 1957).

Although the use of ibogaine is now severely restricted in many countries, several early reports have documented its effects in more controlled settings. The cardiovascular effects of ibogaine include changes in blood pressure and potentiation of the pressor response to adrenaline (Vincent and Sero, 1942). Ibogaine is also reported to stimulate digestion and appetite (Vincent and Sero, 1942). In 1905, Pouchet and Chevalier (cf. Pope, 1969) reported that ibogaine (10 to 30 mg) was used for the treatment of influenza, convalescence from infectious disease, neurasthenia, and a few cardiac disorders. It was found that the drug improved appetite, muscle tone, and the general rate of recovery; a mild euphoria in almost all of patients was also noted and resembled that produced by other stimulants.

Ibogaine or the total *iboga* extract (4 to 5 mg/kg) given orally elicits subjective reactions that last for approximately 6 hr. Fifty percent of subjects are reported to experience dizziness, incoordination, nausea, and vomiting (Naranjo, 1969, 1973; Lotsof, 1995). Typically in these studies, the drug elicited a state of drowsiness in which the subject did not want to move, open the eyes, or attend to the environment. Many subjects were light-sensitive and were covering their eyes or asking that lights be turned off. Sounds or noises were disturbing. Ibogalin (0.1 to 1.2 mg/kg per os), an alkaloid closely related to ibogaine and a constituent of the total *iboga* extract, did not produce psychotomimetic effects in humans (Von Schmid, 1967). Ibogalin also differs from ibogaine in pharmacokinetics and tremorigenic activity (Singbarth et al., 1973).

The psychoactive properties of ibogaine and related compounds were further studied by Naranjo (Naranjo, 1969, 1973), who explored the possibility of using ibogaine to facilitate psychotherapy (see also Stafford, 1978). He used the term "oneirophrenia" to describe the ibogaine-induced state. Such an "oneirophrenic" state differs from the psychotomimetic state by the absence of all psychotic symptoms, yet having in common the prominence of primary process thinking. Naranjo, observing at least 40 sessions conducted with 30 patients, reports that the psychic state produced by ibogaine might be described as similar to a dream state *without* loss of consciousness. Thus, at doses of 4 to 5 mg/kg, subjects experienced an enhancement of fantasy without experiencing changes in the perception of the environment, delusions, depersonalization, or formal alterations of thinking. Ibogaine's fantasies (often described as a "*movie run at high speed*" or "*slide show*" [Lotsof, 1995]) were reported as rich in archetypal contents, involving animals and/or the subject himself with or without other individuals. The fantasies evoked by ibogaine were easy to manipulate by both the subjects and the psychotherapist. The patients were able to respond to the questions of the therapists. It was concluded that ibogaine could act as a psychological catalyst that could compress a long psychotherapeutic process into a shorter time (Naranjo, 1969, 1973).

Ibogaine appears to have a pronounced hallucinogenic action at higher doses. Reference to hallucinatory properties was first made in 1903, when Guien described an initiation ritual performed by inhabitants of the Belgian Congo, in which great quantities of *Tabernanthe iboga* root were chewed (cf. Pope, 1969; Landrin, 1905). More recent studies have demonstrated that ibogaine causes visual and other hallucinations associated with severe anxiety and apprehension (Schneider and Sigg, 1957; Sloviter et al., 1980; Farnsworth, 1968). Sigg described the effects he perceived after ingesting 200 mg of ibogaine (Schneider and Sigg, 1958). He reports: "*Subjectively, the most unpleasant symptoms were the anxiety, the extreme apprehension, and the unheimliche Grundstim-*

mung (~unfamiliar mood) associated with visual and bodily hallucinations. The visual hallucinations appeared only in the dark and consisted of blue disks dancing up and down the walls. Dysesthesia of the extremities, a feeling of light-weightedness, and hyperacusis were other symptoms noted. Autonomic signs, such as dryness of the mouth, increased perspiration, slight pupillary dilation, and increase in pulse rate, as well as extrapyramidal symptoms (fine tremors, slight ataxia, enhanced tendom reflexes and clonus) were also presented [. . .]. The peak effect was reached about 2 hr after swallowing the drug; it subsided gradually, leaving as a residue complete insomnia. No undesirable aftereffects, such as exhaustion or depression occurred." As the hallucinogenic dose appears to be several times higher than the stimulant dose, the user must endure intense and unpleasant central stimulation in order to experience the hallucinogenic effects.

Ibogaine is also reported to affect sexual behavior. Burckhardt (1953) reports that ibogaine is a highly valued aphrodisiac in Africa. Goettlieb (c.f. Stafford, 1978) reported that ibogaine was used as an aphrodisiac and cure for impotence; people consuming large doses of the alkaloid engage in continuous sexual activities for periods ranging from 6 to 17 hr. Although there is no direct pharmacological evidence that ibogaine stimulates sexual function, the reported increase in self-confidence and diminution of fatigue may account for this property.

It is unclear whether ibogaine produces fear, apprehension, and inebriation, as has been reported for *Tabernanthe iboga* extracts. Indeed, little is known about the biological activity of the other alkaloids of the plant including tabernanthine, ibogamine, and ibolutine. Some pharmacological differences have been reported between the whole extract and ibogaine. Thus, Vincent and Sero (1942) report that ibogaine is a less potent inhibitor of serum cholinesterase than a crude *Tabernanthe iboga* extract. It seems likely that disagreement concerning the existence of dysphoric feelings while under the influence of *iboga* extract versus ibogaine (i.e., between initial observations made in the field and anecdotal observations in a more clinical setting) is caused by several factors, including: (*a*) dose; (*b*) differential response to repeated exposure; (*c*) effects of other alkaloids present in the *iboga* root; or (*d*) social influences (ritual vs. clinical or experimental setting).

VI. Lethality and Neurotoxic Effects

The LD_{50} of ibogaine has been determined in guinea pig (82 mg/kg i.p.) and rat (327 mg/kg intragastrically and 145 mg/kg i.p.) (Delourme-Houde, 1946; Dhahir, 1971). Alcohol (2 g/kg) increased the toxicity of ibogaine by a factor of 1.4 in rats (Dhahir, 1971).

Dhahir (1971) reported no significant pathological changes in rat liver, kidneys, heart, and brain following chronic ibogaine treatment (10 mg/kg for 30 days or 40 mg/kg for 12 days, i.p.). Similarly, Sanchez-Ramos and Mash (1994) found no evidence of neurotoxicity in African green monkeys given ibogaine in doses of 5–25 mg/kg per os for four consecutive days. Phase I toxicity studies in people with drug addiction are in progress at the University of Miami (Sanchez-Ramos and Mash, 1994).

O'Hearn et al. (1993) and O'Hearn and Molliver (1993) reported that repeated administration of ibogaine (100 mg/kg i.p.) to rats caused the degeneration of a subset of Purkinje cells in the cerebellar vermis. This degeneration was accompanied by a loss of the microtubule-associated protein 2 and calbindin. The authors suggest that the neurodegenerative actions of ibogaine result from excitation of inferior olivary neurons and release of an excitatory amino acid from climbing fiber synaptic terminals. Thus, whereas the doses used in this study were high relative to the behaviorally active doses of ibogaine in the same species, the authors urge caution before proceeding with clinical trials in humans (Food and Drug Administration Advisory Committee, 1993). In studies from this laboratory, ibogaine also exhibited neuroprotective properties, reducing glutamate-induced neurotoxicity in primary cultures of cerebellar granule cell neurons with an EC_{50} ~4 to 5 μM (Popik et al., in review).

VII. Effects on Neurotransmitter Systems

A. Ibogaine Effects on Dopaminergic Systems

Dopamine pathways are thought to play a crucial role in the rewarding properties of drugs (Wise and Bozarth, 1982) and thus in addiction phenomena. Several laboratories have therefore examined the effects of ibogaine on dopaminergic pathways. Extracellular DA concentrations are consistently elevated in rodent mesolimbic areas, most notably in the nucleus accumbens, in response to drugs known to produce reward and addiction in humans (morphine, amphetamine, cocaine, nicotine, and ethanol) (Di Chiara and Imperato, 1988). Similar effects have been reported for the noncompetitive NMDA antagonists, phencyclidine and MK-801 (Hiramatsu et al., 1989; Rao et al., 1990), although the former compound also binds to the DA transporter and inhibits DA uptake (Schweri et al., 1985). Based on these observations, it has been proposed that increased dopaminergic neurotransmission in mesolimbic/mesocortical pathways plays an important role in reinforcing drug-seeking behavior. Furthermore, both DA antagonists and selective lesions of mesolimbic DA neurons decrease the rewarding properties of many self-administered drugs (Yokel and Wise, 1975, 1976).

Several methods are commonly used to study the activity of DA neurons. The release of DA can be measured directly from isolated tissue. Typically, slices of striatum are isolated and preloaded with [^{3}H]DA (or a precursor like [^{3}H]DOPA or [^{3}H]tyrosine), and subsequently either basal or stimulated (via electrical or chemical stimula-

tion) tritium outflow is measured. Alternatively, areas of interest (such as striatum or nucleus accumbens) are isolated, and tissue levels of DA and its metabolites are measured. A high ratio of metabolites (DOPAC and HVA) to DA suggests that dopaminergic neurons in that region were active. In vivo microdialysis is used to measure the extracellular concentrations of DA and its metabolites (which are thought to reflect synaptic concentrations) and can be done in an "intact", freely behaving animal. In this method, a dialysis probe is inserted into the region of interest, samples collected by dialysis, and DA and its metabolites subsequently measured. The latter technique allows a temporal correlation of changes in DA and metabolite levels with changes in behavior. In vivo voltametry yields similar information but is accomplished by inserting a small electrode into an area of interest that functions as an electrochemical detector. Extracellular DA and metabolites are oxidized at an optimal potential, and the resulting current is measured. Thus, in the present review, unless otherwise indicated, the term *extracellular concentration* refers to results from a microdialysis study, and the term *level* or *tissue concentration* refers to studies using analysis of isolated tissue.

Ibogaine administration to rodents alters both the levels and extracellular concentrations of DA and the DA metabolites DOPAC and HVA. However, there is considerable variability among studies. In rats, different effects were found among brain areas (Maisonneuve et al., 1991a). When administered either acutely or 19 hr before sacrifice, ibogaine (40 mg/kg, i.p.) decreased extracellular DA concentrations in striatum. The effects of this regimen on extracellular DOPAC and HVA concentrations were biphasic: after an initial increase, the concentrations of both metabolites decreased at 19 hr after injection. Whereas no effect on dopamine concentration was observed in nucleus accumbens, this regimen of ibogaine produced a similar biphasic effect on the concentrations of DA metabolites. In the prefrontal cortex, extracellular DA concentrations increased after acute injection, but no change was observed 19 hr after; metabolite concentrations showed the same biphasic increase-decrease pattern. Similar to these findings, Maisonneuve et al. (1992a) found a decrease in DA metabolite levels in rat nucleus accumbens and striatum 19 hr after ibogaine (40 mg/kg i.p.) administration but no change in DA levels in these brain areas.

Consistent with studies in rats, postmortem levels of DOPAC and HVA in mouse striatum were increased for up to 60 min after ibogaine (40 mg/kg i.p.), whereas DA levels were decreased for up to 120 min after ibogaine (Sershen et al., 1992b). Again, consistent with the data obtained in rat studies, the day after ibo-gaine injection, HVA levels remained lower in striatum, frontal cortex, olfactory tubercle and hippocampus; at the same time point, DA levels returned to that seen in control mice (Sershen et al., 1992b). When ibogaine was administered twice (40 mg/kg, 18 hr apart), the levels of DA and DA metabolites were decreased in striatum 3 hr after the second injection (Sershen et al., 1992a).

The effects of ibogaine on DA turnover seem to be both time- and dose-dependent. One hour after ibogaine administration to rats (40 mg/kg i.p.), a 50% decrease in DA levels was observed in striatum, nucleus accumbens, and prefrontal cortex, concomitant with a significant increase in HVA (Maisonneuve et al., 1992b). A decrease in DOPAC levels was seen in nucleus accumbens and striatum at 19 hr and one week (but not one month) after ibogaine administration, suggesting that the differential effects of the alkaloid on DA turnover depend on the time the sampling interval. In another study, ibogaine administered locally as a microdialysis perfusate (10 μM, but not 40 or 80 μM) decreased extracellular concentrations of DOPAC in both rat nucleus accumbens and striatum that was first observed 20 min after the start of perfusion (Glick et al., 1993). Conversely, at high concentrations (200 and 400 μM), ibogaine decreased extracellular concentrations of DA and increased concentrations of DOPAC and HVA in the same areas. The authors suggest that the effects of a low concentration of locally applied ibogaine mimic the delayed effects of systemic ibogaine, whereas those of the locally applied high concentration of ibogaine mimic the acute effects of systemic ibogaine on DA transmission (Glick et al., 1993).

Ibogaine-induced dopamine release from isolated mouse striatum has recently been studied by Harsing et al., (1994). Ibogaine increased basal tritium outflow ([^{3}H]DA and [^{3}H]DOPAC) but was without effect on electrically stimulated tritium overflow. This dopamine-releasing effect was (*a*) reduced by the DA uptake inhibitors cocaine and nomifensine, (*b*) unaltered by omission of Ca^{2+} from the perfusion buffer, (*c*) tetrodotoxin insensitive, (*d*) unaffected by an agonist (quinpirole) or an antagonist (sulpiride) of the D_2 DA receptor, and (*e*) unaffected by pretreatment with reserpine. Ibogaine did not affect dopamine uptake. These data suggest that ibogaine does not increase DA release via an interaction with autoreceptors, and that DA release is from a non-vesicular (cytoplasmic) pool and independent of depolarization. This effect of ibogaine on the isolated striatal slice is inconsistent with its in vivo actions. This inconsistency may be caused by the lack of normal extrastriatal influences in the in vitro preparation.

Ibogaine does not seem to have a direct action on DA receptors (D_1, D_2) (Whitaker and Seeman, 1977; Deecher et al., 1992), and no generalization between ibogaine and CGS 10476B (a DA release-inhibiting agent) was found in a drug-discrimination paradigm (Schechter and Gordon, 1993). In an in vitro study, ibogaine had a moderate (IC_{50} ~1.5 μM) affinity for DA transporters as measured by inhibition of [^{3}H]WIN 35,248 binding in mouse striatal tissue (Sershen et al., 1992b). However, in another study, ibogaine (at concen-

trations up to 100 μM) did not affect [^{3}H]GBR-12935 binding, a ligand that also appears to label DA transporters (Broderick et al., 1992) (see table 1).

Although in the isolated striatal slice preparation, ibogaine seemed to effect a release of DA in a calcium-independent, carrier-mediated process (similar to that of amphetamine), in vivo data suggest that ibogaine does not produce such an effect. Rather, the in vivo effects of ibogaine on the levels of extracellular DA and DA metabolites may be summarized as follows. Initially, extracellular DA concentrations are decreased concomitant with an increase in concentrations of DA metabolites. After some time (up to 1 week), concentrations of DA return to normal, but the concentrations of DA metabolites are decreased. Similar results seem to be found in rats and mice. Based on these data, it is likely that the complex effects of ibogaine on dopamine neurotransmission result from an interaction of ibogaine with several neurochemical and anatomical loci.

1. Ibogaine alters the effects of psychostimulants on dopaminergic systems. Psychostimulants such as cocaine and amphetamine are thought to produce their rewarding effects through an increase in synaptic concentrations of DA, by inhibiting re-uptake and/or stimulating release. Increases in synaptic DA concentrations in different brain regions have distinct behavioral consequences. For example, DA increases in mesolimbic areas are associated with increases in locomotor activity, whereas DA increases in striatum are associated with increased stereotyped behavior. Several laboratories have examined the ability of ibogaine to modify the effects of psychostimulants on both extracellular DA concentrations and locomotor activity, a readily measurable behavioral consequence of this neurochemical action.

Ibogaine (40 mg/kg, i.p.) inhibits the self-administration of psychostimulants such as cocaine and amphetamine in rodents. Cappendijk and Dzoljic (1994) trained male Wistar rats to intravenously self-administer cocaine; a single dose of ibogaine decreased cocaine intake by 40 to 60% for several days, whereas repeated ibogaine administration at 1-week intervals produced a 60 to 80% decrease in cocaine self-administration that was sustained for several weeks. Similar effects were found in mice that developed a preference for cocaine in the drinking water. Thus, ibogaine administration (2 weeks after the beginning of a choice period, 2 doses of 40 mg/kg, 6 hr apart) diminished cocaine preference for 5 days (Sershen et al., 1994a). Recently, Glick et al. (1994) demonstrated that ibogaine and several *iboga* alkaloids reduced cocaine self-administration in rats in a dose-related fashion.

Sex and species of animals are noted here as they may influence the ability of ibogaine to modulate psychostimulant-induced hypermotility and DA metabolism. Sershen et al. (1992a) found that ibogaine (40 mg/kg i.p. 2 or 18 hr before amphetamine) enhanced amphetamine (1 mg/kg)-induced hypermotility in female rats but reduced it in male mice. Because amphetamine was given twice in a 24 hr interval in this study, an inhibitory effect of ibogaine on amphetamine-induced sensitization (Segal et al., 1980) (i.e., on an *increase* rather than decrease of a drug effect during the time it is given) cannot be excluded. In other studies, an amphetamine-induced increase in locomotor activity was potentiated in female rats pretreated with ibogaine (40 mg/kg, i.p.)

TABLE I

Affinities of ibogaine for various [^{3}H]ligands

Receptor	[^{3}H]Ligand	K_i or IC_{50}* [μM]	Reference
Dopamine transporter	WIN 35,248	1.5*	Sershen et al. (1992b)
	GBR-12935	<100*	Broderick et al. (1992)
Muscarinic M_i	pirenzepine	31.6	Repke et al. (1994)
Muscarinic M_2	N-methylscopolamine	50.1	Repke et al. (1994)
Muscarinic M_3	N-methylscopolamine	12.5	Repke et al. (1994)
NMDA ion channel	MK-801	1.0 ± 0.1	Popik et al. (1994)
	TCP	1.5 ± 0.3	Popik et al. (in review)
Opioid (κ)	U69,593	2.1 ± 0.2	Deecher et al. (1992)
		3.2	Repke et al. (1994)
Serotonin 5-HT_{2a}	ketanserin	12.5	Repke et al. (1994)
Sigma	haloperidol	0.003*	Whitaker and Seeman, (1977)
	pentazocine	0.086*	Popik et al., unpublished
Voltage-dependent sodium channels	batrachotoxin A 20-α-benzoate	8.1 ± 1.3	Deecher et al. (1992)
Voltage-dependent calcium channels	isradipine	28*	Popik et al., unpublished

K_i or IC_{50} values > 100 μM were reported for μ and δ (opioid), adrenergic α_1, α_2, β_1, cannabinoid, dopamine D_1, D_2, γ aminobutyric $acid_A$, benzodiazepine, Cl^-, muscarinic, nicotinic, serotonin 5-HT_{1a}, 5-HT_{1b}, 5-HT_{1c}, 5-HT_{1d}, 5-HT_2 and 5-HT_3 binding sites in Deecher *et al.* (1992). Whitaker and Seeman (1977) reported an IC_{50} > 100 μM for [^{3}H]apomorphine binding (nonspecific defined by butaclamol). Whitaker and Seeman (1978a) found no displacement by ibogaine [1 mM] of [^{3}H]serotonin and Whitaker and Seeman (1978b) reported an IC_{50} of 3.5 μM to inhibit [^{3}H]LSD binding. Repke *et al.* (1994) report K_i values for ibogaine > 1 mM to 5-HT_{1a} (8-hydroxy-DPAT) and 5-HT_3 (quipazine) sites. Popik *et al.* (1994) found ibogaine (100 μM) did not alter ligand binding to AMPA, kainate, NMDA-competitive, and metabotropic glutamate receptors. TCP, 1-[1-(2-thienyl)cyclohexyl]piperidine; AMPA, (±)-α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid; DPAT, dipropylaminotetralin.

19 hr earlier (Maisonneuve, 1992; Maisonneuve et al., 1992a). An inhibitory effect of ibogaine on amphetamine metabolism has been proposed (Glick et al., 1992a). However, like amphetamine, cocaine-induced hypermotility in female rats was potentiated by ibogaine (Maisonneuve, 1992; Maisonneuve and Glick, 1992) and ibogaine administration had no effect on brain cocaine levels (Glick et al., 1993). Broderick et al. (1992, 1994) reported that ibogaine (20–40 mg/kg i.p.) administered to male rats for 4 days reduced cocaine (20 mg/kg)-induced hypermotility. Ibogaine (40 mg/kg i.p.) administration reduced also cocaine (25 mg/kg subcutaneous)-induced hypermotility in male mice (Sershen et al., 1992b), a finding in agreement with the amphetamine-ibogaine interaction (Sershen et al., 1992a).

Neurochemical studies were performed on male mice given two doses of ibogaine (40 mg/kg, i.p., 18 hr apart) followed by amphetamine (5 mg/kg) administered 2 hr after the second dose of ibogaine (Sershen et al., 1992a). Striatal levels of DA and DA metabolites (DOPAC, HVA and 3-MT) measured 3 hr after the second dose of ibogaine were decreased in mice that received ibogaine relative to saline-pretreated, amphetamine-treated controls. Thus, in male mice, ibogaine treatment inhibited not only the stimulant-induced hypermotility but also the amphetamine-induced increase in striatal DA levels (Sershen et al., 1992a). Compared with controls, levels of DOPAC and HVA were decreased in the amphetamine and in ibogaine groups and further decreased in the group that received ibogaine and amphetamine.

In female rats, however, the amphetamine-induced increase in extracellular DA concentrations in striatum and nucleus accumbens was further potentiated by ibogaine (40 mg/kg, i.p., 19 hr preceeding amphetamine) (Maisonneuve, 1992; Maisonneuve et al., 1992a). In support of this observation, Glick et al. (1993) found that ibogaine potentiated the amphetamine-induced increase in extracellular DA concentrations in female rat nucleus accumbens and striatum. In this study, however, no effect of ibogaine was seen on amphetamine-induced decreases in extracellular concentrations of DA metabolites. Similarly, ibogaine potentiated cocaine-induced increases in extracellular DA levels in striatum and nucleus accumbens of female rats (Maisonneuve, 1992; Maisonneuve and Glick, 1992). However, quite opposite data were obtained by Broderick et al. (1992, 1994), who studied DA release in male rats using semiderivative in vivo voltametry. In these experiments, ibogaine (40 mg/kg i.p. given for 4 days) reduced the increase in DA release from nucleus accumbens induced by cocaine (20 to 40 mg/kg subcutaneous). A presynaptic mechanism for these actions was suggested.

In toto, these data indicate that the ability of ibogaine to modulate the influence of amphetamine and cocaine on dopamine turnover and hypermotility is dependent on several variables including: (*a*) sex; (*b*) species; (*c*) effective brain concentration; (*d*) treatment regimen (chronic vs. acute, pretreatment interval); (*e*) behavioral status of animals. Although the effects of ibogaine on both dopamine turnover and locomotor activity are similar in male mice and male or female rats, ibogaine interaction with psychostimulants depends upon many variables. No information on ibogaine's effects on dopaminergic transmission in humans is currently available.

B. Ibogaine Effects on Opioid Systems

The impact of drugs on opioid systems has been extensively studied by investigators interested in the process of addiction. Thus, opiates are psychoactive, producing euphoria, analgesia, and in some individuals, addiction. Opiates have also been shown to interact with some of the same neurochemical pathways that mediate the rewarding effects of a variety of other abused drugs. Moroever, physical dependence can be reliably induced and quantified in animals after chronic treatment with opioids.

An important piece of evidence in support of an "anti-addictive" action of ibogaine is the ability of this alkaloid to dose-dependently (2.5 to 40 mg/kg) reduce intravenous morphine self-administration in female Sprague-Dawley rats, both immediately after injection and the next day (Glick et al., 1991). In some animals, a reduced morphine intake was observed for several days, whereas some rats needed several doses of ibogaine to achieve a prolonged reduction. Similar effects were demonstrated for the other *iboga* alkaloids (Glick et al., 1994). However, Dworkin (c.f. [Touchette, 1993]) found that ibogaine alters morphine self-administration in male Fisher rats only on the day it was administered.

Ibogaine (40 mg/kg i.p.) given 19 hr before sampling prevented the increase in extracellular DA concentrations in the striatum and nucleus accumbens of rats following morphine challenge (5 mg/kg) (Maisonneuve et al., 1990; 1991b; Maisonneuve, 1992). Similarly, ibogaine (40 mg/kg i.p. in rats) given 19 hr before morphine (5 mg/kg) prevented the increase in extracellular DA concentration in the striatum, prefrontal cortex, and nucleus accumbens typically observed after a morphine injection (Maisonneuve et al., 1991a). However, in the ibogaine plus morphine group, the levels of DA *metabolites* were increased (as was observed in the morphine group), suggesting that ibogaine did not prevent morphine from activating DA neurons. The authors suggest that ibogaine treatment may change the properties of dopaminergic neurons in such a way that DA release is unaffected under normal conditions but altered when profoundly stimulated (in this case, by morphine). In agreement with this hypothesis, several studies have shown that ibogaine pretreatment (40 mg/kg i.p. 19 hr before measurement in rats) decreased or blocked the locomotor stimulation induced by morphine (0.5 to 20 mg/kg) (Maisonneuve et al., 1991a, 1991b, 1992a, 1992b). In one study (Maisonneuve et al., 1992b), the

same effects were seen if morphine (5 mg/kg) was given a week (but not a month) after ibogaine pretreatment.

Ibogaine may act through a κ opioid receptor mechanism, as it inhibits (K_i ~2.1 μM) [^{3}H]U-69593 (a κ receptor agonist) binding to κ opioid receptors in the calf cortex (Deecher et al., 1992). Consistent with these data, Repke et al. (1994) recently reported a K_i value of 3.16 μM. However, at concentrations of up to 100 μM, ibogaine did not affect [^{3}H]carfentanil or [^{3}H]enkephalin binding, indicating that this alkaloid may act at κ, but not μ or δ opioid receptors (Deecher et al., 1992). The ability of ibogaine to reduce extracellular dopamine levels in the nucleus accumbens of freely moving rats is reversed by norbinaltorphimine, a κ opioid antagonist (Reid et al., 1994). Furthermore, the ability of the κ opioid agonist U-62066 to inhibit stimulation-induced [^{3}H]DA release from mouse striatum was attenuated by pretreatment of mice by ibogaine (40 mg/kg, i.p., 2 hr prior; or 2 × 40 mg/kg, 6 hr apart, killed 18 hr later) (Sershen et al., 1995). Like ibogaine, "anti-addictive" properties have been reported for drugs acting at κ opioid receptors. For example, the κ opioid *antagonist*, MR-2266-BS, decreases both consumption of a diluted ethanol solution and ethanol preference in ethanol-preferring rats (Sandi et al., 1990). The κ *agonist*, U-69593 has been found to attenuate the behavioral sensitization (measured by stereotypy and locomotion) produced by cocaine (Heidbreder et al., 1993). The long-lasting effects of ibogaine (e.g., Glick et al., 1991; Maisonneuve et al., 1992b; Sershen et al., 1994a), however, may not be caused by an action of the drug on κ receptors. Ibogaine did not bind to κ receptors irreversibly, dissociating from brain tissue after a few washes (Deecher et al., 1992). In order to explain the long-lasting effects of ibogaine on morphine-induced motor effects, Maisonneuve and colleagues (1991a) postulated an ibogaine metabolite with a much longer half-life.

In morphine-dependent animals, the opioid antagonist naloxone induces a withdrawal syndrome, characterized (in rats) by increased rearing, digging, jumping, salivation and "wet-dog" head shaking. Ibogaine dose-dependently reduced the frequency of some of these withdrawal symptoms (rearing, digging, head hiding, chewing, teeth chattering, writhing, penile licking) after intracerebroventricular (4 to 16 μg) (Dzoljic et al., 1988) and i.p. administration (40 and 80 mg/kg in rats) (Aceto et al., 1990; Glick et al., 1992b). However, these effects could not be replicated in rats (Sharpe and Jaffe, 1990, 1991) or in mice (Frances et al., 1992). In morphine-dependent monkeys, ibogaine (2 and 8 mg/kg subcutaneous) partially suppressed the total number of withdrawal signs (Aceto et al., 1990). Studies from this laboratory (Popik et al., in review) demonstrate that ibogaine inhibits the morphine withdrawal syndrome in mice in a dose-related fashion (fig. 2). This effect was reversed by combining ibogaine treatment with glycine, which is consistent with this alkaloid acting as an

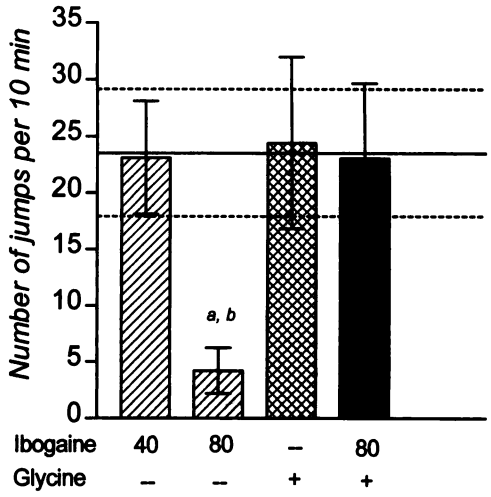

FIG. 2. Jumping behavior is a characteristic feature of opiate withdrawal in mice. Glycine reverses the ability of ibogaine to inhibit naloxone-induced jumping behavior in morphine dependent mice. Male National Institutes of Health Swiss mice were rendered dependent by repeated injections of morphine (30 mg/kg i.p. twice a day for 3 days). Three hours after the last dose of morphine, mice received naloxone (4 mg/kg i.p.) and were placed in transparent plastic cylinders. Each bar represents the mean ± standard error of the mean of the nuber of jumps observed during the following 10 minute period for each group of mice. Ibogaine (45 min before naloxone; hatched bars) inhibited naloxone-induced jumping at 80 but not 40 mg/kg (i.p.). Glycine (800 mg/kg i.p., 15 min before and after ibogaine; cross hatched bar) had no effect alone, but reversed the inhibition of jumping induced by ibogaine (80 mg/kg i.p.; shaded bar). The mean ± standard error of the mean of jumping in control mice is represented by solid and dashed lines, respectively. Statistics: Kruskal-Wallis analysis of variance (Kurshal-Wallis = 10.5, P = 0.03) followed by the Mann-Whitney U test. (a: $P < 0.005$ vs. control, U = 23; b: $P < 0.01$ vs. ibogaine-glycine treated group, U = 32.5). From Popik et al. (1995) with modification.

NMDA antagonist (see section VII. H.). A similar regimen of glycine blocks some of the behavioral actions of phencyclidine (Toth and Lajtha, 1986; Toth 1988), MK-801 (Evoniuk et al., 1991), and memantine (Popik and Skolnick, in review), presumably by increasing stimulatory tone and facilitating drug egress from the NMDA receptor-associated ion channel.

In mice, ibogaine was inactive as an antinociceptive compound as it did not mimic morphine's action in the tail flick (1 to 40 mg/kg i.p.) and hot plate (up to 20 mg/kg i.p.) tests, although it exhibited analgesic activity in the phenylquinone test (ED_{50} 9.7 mg/kg) (Aceto et al., 1990; Schneider and McArthur 1956). Ibogaine either did not affect (Aceto et al., 1990) or increased (Schneider and McArthur, 1956) morphine analgesia in the mouse tail flick test. Ibogaine also did not produce dependence, as measured in the Primary Physical Dependence test after chronic administration of 10 or 40 mg/kg in rats (Aceto et al., 1990). A pharmacokinetic explanation for the effects of ibogaine on morphine-induced actions is unlikely, because ibogaine (40 mg/kg, i.p. 19 hr before measurement) did not modify brain levels of morphine (10 mg/kg) in rats (Maisonneuve et al., 1991a).

In summary, ibogaine treatment reduces the self-administration of morphine in rats and similarly inhibits morphine-induced locomotor activity. Ibogaine inhibits morphine-induced dopamine release in mesolimbic areas. In contrast, ibogaine does not inhibit the analgesic action of morphine. Furthermore, ibogaine can inhibit at least some of the components of the morphine withdrawal syndrome. Although the neurochemical basis for these actions remain unclear, the ability of bind to κ receptors and act as a voltage-dependent NMDA antagonist (see section VII.H.) may be important.

C. Ibogaine Effects on Serotonergic Systems

Several lines of evidence indicate that serotonergic pathways can modulate both the development of opiate dependence and the magnitude of opiate withdrawal. For example, a decrease in severity of morphine withdrawal in rats was achieved when the serotonin antagonists cyproheptadine (Cervo et al., 1981) or methergoline (Samanin et al., 1980) were administered with morphine during the development of dependence. Fenfluramine, a serotonin-releasing agent, reduces jumping behavior (a prominent feature of opiate withdrawal in mice) when given before naloxone challenge (Cervo et al., 1981) or increases it when coadministered with morphine during the development of dependence (Samanin et al., 1980). In another study, mianserin (a serotonin antagonist) decreased naloxone-induced suppression of morphine self-administration and attenuated withdrawal signs precipitated by naloxone (Neal and Sparber, 1986). Fluoxetine, a serotonin uptake inhibitor, has been shown to decrease cocaine self-administration in rats (Richardson and Roberts, 1991). In the 1960s, lysergic acid diethylamide was considered as an adjunctive in treating alcoholism because of its hallucinogenic actions c.f. (Sharpe and Jaffe, 1991), although this was not demonstrated in clinically controlled studies (Denson and Sydiaha, 1970).

Ibogaine (20 mg/kg in mice) does not have a serotonergic profile when assessed in some behavioral studies (Chen and Bohner, 1958). Moreover, when compared with other hallucinogenic drugs, including psilocybin, JB-336, and bufotenine, ibogaine (10 mg/kg) had a negligible effect on the aggressiveness of isolated mice and muricidal behavior in rats (Kostowski et al., 1972). Ibogaine (at concentrations up to 1 μM) had no effect on [^{3}H]serotonin binding (Whitaker and Seeman, 1978a), and concentrations of up to 3.5 μM had no effect on the binding of [^{3}H]LSD (Whitaker and Seeman, 1978b) (table 1). More recently, Deecher et al. (1992) reported that ibogaine did not displace ligands acting at 5-HT$_{1a}$, 5-HT$_{1b}$, 5-HT$_{1c}$, 5-HT$_{1d}$, 5-HT$_2$, or 5-HT$_3$ receptors in concentrations up to 100 μM. However, Repke et al. (1994) reported that ibogaine inhibited binding of 5-HT$_{1a}$, 5-HT$_{2a}$, or 5-HT$_3$ ligands with low affinity (K_i values: >100, 12.5 and >100 μM, respectively) (table 1). There was no generalization between ibogaine and serotonergic ligands (fenfluramine, N-(3-trifluoromethylphenyl)piperazine, 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane, methyl-enedioxymethamphetamine, quipazine or LSD) in a drug-discrimination paradigm (Schechter and Gordon, 1993).

Despite these findings, interactions between ibogaine and serotonergic systems have been reported. Broderick et al. (1994) demonstrated that ibogaine (40 mg/kg i.p. for 4 days) increased 5-HT concentration in rat nucleus accumbens. In another study, ibogaine (40 mg/kg) decreased levels of the serotonin metabolite 5-hydroxyindoleacetic acid in mouse frontal cortex, hippocampus, and olfactory tubercle 2 hr and 24 hr after injection (Sershen et al., 1992b). Long and Lerrin (1962) demonstrated that ibogaine is a reversible inhibitor of the active transport of serotonin into blood platelets. These data may suggest that ibogaine produces a release of serotonin in its terminal fields. Sershen et al. (1994b) demonstrated that the ability of CGS-12066A (a 5-HT$_{1b}$ agonist) to increase stimulation-evoked [^{3}H]DA release from both rat and mouse striatum was inhibited by ibogaine (40 mg/kg, i.p., 2 hr before death). Additionally, ibogaine (40 mg/kg, i.p., 2 hr before sacrifice), increased the ability of phenylbiguanide (5-HT$_3$ agonist) to enhance stimulation-evoked [^{3}H]DA release from the mouse striatal slice (Sershen et al., 1995). Ibogaine (20 mg/kg) partially enhanced the cocaine-induced decrease in serotonin concentration in nucleus accumbens in rats, an action attributed to a presynaptic release mechanism (Broderick et al., 1992, 1994). These data demonstrate that ibogaine can modulate the influence of serotonergic transmission on dopaminergic terminals in a complex manner. Palumbo and Winter (1992) found a generalization between ibogaine (15 to 20 mg/kg) and dimethoxymethylamphetamine (0.6 mg/kg) as well as ibogaine and LSD (0.1 mg/kg) in a two-lever discrimination task. Because pizotyline (BC-105) blocked dimethoxymethylamphetamine- and LSD-appropriate responses, an involvement of 5-HT$_2$ or 5-HT$_1$ receptors in the stimulus properties of dimethoxymethylamphetamine was suggested. Ibogaine has also been shown to inhibit the enzymatic oxidation of peripheral serotonin (Barras and Coult, 1972).

D. Ibogaine Effects on Intracellular Calcium Regulation

L-type calcium channels have been implicated in the rewarding properties of abused drugs. For example, isradipine (an L-type calcium channel blocker) diminished the rewarding properties of cocaine (10 mg/kg i.p. in rats) in a conditioned place preference paradigm (Pani et al., 1991). In addition, an increased number of L- and N-type calcium channels were observed in brain but not heart of morphine dependent animals (Ramkumar and El-Fakahany, 1988; Antkiewicz-Michaluk et al., 1990; Suematsu et al., 1993).

The evidence for an action of ibogaine at L-type calcium channels is equivocal. At 80 μM, ibogaine noncompetitively antagonized calcium-induced contraction of rat aorta and mesenteric artery (Hajo-Tello et al., 1985) that was interpreted as an action on intracellular calcium metabolism. Tabernanthine, an alkaloid related to ibogaine, inhibited depolarization-stimulated ^{45}Ca influx and contractions in the rat aorta (Miller and Godfraind, 1983). Schechter (1993) demonstrated that pretreatment with 10 to 30 mg/kg isradipine dose-dependently decreased the ability of rats to recognize cocaine as a interoceptive stimulus, whereas pretreatment with ibogaine (3.5 to 7.0 mg/kg) was ineffective. Nonetheless, the doses used in this study were lower than those demonstrating efficacy in other behavioral experiments. Ibogaine inhibited the binding of [^{3}H]isradipine (an L-type calcium channel blocker) in the mouse cerebral cortex with an IC_{50} of ~28 μM (table 1).

E. Ibogaine Effects on Cholinergic Systems

Ibogaine inhibits serum cholinesterase activity (Vincent and Sero, 1942). This action may explain its ability to enhance the analgesic activity of morphine (Schneider and McArthur, 1956), as has been shown in other studies (Schneider and Rinehart, 1957). Schneider and Sigg (1957) reported that atropine (2 mg/kg) inhibited the arousal syndrome (as measured by electroencephalogram) produced by ibogaine (3 mg/kg) in cats. Atropine also prevented the rise in blood pressure produced in conscious dogs by ibogaine (Schneider and Rinehart, 1957). In radioligand binding studies, ibogaine (up to 100 μM) did not inhibit the binding of ligands acting at nicotinic or muscarinic receptors (Deecher et al., 1992). However, Repke et al. (1994) demonstrated that ibogaine inhibited binding of muscarinic M_1, M_2 and M_3 ligands at concentrations of ~ 31, 50, and 12.5 μM, respectively. Several synthetic ibogaine derivatives demonstrated 30- to 100-fold higher affinity for these sites.

F. Ibogaine Effects on γ-Aminobutyric Acidergic Systems

The tremorigenic properties of ibogaine and related compounds were attributed to an action on γ-aminobutyric acidergic pathways (King and Tunnicliff, 1990; Roberts et al., 1978; Trouvin et al., 1987). However, Deecher et al., (1992) did not find any effect of ibogaine (at concentrations of up to 100 μM) on [^{3}H]muscimol or [^{3}H]flunitrazepam binding to the $GABA_A$ receptor. In addition, no interaction between ibogaine and $^{36}Cl^-$ uptake through γ-aminobutyric acid-gated channels was observed.

G. Ibogaine Effects on Voltage-dependent Sodium Channels

Several drugs (e.g., chlorinated hydrocarbons and dihydropyrazoles) are thought to act as tremorigens through blockade of voltage-dependent sodium channels, and a similar effect could also explain the tremorigenic actions of ibogaine. Ibogaine inhibited (K_i ~8.1 μM) [^{3}H]batrachotoxin A 20-α-benzoate binding to voltage-dependent sodium channels in depolarized mouse neuronal preparations (Deecher et al., 1992). Ibogaine analogs, including ibogamine, tabernanthine, and coronaridine exhibited potencies similar to ibogaine in this assay.

H. Ibogaine Effects on Glutamatergic Systems

Several lines of evidence suggest that NMDA receptors are involved in mediating the effects of abused drugs. Various studies have demonstrated a role for excitatory amino acids in the effects of morphine. Perhaps the first notion supporting this hypothesis came from studies showing that aspartate, glutamate, and glycine may antagonize some of the actions of morphine (Koyuncuoglu et al., 1974, 1976). Aanonsen and Wilcox (1987) demonstrated that various glutamate receptor agonists administered into the spinal subarachnoid space produced hyperalgesic effects that could be blocked by various μ and σ agonists as well as by NMDA antagonists.

Another independent line of evidence linking drug-seeking behavior to glutamatergic transmission comes from studies involving NMDA antagonists. Thus, NMDA antagonists acting at the glutamate, MK-801 and glycine binding sites suppress symptoms of morphine withdrawal in rodents (Koyuncuoglu et al., 1990; 1992; Trujillo and Akil, 1991; Rasmussen et al., 1991; Cappendijk et al., 1993), attenuate the development of the tolerance to morphine (Marek et al., 1991; Trujillo and Akil, 1991; Ben-Eliyahu et al., 1992; Gutstein and Trujillo, 1993; Lutfy et al., 1993; Kolesnikov et al., 1994), and block sensitization to several psychostimulants (Karler et al., 1989; Shoaib and Stolerman, 1992; Khanna et al., 1993a; 1993b; Pudiak and Bozarth, 1993). Furthermore, the data demonstrating an interaction between ibogaine and amphetamine in rats parallel the potentiating effect of MK-801 on apomorphine- or amphetamine-induced hypermotility (Maj et al., 1991).

Studies from this laboratory (fig. 3) (table 1) indicate that ibogaine is a competitive inhibitor of [^{3}H]MK-801 binding (K_i ~1 μM) to NMDA receptor coupled ion channels. In contrast, ibogaine did not affect [^{3}H](±)-α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid, [^{3}H]kainate or [^{3}H]glutamate (to the competitive or metabotropic sites) binding, consistent with a specificity for NMDA receptor coupled cation channels (Popik et al., 1994). The potency of ibogaine to inhibit [^{3}H]MK-801 binding was also examined in eight distinct brain regions of Sprague-Dawley male rats and compared with the dissociation constants for [^{3}H]MK-801 estimated using saturation analyses. A high correlation ($r = 0.976$, $P = 0.0004$) was obtained between the K_i of ibogaine and K_d of [^{3}H]MK-801, consistent with the notion that these

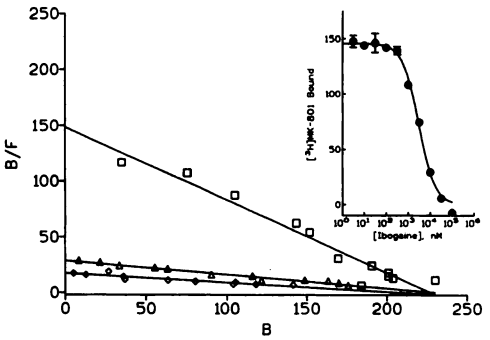

FIG. 3. Ibogaine competitively inhibits [^{3}H]MK-801 binding to NMDA receptors. [^{3}H]MK-801 binding was assayed in extensively washed rat forebrain membranes (~70 μg protein/tube) in the presence of 30 μM glutamate and 30 μm glycine. In this representative experiment, addition of 0 (□), 5 μM (△) and 10 μM (◇) ibogaine increased the K_d of [^{3}H]MK-801 from 1.3 nM to 8.6 and 16.1 nM, respectively. The corresponding B_{max} values were: 3.6, 3.9, and 4 pM/mg protein, respectively. Symbols: B, [^{3}H]MK-801 bound (fmol/assay); F, free radioligand (nM). Inset: Competition curve. In this representative experiment, [^{3}H]MK-801 (4 nM) binding was inhibited by ibogaine with a K_i of 0.90 nM (n_H 1.17). Both types of experiments were repeated three times. Data were analyzed using Inplot 4.0. From Popik et al. (1994).

compounds share a common binding site. The ability of ibogaine to act as a noncompetitive NMDA antagonist can also be demonstrated using [^{3}H]1-[1-(2-thienyl)cyclohexyl]piperidine, a thienyl derivative of phencyclidine, resulting in a K_i ~1.5 μM in rat forebrain (Popik et al., in review). Consistent with these neurochemical studies, ibogaine produced a voltage dependent block of NMDA evoked currents in hippocampal cultures. Moreover, in drug-discrimination studies, ibogaine substituted as an interoceptive cue in mice trained to recognize MK-801 (dizocilpine) in a T-maze drug discrimination paradigm (Popik et al., in review).

Ibogaine-induced alterations in DA and DA metabolites are comparable to those observed after MK-801 or phencyclidine administration (Hiramatsu et al., 1989; Rao et al., 1990). Like ibogaine, MK-801 blocks cocaine self-administration in rats (Schenk et al., 1993). However, differences between phencyclidine or MK-801 and ibogaine have been reported. Thus, unlike phencyclidine (Bowyer et al., 1984), ibogaine (1 μM) had no effect on DA re-uptake by striatal P_2 fraction (Broderick et al., 1992). Unlike MK-801 (Rao et al., 1990), application of ibogaine (1–400 μM) to dopaminergic cell body regions (substantia nigra and ventral tegmental area) was ineffective in changing DA or DA metabolite levels in striatum and nucleus accumbens (Glick et al., 1993).

Taken together, the similarity between ibogaine and noncompetitive NMDA antagonists such as MK-801 may explain several effects of this alkaloid, and in particular, its putative "anti-addictive" properties (see VII., Conclusions). Differences between ibogaine and the other noncompetitive NMDA antagonists may reflect properties at other sites of action that these drugs do not have in common.

I. Ibogaine Effects on σ Receptors

Several lines of evidence indicate that σ receptors may be involved in the effects of abused drugs. σ Receptors are considered potential therapeutic targets for treatment of cocaine abuse, because the σ ligands rimcazole and BMY 14802 were shown to block the locomotor stimulant effects of cocaine in mice (Menkel et al., 1991). Cook et al. (1992) obtained similar results using the σ receptor ligand DuP 734. Ujike et al. (1992a) have shown that in rats sensitized to methamphetamine, the σ ligand (+)-3-(3-hydroxyphenyl)-N-propylpiperidine stimulated stereotyped behavior. The same authors reported supersensitivity of σ receptors after chronic administration of cocaine (Ujike et al., 1992b). Some σ ligands (rimcazole, (+)-3-(3-hydroxyphenyl)-N-propylpiperidine inhibited (K_i < 1 μM) [^{3}H]WIN 35,428 binding to DA transporters, sites implicated in amphetamine and cocaine action (Izenwasser et al., 1993). The K_i values for rimcazole and (+)-3-(3-hydroxyphenyl)-N-propylpiperidine at the DA transporter are, however, significantly higher than corresponding values at σ receptors.

Ibogaine has been reported to produce hallucinations or fantasies in man (see Section V.B.). Several σ receptor ligands (e.g., cyclazocine and N-allylnormetazocine [SKF 10,047]) also produce psychotic symptoms in humans (Haertzen, 1974), whereas the major effect of σ receptor antagonists in humans is attenuation of hallucinations (both drug-induced and illness-related) [Snyder, 1982]. Whitaker and Seeman (1977) showed that ibogaine inhibited [^{3}H]haloperidol binding with high affinity (IC_{50} ~3 nM), but only weakly (IC_{50} 450 μM) inhibited [^{3}H]apomorphine binding. These findings suggest that the high affinity inhibition of [^{3}H]haloperidol binding may be caused by an action at σ rather than DA receptors. In another study (Deecher et al., 1992), ibogaine did not inhibit binding of dopaminergic ligands. Taken together, these data suggest that ibogaine may act at σ receptors.

In our studies, ibogaine inhibited the binding of [^{3}H]pentazocine (a σ_1 receptor ligand) to high (IC_{50} ~86 nM) and low (IC_{50} ~5.6 μM) affinity sites in mouse cerebellum. In the same experiment, haloperidol inhibited [^{3}H]pentazocine binding with IC_{50} values of ~76 nM and ~24 μM to these high and low affinity sites, respectively, (see Table 1). As the physiology and pharmacology of the σ receptor is not well understood, the significance of these findings remains unclear.

J. Ibogaine Effects on Adrenergic Systems

Clonidine (an α_2-adrenoceptor agonist) attenuates morphine withdrawal in rats (Vetulani and Bednarczyk, 1977) and has been used for treating the opiate abstinence syndrome in humans (Gold et al., 1978). These observations suggest a role for noradrenergic neurons in opiate withdrawal. Noradrenergic cells in the locus coeruleus increase their activity during antagonist-precip-

itated opiate withdrawal (Aghajanian, 1978; Valentino and Wehby, 1989). In radioligand binding studies, no effect of ibogaine has been found on α_1, α_2 or β_1 adrenergic receptors (Deecher et al., 1992). Moreover, ibogaine (20 mg/kg) did not modify cerebral noradrenaline levels in rats (Cretet et al., 1980). NMDA receptor antagonists (MK-801 and LY274614) attenuate opiate withdrawal without affecting either the withdrawal-induced activation of locus coeruleus neurons or the increase in noradrenaline turnover in several brain areas innervated by the locus coeruleus (Rasmussen et al., 1991).

K. Miscellaneous Actions of Ibogaine

Deecher et al. (1992) found that ibogaine (up to 100 μM) did not inhibit the binding of cannabinoid receptor ligands, [^{3}H]CP 55,940 or [^{3}H]WIN 5212–2. In the anesthetized rat, ibogaine caused slight hypoglycemia (Dhahir, 1971). Bunag and Walaszek (1968) reported that ibogaine antagonized the contractile responses produced in guinea pig ileum by substance P and angiotensin.

VIII. Conclusions

Pharmacological strategies for the treatment of addiction include substitution, blockade and extinction, and aversion (Jaffe, 1985). In substitution strategies, a less "dangerous" drug is substituted for the abused drug as in the treatment of heroin addiction with methadone. Blockade and extinction involve the administration of an antagonist. In this strategy, it is hypothesized that blockade of the euphoric effects of an abused drug (such as heroin) by an antagonist such (as naltrexone) will lead to the extinction of the need to use the abused drug. In the strategy of aversion, a drug (such as disulfiram) produces severe discomfort whenever the subject uses the abused drug (alcohol). Although these strategies have been widely used to treat addiction, they have not been proven very efficacious. Ibogaine presents a potential new strategy for treating addiction to diverse drug classes. Although there are currently no controlled clinical data supporting the "anti-addictive" properties of ibogaine, both anecdotal reports in humans and preclinical data from several laboratories are consistent with these therapeutic claims.

The preclinical pharmacological effects of ibogaine may be summarized as follows: (*a*) a decrease in self-administration of cocaine and morphine in rats, (*b*) reduction of morphine withdrawal syndrome, (*c*) a decrease in locomotor activity (both spontaneous and morphine-induced), cardiovascular effects, and tremor. Ibogaine decreases the hypermotility and dopamine turnover elicited by stimulants in male mice and rats, but has opposite effects in female rats. Neurochemical effects of ibogaine on mesolimbic and mesocortical DA systems can be summarized as follows: *high concentrations* decrease extracellular DA concentrations and increase concentrations of DA metabolites; *low concentrations* do not affect DA concentrations but decrease DA metabolite concentrations. Ibogaine may also affect the activity of voltage-dependent sodium channels, opioid κ, σ and NMDA receptors, and, in one study, dopamine transporters. In addition, high doses of ibogaine seem to be toxic to Purkinje cells in the rat cerebellum.

In humans, it has been reported that ibogaine reduces craving and attenuates narcotic dependence. Ataxia, nausea, vomiting, and hypertension have also been attributed to its action. It also has been reported that ibogaine will produce tremors, hallucinations or "fantasies" and apprehension, increase strength and appetite, and possibly increase libido.

The pharmacological profile of ibogaine, including its putative "anti-addictive" effects, are likely to result from actions at multiple loci. For example, the effects of ibogaine on voltage-dependent sodium channels could explain its tremorigenic actions, whereas an anticholinesterase activity may explain its effects on blood pressure as well as stimulation of digestion and appetite. The neurochemical basis (or bases) for the putative "anti-addictive" actions of ibogaine remains unclear. However, several hypotheses can be considered. O'Hearn and Molliver (1993) have shown that ibogaine produces a degeneration of Purkinje cells in the parasagittal zone of the cerebeller vermis. They hypothesize (see Touchette, 1993) that this toxicity may interfere with addictive behavior. At present, there is no experimental evidence to support this hypothesis. Based on its neurochemical profile, ibogaine may produce "anti-addictive" actions through multiple effects at κ receptors, σ receptors, or dopamine transporters (see VII.B. and VII.I.). Alternatively, ibogaine, or an unidentified active metabolite might act at pathways that have not been previously linked to addictive processes.

Although these hypotheses all merit further investigation, at present, there are converging lines that link the NMDA-antagonist action of ibogaine to its putative "anti-addictive" properties. NMDA antagonists are structurally diverse, acting at multiple, allosterically coupled recognition sites on this family of ligand-gated ion channels (for reviews see Kutsuwada et al., 1992; Meguro et al., 1992; Carter, 1992). Like ibogaine (see Section VII.B.), NMDA antagonists acting at each of these sites (glutamate, glycine, polyamine, open channel) attenuate morphine withdrawal (Koyuncuoglu et al., 1990, 1992; Trujillo and Akil, 1991; Rasmussen et al., 1991; Rossetti et al., 1992; Cappendijk et al., 1993; Kolesnikov et al., 1994). Although evaluation of the "anti-addictive" effects of a drug in animals is by definition fraught with difficulties, many of the phenomena that accompany addiction in humans can be modeled in animals. For example, repeated treatment with opioids produces tolerance to several of its effects; NMDA antagonists reduce tolerance to the analgesic action of opioids (Marek et al., 1991; Trujillo and Akil, 1991; Ben-Eliyahu et al., 1992; Gutstein and Trujillo, 1993; Lutfy et al.,

1993; Kolesnikov et al., 1994). It has also been demonstrated that NMDA antagonists attenuate the tolerance to a variety of other addictive substances including alcohol (Khanna et al., 1993a, 1993b, 1994; Wu et al., 1993) and benzodiazepines (File and Fernandes, 1994).

Repeated administration of cocaine, amphetamine, or nicotine leads to sensitization or "reverse tolerance." Reverse tolerance describes the condition in which the response to drug, such as locomotor stimulation, stereotypy and/or convulsions, is increased after repeated administration. The use-dependent channel blocker, MK-801 has been shown to inhibit the development of reverse tolerance to stimulants (Karler et al., 1989; Shoaib and Stolerman, 1992; Pudiak and Bozarth, 1993). Although the direct effects of ibogaine on sensitization have not been investigated, ibogaine shares other "anti-addictive" properties with other NMDA antagonists that can block "reverse tolerance." Thus, similar effects of ibogaine on reverse tolerance must be considered in interpretation of studies using repeated administration of drugs (see Section VII.A.).

It is unknown whether the hallucinogenic actions of ibogaine are caused by its effects on NMDA receptors. Drugs with high affinities to the open-channel binding site on NMDA receptors (e.g., phencyclidine, MK-801) have profound behavioral actions in animals and produce psychotomimetic effects in humans (Luby, 1959; Domino, 1964; Fauman and Fauman, 1978). Furthermore, phencyclidine and ketamine are recreationally used and sold on the illicit drug market (Davies, 1963; Stafford, 1978; Fauman and Fauman, 1978; Snyder, 1980; Gintzler et al., 1982). There are some similarities between the psychoactive effects of ibogaine (which binds to the open NMDA receptor channel) (Popik et al., 1994, in review) and those produced by phencyclidine or ketamine (Luby, 1959; Stafford, 1978). Nonetheless, ibogaine binds with high affinity to σ receptors (see above, Section VII.I.), whereas NMDA antagonists such as MK-801 (which also acts at the open channel site) do not affect σ receptors at pharmacologically relevant concentrations. Based on this information and the ability of parenterally administered glycine to block the effect of ibogaine to diminish naloxone-precipitated opiate withdrawal (Popik et al., in review), it may be hypothesized that the "anti-addictive" properties of ibogaine are related to a blockade of NMDA receptors. The hallucinogenic effects of ibogaine could be related to action at σ receptors, because the psychotomimetic properties of other σ ligands are well known (Haertzen, 1974).

The observation that ibogaine acts as an NMDA antagonist resolves in part the issue of its reported long-lasting effects. The behavioral and neurochemical effects of ibogaine seem to significantly outlast its presence in the brain, suggesting either the existence of a long-lasting metabolite or a neurochemical change of a long-lasting nature. Despite several attempts, a metabolite that acts at either κ (Deecher et al., 1992) or NMDA receptors (our unpublished observations) has not been demonstrated, although the possibility that a metabolite exists that acts at another locus cannot be excluded. However, many effects mediated by NMDA receptors outlast the presence of the drug that induces them. Such changes are thought to underlie many of the physiological (e.g., memory) (Morris et al., 1986; Danysz et al., 1988; Sierociska et al., 1991), pathological (epileptogenesis) (Williamson and Lothman, 1989), and neurotoxic (Rothman et al., 1987; Foster et al., 1988; Roberts-Lewis et al., 1993) processes that can be prevented or modulated by NMDA antagonists (Andine et al., 1988; Foster et al., 1988; Monaghan et al., 1989). If ibogaine attenuates drug addiction by modulation of long-lasting processes (such as learning and memory), then this hypothesis may support theories relating learned factors in drug dependence (Siegel, 1975, 1976) as some learning processes are blocked by NMDA antagonists (Morris et al., 1986; Danysz et al., 1988; Sierociska et al., 1991). However, because NMDA antagonists block learning processes but not memories that are already well established (Shapiro and Caramanos, 1990), the "amnestic" hypothesis invoked to explain the "anti-addictive" effects of NMDA antagonists apparently requires refinement.

Based on these observations, it may also be hypothesized that the "anti-addictive" effects of other drugs previously reported to decrease drug-seeking phenomena might also be explained by inhibition of glutamatergic transmission. Thus, chronic administration of the tricyclic antidepressant desipramine (reported to act as a use-dependent NMDA channel blocker (K_i ~7.4 μM) (Reynolds and Miller, 1988; Wdzony and Goembiowska, 1993) reduced cocaine use and craving (Gawin et al., 1989; Gawin, 1991) and attenuated the phencyclidine withdrawal syndrome (Tennant et al., 1981) in man. Dextromethorphan, another use-dependent NMDA channel blocker (K_i ~1.9 μM) (Reynolds and Miller, 1988), has been used to treat people with heroin addiction (Saydam and Koyuncuoglu, 1989; Koyuncuoglu and Saydam, 1990).

From the reports of humans with heroin addiction who have taken ibogaine, it seems that several features of the ibogaine experience are important in interrupting addiction. Thus, Dutch addicts who used ibogaine described the experience as having a dream with full consciousness, together with anxiety and the recall of memories (Kaplan et al., 1993; Lotsof, 1995). After this experience, the people with addiction did not feel compelled to use heroin. Although these insights are intriguing, they are at present without heuristic value. Further studies are required to determine the importance of such experiences in the treatment of drug abuse. In conclusion, the claimed "anti-addictive" properties of ibogaine require rigorous validation in humans, after careful assessment of its neurotoxic potential. If the "anti-addictive" properties of ibogaine are dependent upon the

blockade of NMDA receptors, the use of more specific NMDA antagonists might be considered.

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