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REVIEW ARTICLE

Ibogaine and Cocaine Abuse: Pharmacological Interactions at Dopamine and Serotonin Receptors

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ABSTRACT: Ibogaine is an indole alkaloid that has been of interest in recent years due to its putative efficacy in the treatment of drug dependence. For the most part, animal data have shown attenuation of some of the effects of stimulant drugs, for example, motor stimulation and self-administration. The mechanism of this inhibition of drug-induced behavior seems to suggest the action of the dopamine, serotonin, NMDA, kappa, and/or sigma receptor sites, as indicated by the affinity of ibogaine to receptor selective ligands in binding competition studies. However, affinity for receptors does not in itself indicate their involvement. In vitro perfusion studies have proven a useful model to study the effect of ibogaine on neurotransmitter systems and the functional effects of such interactions. This review summarizes these data and the support of multiple effects of ibogaine, and the potential importance of its action on serotonergic modulation of dopamine release. Copyright © 1997 Elsevier Science Inc.

KEY WORDS: Ibogaine, Dopamine, Serotonin, 5-HT$_{1b}$ receptor, In vitro perfusion, NMDA, Kappa-opioid, Sigma receptor, Presynaptic transmitter regulation.

INTRODUCTION

Ibogaine (NIH 10567, Endabuse™), the principal alkaloid of *Tabernathe iboga*, has recently been suggested to interrupt the physiological and psychological aspects of the opiate withdrawal and cocaine and amphetamine abuse syndromes in humans. Early studies in the first part of this century were mostly focused on its stimulant properties. The discovery of reserpine in the 1950s in *Rauwolfia*, stimulated a new interest in plants containing indole alkaloids. The early pharmacological studies were influenced by its similarity to serotonin [18] (Fig. 1). It was used as a psychoactive drug in psychotherapy [47], and as a hallucinatory LSD substitute; it was later classified as a controlled substance by the FDA.

Recent studies during the past 5 years were prompted by anecdotal reports of observations on humans suggesting that ibogaine could interrupt addiction to both heroin and cocaine without symptoms of withdrawal. Based on these limited reports, a number of investigators have examined ibogaine's action using several animal models to characterize its site and mechanism of action. The early history and pharmacological actions of ibogaine were recently reviewed by Popik et al. [53], whose own work suggests that ibogaine may act by blockage of NMDA receptors, based on the affinity of ibogaine to the MK-801 binding site [52,54]. Others have proposed that on the basis of ligand binding affinities the kappa-opioid [17] or sigma [38] receptors are involved in its action. The present review will describe studies that attempt to characterize the site(s) and action of ibogaine that may relate to its interaction with mechanisms involved in cocaine abuse. This review is not intended to cover all the effects of cocaine on neurotransmitter systems, but to focus on the effects of cocaine that can be related to recent studies on aspects of the pharmacology of ibogaine associated with its putative antiaddictive properties. Although many investigators have focused on central dopamine mechanisms underlying the behavioral effects of cocaine, it is likely that other nondopaminergic sites are also involved, independently or via their modulation of dopamine release, in producing cocaine dependence. Ibogaine seems to have influence at these nondopaminergic sites.

EFFECT OF IBOGAINE ON COCAINE-INDUCED BEHAVIORS

At present, ibogaine's usefulness in treating human drug dependence is perceived as being based on anecdotal evidence. A preliminary study in humans reported the absence of withdrawal signs and variable periods of abstinence from opiates [69]. To substantiate such usefulness, a number of animal models have been studied to test its effect on drug-induced motor activity or self-administration (summarized in Table 1). One to five injections of ibogaine (injections of 40 mg/kg, intraperitoneal) decreased morphine self-administration by Sprague–Dawley female rats for several days [24,26]. In studies on rats, ibogaine dose dependently reduced the frequency of withdrawal symptoms induced by naloxone in morphine-dependent (Wistar male and Sprague–Dawley female) rats [20,25]. Recently, ibogaine (intraperitoneal) was also reported to decrease intravenous cocaine self-administration in Wistar rats [11], and to reduce cocaine consumption in a drinking preference model

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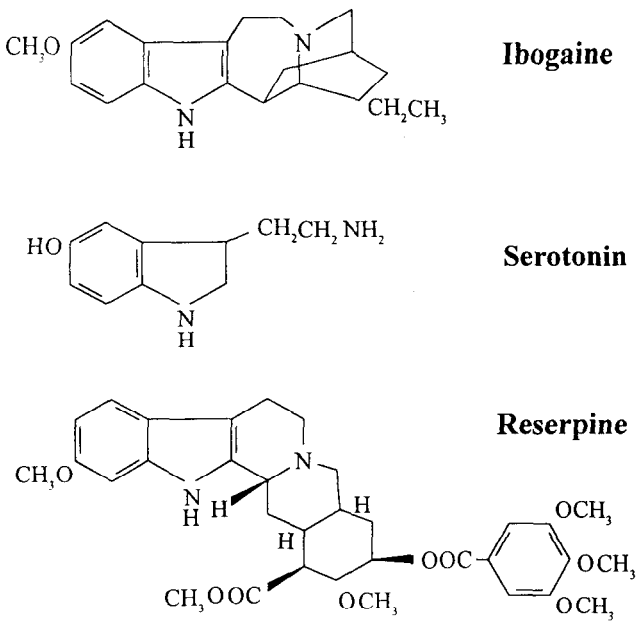

FIG. 1. Chemical structures of ibogaine, serotonin, and reserpine.

after one to two injections of 40 mg/kg IP ibogaine (C57BL/6By mice) [63].

Not all studies have been supportive: ibogaine (subcutaneous injection) failed to reduce withdrawal symptoms in Sprague–Dawley male rats [67,68]. In morphine-dependent mice (CDF1), ibogaine did not eliminate withdrawal symptoms, but significantly increased the number of repetitive vertical jumps induced by naloxone [21]. Dworkin et al. [19] reported predominantly only short-term reduced response to cocaine and heroin after ibogaine administration to Fisher 344 male rats (on reversed light cycle), possibly accounted for by development of abnormal motor behavior that was due to administration of ibogaine. Carol Hubner (communication at meeting of NIDA/Medical Development Division (MDD) in Washington, DC) reported that ibogaine had no effect on cocaine-induced locomotor behavior in BALB/c mice. Our lab reported reduced locomotor responses to cocaine and long-term reduction of oral cocaine consumption in C57BL/6By male mice [61,63].

The reported effects of ibogaine on drug-induced motor activity are heterogeneous. Ibogaine reduced amphetamine-induced locomotor activity in C57BL/6By mice, but not in BALB/c mice [60], and ibogaine pretreatment blocked locomotor stimulation induced by morphine in rats [40,41,43]. In another study, ibogaine pretreatment of female rats (note: many of the initial studies from the Glick laboratory used female rats) potentiated the motor activity induced by *d*-amphetamine and enhanced the rise of extracellular dopamine induced by *d*-amphetamine in the striatum [42]. In this study ibogaine slightly potentiated cocaine-induced motor activity and potentiated the increase in the extracellular level of dopamine induced by cocaine in female rats [39]; in other studies it reduced the cocaine-induced increase in dopamine and in locomotor behavior in male Sprague–Dawley rats [9,10], and significantly inhibited cocaine-induced hyperactivity in rats [9–11]. Similar variable responses to ibogaine have been reported for morphine self-administration and withdrawal symptoms [21,24–26,67].

Overall, however, ibogaine does appear to attenuate some of the behavior associated with cocaine administration or withdrawal. It is important to recognize that there are short-term acute nonspecific motor affects that will appear as altered drug responses. The more relevant studies should take into account the prolonged effect of ibogaine, its route of administration, and the species, strain, and sex of the experimental animals.

At present, it is unclear how such variables alter the responses to ibogaine. It appears that there are differences between rats and mice in the effect of ibogaine on the *d*-amphetamine-induced release of dopamine. *d*-Amphetamine stimulates the basal release

TABLE 1

EFFECTS OF IBOGAINE ON DRUG-INDUCED BEHAVIOR

Drug	Animals	Route	Effects	Author	Ref.
Opiates	Human	or	withdrawal/not present abstinence/variable	Sheppard et al.	[69]
Morphine	Sprague–Dawley rats	ip	motor activity/inhibit	Maisonneuve et al.	[43]
	Sprague–Dawley rats	ip	self-admin./inhibit	Glick et al.	[24,26]
	Wistar rats	ip	withdrawal/inhibit	Dzoljic et al.	[12,20]
	Sprague–Dawley rats	sc	withdrawal/**no effect**	Sharpe and Jaffe	[68,69]
	Sprague–Dawley rats	ip	withdrawal/inhibit	Glick et al.	[25]
	CDF1 mice	ip	withdrawal/**no effect**	Frances et al.	[21]
Amphetamine	Sprague–Dawley rats	ip	motor activity/stimulate	Maisonneuve et al; Sershen et al.	[42,60]
	C57BL/6By mice	ip	motor activity/inhibit	Sershen et al.	[60]
	BALB/cBy	ip	motor activity/**no effect**	Sershen et al.	[60]
Cocaine	C57BL/6By mice	ip	motor activity/inhibit	Sershen et al.	[61]
	C57BL/6By mice	ip	consumption/inhibit	Sershen et al.	[63]
	BALB/cBy	ip	motor activity/**no effect**	Hubner (MDD report)	
	Sprague–Dawley rats	ip	motor activity/stimulate	Maisonneuve and Glick	[39]
	Wistar rats	ip	self-admin./inhibit	Cappendijk and Dzoljic	[11]
	Sprague–Dawley rats	ip	motor activity/inhibit	Broderick et al.	[9,10]
	Fischer 344 rats (+Heroin, Food)	ip	self-admin./**nonspecif. effect**	Dworkin et al.	[19]

Summary of the effects of ibogaine on drug-induced behaviors. Bold indicates the absence of any reported effect or highlights a difference in route of administration or strain of animal.

TABLE 2
AFFINITY OF IBOGAINE AT BINDING SITES

Binding Site	Ligand	Affinity	Author	References
Dopamine Transporter	(WIN 35,248)	1.5 μM	Sershen et al.	[61]
	(WIN 35,248)	3.5 μM	Sweetnam et al.	[72]
	(GBR-12935)	>100 μM	Broderick et al.	[9]
	(RTI-121)	2.0 μM	Mash et al.	[44]
Serotonin Transporter	(RTI-55)	0.55 μM	Mash et al.	[44]
	*(RTI-55)	40.7 nM	Mash et al.	[44]
κ-Opioid	(U-69593)	2.0 μM	Deecher et al.	[17]
	(U-69593)	16.0 μM	Sweetnam et al.	[72]
	(U-69593)	3.8 μM	Pearl et al.	[51]
	**(U-69593)	1.0 μM	Pearl et al.	[51]
Mu	(carfentanil)	>100 μM	Deecher et al.	[17]
	(DAGO)	16 or 26 μM	Sweetnam et al.	[72]
	(naloxone)	130 nM and 4 μM	Codd	[14]
	(DAMGO)	11 μM	Pearl et al.	[51]
	*(DAMGO)	2.7 μM	Pearl et al.	[51]
Sigma	(pentazocine)	86 nM	Popik et al.	[53]
	(pentazocine)	9.3 μM	Mach et al.	[38]
	(pentazocine)	8.5 μM	Bowen et al.	[8]
	(DTG)	90 nM	Mach et al.	[38]
	(DTG)	38 μM	Sweetnam et al.	[72]
	(DTG)	201 nM	Bowen et al.	[8]
NMDA	(MK-801)	1.0 μM	Popik et al.	[52,54]
	(TCP)	1.5 μM	Popik et al.	[52]
	(MK-801)	3.2 or 5.6 μM	Sweetnam et al.	[72]
	(CGS-19755)	>100 μM	Sweetnam et al.	[72]
	(MK-801)	4–10 μM	Mash et al.	[45]

Competition studies using. *12-hydroxyibogamine, **noribogaine

Summary of reported affinities (K_i or IC_{50}) of ibogaine to ligand binding sites.

of dopamine in vitro in mouse and rat striatum, but inhibits the electrically evoked release of dopamine in rat (but not mouse) striatum [60]. Kamal et al. [36] reported a similar enhancement of basal release and inhibition of stimulation-evoked release of dopamine in rabbit caudate nucleus slices by *d*-amphetamine. Ibogaine has an opposite effect on the changes in electrically evoked release of dopamine induced by amphetamine in these two species; it caused inhibition in the mouse and reversed or prevented the inhibition seen in the rat. These species-related differences could account for the different behavioral effects of ibogaine seen in amphetamine-treated mice and rats. The inhibition of *d*-amphetamine-induced locomotor activity in mice can relate to the ibogaine-induced inhibition of stimulation-evoked release of dopamine, and the enhanced stimulation of locomotor activity in rats to ibogaine's reversal of *d*-amphetamine-induced inhibition of stimulation-evoked release of dopamine, suggesting that ibogaine alters the releasable pools of dopamine. Its structural similarity to reserpine (Fig. 1) also supports an effect on the transmitter pools. Harsing et al. [29] confirmed an action of ibogaine on a transmitter pool, reporting that ibogaine acts to release dopamine from the cytoplasmic pool.

Strain differences in opiate withdrawal syndromes are reported, for example, Lewis and Fischer rats, with differences in the cyclic AMP pathway responses to chronic morphine [28], which may account for variable responses to ibogaine. Metabolism of ibogaine to noribogaine is produced at concentrations that are 50% higher in females than in male rats [73], which is another variable to be considered. Metabolism of the abused drug may also be affected. Amphetamine levels are higher in female rats after ibogaine administration and that may account for the increased motor response; however, morphine levels were unchanged [23,27]. Cocaine levels may even be slightly higher in ibogaine treated mice, but motor responses were reduced [63].

RECEPTOR BINDING

Ibogaine was shown to have complex action on neurotransmitter systems, affecting noradrenergic [22], dopaminergic [39,40,43,61,62], and 5-HT receptors [70]. In attempts to characterize its site of action, radioligand screenings were conducted (Table 2). A radioligand screen conducted by Deecher et al. [17], in bovine and rat brain tissue, found affinity for ibogaine in the μM range for the voltage-dependent sodium channel ([^{3}H]BTX-B) and the kappa-opiate receptor ([^{3}H]U-69593 binding site). Subsequently, Popik et al. [52] reported an affinity of ibogaine to the MK-801 binding site. Mach et al. [38] found a 6- to 30-fold higher affinity to the sigma receptors than to kappa receptors. Codd [14] noted a high affinity to the mu opioid agonist site, a nM and mM site based on a two-site model. We reported a relatively weak affinity of ibogaine to the dopamine transporter (WIN 35,248 binding site; affinity 10 times higher than that of cocaine) [61], and Broderick et al. [9] found no significant affinity of ibogaine to the GBR-12935 site. Sweetnam et al. [72] reported interaction of ibogaine with a variety of receptors, including mu, delta, kappa, opiate, 5-HT_2, 5-HT_3, muscarinic1 and 2, and NMDA (MK-801) receptors, and dopamine, norepinephine, and serotonin uptake sites. Mash et al. [44,45] suggested that in addition to the NMDA site, ibogaine or its me-

tabolite 12-hydroxyibogamine has high affinity to the serotonin transporter; 50-fold more potent than that to the dopamine transporter.

These results are summarized in Table 2, focusing on affinities in the micromolar or lower range, perhaps indicative of a functionally relevant interaction with these sites. It is apparent that there are some variations in the reported affinities from different laboratories. Some of the differences may relate to the ligand used; others may relate to the assay conditions. To date, the highest affinities (nM range) are seen at the sigma and mu sites. Brain levels of ibogaine or its metabolites have been estimated to be in the micromolar range [77], sufficiently high to affect those systems showing affinities in the low micromolar range.

Ibogaine was reported to have no long-term effect (1–2 days after administration) on WIN-35, 248 binding [61]. Other than this study, there have been no detailed studies on the long-term effect of ibogaine on the kinetic properties (up-regulation) of the NMDA. kappa, and sigma sites that can be related to its drug action.

EFFECT OF IBOGAINE ON RELEASE OF NEUROTRANSMITTERS

A problem with the binding assay is that it does not give an indication of the functional activity of a drug at the binding site. We attempted to test the functional effect of ibogaine action at some of these sites by measuring their ability to modulate dopamine and serotonin release in vitro after ibogaine administration. The dopamine system was selected because it is a predominant site of action for cocaine, involved in the central action and rewarding properties [75]. Additionally, a number of receptor sites identified in the binding assay are known to be located presynaptically on dopamine terminals that can modulate its release, and not surprisingly, agonists/antagonists of these sites, for example, NMDA, sigma, kappa, serotonin receptors, can in some way alter behavioral and biochemical responses to cocaine. Table 3 summarizes the effects of various agents for these sites, and the effect of copresence of ibogaine on dopamine and serotonin release.

Kappa Receptor

Initial radioligand surveys suggested that ibogaine had high affinity to the kappa receptor [17,51,72]. Although mu and delta receptors often seem to modulate the neurotransmission process by a comparable mechanism, for example, inhibition of adenylate cyclase and enhancement of potassium conductance, kappa-opioid receptors differ from mu- and delta-opioid receptors in the way they affect signal transduction [33]. Kappa receptors appear to mediate inhibition of evoked [^{3}H]dopamine release from nucleus accumbens via a decrease in Ca^{2+} conductance rather than the enhancement of K^+ conductance seen with the activation of mu and delta opioid receptors, resulting in inhibition of [^{3}H]ACh release [33], an effect that may be modulated by ibogaine via its affinity to the kappa receptor. Activation of kappa-opioid receptors attenuates the behavioral effects of cocaine, possibly by restricting its ability to enhance dopaminergic neurotransmission [30–32]. Repeated activation of kappa receptors prevents the locomotor activation that occurs in response to acute cocaine in addition to sensitization that develops after repeated administration of cocaine [30]. Such effects may be related to the kappa receptor modulation of dopamine release and dopamine uptake [71], although the latter action may not be its major role [15]. Alternatively, ion channel inhibitors may function as potential modulators of cocaine binding; for example, Ca^{2+} antagonists inhibit cocaine-induced increase in dopamine and locomotor stimulation [49] and various ionic channel blockers inhibit the binding of cocaine without inhibition of dopamine reuptake [5]. The lack of effect of ibogaine on dopamine uptake [9,10,29] does not therefore discount its efficacy in treatment of cocaine addiction.

Ibogaine eliminated the kappa agonist-mediated inhibition of dopamine and serotonin release measured after electrical stimulation in vitro [64] (Table 3). With the addition of cocaine, the efflux of dopamine and of serotonin is increased (the increase may reflect the release or reuptake blockade) [66]. Ibogaine attenuates the cocaine-induced increase in serotonin release, which is normalized by addition of the kappa agonist, suggesting that the kappa agonist effect is mediated via the serotonin system. The serotonergic system appears to have a prominent role in the discriminative effects of kappa-opioid agonists in some species; the antinociceptive effects of kappa-opioid agonists are due, in part, to activation of the 5-HT_2 type of serotonin receptor [34].

NMDA-Sigma Receptors

Relatively high affinity of ibogaine to the NMDA and sigma receptors has been reported (Table 2). Ibogaine produces a voltage-dependent block of NMDA receptors in hippocampal culture

TABLE 3

EFFECTS OF IBOGAINE ON [^{3}H]DOPAMINE AND [^{3}H]SEROTONIN RELEASE

		[^{3}H]Dopamine		[^{3}H]Serotonin	
	[References]	Control	Ibogaine	Control	Ibogaine
5-HT (basal)	[Table 4]	↑increase	↑↑increase		
5-HT_{1B} agonist (evoked) (CGS-12066A)	[62,66]	↑increase	block	no effect	no effect
5-HT_3 agonist (basal and evoked) (phenylbiguanide)	[64]	↑↓biphasic	no effect		
K-opioid agonist (evoked) (U-62066)	[64,66]	↓inhibit	block	↓inhibit	block
Sigma agonist (evoked) (pentazocine)	[65]	↑increase	inhibit 50%		
NMDA agonist (basal) (NMDA)	[65]	↑increase	partial inhibition		
DA Autoreceptor (evoked) antagonist (Sulpiride)	[29,72]	↑increase	no effect		
DA Uptake Blocker (evoked) (cocaine)	[66]	↑increase	no effect	↑increase	block

Summary of effects of indicated agents and ibogaine on labeled dopamine or serotonin efflux from striatal tissue after electrical stimulation (evoked) or on basal efflux. Control condition refers to effect on labeled dopamine or serotonin release with addition of indicated agents. The column under ibogaine indicates the effect seen when ibogaine was added before addition of the indicated agent. "no effect" indicates no change from control response.

[52], blocks NMDA-depolarization in frog motorneurons [45], and substitutes as a discriminative stimulus in mice trained to discriminate dizocilpine [52].

NMDA was shown to stimulate the basal release of [^{3}H]dopamine from striatal tissue [65] (Table 3). This release was subject to inhibition by MK-801, and also ibogaine at a concentration that by itself did not affect release partially inhibited NMDA-evoked release of dopamine [65]. Inhibition was not seen in animals pretreated with ibogaine. The NMDA-evoked release was also inhibited by the kappa agonist U62066 [65], in agreement with similar inhibition of dopamine release from cultured neurons [56]. In addition, the level of basal release of dopamine after the NMDA-evoked release remained higher in the tissue exposed to ibogaine. Because the kappa system is inhibitory on the NMDA receptor (inhibition by U62066), and the elevated basal release of dopamine seen in the presence of ibogaine after NMDA-evoked release may reflect the blockade of a tonic inhibitory kappa influence by ibogaine.

It has been questioned whether the stimulatory effect of excitatory amino acid receptor agonists on striatal dopamine release reflect a more pathophysiological condition, rather than representing physiologically relevant presynaptic interaction between excitatory amino acid efferents and dopamine terminals, because there is no anatomical evidence to support such axoaxonic connections [46]. The influence of tonic NMDA receptor activation in determining the basal level of dopamine release has, therefore, been suggested to involve two mechanisms, one dependent and one independent of the involvement of the basal ganglion [46]. Involvement of the basal ganglion would support an inhibitory influence of NMDA receptors on striatal dopamine basal release. If ibogaine were an NMDA antagonist, it could be hypothesized that the basal release of dopamine would be increased. Dopamine release would also be elevated with removal of the kappa inhibitory influence. The resulting increase in basal dopamine release could function in attenuating drug-induced withdrawal symptoms.

Ibogaine showed the highest binding affinity to the sigma site (Table 2). The sigma agonist pentazocine also evoked dopamine release [65] (Table 3). This effect was inhibited approximately 50% by ibogaine, MK-801, or U62066, suggesting that there are interactions between the NMDA, kappa, and sigma receptors that modulate dopamine release. However, because the maximal effect of ibogaine (1 μM) on (+)-pentazocine-induced release of dopamine was about 50% inhibition, at a concentration of ibogaine expected to fully saturate the receptor (K_i = ~90 nM), the sigma receptor was not thought to be a major site of action. Since the sigma and kappa receptors also bind the same opioids (pentazocine) [74], the effect seen may be more related to ibogaine's kappa activity.

Serotonin Receptor

Although binding assays have not shown a clear association of ibogaine with the serotonin receptors, there is experimental evidence showing an effect on this system. For example, microdialysis studies or brain tissue concentrations after ibogaine administration have suggested that ibogaine is able to increase serotonin release [10,61]. Long and Lerrin [37] have shown that ibogaine is a reversible competitive inhibitor of the active transport of serotonin into blood platelets, as are cocaine, amphetamine, and imipramine. Potentiation of the hexobarbital hypnosis produced by serotonin and reserpine was blocked by ibogaine [57]. The stimulus properties of ibogaine were suggested to involve 5-HT$_2$ and 5-HT$_{1A}$ receptor activity; ibogaine mimicked LSD, DOM, and yohimbine appropriate responses in two-lever discrimination task [48]. The cocaine binding site has been associated with both the dopamine and the serotonin reuptake carrier [55]. Broderick et al. [10] indicated that ibogaine releases serotonin, which in the presence of cocaine appears to inhibit dopamine cells. Studies indicate that presynaptic serotonin sites can modulate dopamine release; for example, serotonergic innervation of the dorsal striatum may exert a facilitatory influence on dopamine release [2,3]. Our studies report long-term effects of ibogaine on serotonergic receptor modulation of dopamine release. Ibogaine administration lowers the brain level of the serotonin metabolite 5-HIAA 24 h later [61], blocks the 5-HT$_{1b}$ agonist-mediated increase in dopamine efflux [62], and blocks the cocaine-mediated efflux of serotonin from striatal tissue in vitro [66].

Numerous studies have reported that nondopaminergic mechanisms are involved in cocaine dependence. It has been reported that deficient serotonin neurotransmission could be a significant factor in cocaine withdrawal symptoms [50]. Drugs that antagonize postsynaptic serotonin receptors alter cocaine-induced convulsions [59]. Serotonin has also been proposed to be involved in mediating the euphorigenic and anxiogenic effects of cocaine; serotonin depletion significantly reduces subjective ratings of cocaine high [1] and cue-induced craving for cocaine [58]. Cocaine self-administration produces sustained increases in both serotonin and dopamine; however, during withdrawal serotonin neurotransmission may be deficient [50]. Elevated serotonin in prefrontal cortex was suggested to have a role in the mediation of conditioned stimulus effects of cocaine [13]. Mash et al. [44] reported that 12-hydroxyibogamine, a primary metabolite of ibogaine, displayed high affinity to the serotonin transporter and elevated extracellular levels of serotonin.

Serotonin dose dependently increases the release of dopamine (Table 4). Part of this effect is related to the dopamine uptake site; serotonin is taken up by the dopamine transporter and displaces vesicular dopamine, inducing dopamine release [4,16,35]. Dopamine uptake blockers (cocaine, mazindol, Table 4) would, therefore, be expected to attenuate this effect. Ibogaine, at a concentration (1 μM) that has no effect on dopamine release, or given in vivo, potentiates the serotonin-mediated release of dopamine. Cocaine can also prevent this increase (Table 4). The kappa (U62066) agonist or NMDA (MK-801) antagonist have no effect on serotonin-mediated dopamine release. Striatal 5-HT$_{1b}$ receptors are partially implicated in the facilitatory control of dopamine release induced by serotonin [2,16,76]. The serotonin 5-HT$_{1b}$ agonist CGS-12066A increased the release of dopamine evoked by electrical stimulation [62,66] (Table 3). CGS-12206A also inhibits the serotonin-mediated release of dopamine, but does not completely reduce the potentiation by ibogaine (Table 4), suggesting that the potentiated release is secondary to the uptake of serotonin and its displacement of dopamine. This would account for the ability of cocaine to block the effect of serotonin and ibogaine, because it blocks the initial uptake of serotonin. The secondary response effect must be mediated by the 5-HT$_{1b}$ receptor, because ibogaine greatly reverses the CGS-12066B induced inhibition of 5-HT–mediated dopamine release. Comparable effects were seen in studies by Bolanos–Jimenez et al. [6,7] where antidepressants interact with presynaptic 5-HT$_{1b}$ heteroreceptors located on cholinergic terminals, to reduce the inhibitory effect of CGS-12066B on stimulation-induced release of acetylcholine, through a mechanism independent of synaptic availability of serotonin. The 5-HT$_3$ agonist phenylbiguanide (10^{-5} M)-mediated release of dopamine is not potentiated by ibogaine [64] (Table 3). At lower concen-

TABLE 4

EFFECT OF IBOGAINE ON SEROTONIN-EVOKED DOPAMINE RELEASE

	FR (mean ± SEM)	(*n*)
5-HT 5 μM	5.22 ± 1.16	(6)*
5-HT 10 μM	9.56 ± 0.66	(30)*
5-HT 20 μM	17.6 ± 3.6	(6)*
5-HT 10 μM + Cocaine 1 μM	5.45 ± 0.46	(12)†
5-HT 10 μM + Cocaine 10 μM	2.94 ± 0.20	(17)†
5-HT 10 μM + Mazindol 20 μM	5.25 ± 0.7	(6)†
5-HT 10 μM + Ibogaine 1 μM + Cocaine 1 μM	4.67 ± 0.45	(12)
5-HT 10 μM + Ibogaine 1 μM + Cocaine 10 μM	2.96 ± 0.55	(6)
5-HT 10 μM + Ibogaine 1 μM	16.5 ± 0.63	(6)‡
5-HT 10 μM + Ibogaine (Pretreatment 40 mg/kg-2 hr)	15.1 ± 2.03	(11)‡
5-HT 10 μM + U62066 1 μM	9.67 ± 1.42	(6)
5-HT 10 μM + MK-801 5 μM	9.03 ± 0.09	(6)
5-HT 10 μM + CGS-12066A 10 μM	1.68 ± 0.27	(12)§
5-HT 10 μM + Ibogaine 1 μM + CGS-12066A 10 μM	11.9 ± 3.02	(6)#

The effect of serotonin on efflux of labeled dopamine from striatal tissue. Striata were incubated with [^{3}H]dopamine (see [63] and [64] for details on methods). Serotonin was added starting at fraction 5 for 2 min, and fractional release (FR, release of radioactivity as a percentage of the radioactivity in the tissue at the time the release was determined) was measured. The peak was calculated from the counts released, starting from the fraction during which serotonin was added until the fraction the counts returned to basal. Competing drugs were added during fraction 3 and maintained until the end of the experiment (fraction 15). Animals treated with ibogaine were killed 2 h after ibogaine administration.

* $p < 0.01$ vs. no addition.
† $p < 0.05$ vs. 5-HT 10 μM.
‡ $p < 0.01$ vs. 5-HT 10 μM.
§ $p < 0.01$ vs. 5-HT 10 μM.
# $p < 0.01$ vs. 5-HT 10 μM + CGS-12066A 10 μM.

trations (10^{-6} M) and activation by electrical stimulation, ibogaine was shown to elevate the basal release of dopamine [64].

Thus, ibogaine acting at the 5-HT$_{1b}$ site can alter dopamine release through other effects than those related to cocaine reuptake blockade. Such effects may have significance in the antiaddictive effects of ibogaine.

CONCLUSIONS

Although many of the locomotor stimulant effects of drugs of abuse are thought to be mediated via dopamine release, and several hypotheses associate the dopaminergic system with the reinforcing effects of these drugs, it is important to recognize that many neurotransmitter systems interact to produce the effects, and all of these need to be considered in the evaluation of the mechanism of action of ibogaine. Ibogaine apparently has some effects that inhibit motor responses to several drugs of abuse, such as to cocaine, and also inhibitory effects in self-administration paradigms and models testing withdrawal effects. Although there are a number of negative findings, the positive findings at present outweigh them. When evaluating ibogaine's effects on drug-mediated behaviors, it is important to recognize that its acute nonspecific effects can influence activity. Some of these nonspecific effects may depend on the route of administration, sex, strain, and species of animal tested. Metabolism of ibogaine is an important variable, because it has been reported that its metabolism is two times faster in females [73].

The present review focuses on the effects of ibogaine itself. However, in view of the relatively short half-life of ibogaine [18,44], the effects of possibly active long-lasting metabolites, 12-hydroxyibogamine, should not be excluded [44,45]. Because in some of our studies ibogaine was added in vivo and responses were tested in vitro after a washout period, ibogaine may by itself produce some long-lasting receptor-mediated changes, maintained after washout of ibogaine. Long-term effects of ibogaine administration on receptor properties should be examined, for example the NMDA, 5-HT$_{1b}$, and kappa sites, to determine if functional changes occur.

It is difficult at present to determine the primary, or more relevant, site of action of ibogaine. Radioligand binding studies suggests that the affinity of ibogaine to the kappa, mu, sigma, and NMDA receptors may be physiologically relevant to its action. But studies of binding affinity do not indicate functional relevance. Our laboratory has conducted a number of in vitro perfusion-release studies to characterize the functional effects of ibogaine on dopamine- and serotonin-mediated release, and their modulation, and its effect on cocaine-mediated changes in transmitter release. What is clear is that nondopaminergic receptor sites are capable of modulating dopamine and serotonin release. Such sites also interact with each other to finally control dopamine release and modulate responses to cocaine. The weak affinity to the dopamine transporter binding site and lack of effect on the cocaine-mediated reuptake blockade of dopamine indicate that ibogaine does not act directly at the dopamine transporter. Because cocaine is also a serotonin reuptake blocker, it is of interest that the increased efflux of serotonin in the presence of cocaine was attenuated by ibogaine. This effect may not be at the transporter, because in vitro perfusion studies do not only measure reuptake blockade; however, it is difficult to distinguish with this technique between release enhancement and reuptake blockade. Ibogaine potentiates the serotonin-induced increase in dopamine release and attenuates the 5-HT$_{1b}$ agonist-induced inhibition of serotonin-mediated efflux of dopamine, suggesting

that serotonin modulation of dopamine is a primary site of action. In addition, ibogaine has affinity to the NMDA and sigma sites. However weaker effects were seen with ibogaine on NMDA- and sigma-mediated dopamine release, in comparison with ibogaine's effect on the kappa-mediated inhibition of dopamine release. Which effects are the relevant ones is not clear; it may be ibogaine's cumulative effect at all these sites that alters the subsequent responses to cocaine. Nevertheless, the results suggest a more prominent effect of ibogaine on serotonergic mechanisms. Such interactions may be the basis for ibogaine's antiaddictive properties. As we gain a better understanding of the mechanisms involved in the modulation of dopamine release, we will learn how to characterize ibogaine's action in antagonizing the effects of drugs.

REFERENCES

1. Aronson, S. C.; Black, J. E.; McDougle, C. J.; Scanley, B. E.; Jatlow, P.; Kosten, T. R.; Heninger, G. R.; Price, L. H. Serotonergic mechanisms of cocaine effects in humans. Psychopharmacology (Berlin) 119:179–185; 1995.
2. Benloucif, S.; Galloway, M. P. Facilitation of dopamine release in vivo by serotonin agonists: Studies with microdialysis. Eur. J. Pharmacol. 200:1–8; 1991.
3. Benloucif, S.; Keegan, M. J.; Galloway, M. P. Serotonin-facilitated dopamine release in vivo: Pharmacological characterization. J. Pharmacol. Exp. Ther. 265:373–377; 1993.
4. Benuck, M.; Reith, M. E. Dopamine releasing effect of phenylbiguanide in rat striatal slices. Naunyn Schmiedebergs Arch. Pharmacol. 345:666–672; 1992.
5. Boja, J. W.; Kopajtic, T. A. Ion channel inhibitors may function as potential modulators of cocaine binding. Neuropharmacology 32:229–234; 1993.
6. Bolanos–Jimenez, F.; de Castro, R. M.; Fillion, G. Antagonism by citalopram and tianeptine of presynaptic 5-HT_{1B} heteroreceptors inhibiting acetylcholine release. Eur. J. Pharmacol. 242:1–6; 1993.
7. Bolanos–Jimenez, F.; Manhaes de Castro, R.; Fillion, G. Effect of chronic antidepressant treatment on 5-HT_{1B} presynaptic heteroreceptors inhibiting acetylcholine release. Neuropharmacology 33:77–81; 1994.
8. Bowen, W. D.; Vilner, B. J.; Williams, W.; Bertha, C. M.; Kuehne, M. E.; Jacobson, A. E. Ibogaine and its congeners are sigma 2 receptor-selective ligands with moderate affinity. Eur. J. Pharmacol. 279:R1–R3; 1995.
9. Broderick, P. A.; Phelan, F. T.; Berger, S. P. Ibogaine alters cocaine-induced biogenic amine and psychostimulant dysfunction but not [^{3}H]GBR-12935 binding to the dopamine transporter protein. NIDA Res. Monographic 96. US Government Printing Office, Washington, DC; 1992.
10. Broderick, P. A.; Phelan, F. T.; Eng, F.; Wechsler, R. T. Ibogaine modulates cocaine responses which are altered due to environmental habituation: In vivo microvoltammetric and behavioral studies. Pharmacol. Biochem. Behav. 49:711–728; 1994.
11. Cappendijk, S. L.; Dzoljic, M. R. Inhibitory effects of ibogaine on cocaine self-administration in rats. Eur. J. Pharmacol. 241:261–265; 1993.
12. Cappendijk, S. L.; Fekkes, D.; Dzoljic, M. R. The inhibitory effect of norharman on morphine withdrawal syndrome in rats: Comparison with ibogaine. Behav. Brain Res. 65:117–119; 1994.
13. Carey, R. J.; Damianopoulos, E. N. Conditioned cocaine induced hyperactivity: An association with increased medial prefrontal cortex serotonin. Behav. Brain Res. 62:177–185; 1994.
14. Codd, E. E. High affinity ibogaine binding to a mu opioid agonist site. Life Sci. 57:315–320; 1995.
15. Das, D.; Rogers, J.; Michael–Titus, A. T. Comparative study of the effects of mu, delta and kappa opioid agonists on ^{3}H-dopamine uptake in rat striatum and nucleus accumbens. Neuropharmacology 33:221–226; 1994.
16. De Deurwaerdère, P.; Bonhomme, N.; Lucas, G.; Le Moal, M.; Spampinato, U. Serotonin enhances striatal dopamine outflow in vivo through dopamine uptake sites. J. Neurochem. 66:210–215; 1996.
17. Deecher, D. C.; Teitler, M.; Soderlund, D. M.; Bornmann, W. G.; Kuehne, M. E.; Glick, S. D. Mechanisms of action of ibogaine and harmaline congeners based on radioligand binding studies. Brain Res. 571:242–247; 1992.
18. Dhahir, H. I. A comparative study of the toxicity of ibogaine and serotonin. Dissert. Abstr. Int. 32:2311; 1971.
19. Dworkin, S. I.; Gleeson, S.; Meloni, D.; Koves, T. R.; Martin, T. J. Effects of ibogaine on responding maintained by food, cocaine and heroin reinforcement in rats. Psychopharmacology (Berlin) 117: 257–261; 1995.
20. Dzoljic, E. D.; Kaplan, C. D.; Dzoljic, M. R. Effect of ibogaine on naloxone-precipitated withdrawal syndrome in chronic morphine-dependent rats. Arch. Int. Pharmacod. Ther. 294:64–70; 1988.
21. Frances, B.; Gout, R.; Cros, J.; Zajac, J. M. Effects of ibogaine on naloxone-precipitated withdrawal in morphine-dependent mice. Fund. Clin. Pharmacol. 6:327–332; 1992.
22. Gershon, S.; Lang, W. J. A psycho-pharmacological study of some indole alkaloids. Arch. Int. Pharmacodyn. 135:31–56; 1962.
23. Glick, S. D.; Gallagher, C. A.; Hough, L. B.; Rossman, K. L.; Maisonneuve, I. M. Differential effects of ibogaine pretreatment on brain levels of morphine and (+)-amphetamine. Brain Res. 588:173–176; 1992.
24. Glick, S. D.; Kuehne, M. E.; Raucci, J.; Wilson, T. E.; Larson, D.; Keller, R. W., Jr.; Carlson, J. N. 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. Brain Res. 657:14–22; 1994.
25. Glick, S. D.; Rossman, K.; Rao, N. C.; Maisonneuve, I. M.; Carlson, J. N. Effects of ibogaine on acute signs of morphine withdrawal in rats: Independence from tremor. Neuropharmacology 31:497–500; 1992.
26. Glick, S. D.; Rossman, K.; Steindorf, S.; Maisonneuve, I. M.; Carlson, J. N. Effects and aftereffects of ibogaine on morphine self-administration in rats. Eur. J. Pharmacol. 195:341–345; 1991.
27. Glick, S. D.; Rossman, K.; Wang, S.; Dong, N.; Keller, R. W., Jr. Local effects of ibogaine on extracellular levels of dopamine and its metabolites in nucleus accumbens and striatum: interactions with D-amphetamine. Brain Res. 628:201–208; 1993.
28. Guitart, X.; Kogan, J. H.; Berhow, M.; Terwilliger, R. Z.; Aghajanian, G. K.; Nestler, E. J. Lewis and Fischer rat strains display differences in biochemical, electrophysiological and behavioral parameters: Studies in the nucleus accumbens and locus coeruleus of drug naive and morphine-treated animals. Brain Res. 611:7–17; 1993.
29. Harsing, L. G., Jr.; Sershen, H.; Lajtha, A. Evidence that ibogaine releases dopamine from the cytoplasmic pool in isolated mouse striatum. J. Neural Transm. 96:215–225; 1994.
30. Heidbreder, C. A.; Babovic–Vuksanovic, D.; Shoaib, M.; Shippenberg, T. S. Development of behavioral sensitization to cocaine: Influence of kappa opioid receptor agonists. J. Pharmacol. Exp. Ther. 275:150–163; 1995.
31. Heidbreder, C. A.; Shippenberg, T. S. U-69593 prevents cocaine sensitization by normalizing basal accumbens dopamine. Neuroreport 5:1797–1800; 1994.
32. Heidbreder, Ch. A.; Goldberg, S. R.; Shippenberg, T. S. The kappa-opioid receptor agonist U-69593 attenuates cocaine-induced behavioral sensitization in the rat. Brain Res. 616:335–338; 1993.
33. Heijna, M. H.; Hogenboom, F.; Mulder, A. H.; Schoffelmeer, A. N. M. Opioid receptor-mediated inhibition of ^{3}H-dopamine and ^{14}C-acetylcholine release from rat nucleus accumbens slices. Naunyn Schmiedebergs Arch. Pharmacol. 345:627–632; 1992.
34. Holtzman, S. G.; Steinfels, G. F. Monoamine systems in the discriminative effects of spiradoline, a kappa-opioid agonist. Pharmacol. Biochem. Behav. 47:575–578; 1994.
35. Jacocks, H. M., III; Cox, B. M. Serotonin-stimulated release of [^{3}H]dopamine via reversal of the dopamine transporter in rat striatum and nucleus accumbens: A comparison with release elicited by potassium, *N*-methyl-D-aspartic acid, glutamic acid and D-amphetamine. J. Pharmacol. Exp. Ther. 262:356–364; 1992.
36. Kamal, L. A.; Arbilla, S.; Galzin, A. M.; Langer, S. Z. Amphetamine inhibits the electrically evoked release of [^{3}H]dopamine from slices of the rabbit caudate. J. Pharmacol. Exp. Ther. 227:446–458; 1983.

37. Long, R.; Lerrin, A. W. Inhibition of 5-hydroxytryptamine uptake by platelets in vivo and in vitro. Biochem. J. 82:4P–5P; 1962.
38. Mach, R. H.; Smith, C. R.; Childers, S. R. Ibogaine possesses a selective affinity for sigma 2 receptors. Life Sci. 57:57–62; 1995.
39. Maisonneuve, I. M.; Glick, S. D. Interactions between ibogaine and cocaine in rats: In vivo microdialysis and motor behavior. Eur. J. Pharmacol. 212:263–266; 1992.
40. Maisonneuve, I. M.; Keller, R. W., Jr.; Glick, S. D. Blockade of morphine induced stimulation of mesolimbic and striatal dopamine release by ibogaine. Soc. Neurosci. Abstr. 382:15; 1990.
41. Maisonneuve, I. M.; Keller, R. W., Jr.; Glick, S. D. Interactions between ibogaine, a potential anti-addictive agent, and morphine: An in vivo microdialysis study. Eur. J. Pharmacol. 199:35–42; 1991.
42. Maisonneuve, I. M.; Keller, R. W., Jr.; Glick, S. D. Interactions of ibogaine and D-amphetamine: In vivo microdialysis and motor behavior in rats. Brain Res. 579:87–92; 1992.
43. Maisonneuve, I. M.; Rossman, K. L.; Keller, R. W., Jr.; Glick, S. D. Acute and prolonged effects of ibogaine on brain dopamine metabolism and morphine-induced locomotor activity in rats. Brain Res. 575:69–73; 1992.
44. Mash, D. C.; Staley, J. K.; Baumann, M. H.; Rothman, R. B.; Hearn, W. L. Identification of a primary metabolite of ibogaine that targets serotonin transporters and elevates serotonin. Life Sci. 57:45–50; 1995.
45. Mash, D. C.; Staley, J. K.; Pablo, J. P.; Holohean, A. M.; Hackman, J. C.; Davidoff, R. A. Properties of ibogaine and its principal metabolite (12-hydroxyibogamine) at the MK-801 binding site of the NMDA receptor complex. Neurosci. Lett. 192:53–56; 1995.
46. Miller, D. W.; Abercrombie, E. D. Effects of MK-801 on spontaneous and amphetamine-stimulated dopamine release in striatum measured with in vivo microdialysis in awake rats. Brain Res. Bull. 40:57–62; 1996.
47. Naranjo, C. Psychotherapeutic possibilities of new fantasy-enhancing drugs. Clin. Toxicol. 2:209–224; 1969.
48. Palumbo, P. A.; Winter, J. C. Stimulus effects of ibogaine in rats trained with yohimbine, DOM, or LSD. Pharmacol. Biochem. Behav. 43:1221–1226; 1992.
49. Pani, L.; Kuzmin, A.; Stefanini, E.; Gessa, G. L.; Rossetti, Z. L. Flunarizine potentiates cocaine-induced dopamine release and motor stimulation in rats. Eur. J. Pharmacol. 190:223–227; 1990.
50. Parsons, L. H.; Koob, G. F.; Weiss, F. Serotonin dysfunction in the nucleus accumbens of rats during withdrawal after unlimited access to intravenous cocaine. J. Pharmacol. Exp. Ther. 274:1182–1191; 1995.
51. Pearl, S. M.; Herrick-Davis, K.; Teitler, M.; Glick, S. D. Radioligand-binding study of noribogaine, a likely metabolite of ibogaine. Brain Res. 675:342–344; 1995.
52. Popik, P.; Layer, R. T.; Fossom, L. H.; Benveniste, M.; Geter-Douglass, B.; Witkin, J. M.; Skolnick, P. NMDA antagonist properties of the putative antiaddictive drug, ibogaine. J. Pharmacol. Exp. Ther. 275:753–760; 1995.
53. Popik, P.; Layer, R. T.; Skolnick, P. 100 years of ibogaine: Neurochemical and pharmacological actions of a putative anti-addictive drug. Pharmacol. Rev. 47:235–253; 1995.
54. Popik, P.; Layer, R. T.; Skolnick, P. The putative anti-addictive drug ibogaine is a competitive inhibitor of [^{3}H]MK-801 binding to the NMDA receptor complex. Psychopharmacology (Berlin) 114:672–674; 1994.
55. Reith, M. E. A.; Meisler, B. E.; Sershen, H.; Lajtha, A. Structural requirements for cocaine congeners to interact with dopamine and serotonin uptake sites in mouse brain and to induce stereotyped behavior. Biochem. Pharmacol. 35:1123–1129; 1986.
56. Ronken, E.; Van Muiswinkel, F. L.; Mulder, A. H.; Schoffelmeer, A. N. Opioid receptor-mediated inhibition of evoked catecholamine release from cultured neurons of rat ventral mesencephalon and locus coeruleus. Eur. J. Pharmacol. 230:349–355; 1993.
57. Salmoiraghi, G. C.; Page, I. H. Effects of lysergic acid diethylamide (LSD25), 2-bromolysergic diethylamide (BOL148), bufotenine, mescaline and ibogaine on the potentiation of hexobarbital hypnosis produced by serotonin and reserpine. J. Pharmacol. Exp. Ther. 120:20–27; 1957.
58. Satel, S. L.; Krystal, J. H.; Delgado, P. L.; Kosten, T. R.; Charney, D. S. Tryptophan depletion and attenuation of cue-induced craving for cocaine. Am. J. Psychiatry 152:778–783; 1995.
59. Schechter, M. D.; Meehan, S. M. Serotonergic mediation of cocaine seizures in mice. Pharmacol. Biochem. Behav. 51:313–316; 1995.
60. Sershen, H.; Harsing, L. G., Jr.; Hashim, A.; Lajtha, A. Ibogaine reduces amphetamine-induced locomotor stimulation in C57BL/6By mice, but stimulates locomotor activity in rats. Life Sci. 51:1003–1011; 1992.
61. Sershen, H.; Hashim, A.; Harsing, L.; Lajtha, A. Ibogaine antagonizes cocaine-induced locomotor stimulation in mice. Life Sci. 50:1079–1086; 1992.
62. Sershen, H.; Hashim, A.; Lajtha, A. Effect of ibogaine on serotonergic and dopaminergic interactions in striatum from mice and rats. Neurochem. Res. 19:1463–1466; 1994.
63. Sershen, H.; Hashim, A.; Lajtha, A. Ibogaine reduces preference for cocaine consumption in C57BL/6By mice. Pharmacol. Biochem. Behav. 47:13–19; 1994.
64. Sershen, H.; Hashim, A.; Lajtha, A. The effect of ibogaine on kappa-opioid- and 5-HT$_3$-induced changes in stimulation-evoked dopamine release in vitro from striatum of C57BL/6By mice. Brain Res. Bull. 36:587–591; 1995.
65. Sershen, H.; Hashim, A.; Lajtha, A. The effect of ibogaine on sigma- and NMDA-receptor-mediated release of [^{3}H]dopamine. Brain Res. Bull. 40:63–67; 1996.
66. Sershen, H.; Hashim, A.; Lajtha, A. Effect of ibogaine on cocaine-induced efflux of [^{3}H]dopamine and [^{3}H]serotonin from mouse striatum. Pharmacol. Biochem. Behav. 53:863–869; 1996.
67. Sharpe, L.; Jaffe, J. Ibogaine fails to reduce naloxone-precipitated withdrawal in the morphine dependent rat. NIDA Res. Monogr. 105:477; 1991.
68. Sharpe, L. G.; Jaffe, J. H. Ibogaine fails to reduce naloxone-precipitated withdrawal in the morphine-dependent rat. Neuroreport 1:17–19; 1990.
69. Sheppard, S. G. A preliminary investigation of ibogaine: Case reports and recommendations for further study. J. Subst. Abuse Treat. 11:379–385; 1994.
70. Sloviter, R. S.; Drust, E. G.; Damino, B. P.; Connor, J. D. A common mechanism for lysergic acid, indoealkylamine and phenethylamine hallucinogens: Serotonergic mediation of behavioral effects in rats. J. Pharmacol. Exp. Ther. 214:231–238; 1980.
71. Spanagel, R.; Almeida, O. F.; Bartl, C.; Shippenberg, T. S. Endogenous kappa-opioid systems in opiate withdrawal: Role in aversion and accompanying changes in mesolimbic dopamine release. Psychopharmacology (Berlin) 115:121–127; 1994.
72. Sweetnam, P. M.; Lancaster, J.; Snowman, A.; Collins, J. L.; Pershke, S.; Bauer, C.; Ferkany, J. Receptor binding profile suggests multiple mechanisms of action are responsible for ibogaine's putative anti-addictive activity. Psychopharmacology (Berlin) 118:369–376; 1995.
73. Touchette, N. Anti-addiction drug ibogaine on trial. Nature 1:288–289; 1995.
74. Walker, J. M.; Bowen, W. D.; Walker, F. O.; Matsumoto, R. R.; De Costa, B.; Rice, K. C. Sigma receptors: Biology and function. Pharmacol. Rev. 42:355–402; 1990.
75. Wise, R. A.; Bozarth, M. A. Brain mechanisms of drug reward and euphoria. Psychiatr. Med. 3:445–460; 1985.
76. Yadid, G.; Pacak, K.; Kopin, I. J.; Goldstein, D. S. Endogenous serotonin stimulates striatal dopamine release in conscious rats. J. Pharmacol. Exp. Ther. 270:1158–1165; 1994.
77. Zetler, G.; Singbartl, G.; Schlosser, L. Cerebral pharmacokinetics of tremor-producing harmala and iboga alkaloids. Pharmacology 7:237–248; 1972.