——Chapter 6——

CHARACTERIZATION OF MULTIPLE SITES OF ACTION OF IBOGAINE

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I. Introduction

Ibogaine, the principal alkaloid of *Tabernathe iboga*, has been studied for the past 100 years. Early in the past century (1900) it was isolated in crystalline form and was later marketed in Europe as the mild stimulant "Lamberene" (8 mg tablet). There was renewed interest in indole alkaloids with the discovery of reserpine, and the structural similarity of ibogaine to serotonin was the basis for Dhahir's 1970s thesis studies (*1*). However, the hallucinogenic properties of ibogaine had moved the FDA to ban its use in the United States. The renewed interest in ibogaine in the past 10 years is related to its putative antiaddictive properties. Several review articles have been published recently describing the historical and pharmacological perspective of ibogaine (*2-4*).

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Unfortunately, the reports of ibogaine's antiaddictive effects have been termed "anecdotal" for the past 10 to 15 years, and although there have been over 150 publications related to its purported effects and action, clinical trials have not been forthcoming. There have been concerns related to its hallucinogenic effects and possible cerebellar toxicity (*5-9*). The First International Conference on Ibogaine brought together the addict, the researcher, and grant-funding source, in the hope of reviewing the current findings and status of ibogaine in the treatment of substance abuse.

Our own studies focused on the behavioral and biochemical effects of ibogaine related to cocaine administration and pharmacological responses. Our results suggest that ibogaine can act at multiple sites and that attempts to focus on one site as the primary site of action can be misleading. Interaction at several sites is more than likely to be important for its antiaddictive properties. In addition to being an overview of these studies, this chapter attempts to demonstrate that to understand the action of ibogaine one must also consider the multifaceted pharmacology of the drugs of abuse themselves. Most recent conceptual views accept that drugs of abuse involve multiple neural mechanisms. Any given behavior is likely to be influenced by a number of neurotransmitter systems, and transmitter systems do not work independently, but rather interact with one another by stimulating, inhibiting, or modulating each other. Various brain structures and components, receptors, and neurotransmitters are involved. Their participation in the reward mechanism is not the same for all drugs of abuse. Genetic risk factors in drug abuse have also been identified. The action of ibogaine could be an important paradigm for further characterizing the action of drugs of abuse.

It is also important to recognize that there are multiple and complex behavioral responses associated with acute and chronic drug administration, and that there are different behaviors associated with drug initiation, maintenance, withdrawal, and extinction. Each of these responses is probably mediated by a different neural mechanism and varies with different drugs, and therefore it is not surprising that a number of varied receptor type agonists and antagonists appear to have some remediation of a particular drug response. A therapeutic approach that targets more than one system is possibly more efficacious, if addiction is a multifactorial disease. This chapter will describe findings that indicate support for the use of ibogaine, its metabolite, and/or ibogaine-related compounds in the treatment of addiction, based on their ability to target relevant multiple neurotransmitter sites appropriate for the drug of abuse examined. Because of the multiple components of reward systems, a "dirty" drug like ibogaine that affects multiple neurotransmitter systems should not be excluded from consideration. Indeed, it is a likely positive attribute.

II. Issues Related to Ibogaine in the Treatment of Drug Dependence

Although the results have been discrepant at times, in the majority of studies, ibogaine has been proposed to have antiaddictive properties, modifying behavioral effects of various drugs and their self-administration in rodent models. Based on radioligand binding and other *in vivo*/*in vitro* studies, and several behavioral assays, to characterize its effects, ibogaine has been reported to have affinities to at least the dopamine and serotonin transporters, and to the glutamatergic (NMDA), sigma, kappa- and mu-opioid, and nicotinic acetylcholine receptors (see the references listed later in Table I). This raises the question of whether the action of ibogaine at a single site relates to its antiaddictive properties, or whether multiple sites are implicated in its action. Alternatively, ibogaine's affinity to ligand binding sites may not necessarily indicate the functionally relevant site.

A. Dopamine as a Primary Site of Drug-Mediated Responses

Despite the pronounced involvement of dopamine in stimulant drug-mediated behavioral effects, it is important to recognize that many of the addictive drugs have affinity to multiple neurotransmitter sites; for example, cocaine is not a selective dopamine reuptake inhibitor. Cocaine also binds and inhibits the uptake of serotonin and norepinephrine, with equal potency. "Knockout" models of rodents missing dopamine reuptake transport still self-administer cocaine (*10,11*). We should also recognize that the neurobiology associated with addictive behaviors (cognition, reward, withdrawal, craving, sensitization) involve multiple neurotransmitter systems and their interactions. For example, serotonin transmission and the subsequent activation of serotonin receptor(s) (numbering 14 serotonin receptor subtypes) have a strong modulatory role, either stimulatory or inhibitory, in dopaminergic neurotransmission. Although nicotine and cocaine both increase dopamine, their actions are not similar, and we recently reported that selective neurotransmitter antagonists can block response to one and not the other (*12*).

It needs to be considered that although the prevailing theory is that elevated extracellular dopamine is the primary mediator of cocaine's reinforcing effects, this has been challenged by the finding that in mice lacking the dopamine transporter who still self-administer cocaine (*10,11*), cocaine has no effect on dopamine levels, further supporting the involvement of other neurotransmitter systems in drug behavior. Serotonin, acting through many receptors can modulate the activity of neural reward pathways and thus the effects of various drugs of abuse. Mice lacking one of the serotonin-receptor subtypes, the 5-HT_{1B} receptor,

display increased locomotor responses to cocaine, and they are more motivated to self-administer cocaine (*13*). In mice in which the beta-2 subunit of the nicotinic receptor is lacking, the normal increase in dopamine after nicotine injection is not seen, and nicotine fails to be self-administered, but cocaine is self-administered (*14*), showing differences between nicotine and cocaine reward mechanisms.

B. Ibogaine and Its Metabolite and Acute Versus Long-Term Effect

There are other issues to consider; for example, what is the importance of ibogaine's acute versus long-lasting effects on transmitter functioning? Why and how does ibogaine produce its long-lasting effect? Is it just slow release of a metabolite from lipid stores or long-term block/conformational change in some receptor? Understanding apparent gender and genetic differences in behavioral responses to and metabolism of drugs and ibogaine is also of importance. The issue of increased sensitivity of females to ibogaine has been raised. Female rodents have a higher brain level of ibogaine after administration (*15*), and female mice show increased locomotor responses to cocaine (*16*). Gender differences were also observed in kappa-opioid and NMDA-mediated dopamine release (*16*) and in human reactions to nicotine and cocaine. In humans, genetic differences in nicotine metabolism have been observed (*17*).

The data and discussions presented emphasize the importance of investigating the interaction of multiple neurotransmitter systems and multiple neuronal pathways in the mediation of drug-induced behaviors, with differences among the various drugs of abuse justifying the use of drugs that target multiple sites in protocols for drug-dependence treatment. The difficulties in devising appropriate therapy are compounded by genetic and sex variations in drug responsiveness.

C. Single or multiple Sites of Action of Ibogaine

Ibogaine has been suggested to inhibit the physiological and psychological effects of a number of drugs of abuse: heroin, morphine, amphetamine, cocaine, alcohol, and nicotine. This suggests a common site(s) of action of the drugs of abuse and that of ibogaine, or that ibogaine acts at some common pathway(s), secondary to the initial site of drug action, that affects some common behavior associated with addictive drugs. Alternatively, ibogaine may act at multiple sites one or more of which may "coincidentally" involve a common site of action of several addictive drugs. As studies move away from the simplistic approach based on the notion that a drug acts at only one specific site and that drug behaviors involve individual neural systems, to one that explores more complex multiple interactive neural systems, we will be able to better understand the

action of ibogaine and that of drugs of abuse.

III. Effect of Ibogaine on Drug-Induced Behavior

Initial studies of the effects of ibogaine on drug self-administration behavior in animals were received with some skepticism, as were the varied case reports on human experiences. Early NIDA-funded projects did not find any effects of ibogaine in rodent models, or the effects consisted of nonspecific inhibition of overall activity, for example, inhibition of food consumption at high doses.

Dworkin *et al*. (*18*) found suppression of responding to cocaine or heroin at 60 minutes after treatment with high doses of ibogaine, but responding to food was also suppressed, suggesting nonspecific effects. No long-term effects were seen, except at the 80 mg/kg dose with 60-minute pretreatment, where cocaine self-administration was suppressed at 48 hours. The literature is also mixed on ibogaine reduction of naloxone-precipitated morphine withdrawal; in some cases it blocked expression of withdrawal, or it had no effect (*19-22*). Locomotor activity is reportedly either inhibited or enhanced after stimulant drugs such as cocaine and amphetamine (*23-25*).

Clearly, the initial behavioral responses to ibogaine (high dose) were disruptive to overall behavior and could not be clearly interpreted, but some long-term effects have been suggestive of antiaddictive properties (*24-29*). It is not known why there was such variability in results. Species and sex differences, and treatment protocols have been suggested. Possibly the batches (pure or semisynthetic extract) of ibogaine were somewhat different. However, the potency of samples of ibogaine obtained from Sigma Chemical Company or NIDA appears to have been similar (*30*), which would suggest that there are no significant differences between batches of ibogaine.

IV. Binding Site Activity

There have been a number of studies reporting on the "affinity" of ibogaine and some analogs to known receptor systems utilizing a radiolabeled ligand that has specificity for a binding site of a particular receptor site. These affinities have been reviewed elsewhere (*2,4,31*). Additionally, *in vitro* assays to measure functional changes, for example, transmitter release or channel blockade, have been used to assess the site of action of ibogaine (*3,25*). The most recent addition

is the report that ibogaine has affinity to the nicotinic-acetylcholine receptor (*32,33*). These results are summarized in Table I.

Clearly, the diversity of potential interactions of ibogaine can be inferred from these binding site affinities. However, a question to be asked is how does the binding site affinity of ibogaine relate to its pharmacological action? Although ibogaine has affinity to the kappa-opioid receptor, it was concluded that it does not produce such an action by interacting directly with multiple opioid receptors. Ibogaine injected 10 minutes before the opioid drugs did not modify the antinociceptive actions of morphine, kappa-opioid agonist U-50,488H, or delta-opioid agonist DPDPE. However, the metabolite of ibogaine enhances the antinociception of morphine, but not of U-50,488H or DPDPE. Thus, it was concluded that that there is an interaction of ibogaine with the mu-opioid receptor following its metabolism to noribogaine (*34*).

Brain levels of ibogaine or its metabolites have been estimated to be in the micromolar range, sufficiently high to affect those systems showing affinities in the low micromolar range. However, ibogaine is metabolized very rapidly, raising the question of a long-lasting metabolite (that would also have to be at a sufficiently high level to affect some receptors) (*35*). Since the half-life of ibogaine is relatively short, how this would relate to its long-term effects is not

TABLE I.
REPORTED SITES OF ACTIVITY OF IBOGAINE FROM BINDING AND FUNCTIONAL ASSAYS: MULTIPLE NEUROTRANSMITTER SITES

Receptor Systems	Binding Aassays	Functional Assays
DA (receptors/transporter)	(*36,39,40*)	(*25,41-45*)
5-HT (receptors subtypes/transporter)	(*36,39,40,46*)	(*42,45-52*)
NMDA	(*39,40,53-58*)	(*16,53,58-61*)
Kappa-opioid	(*39,40*)	(*16,51,60,62*)
Mu-opioid	(*39,63*)	(*34,64,65*)
Sigma (1 and 2)	(*54,66,67*)	(*68,69*)
Na^+ Channel	(*40*)	
Muscarinic	(*40*)	
Nic-ACh		(*32,33,70,71*)
Adrenergic	(*40*)	(*72*)
Purinergic		(*73*)
Neuropeptides		(*74-76*)
Early genes		(*77*)

Receptor/neurotransmitter system sites showing binding affinities (in the range of levels reached by ibogaine) for ibogaine or metabolite(s) and suggested sites of action based on functional assays, for example, *in vitro*/*in vivo* transmitter release, isolated tissue contractions, discriminative stimulus, and anticonvulsant efficacies (*indicated references*).

clear. Possibly a long-lasting metabolite, for example, noribogaine (10-hydroxy-ibogamine), is present, or its slow release from lipid depots may play a role (*4,36,37*).

Are there long-lasting changes in any of these receptor systems or second messenger systems to account for its long-lasting effects? Such studies have not been conducted. Again, ibogaine itself has several pharmacological effects, for example, its stimulatory or hallucinogenic effects, in addition to, or part of, its antiaddictive properties, that each may involve single or multiple interactions at several neurotransmitter sites. Alternatively, ibogaine or its metabolite may act to alter the receptor, similarly to metaphit, a proposed phencyclidine receptor acylator (*38*). It is still unclear how one or two doses of ibogaine can produce such long-lasting effects.

Even the depot release of a metabolite(s) is difficult to accept as having profound and long-lasting effects (effects reported to last for months in humans). Most rodent studies have not been conducted beyond a duration of one week. One could also speculate that the long-lasting effect(s) of ibogaine "restores" neurotransmitter interactions back to some pre-drug, pre-craving, or pre-withdrawal level, resulting from its diversified effects on multiple neurotransmitter systems, somewhat similar to the diversified effects of electroconvulsive therapy (ECT) in the treatment of depression unresponsive to standard antidepressant therapy. Although unknown, the mechanism of action is thought to result from distinct combinations of neuropeptide and neurotransmitter changes and changes in gene expression in selected neuronal populations (*78-81*). For example, a single electroconvulsive shock (ECS) pretreatment suppresses the inhibition of dopamine release mediated by kappa-opioid receptors, suggesting that a single ECS treatment modifies the sensitivity of the kappa-opioid receptors located on the presynaptic dopamine terminals in the rat striatum (*82*). The simultaneous action of ibogaine at multiple sites induces a major resetting of transmitter interactions, and there is no need for it to be present long term. Effects of ibogaine on changes in second messenger systems and gene expression need to be examined as mechanisms of its long-lasting effects.

A. Relevant Site of Action

There have been a number of studies attempting to determine which neurotransmitter system is *most* affected by ibogaine or a metabolite that relates to its antiaddictive property. The dopamine transporter is a target for cocaine; we reported affinity of ibogaine for the transporter in the low micromolar range. This affinity, however, is ten times higher (weaker) than that of cocaine (*29*). The studies of Popik *et al*. (*57,58*) indicated that the NMDA receptor plays a major role, whereas Glick's (*25*) laboratory suggest a strong involvement of both the kappa-opioid and NMDA receptor (*60*). Helsley *et al*. (*69*) reported some

interaction with the sigma-2 and opiate receptors, while the NMDA antagonist activities do not play a major role in the ibogaine discriminative stimulus. Their later studies also suggest multiple interactions and a role of the 5-HT_{2c} receptor in ibogaine discriminative stimulus (*47*). The antagonist action of ibogaine at the nicotinic receptor may be involved in reducing nicotine preference and action at the serotonin transporter affecting alcohol consumption (*25*). Mah *et al*. (*71*) suggested that ibogaine at an initially high concentration acts at multiple sites and then, after metabolism to lower levels, has a selective action at the nicotinic acetylcholine receptor to inhibit catecholamine release. We also reported that ibogaine can block cocaine-mediated effects on serotonin transmission and block the kappa-opioid inhibitory effect on dopamine and serotonin release (*62*). Mash *et al*. (*36,83*) have suggested involvement of the serotonin transporter and NMDA receptor site in the action of ibogaine and its metabolite (noribogaine). Noribogaine has an affinity to the serotonin transporter 50-fold more potent than to the dopamine transporter (*36*). However, studies with the ibogaine congener, 18-methoxycoronaridine (18-MC), suggested that the serotonin system might not be essential for 18-MC antiaddictive action, although the serotonin system may be involved in the action of ibogaine and its metabolite (*52*). The NMDA receptor and D1 dopamine receptor are suggested to be involved in the release of neurotensin by ibogaine, and that neurotensin may contribute to the interaction of ibogaine and the dopamine system (*75*).

Clearly, complex interactions occur, each probably related to some different aspect of drug-induced behavior. Whether the dopamine system is the final common denominator—that is, can ibogaine act at some site(s), the final action of which is to reduce drug-induced changes in dopamine release without affecting overall dopaminergic responses?—is far from understood.

V. Functional Activity

Binding to a specific site suggests sites of action, but does not indicate functional activity. The functional effects of ibogaine were studied in our laboratory by utilizing an *in vitro* perfusion technique that enabled us to study mechanisms of regulation and modulation of dopamine transmitter release processes. The results are summarized in Table II.

At the nerve terminal level, ibogaine added *in vitro* released dopamine from the cytoplasmic pool (*43*). This release was not subject to presynaptic autoreceptor regulation (dopamine D2 antagonist sulpiride-stimulated dopamine release is not affected) (*50,43*). Cocaine as a reuptake blocker increases the level of dopamine; this response was not affected by ibogaine. However, the cocaine-induced

increase in serotonin level (reuptake blockade?) was blocked by ibogaine. The NMDA-mediated dopamine release was partially inhibited by ibogaine (*61*). The kappa-opioid agonist-induced inhibitions of dopamine and serotonin release were both blocked by ibogaine pretreatment (*51*). The sigma agonist-stimulated dopamine release was inhibited 50% by ibogaine (*61*). A strong serotonergic component of ibogaine's effects was also reported, involving both the reuptake transporter and 5-HT_{1b} receptor, increasing the exchange of dopamine for serotonin via the dopamine transporter and inhibition of serotonin 5-HT_{1b} agonist-mediated inhibition of dopamine release (*3,51*). The studies of Mah *et al.* (*71*) showed that ibogaine also blocks the nicotinic receptor-mediated stimulation (acetylcholine) of catecholamine (norepinephrine) release in bovine chromaffin cells. This is also supported by microdialysis studies showing attenuation of nicotine-induced dopamine release (*84,85*). Glick's (*25*) *in vivo* studies also show stimulation with amphetamine or cocaine and block with nicotine or morphine of dopamine release by ibogaine (Table II, bottom). Utilizing other methods, Broderick *et al.* (*26*) and French *et al.* (*90*) suggested either a decrease or no effect of ibogaine on cocaine-mediated dopamine increase. Our results show a number of interactions of ibogaine with various neurotransmitter systems that can regulate dopamine release. It is interesting that although many of the studies were conducted with the addition of ibogaine to an *in vitro* preparation, most showed the same effect when animals were treated *in vivo* with ibogaine and tissue responses tested later *in vitro*. Since the tissue preparation is extensively washed in the latter experiments, it is unlikely that ibogaine or its metabolite is present during the release portion of the study. This could be suggestive of some receptor conformational change that is long lasting, beyond the period of exposure to ibogaine or the "resetting" ability.

From studies over the past 10 years, it is clear that ibogaine can act at different neural sites (via neurotransmitters and ion channels), which can modulate terminal dopamine release (Table II and Figure 1). Figure 1 is a model of a dopamine terminal, which is offered to diagrammatically represent these multiple interactions on presynaptic terminal dopamine responses. Receptor-induced stimulation (+) or inhibition (–) of dopamine release is shown. There are also interactions/modulation between different receptors; for example, the kappa-opioid receptor is inhibitory on the NMDA and acetylcholine receptors, inhibitory and excitatory on the serotonin system, and can inhibit calcium channels. Ibogaine effects on these receptor responses are indicated. In most cases, ibogaine inhibits (–) these receptor-mediated excitatory or inhibitory responses. The resultant effects of ibogaine on drugs that increase extracellular dopamine level are indicated on the right. The responses are either further stimulated by ibogaine (cocaine and amphetamine) or inhibited by ibogaine (nicotine and morphine). The literature is mixed on the effect of ibogaine on cocaine-mediated increase in dopamine.

VI. Stimulant Drug Actions/Behaviors

Psychostimulants act predominantly to elevate brain dopamine, either by their ability to release dopamine, as is the case for amphetamine, or by blockade of the

TABLE II.
SUMMARY OF EFFECTS OF IBOGAINE ON [^{3}H]DOPAMINE AND [^{3}H]SEROTONIN RELEASE: *In Vitro* PERFUSION AND BRAIN MICRODIALYSIS STUDIES ON REGULATION OF TRANSMITTER RELEASE

	[^{3}H]Dopamine		[^{3}H]Serotonin	
	Control	Ibogaine	Control	Ibogaine
In Vitro Studies				
DA autoreceptor (electrical-evoked) (Sulpiride)	↑ Increase	No effect		
DA transporter (electrical- evoked) (Cocaine)	↑ Increase	No effect	↑ Increase	Block
NMDA receptor (basal) (NMDA)	↑ Increase	Partial inhibition		
Kappa-opioid receptor (electrical-evoked) (U-62066)	↓ Inhibit	Block	↓ Inhibit	Block
Sigma receptor (electrical-evoked) (pentazocine)	↑ Increase	Inhibit 50%		
Serotonin transporter (basal) (serotonin)	↑ Increase	↑↑ Increase		
Serotonin 5-HT$_{1b}$ receptor (basal) (CGS-12066A)	↑ Increase	Block		
Nicotinic receptor (acetylcholine)	↑ Increase (Norepinephrine release in chromaffin cells)	Block		
In Vivo Studies				
Cocaine	↑ Increase	↑↑ Increase ↓ Inhibit, no effect		
Amphetamine	↑ Increase	↑↑ Increase		
Morphine	↑ Increase	Block		
Nicotine	↑ Increase	Block		

Summary of *in vitro* studies on the effect of ibogaine on electrical stimulation or drug-induced release of dopamine and serotonin release in the presence of selective neurotransmitter system agonists/antagonists (*3,16,43,50,51,61,62*) and *in vivo* brain microdialysis studies examining drug-induced changes in dopamine level (*25-28,37,85-90*).

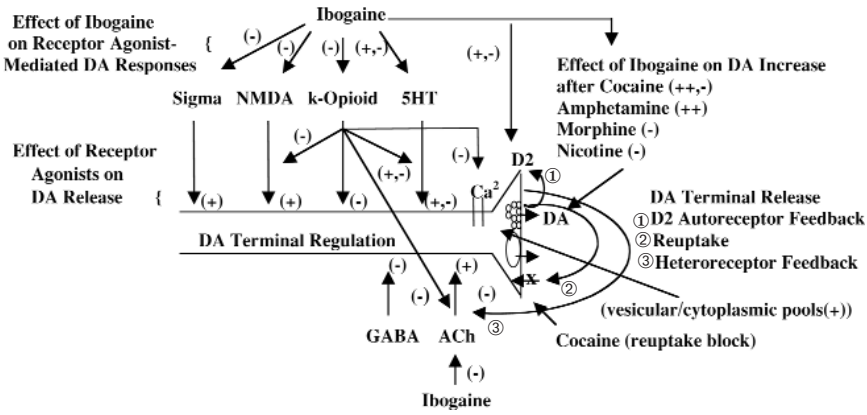

FIGURE 1. REPORTED MULTIPLE SITES OF ACTION OF IBOGAINE ON DOPAMINERGIC FUNCTION. The effect of ibogaine on stimulatory and inhibitory modulation of dopamine terminal release by sigma, NMDA, kappa-opioid, 5-HT, and ACh receptor agonists, and the effect of ibogaine on the increase in dopamine level after stimulant drug administration. The above figure represents a dopamine terminal showing inhibitory (-) and stimulatory (+) interactions of multiple neurotransmitter systems that modulate dopamine release (from Table II). Dopamine release is under excitatory (+) modulation by agonists to the sigma (*61*), NMDA (*61*), ACh (*32*), and 5-HT (*3,51*) receptors or inhibitory (-) modulation by kappa-opioid agonists (*51*), and also 5-HT (*51*). There are interactions/modulation between receptors; the kappa-opioid system interacts with the NMDA, 5-HT, and ACh receptors, and calcium channels (*51,16*). The effect of ibogaine on these receptor system interactions is shown (predominantly inhibition or blockade, except some stimulation of 5-HT function) (see Table II). Also indicated are the stimulatory and inhibitory effects of ibogaine on dopamine release (*43*) and extracellular level after stimulant drugs (right side) (*25*). Terminal DA release is subject to inhibitory ① auto- and ③ heteroreceptor feedback control and ② reuptake. Updated from Sershen *et al*. (*3*).

reuptake transporter, as in the case of cocaine. The elevation of dopamine resulting from release or reuptake inhibition is thought to be the basis of the rewarding effects of stimulant drugs. However, some direct reuptake blockers are not self-administered, for example, mazindol, suggesting that either other sites of action are also involved, or that there are different sites on the dopamine transporter which, depending on the conformational sites that are occupied, might determine the potential for self-administration. Stimulant drugs can also act at other neurotransmitter systems. As mentioned earlier, dopamine transporter knockout studies raise questions as to whether the dopamine transporter is solely responsible for self-administration. However, caution should be taken with interpretation of these studies because they do not take into consideration compensatory changes that occur during development in the knockout animal.

The final common pathway may be dopamine, but most likely other pathways are also involved in different drug-induced behaviors. The pathways indicated in

Figure 1 are all affected in some way by ibogaine and are briefly discussed in this chapter. Another important area for future studies will be changes in gene expression as involved in the long-term effects of drugs and ibogaine action.

In addition to targeting the dopamine transporter directly, a number of studies have attempted to target neurotransmitter sites that can modulate the dopaminergic response, in an effort to attenuate the stimulant drug-induced increase in dopamine. Glutamate antagonists (MK-801) can antagonize cocaine stimulant responses (*91*). The inhibitory neurotransmitter GABA, elevated by administering gamma-vinyl-GABA, can also attenuate effects of cocaine in increasing extracellular dopamine (*92,93*).

In addition to stimulating the dopamine reward system, stimulant drugs produce other behaviors. Sensitization-tolerance are behavioral responses generally observed with repeated stimulant administration, either an enhanced response to subsequent exposure as in the case of sensitization, or less of a response, requiring more drug to produce a similar behavioral response as in the case of tolerance. The dopamine receptor exists as several subtypes; some of them, the D1 and D4 dopamine receptors, have been implicated in sensitization, either its initiation or maintenance. Other neurotransmitter systems can alter this process, for example, the serotonin, NMDA, and kappa-opioid receptors (*94*). With craving/reinforcing effects of drugs, the dopamine, serotonin, glutamate, opioid, GABA, and cAMP systems have all been implicated. Drug withdrawal symptoms have been associated with a transmitter depletion response after removal of a drug. Implicated in this behavior are the dopamine and serotonin systems, excitatory amino acids (NMDA), and interactions with nitric oxide (NO), and cGMP.

Behavioral studies involving diverse drugs of abuse suggest that ibogaine may affect multiple neurotransmitter systems which are involved in the modulation of dopaminergic responses to stimulants:

Opioid Withdrawal: Noribogaine has been shown to have a lower affinity than, but an increased intrinsic activity over, buprenorphine as a mu-agonist. In addition, it was reported that noribogaine has weak intrinsic activity (partial agonist) or antagonist actions at kappa-opioid receptors; together suggesting that the ability of ibogaine to inhibit opiate withdrawal symptoms may be explained by a mixed mu- and kappa-opioid receptor profile and an affinity for the serotonin transporter of the active metabolite noribogaine (*65*). Pablo and Mash (*65*) also suggested that the capacity for noribogaine to reset multiple opioid receptors and the serotonin transporter mechanism may explain the reportedly easy transition after only a single dose of ibogaine following the abrupt discontinuation of opiates.

Drug Discrimination: Drug discrimination studies with ibogaine did not show

substitution with mu- or kappa-opioid receptor agonists, although sigma-2 receptors may be involved (*69*). At low doses of ibogaine, NMDA receptor antagonists did not show any substitution. For the metabolite noribogaine, NMDA antagonists did not show substitution in discriminative effects (*95*).

Cocaine and Morphine Self-Administration: Ibogaine effects on both the kappa-opioid and NMDA receptor have been shown to be involved in its effects on cocaine self-administration (*25*).

Alcohol Consumption: Rezvani *et al.* (*96,97*) reported that ibogaine reduces alcohol consumption, although mechanisms involved were not determined. It was found that the novel, nontoxic ibogaine analog 18-methoxycoronaridine also reduces alcohol consumption (*96*). Although, Glick and Maisonneuve suggested that the serotonergic effects of ibogaine might mediate some of the shorter-lasting effects of ibogaine, for example, effects on alcohol intake (*25*), they also report that 18-methoxycoronaridine had no effect on the serotonin transporter (*52*). The opioid antagonist naltrexone and serotonin uptake inhibitor fluoxetine have been used for treatment of alcohol abuse. Rezvani (*98*) has shown that combination therapy (naltrexone, fluoxetine, and a TRH analogue (TA091)) reduces ethanol intake in rats. Opioid antagonists in combination with isradipine (Ca^{2+} channel blocker) showed sustained effects in reducing cocaine and alcohol intake (*99*). The kappa-opioid receptor appears to mediate inhibition of dopamine release via a decrease in calcium conductance (*100*). The action of ibogaine at the kappa-opioid receptor may be mediated by this effect. Acamprosate for the treatment of alcohol abuse is thought to act at the NMDA receptor and to reduce calcium fluxes through voltage-dependent channels (*101*). It is also thought to inhibit GABAB receptors (*102*). Interestingly, ibogaine has been reported to act at all these sites.

These results suggest that stimulant drugs have multiple actions and behaviorial effects, and that targeting sites that can modulate dopamine responses is one approach to treatment development. Such sites may be involved directly in modulating the dopaminergic response or act via other neurotransmitters.

VII. Current Non-Ibogaine Drug Treatment Protocols

Further support for a multiple-site-target approach to drug treatment development can be inferred from recent treatment protocols tested against different behaviors associated with drug use. With cocaine abuse, a variety of approaches have been proposed, depending on the behavior being studied. The

dopaminergic, serotonergic, GABAergic, opioid, and excitatory amino acid receptors have received the most attention. For example, treatment for cocaine addiction has focused on the dopamine transporter, developing drugs that can bind to the receptor without elevating synaptic dopamine. Dopamine knockout-mouse studies have suggested the importance of the serotonin system (*10,13*). Cocaine is also a serotonin and norepinephrine uptake blocker.

The development of effective pharmacotherapy of substance abuse and dependence considers specific drug-related behaviors, for example, medication for the withdrawal syndromes. Treatment must also consider craving, especially early during the withdrawal period. Effective anticraving medication has been limited. The opioid antagonists have been tested, since the opioid receptors are associated with the reward pathways. Methadone and other long-lasting opiates, such as buprenorphine or levo-alpha-acetylmethadol (LAAM), induce tolerance to the effects of opiates (*103*). Naltrexone is used to block the euphoria that occurs when opiates are administered (*104*). The euphoria component for drug behavior has also been targeted by the use of calcium channel blockers; verapamil reduces the subjective effects of morphine in humans (*105*). Attempts at maintenance therapy have used such drugs as amantadine, bromocriptine, and methylphenidate that act to release dopamine (*106*). The use of dopamine antagonists is based on the premise that stimulant drug euphoria appears to be mediated by a rapid increase in dopamine; blockade of specific dopamine receptors may change stimulant effects. Studies have suggested that dopamine receptor subtypes play a role in the reinforcing effect of cocaine. In general, the D1 and D2 antagonists can maintain cocaine responding, whereas D1 and not D2 agonists have been reported to block cocaine self-administration. However, chronic dopamine antagonist treatment may lead to receptor supersensitivity and enhanced responses to stimulants (*107*).

Dopamine hypofunction and depletion occurring during stimulant withdrawal have been the basis for dopamine agonist (or drugs that release, block reuptake, or inhibit dopamine metabolism) treatment. A recent review of preclinical trials by McCance (*108*) suggested that agonist-type treatments have low efficacy against stimulant dependence. Cocaine-type antagonists such as mazindol to block dopamine reuptake; carbamazepine, an anticonvulsant, to block kindling; and naltrexone, an opioid antagonist to block some of the opiate pathways involved in reinforcing effects of cocaine had no effect. However, fluoxetine to block serotonin reuptake had some effectiveness. A D1 antagonist (SCH22390) and an NMDA antagonist (dextrophan) have some effect in animal models.

Studies of antagonism of the different serotonin receptor subtypes have yielded mixed results. Many of the serotonin drugs are also thought to treat depression, anxiety, and obsessive-compulsive behaviors that may underlie cocaine abuse. A number of studies have examined the effects of altering serotonin levels, for example, with L-tryptophan (serotonin precursor) or specific serotonin reuptake

inhibitors (SSRI, a class of antidepressants) such as sertraline. Serotonin reuptake inhibitors have been reported to decrease cocaine self-administration, but may also decrease food-maintained behavior. Continuous cocaine administration induces tolerance to its behavioral effects (*109,110*) and a functional down-regulation of accumbens 5-HT_3 receptors. Agonists at the 5-HT_{1b} receptor partly generalize to cocaine in drug-discrimination experiments (*111*) and enhance the reinforcing effects of cocaine (*112*). Mice lacking the 5-HT_{1b} receptor consume more ethanol than controls (*13*). Undoubtedly, one or more of the 5-HT receptor subtypes could appear as a key component in drug dependence.

Since there has been association of anxiety with cocaine use, GABAergic agents have been tested. Anticonvulsants have also shown some clinical or anecdotal effectiveness. The blockade of the NMDA glutamate receptors in the nucleus accumbens appears to reduce the reinforcing effects of cocaine. As reviewed recently (*113*), to date none of the medications have singly been accepted as efficacious for treating cocaine abuse. This may be because there are several different aspects to the problem of cocaine abuse, each potentially treatable by different medications (*113*).

Since it has been shown that the neural systems involved are complex in drug behaviors, it is surprising that strategies for drug treatments have not, until recently, targeted multiple sites.

VIII. Conclusions

Ibogaine has a history of at least 100 years from its discovery and isolation in the early 1900s. Its use in Africa for ritual ceremonies may well extend before this. Its use as a mild stimulant was not much noticed, but its reported psychedelic properties in the 1960s gave it renewed interest. Although banned by the FDA, ibogaine has had a curious attraction over the past 20 to 30 years, suggesting it may have antiaddictive properties. While concerns have been raised regarding potential neurotoxicity and hallucinogenic properties, such concerns must be weighed against the devastating morbidity associated with drug dependence. Case reports in humans and animal data indicating significant potential would appear to argue in favor of the further development of ibogaine, especially in view of the high cost of the disorder that it is intended to treat. The possibility of a novel treatment of drug addiction deserves attention, and studies have to go beyond the anecdotal.

The primary aims of our studies were to examine ibogaine in rodent models to see whether there is any validity to its use, and how it works, and also to enhance our understanding of mechanisms that are involved in drug dependence. That

ibogaine works can be further suggested from the reported summary of results of a subset of patients treated in nonmedical settings for acute opioid withdrawal with ibogaine between 1962 and 1993; these case studies appeared to provide some evidence for the efficacy of ibogaine in acute opioid withdrawal (*114*). Maybe further studies with ibogaine would give suggestions for the development of other drug-treatment protocols.

Our current understanding of dopaminergic function and response suggests that there are many complex modulatory influences on dopamine release, and that many neural systems are involved in the different behaviors associated with drug dependence. These modulatory regulations can be both stimulatory and inhibitory. Certain drugs, for example, stimulants like amphetamine and cocaine, unlike opioids like morphine, may act at some of the same sites, but also at different sites. Clearly, drug abuse is a complex behavioral and neurobiological process that lends itself to complex treatment protocols. Maybe what we learn from the action of ibogaine will lead us in the direction of new treatment approaches.

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