——Chapter 3——

IBOGAINE AS A GLUTAMATE ANTAGONIST: RELEVANCE TO ITS PUTATIVE ANTIADDICTIVE PROPERTIES

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I. Overview

Beginning in the mid 1980s, Howard Lotsoff (*1-4*) filed a series of patents claiming that ibogaine, an alkaloid derived from *Tabernanthe iboga*, possessed antiaddictive qualities. At the time, the concept that a single molecule could treat dependence across classes of abused drugs (e.g., cocaine, nicotine, ethanol, opiates) was viewed as radical, if not revolutionary. In the absence of rigorously controlled, double-blind clinical trials, these claims have engendered skepticism and controversy. During the past 5 to 7 years, the biomedical research community has made a concerted effort to characterize the neurochemical actions of ibogaine with the implicit understanding that such studies may provide insight into the putative antiaddictive actions of this compound. In parallel with these neurochemical studies, preclinical behavioral studies have established that ibogaine can interfere with tolerance and dependence phenomena (reviewed in reference *5*).

If the dictum, "Clinical data trumps preclinical data" has merit, then the pragmatist may legitimately question the value of such preclinical studies in the face of anecdotal reports that ibogaine does possess antiaddictive properties.

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Certainly, there are many examples where safe and effective drugs have been used for decades (e.g., benzodiazepines, NSAIDs) before a molecular mechanism of action was evinced. However, in view of the safety concerns raised by both preclinical and clinical reports (e.g., reference *6*), and in the absence of controlled clinical studies, basic research on ibogaine is clearly mandated.

Pharmacologically relevant concentrations (doses) of ibogaine can affect several neurotransmitter systems (reviewed in reference *5*). These multiple actions pose the challenge of separating "wheat from chaff"—that is, discriminating those effects relevant to the putative antiaddictive properties of ibogaine from epiphenomena. The majority of these "mechanism of action" investigations, including work from our studies at the NIH, have focused on "traditional" targets, such as ion channels, transporters, and the seven transmembrane superfamily of transmitter receptors. Such studies have largely neglected a host of potential intracellular targets that may either act independently, or in concert with, extracellular targets to produce the antiaddictive properties described anecdotally in the clinic and documented in preclinical studies. Absent these studies, there remain sufficient *in vitro* and *in vivo* data to both formulate testable hypotheses and create a diversity of opinion (clearly evident at the First International Congress on Ibogaine) about the neurochemical processes responsible for these antiaddictive actions. This contribution will overview data demonstrating that pharmacologically relevant concentrations of ibogaine produce a blockade of *N*-methyl-D-aspartate (NMDA) receptors, and relate the relevance of these findings to its antiaddictive properties.

II. NMDA Antagonist Properties of Ibogaine

There is a striking similarity between the claims that have been made for ibogaine and an emerging body of preclinical evidence that NMDA antagonists interfere with tolerance and dependence phenomena to a wide variety of abused drugs. This prompted us to determine if the basis for the apparent mimicry between ibogaine and NMDA antagonists could be due to an identical locus of action. In our initial studies, we examined the ability of ibogaine to inhibit radioligand binding to native NMDA receptors from rat brain (*7*). Ibogaine inhibited the binding of [^{3}H]dizocilpine (MK-801) in a concentration-dependent manner with a K_i of ~1 μM. This inhibition by ibogaine reflected an increase in the K_d of [^{3}H]MK-801 without striking changes in B_{max}, characteristic of two ligands acting at the same site (i.e., a competitive interaction). Subsequent neurochemical studies from our laboratory and others confirmed that the apparent affinity of ibogaine is in the low μM range using other radioligands acting at the

same locus as MK-801 (e.g., [^{3}H]TCP) and NMDA receptors derived from a variety of sources, including human brain (*8-11*). In contrast, ibogaine does not remarkably affect radioligand binding to other members of the ionotropic glutamate receptor family (i.e., kainate and AMPA receptors), nor does it inhibit radioligand binding to the glutamate recognition site on NMDA receptors (*7*). While the affinity of ibogaine for NMDA receptors is low relative to MK-801 (and other NMDA antagonists belonging to this same class such as TCP and PCP), brain concentrations of the parent alkaloid are in the range of 1 to 10 μM after administering pharmacologically relevant doses (i.e., doses capable of interfering with tolerance and/or dependence phenomena) to rodents (*12*).

Such neurochemical studies are valuable because they provide a mechanistic link between ibogaine and a class of uncompetitive NMDA antagonists (including MK-801, PCP, memantine, and ketamine) that has been extensively characterized both *in vitro* and *in vivo*. Uncompetitive NMDA antagonists can be envisioned as channel "plugs" (analogous to placing a cork in one end of a tube) and exhibit a number of characteristic features including use (i.e., the channel lumen must be open in order for such compounds to enter and bind) and voltage (the "block" is relatively more efficient at hyperpolarized membrane potentials) dependence. Because of the potential therapeutic applications of uncompetitive NMDA antagonists, this class of compound has been extensively studied at all levels of cellular organization (ranging from effects on single channel activity to behavior). This "prior art" allows us to make predictions about the pharmacological actions of ibogaine that may be NMDA receptor-mediated, and provides strategies to isolate and assess the contribution of this effect relative to its putative antiaddictive actions.

While radioligand binding studies indicate that ibogaine acts as an uncompetitive NMDA antagonist (i.e., acting at the same locus and by the same mechanism as, for example, dizocilpine and phencyclidine), several independent lines of investigation have provided compelling evidence that supports this hypothesis. Thus, in electrophysiological studies, the inhibition of NMDA responses by ibogaine exhibits the voltage and use dependence characteristic of this class of compounds (*8,10,11*). Further, there is very good agreement between the estimated potencies of ibogaine obtained in neurochemical and electrophysiological studies. For example, analysis of the NMDA receptor block using the Woodhull equation permits a calculation of the K_d of ibogaine as a function of membrane potential. In cultured hippocampal neurons, the K_d of ibogaine ranged from ~8.6 μM at 0 mV to ~2.3 μM at –60 mV (8).

The neuroprotective effects of NMDA antagonists are perhaps the best described pharmacological actions produced by this class of compounds (*13*). These neuroprotective actions can readily be demonstrated in both simple systems and whole animals using a variety of insults, ranging from glutamate-induced cell death in primary neuron culture to animal models of focal ischemia.

If the neurochemical and electrophysiological studies with ibogaine are pharmacologically meaningful, then like other NMDA antagonists, ibogaine should protect against NMDA receptor-mediated neurotoxicity. To test this hypothesis, we examined (*8*) the ability of ibogaine to prevent glutamate-induced death of cerebellar granule neurons in primary culture. Many studies have shown that activation of NMDA receptors is a necessary condition for glutamate-induced death of these neurons, and as such, NMDA antagonists (including uncompetitive antagonists such as MK-801) are effective in blocking this "excitotoxic" process. In our hands, ibogaine decreased glutamate-induced neurotoxicity in a concentration dependent manner with an IC_{50} of ~4.9 μM; this value closely approximates the potency of ibogaine as an NMDA antagonist estimated by neurochemical and electrophysiological techniques. By comparison, MK-801 was ~500-fold more potent, with an IC_{50} value of ~9.6 nM . At face value, a neuroprotective action of ibogaine appears at variance with reports that this alkaloid produces degeneration of cerebellar Purkinje neurons (*14,15*). However, it is unlikely that this latter action is a consequence of NMDA receptor blockade since the prototypic uncompetitive NMDA antagonist, MK-801, does not produce a similar effect (*16*). Based on its side effect profile, it is unlikely that the neuroprotective properties of ibogaine will be reduced to clinical practice. Nonetheless, Olney (*17*) has patented the use of ibogaine as a neuroprotective agent!

III. Are the NMDA Antagonist Actions of Ibogaine Relevant to Its Putative Antiaddictive Properties?

These *in vitro* data provide compelling evidence that ibogaine can act as an NMDA antagonist. Further, ibogaine concentrations that are required to produce this action are well within the range found in the rodent central nervous system (*12*) at doses that affect both tolerance and dependence phenomena. This same dose range of ibogaine can substitute as a discriminate stimulus in mice trained to recognize the prototypic uncompetitive NMDA antagonist, MK-801 (*8*). These findings, coupled with an emerging preclinical literature (*18-20*) demonstrating that NMDA antagonists interfere with tolerance and dependence phenomena to a variety of abused drugs (*7,8*), indicate that it is this NMDA antagonist action that is responsible, either wholly or in part, for the antiaddictive properties of ibogaine. If ibogaine produces its antiaddictive actions via a voltage-dependent block of NMDA receptors, then reversal of this block should reduce or abolish these actions. One strategy that has been employed to relieve this block relies on increasing brain concentrations of glycine (or a glycine-mimetic such as D-serine)

at strychnine-insensitive glycine receptors. Glycine is a coagonist at NMDA receptors. Due to the presence of specific transporters that appear colocalized with NMDA receptors (*21*), it is unlikely that these strychnine-insensitive glycine sites are saturated under physiological conditions (*22*). Thus, raising glycine concentrations increases the probability of NMDA receptor-coupled channel opening, which in turn increases the likelihood that ibogaine (and other channel blockers) will dissociate from the binding site. This "unblocking" strategy has been shown to reduce some of the pharmacological effects of dizocilpine and phenyclidine (*23-25*).

It was demonstrated that like other NMDA antagonists, memantine (a low-affinity, uncompetitive NMDA antagonist) blocks the expression of morphine withdrawal in mice (*18*). This is evidenced by a dose-dependent reduction in naloxone-precipitated jumping in morphine-dependent animals. Parenteral administration of glycine (at doses that significantly elevate brain glycine levels [*26*]) blocked this action of memantine, but did not remarkably affect naloxone-precipitated jumping when administered alone (*18*). Similarly, this regimen of glycine abolished the ability of ibogaine to reduce naloxone-precipitated jumping (*8*). Clearly, it is not possible to extrapolate the importance of this single measure of morphine withdrawal in mice to the complex phenomena associated with opiate dependence in humans. Nonetheless, these data indicate that the NMDA antagonist properties of ibogaine are responsible for its "antiaddictive actions" in this measure.

This "unblocking" paradigm may be useful as a means of examining the relative contribution of NMDA receptor blockade to a particular "antiaddictive" property of ibogaine (or an ibogaine derivative). This issue transcends academic minutiae because there are a number of NMDA antagonists that are in clinical use with an established safety and side effect profile. For example, memantine has been used in Europe to treat neurodegenerative disorders such as senile dementia (*27*). Thus, if the putative antiaddictive properties of ibogaine are due to its NMDA antagonist action, then there are established therapeutic alternatives. In support of this hypothesis, the ability of a low affinity NMDA antagonist (dextromethorphan) to attenuate opiate withdrawal and craving has already been examined in a small, open clinical trial. In this study (*28*), six patients addicted to heroin were detoxified using dextromethorphan. Two patients requested methadone on the first day of the study, but the four patients completing the study: "had a rapid and complete attenuation of signs, symptoms, and craving by the fourth day of treatment." Particular improvement in the alleviation of craving was noted during the first 2 days (*28*). This report, while preliminary, is consistent with preclinical data demonstrating that NMDA antagonists block the expression of opiate withdrawal (*18,29*). However, in view of the number of targets that can be affected by pharmacologically relevant concentrations of ibogaine (*5,9,30*), it may be argued that NMDA antagonists may only be effective in treating a subset

of abused drugs (or a subset of signs and symptoms), despite the striking similarities between this class of compounds and ibogaine in preclinical studies.

Several ibogaine derivatives (*31*) were synthesized in an attempt to relate the potency of these compounds to the expression of morphine withdrawal in mice (i.e., blockade of naloxone-precipitated jumping) and to NMDA receptor affinity. All of these derivatives (including a number of coronaridine derivatives) were less potent than ibogaine as NMDA antagonists *in vitro*. Notably, the K_i values of noribogaine, (±)-ibogamine, and (±)-coronaridine were ~5-fold lower than ibogaine (i.e., 5 to 6 μM). At the highest "nontoxic" doses tested (80 mg/kg), none of these compounds significantly reduced naloxone-precipitated jumping in morphine-dependent mice. Limiting side effects, such as profound ataxia and convulsions, prevented testing higher doses (i.e., 120 mg/kg) of several of these alkaloids (e.g., noribogaine). At face value, it may be argued that this study supports the hypothesis that the NMDA antagonist properties of ibogaine are essential to its "antiaddictive" actions. However, in the absence of pharmacokinetic data (e.g., brain levels of these alkaloids), these data may be considered inconclusive. The affinity of noribogaine (also known as desmethylibogaine and 10-hydroxy-ibogamine) at NMDA receptors (K_I of 5 to 6 μM) is noteworthy since this compound appears to be the primary metabolite of ibogaine (*30*). If this metabolite enters the central nervous system as readily as its parent, then the NMDA antagonist action of noribogaine could also contribute to its pharmacological properties.

Glick and coworkers (*32*) have reported that addition of a methoxy moiety to coronaridine results in a compound that lacks the tremorigenic properties of ibogaine, but retains many of its putative antiaddictive properties in animals. Thus, like ibogaine, 18-methoxycoronaridine has been reported to reduce morphine and cocaine self-administration in rats (*32*), attenuate alcohol consumption in alcohol-preferring rats (*33*), and reduce nicotine intake (*34*). It has been reported that neither racemic 18-methoxycoronaridine nor its optically active isomers (i.e., (+)- and (-)-18-methoxycoronaridine) possess NMDA antagonist properties, but retain μM affinities for opioid (κ, μ, and δ) receptors, sodium channels, 5HT-3 receptors, and $sigma_2$ sites (*35*). Because it seems unlikely that ibogaine and 18-methoxycoronardine produce their antiaddictive actions through different mechanisms, it may be concluded that one or more of the neurochemical properties common to these closely related compounds are necessary for these effects. However, following intravenous administration, 18-methoxycoronaridine has a very short half-life (~5 to 10 minutes) (*35*). This raises the possibility that it is not the parent alkaloid, but rather a metabolite of 18-methoxycoronaridine that is responsible for the observed antiaddictive actions. Short of identifying an active metabolite(s), there are several experiments that could be done to determine if administration of the parent compound produces an NMDA antagonist. One simple experiment would be to determine if

the ability of 18-methoxycoronaridine to interfere with morphine withdrawal can be attenuated by glycine administration. This experimental strategy was successfully employed to link the antiaddictive properties of ibogaine and memantine to an NMDA antagonist action. Second, if rodents trained to recognize MK-801 as a discriminative stimulus (*8*) also recognize 18-methoxycoronaridine at doses that interfere with tolerance/dependence phenomena, then it is likely that a metabolite with NMDA antagonist properties is formed in vivo. Such experiments are necessary to critically assess the contribution of NMDA receptor blockade in the putative antiaddictive actions of 18-methoxycoronaridine. This compound appears to lack the tremorigenic actions of ibogaine (*32*). However, in the absence of basic toxicological studies, the claim that 18-methoxycoronaridine is nontoxic (*32*) must be viewed as premature.

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