——Chapter 2——

MECHANISMS OF ACTION OF IBOGAINE: RELEVANCE TO PUTATIVE THERAPEUTIC EFFECTS AND DEVELOPMENT OF A SAFER IBOGA ALKALOID CONGENER

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I. Introduction

Ibogaine, an alkaloid extracted from *Tabernanthe iboga* (Apocynaceae), is being used in uncontrolled clinical trials as a long-acting treatment for opioid and stimulant abuse, alcoholism, and smoking. In this laboratory, animal models have been used to study ibogaine's interactions with drugs of abuse, to investigate its mechanisms of action, and to help develop an ibogaine derivative that will have an improved safety profile. An outline illustrating the kinds of studies we have conducted is shown in Table I. In this review, we will describe, in parallel, the results of these studies with ibogaine and with 18-methoxycoronaridine (18-MC), a novel *iboga* alkaloid congener.

The structures of ibogaine and 18-MC are shown in Figure 1. It is of interest

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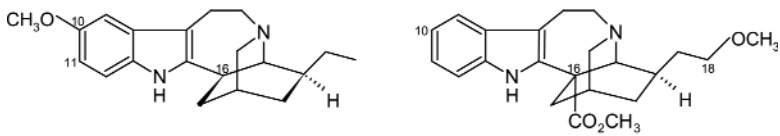
TABLE I. PRECLINICAL EVALUATION OF IBOGAINE AND 18-MC

Strategies	Methods
Efficacy	Animals
• Addiction (drug-self-administration)	• Rats (Sprague-Dawley and Long-Evans)
• Dependence (opioid withdrawal)	• Ns = 4-9 (usually 6)
Safety	Route of administration
• Side effects	• i.p. and p.o. routes
• Pharmacokinetics	
Mechanisms of action	Techniques
• Receptor interactions	• Intravenous and oral drug self-administration, morphine withdrawal signs
• Effects on neurotransmitters	• Cerebellar morphology, heart rate and blood pressure, GCMS
	• Radioligand binding, in vivo microdialysis, locomotor activity

that the structure-activity relationships elucidated in the 1970s suggested that 18-MC might have fewer side effects than ibogaine. Singbartl *et al*. (*1*) found that, when injected intracerebrally, several *iboga* alkaloids caused tremors in mice. Tremorigenic activity was increased by the addition of a methoxy group at position 10 or 11 and was reduced or abolished by the addition of a carbomethoxy group at position 16 (note that an alternative numbering scheme refers to these positions as 12, 13, and 18, respectively). 18-MC has both of these non-tremorigenic features (i.e., lacking ibogaine's 10-methoxy group and having a 16-carbomethoxy group) and thus, in at least one respect, should be safer than ibogaine.

Ibogaine has an active metabolite, noribogaine (*2*,*3*), and both ibogaine and noribogaine appear to have multiple mechanisms of action in the nervous system. 18-MC also appears to have multiple targets. Table II shows the reported affinities of ibogaine and noribogaine for several binding sites, as well as the affinities of 18-MC for these same sites. The evidence to date suggests that actions at several of these sites may together mediate the putative antiaddictive effects of these



Ibogaine (±)-18-Methoxycoronaridine

FIGURE 1. Structures of ibogaine and 18-methoxycoronaridine.

TABLE II. INTERACTIONS OF 18-MC, IBOGAINE, AND NORIBOGAINE WITH THE INDICATED TARGET SITES (VALUES ARE μM K_i)

Site	Ligand	Tissue	18-MC	Ibogaine	Noribogaine
κ opioid	[^{3}H]-U69593	Calf cortex	5.1 ± 0.50	2.2 ± 0.10	0.61 ± 0.015
μ opioid	[^{3}H]-DAGO	Calf cortex	1.1 ± 0.30	2.0 ± 0.15	0.68 ± 0.016
δ opioid	[^{3}H]-DPDPE	Calf caudate	3.5 ± 0.05	>10	5.2 ± 0.64
Nociceptin	[^{3}H]-nociceptin	Bovine cortex	>100	>100	>100
NMDA	[^{3}H]-MK801	Bovine cortex	>100	3.1 ± 0.30	15 ± 2.0
D1	[^{3}H]-SCH23390	Calf caudate	>100	>10	>10
D2	[^{3}H]-N-methyl-spiperone	Calf caudate	16 ± 0.60	>10	>10
D3	[^{3}H]-7-OH-DPAT	Calf caudate	25 ± 2.5	70 ± 1.7	>100
M1	[^{3}H]-pirenzepine	Calf cortex	32 ± 3	16 ± 1.0	15 ± 1.0
M2	[^{3}H]-QNB	Calf cortex	>100	31± 3.4	36 ± 3.7
5-HT1A	[^{3}H]-8-OH-DPAT	Rat hippocampus	46 ± 4.9	>100	>100
5-HT1B	[^{3}H]-serotonin	Calf caudate	>100	>100	>100
5-HT1C	[^{3}H]-mesulergine	Calf cortex	>100	>100	>100
5-HT1D	[^{3}H]-serotonin	Calf caudate	>10	>100	>100
5-HT2A	[^{3}H]-ketanserin	Gf-6 cells	40 ± 3.4	16	>100
5-HT2C	[^{3}H]-mesulergine	J-1 cells	>100	>10	>10
5-HT3	[^{3}H]-GR-65,630	NG-108 cells	3.8 ± 0.067	2.6 ± 0.23	>100
Sodium channel	[^{3}H]-BTX-B	Bovine cortex	6.4 ± 0.68	3.6 ± 0.35	17 ± 0.6
Sigma 1	[^{3}H]-(+)-pentazocine	Calf caudate	>100	2.5 ± 0.6	11 ± 1.7
Sigma 2	[^{3}H]-DTG	Calf hippocampus	13 ± 1.2	0.4 ± 0.036	19 ± 1.3
GABA B	[^{3}H]-GABA	Calf cortex	>100	>100	>100
NE uptake	[^{3}H]-nisoxetine	Bovine cortex	>10	>100	39 ± 1.5
5-HT uptake	[^{3}H]-paroxetine	Bovine brain stem	>10	4.1 ± 0.83	0.57 ± 0.083

drugs. While most pharmaceutical development efforts focus on single mechanisms of action, a drug capable of treating diverse addictions may, of necessity, have to have multiple actions. Hence, as reviewed below, the peculiarly broad efficacy of ibogaine and 18-MC may be precisely attributable to their peculiarly complex pharmacology.

II. Behavioral and Neurochemical Methods

All subjects were naïve female Sprague-Dawley (Taconic) or Long-Evans (Charles River) rats, approximately 3 months old and weighing 230-250 g at the beginning of an experiment. Rats were maintained on a normal light/dark cycle (lights on/off at 0700 h/1900 h).

The intravenous self-administration procedure was described previously (*4-6*).

The intravenous self-administration system consisted of polyethylene-silicone cannulas constructed according to the design of Weeks (*7*), Instech harnesses and commutators, and Harvard Apparatus infusion pumps (#55-2222). Responses on either of two levers produced a 10 or 50 µl infusion of drug solution, 0.01 mg (0.04 mg/kg) morphine sulfate, or 0.1 mg (0.4 mg/kg) cocaine hydrochloride, respectively, in 0.2 to 1.0 second.

Nicotine was self-administered via the oral route using an operant procedure previously described (*8*). Rats received nicotine (1.4 µg/µl of the base; 0.1 ml per response) by pressing one lever and water by pressing another lever.

Locomotor activity was assessed using cylindrical photocell activity cages (60 cm, three crossing beams) interfaced to an IBM compatible computer (*9*).

The microdialysis procedures used to assess the effects of drug treatments on extracellular levels of dopamine and its metabolites have been used extensively in this laboratory (*3,5,6,10-14*). Rats were implanted stereotaxically with guide cannulae so that, when inserted, the tips of the dialysis probes would be located in the intended brain areas (e.g., nucleus accumbens, striatum, medial prefrontal cortex). All microdialysis experiments were carried out in freely moving animals. Perfusate samples were analyzed by HPLC with electrochemical detection.

III. Opioid Interactions

The acute intraperitoneal (i.p.) administration of either ibogaine or 18-MC, 15 minutes prior to testing, dose-dependently decreased the self-administration of morphine (*4,6*) in rats. As shown in Figure 2, although ibogaine and 18-MC were about equally potent, 18-MC was more selective in that ibogaine, but not 18-MC, acutely (on the day of treatment) depressed responding for a nondrug reinforcer (water). The effects of ibogaine and 18-MC on morphine self-administration were protracted; pretreatment with 40 mg/kg ibogaine or 18-MC had significant effects for 24 and 48 hours, respectively (*4-6*). Although the acute effects of ibogaine on morphine self-administration can be attributed to the induction of whole body tremors, the protracted effects of ibogaine occur at times when the drug is eliminated from the body and tremors are absent (*4*). 18-MC does not induce tremors, but its effects on morphine self-administration also persist long after 18-MC itself is eliminated (*6,14*).

Comparable effects of 18-MC on morphine self-administration were also observed following oral treatment (*14*), suggesting that 18-MC, like ibogaine, will be pharmacologically active when given orally to humans. Furthermore, in a recent study, oral 18-MC treatment (40 mg/kg) was found to produce a downward shift in the entire dose-response relationship for self-administered morphine (*13*).

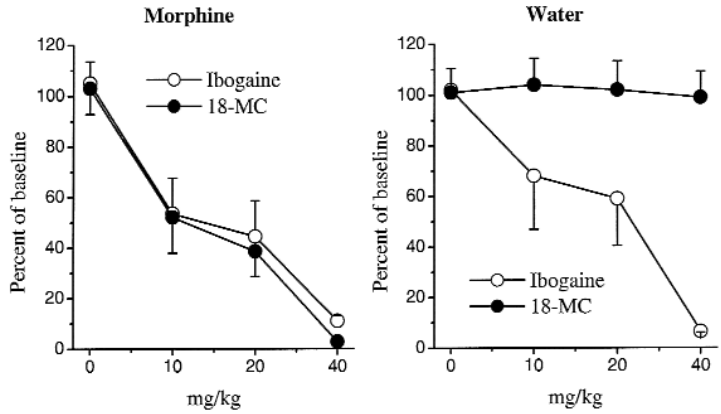


FIGURE 2. Comparison of acute effects of ibogaine and 18-MC on morphine self-administration and on responding for water.

This indicated that 18-MC, and probably ibogaine as well (*15*), decreases the reinforcing efficacy of morphine. Prolonged access to opioids (*16*), as well as to stimulants (*17*), has been shown to result in an "escalation" of drug intake such that the drug becomes more reinforcing and the dose-response relationship is shifted higher. Our results (*13*) suggest that 18-MC may reverse this trend, counteracting the neural adaptations produced by chronic drug administration.

Consistent with human anecdotal reports, the antiaddictive efficacies of both ibogaine and 18-MC seem to increase with repeated treatment. Weekly or biweekly injections of ibogaine (3-4 injections of 40 mg/kg, i.p.) can increasingly suppress morphine intake for up to a week in some rats (*4*), and repeated daily administration of low doses of 18-MC (e.g., 5 injections of 20 mg/kg, p.o.), while having little or no effect on self-administration on day 1 of treatment, decreased morphine intake by day 4 (*14*). This suggests that rather than giving people ibogaine or 18-MC in a single large dose, as is currently done for ibogaine, it might be advisable, at least for reasons of safety, to give smaller doses repeatedly.

Ibogaine has been claimed to "suppress the multiple symptoms and physical discomfort of narcotic withdrawal" (ENDABUSE™ product information). Accordingly, we assessed the effects of ibogaine (*18*) and 18-MC (*19*) treatment in an animal model of morphine withdrawal, in which signs of withdrawal were induced in morphine-dependent rats by the acute administration of a μ-opioid receptor antagonist (naltrexone). Both ibogaine and 18-MC reduced the intensity of several signs of morphine withdrawal. However, their effects were not identical, suggesting that ibogaine and 18-MC may act via somewhat different mechanisms.

Ibogaine and 18-MC also differ with regard to their acute effects on morphine-induced locomotion. Ibogaine decreased morphine's efficacy to induce locomotion, shifting morphine's dose-response curve downward (*9,15,20*), whereas 18-MC enhanced morphine's potency, shifting its dose-response curve to the left (*21*). Ibogaine (40 mg/kg, i.p., 19 hours beforehand) also produced a greater attenuation of morphine-induced (5 mg/kg, i.p.) locomotion in rats previously (2-4 times) administered morphine (30 mg/kg, i.p.) compared to acutely treated rats (*9*). Interestingly, however, 18-MC (40 mg/kg, i.p., 19 hours earlier) blocked the expression of locomotor sensitization following chronic morphine administration (*21*). The dose-effect curve of control rats sensitized by chronic morphine administration was shifted to the left of control rats that did not sensitize in response to chronic morphine, whereas the dose-effect curves of 18-MC-pretreated sensitized and nonsensitized rats were virtually identical. Thus, it appears that whereas ibogaine produces a greater effect on morphine-induced locomotion in drug-experienced animals, compared to naïve animals, 18-MC masks, or possibly reverses, the alterations in behavior produced by chronic morphine experience, apparently returning the animal to its initial nonsensitized state.

Some of the effects of ibogaine appear to be at least partially mediated by a combination of κ-opioid agonist and NMDA antagonist actions. Thus, a combination of a κ-opioid antagonist (nor-binaltorphimine; norBNI) and an NMDA agonist (NMDA) significantly antagonized the effect of ibogaine on morphine self-administration, while neither norBNI nor NMDA alone had this

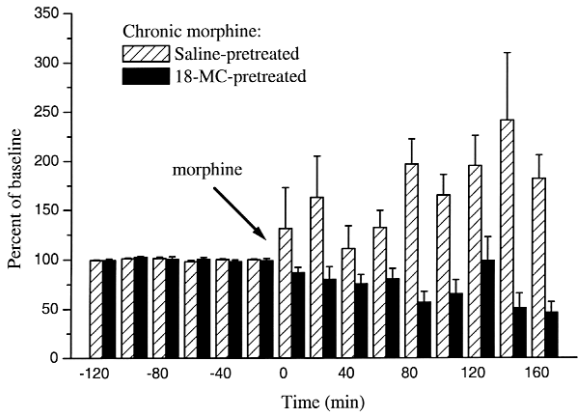


FIGURE 3. Effects of 18-MC (40 mg/kg, 19 hours beforehand) on the sensitized dopamine response to morphine (20 mg/kg, i.p.); morphine was administered daily for 5 consecutive days and, again (test for sensitization), after a 3-day withdrawal period.

effect (*22*). Other effects of ibogaine were also blocked by a combination of norBNI and NMDA (*22*). These included ibogaine (40 mg/kg, i.p., administered 19 hours beforehand) inhibition of morphine-induced (5 mg/kg, i.p.) locomotor stimulation and ibogaine inhibition of dopamine release in the striatum. Comparable studies with 18-MC have not been conducted.

All addictive drugs (including opioids, stimulants, ethanol, and nicotine) examined to date share an ability to enhance dopamine transmission in the nucleus accumbens (*23,24*), a critical mediator of the "rewarding" or "incentive motivational" effects of drugs (*25,26*). Consistent with their putative antiaddictive actions, ibogaine and 18-MC (40 mg/kg, i.p.) were both found to decrease accumbal dopamine release during the first 3 hours after their administration (*6,10*). Both compounds, administered 19 hours earlier, also blocked acute morphine-induced (*6,10*) increases in extracellular levels of dopamine in the nucleus accumbens.

Like its effects on sensitized locomotor behavior, we have recently found that 18-MC (40 mg/kg, i.p., 19 hours earlier) similarly abolishes the sensitized dopamine response to morphine in rats chronically administered morphine (Figure 3). Again, the data suggest that 18-MC (and probably ibogaine) counteracts or reverses the homeostatic disturbances that are a consequence of repetitive opioid use.

IV. Stimulant Interactions

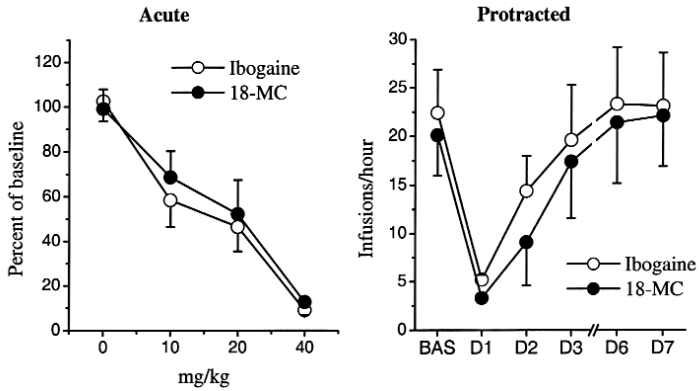


FIGURE 4. Comparison of acute and protracted effects of ibogaine and 18-MC on cocaine self-administration.

The acute intraperitoneal (i.p.) administration of either ibogaine or 18-MC, 15 minutes prior to testing, dose-dependently decreased the self-administration of cocaine (*5,6*) in rats. As shown in Figure 4, ibogaine and 18-MC were again about equally potent; and similar to previous results with morphine, their effects on cocaine self-administration were protracted, lasting for approximately 24 hours. In contrast, 18-MC seemed to be approximately twice as potent as ibogaine in decreasing oral nicotine preferences (*12*), and recent work with an intravenous nicotine self-administration paradigm suggests that 18-MC is at least twice as potent in decreasing nicotine intake as in decreasing either morphine or cocaine intake.

With respect to stimulant-induced locomotion, both ibogaine and 18-MC augmented the expression of locomotor behavior in response to cocaine (*27-30*) and amphetamines (*31,32*). Ibogaine and 18-MC both shifted the dose-response curve of acute cocaine-treated animals to the left of controls (*30*), indicating that pretreatment with these agents renders an animal more sensitive to cocaine's acute locomotor effects (Figure 5). In an early study, ibogaine (40 mg/kg, i.p., 24 hours beforehand) attenuated the locomotor response to *d*-amphetamine (1.5 mg/kg, i.p.) in rats repeatedly administered *d*-amphetamine (4 x 1.5 mg/kg, every other day) (*34*). More recently, pretreatment with ibogaine or 18-MC (40 mg/kg, i.p., 19 hours earlier) was found to shift the inverted U-shaped dose-response curves for locomotion in chronic cocaine-treated rats to the left of controls such that *iboga*-pretreated rats displayed augmented locomotor activation at lower cocaine doses (e.g., 5 and 10 mg/kg) (*29,30*) and lower levels of locomotor

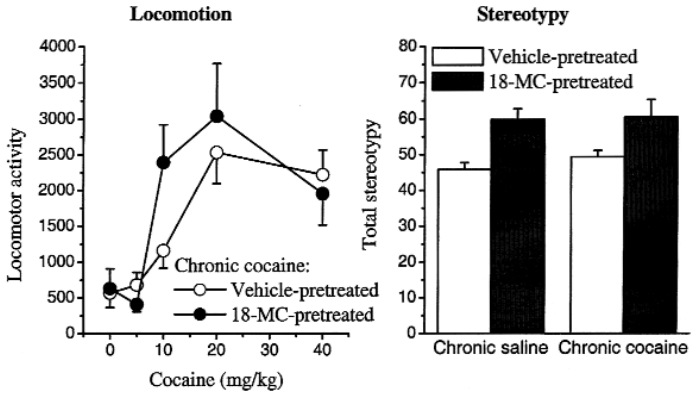


FIGURE 5. 18-MC (40 mg/kg, 19 hours before test doses of cocaine) shifted the chronic cocaine locomotor dose-response curve to the left and enhanced the stereotypic response to cocaine (40 mg/kg); similar findings occurred with ibogaine.

activation at higher cocaine doses (e.g., 20 and 40 mg/kg) (*30*), compared to control animals (Figure 5). The locomotor-attenuating effects of *iboga* pretreatment at higher cocaine doses can be attributed to the induction of repetitive, species-specific behaviors (stereotypy), which can be physically incompatible with locomotion (e.g., focused sniffing, grooming, gnawing). Ibogaine and 18-MC (40 mg/kg, i.p., 19 hours earlier) promoted the expression of high levels of cocaine-induced stereotypic behavior in both acute and chronic cocaine-treated rats, compared to controls (Figure 5).

Virtually identical effects of ibogaine and 18-MC pretreatment were observed for methamphetamine-induced stereotypy. This latter finding may possibly account for the previously reported (*32*) attenuating effect of ibogaine on *d*-amphetamine-induced locomotion in chronic d-amphetamine-treated rats. Combined, these findings indicate that pretreatment with either ibogaine or 18-MC will enhance rats' sensitivity to the behavioral-activating effects of stimulant drugs, and that this increase can be above and beyond the sensitization produced by chronic stimulant administration alone.

Distinctions between ibogaine and 18-MC have been reported with respect to some of their neurochemical effects. For one, acute ibogaine, as well as noribogaine, increase extracellular levels of serotonin in the nucleus accumbens, whereas 18-MC has no effect (*33*). Secondly, ibogaine pretreatment (19 hours earlier) augments (*27*), whereas 18-MC has no effect on (*14*), acute cocaine-induced increases in extracellular levels of dopamine in the nucleus accumbens. Curiously, however, both agents block acute nicotine-induced dopamine release

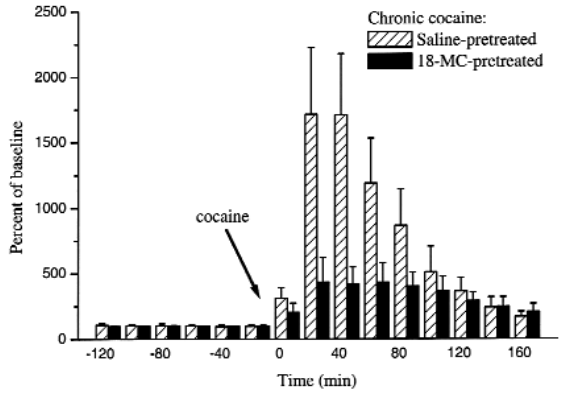


FIGURE 6. Effects of 18-MC (40 mg/kg, 19 hours beforehand) on the sensitized dopamine response to cocaine (15 mg/kg, i.p.); cocaine was administered daily for 5 consecutive days and, again (test for sensitization), after a two-week withdrawal period.

in the nucleus accumbens (*11,12*). The studies with 18-MC have recently been extended to animals sensitized by chronic cocaine and, interestingly, 18-MC pretreatment blocked the sensitized dopamine response to chronic cocaine (Figure 6). Although the effect of ibogaine pretreatment on cocaine-sensitized levels of dopamine in the nucleus accumbens has not yet been assessed, the 18-MC results suggest that different mechanisms may mediate the interactions of ibogaine and related agents with the effects of acute versus chronic cocaine. The data also suggest that the changes in nucleus accumbens dopamine are more directly related to cocaine's reinforcing or addictive property than to its locomotor stimulant effects, since, as reviewed earlier, 18-MC decreased cocaine self-administration, but enhanced both acute and chronic cocaine-induced locomotor behavior.

V. Metabolism and Distribution of Ibogaine and 18-MC

Plasma and tissue levels of both ibogaine and 18-MC have been determined using gas chromatography-mass spectrometry (*14,34*). Both compounds have short initial half-lives of 5 to 10 minutes and terminal half-lives of slightly over 100 minutes. Consistent with a two-compartment model of their elimination, both ibogaine and 18-MC are highly sequestered in fat (*14,34*). In absolute terms, however, the fat levels of either ibogaine or 18-MC account for only a small fraction of the administered dose (approximately 10%), suggesting that both compounds are rapidly metabolized. Indeed, an active metabolite of ibogaine, noribogaine, has already been well characterized both *in vivo* (e.g., *2,3*) and *in vitro* (e.g., 35,36). Although some investigators (*37*) consider noribogaine to be the major determinant of ibogaine's pharmacology *in vivo*, studies in this laboratory (*20*) indicated that the elimination of noribogaine was also too fast for it to be responsible for all of ibogaine's prolonged effects. Recent work in this laboratory has provided evidence that 18-MC also has metabolites, but it remains to be determined whether they are active, and whether they contribute to the protracted behavioral effects of 18-MC.

VI. Toxicity

Ibogaine induces whole body tremors at moderate doses (20-40 mg/kg) and Purkinje cell loss in the cerebellum at high doses (≥100 mg/kg) (*38-40*).

However, 18-MC (40 mg/kg) is non-tremorigenic, and even multiple, high-dose (100 mg/kg) injections of 18-MC fail to produce damage to cerebellar Purkinje cells (*6*). The neurotoxic effect of ibogaine appears to be mediated by an agonist action at sigma-2 receptors (*41*). Consistent with this, 18-MC has a much lower affinity than ibogaine for sigma-2 sites (Table II and ref. *42*).

Anecdotal reports in humans indicate that ibogaine can slow heart rate. Consistent with these reports, recent work in this laboratory showed that, in awake and freely moving rats, high doses (100 and 200 mg/kg, i.p.) of ibogaine decreased heart rate, without altering blood pressure. In contrast, even at 200 mg/kg (i.p.), 18-MC had no effect on either heart rate or blood pressure (*14*).

Noribogaine has about a 10-fold higher affinity for the serotonin transporter than ibogaine and, consistent with this, noribogaine is more potent than ibogaine in raising extracellular levels of serotonin in the nucleus accumbens (*2*). However, the efficacy of ibogaine to increase serotonin levels appears to be substantially greater than that of noribogaine (*33*). Ibogaine may directly release serotonin. Compared to its effects on the dopamine systems, these serotonergic effects of ibogaine and noribogaine appear to be relatively short lasting, dissipating within 3 hours. Similarly, while effects of ibogaine on tissue levels of dopamine metabolites are still apparent on the day after administration (*15,43*), there are no effects on tissue levels of serotonin's metabolite (*43*). Serotonin would thus seem to have a role in mediating only the acute behavioral effects of ibogaine. These might include its acute discriminative stimulus effect in rats (*44,45*) and possibly its acute hallucinogenic effect in humans. 18-MC neither inhibits the reuptake of (Table II), nor releases, serotonin (*33*) and, to the extent that these actions are involved in ibogaine-induced hallucinations, it is predicted that 18-MC will not be hallucinogenic.

VII. Mechanisms

Table II shows the results of a receptor screen comparing the binding affinities of 18-MC, ibogaine, and its active metabolite, noribogaine. The binding profiles for 18-MC are somewhat different from that of its parent compound. Similar to results reported by others (cf. *46*), our studies show that ibogaine and noribogaine have low micromolar affinities for the κ- and μ-opioid receptors, the NMDA-subtype of glutamate receptor, 5-HT3 receptors, sigma-2 sites, sodium channels, and the serotonin transporter. In contrast, 18-MC has low micromolar affinities at all three opioid receptors (κ, μ, and δ) and at the 5-HT3 receptor, and no affinity at NMDA receptors, or the serotonin transporter (*14*). For both ibogaine and 18-MC, all of these receptor affinities are in the low micromolar range and therefore

are not likely to be responsible for effects lasting 24 to 48 hours. However, some of the differences between ibogaine and 18-MC might account for a potentially higher therapeutic index for 18-MC. Ibogaine's affinities at muscarinic (M1 and M2) receptors and at sodium channels, which are two to three times greater than those of 18-MC, may mediate its tendency to lower heart rate. Ibogaine's action at sigma-2 sites has been linked to its neurotoxicity (*42*), and 18-MC has a 30-fold lower affinity for this site. In addition, as suggested previously, the hallucinogenic effect of ibogaine may be mediated via serotonin release, an effect not produced by 18-MC (*33*). Lastly, in functional assays, ibogaine was reported to be a noncompetitive antagonist at nicotinic receptors, possibly acting as an open channel blocker (*47,48*). The latter, as well as preliminary data from this laboratory, suggest that both ibogaine and 18-MC might have nanomolar affinities for nicotinic channels—and this action could well contribute to prolonged antiaddictive effects.

VIII. Discussion

Most drug development programs focus on single mechanisms of action, and the development of pharmacotherapies for drug addiction has been no exception to this practice. The use of methadone to treat heroin addiction and the use of nicotine formulations (e.g., gum, patch, nasal spray) to treat smoking are representative of a pharmacokinetic approach in which long-acting replacement therapies are used to dampen both the "highs" and "lows" associated with the short-acting addictive substances. This approach has limitations in that replacement therapies maintain physical dependence and often have other significant side effects as well. Newer, and still mostly experimental, approaches to this problem have attempted to develop agents that should modulate or directly interfere with the action of the abused drug. Representatives of such potential therapies are dopamine transporter inhibitors, dopamine receptor agonists and antagonists, GABA B receptor agonists, and partial μ-opioid receptor agonists. In general, treatments have been sought that are site specific, usually acting selectively at a particular receptor or receptor subtype; and most often, treatments are targeted to one particular addictive disorder.

Viewed in relationship to a "normal" pharmaceutical development program, the proposed use of ibogaine, 18-MC, and possibly their metabolites, to treat several varieties of drug addiction may appear, depending on one's bias, to be extraordinarily innovative or outrageously foolish. However, if the many anecdotal reports of efficacy are ever substantiated in well-controlled clinical trials, ibogaine will have taught us at least one important if not obvious truth—

namely, that addiction is a multifaceted brain disorder, and that to be effective, a treatment or treatments having multiple actions may be required. Certainly science, rather than politics, should determine whether or not ibogaine will have any clinical utility. Moreover, the apparent advantages of 18-MC, and perhaps other congeners yet to be tested, have already highlighted the significance of ibogaine's discovery. If only because it is the prototype, ibogaine would still merit a great deal of investigation.

The data reviewed here indicate that there are several ways in which ibogaine and 18-MC could exert antiaddictive effects. Both compounds have affinities for 5-HT3 receptors, the manipulation of which has been reported to alter amphetamine-induced euphoria in humans (*49*) and cocaine-induced locomotion, cocaine discrimination, alcohol consumption, and morphine withdrawal signs in rodents (*50-54*). These alkaloids also have similar affinities for μ-and κ-opioid receptors, and other data (*55-57*) have indicated that μ-antagonists and κ-agonists can modulate the self-administration of cocaine and morphine. However, as noted earlier, the protracted antiaddictive effects of ibogaine and 18-MC are hard to reconcile with their micromolar affinities for these receptors. In addition, both ibogaine (*18*) and 18-MC (*19*) attenuate naltrexone-precipitated withdrawal symptoms in morphine-dependent rats, findings that are inconsistent with μ-antagonist activity; and both ibogaine (*58*) and 18-MC have little or no analgesic activity, findings that are inconsistent with μ-agonist activity. Although NMDA antagonist (*59*) and serotonergic (*2*) actions of ibogaine have been invoked to explain ibogaine's effects, it is noteworthy that 18-MC appears to have neither action. The possibility that ibogaine and 18-MC have important actions at nicotinic receptors requires further investigation.

The short-half lives of ibogaine and 18-MC strongly suggest that the pharmacological actions of both alkaloids are attributable to one or more active metabolites; although noribogaine has been proposed (*2,37*) as the mediator of ibogaine's prolonged action, it would appear that noribogaine alone cannot account for ibogaine's effects since brain levels of noribogaine also decline rapidly after ibogaine administration to rats (*20*). As both ibogaine and 18-MC are deposited in fat (*14,34*), it is possible that the slow release of these compounds, or perhaps their metabolites, may contribute to their protracted effects.

In summary, although the pharmacology of ibogaine and 18-MC is complex, the study of their pharmacology represents an entirely novel approach to the development of pharmacotherapies for drug addiction. This approach will indeed have proven its worth if 18-MC, or another structural congener, is eventually found to be a safe and effective treatment for multiple forms of drug abuse. At the very least, continued investigation of ibogaine and 18-MC should help us further understand the neurobiology of addiction; and this, in the long term, may be a prerequisite for developing optimal antiaddictive agents.

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