——Chapter 4——

DRUG DISCRIMINATION STUDIES WITH IBOGAINE

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I. Introduction

Drug discrimination is a useful technique in the search for the mechanism of action of psychotropic drugs. Perhaps its utility has been best demonstrated in efforts to elucidate those neurotransmitter receptors involved in the mediation of the perceptual effects of phenethylamine (DOM) and indoleamine (LSD) hallucinogens (*1*).

As far as biological assays of pharmacological activity are concerned, drug discrimination is relatively easy to understand. Specifically, the goal of such

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studies is to produce drug-induced stimulus control. This condition is said to exist when, in the presence of a stimulus, an animal subject emits a conditioned response (*2*). An example of a conditioned response might be pressing a specific lever when presented with a two-lever choice, or entering a specific arm of a two-arm maze (T-maze). The stimulus (or discriminative stimulus) is the interoceptive state produced by the drug used to establish stimulus control. To illustrate this by way of example, assume that one wishes to establish stimulus control with drug X. The discriminative stimulus will be the interoceptive cue, which is simply the effect experienced by the subject after receiving drug X. In this case the subject is a rat. However, pigeons, other rodents, and primates can also be used. The subject, over several weeks, has been taught to press levers in a two-lever operant chamber for a food reward in a process known as shaping. During this process, the ratio of response to reward is gradually increased from 1 to 10 or more. Since a certain fixed number of responses is required for a reward, this is known as a fixed ratio schedule of reinforcement. If 10 responses are required for a reward, then a fixed ratio of 10 (FR 10) is the schedule. Once the rat has mastered this, it is time to establish stimulus control.

In order to accomplish this, the rat is trained with once daily sessions, which alternate between drug and vehicle treatment. Thus, using a specific pretreatment time (e.g., 15 minutes prior to the session), the training drug (drug X) or its vehicle are given on alternating days. On days when drug X is given, only responses on one lever (left or right) are rewarded. On vehicle days, only responses on the other lever are rewarded. After a number of sessions the subject will learn to press the drug appropriate lever only on those days when that drug is administered. On vehicle days, the subject should only respond on the vehicle-appropriate lever. Once the subject is responding reliably in a treatment-appropriate manner, stimulus control is said to be present. Having established stimulus control in a given subject investigations can begin regarding the receptor interactions mediating the discriminative cue of drug X. Test drugs (drug Y) that are known agonists or antagonists at certain receptors can be given during test sessions. If these produce responses on the drug X-appropriate lever, then the test drug is said to substitute for the training drug, alternatively, by convention, the training drug stimulus is said to generalize to that of the test drug. This terminology is often reversed by some authors resulting in confusion on the part of the readers. If responding is on the vehicle-appropriate lever then no substitution or generalization is present. Often there is an intermediate degree of substitution or generalization (partial generalization) suggesting that the interoceptive cues are similar, but not identical. Another test is that of antagonism. In these tests, a drug with known receptor binding properties is given with the training drug (e.g., drugs X and Y together). If responding is seen only on the vehicle appropriate-lever then drug Y has antagonized the interoceptive cue produced by drug X. Alternatively, responding on the drug X-appropriate

lever would indicate absence of antagonism. During test sessions, rewards should not be given and the session should be terminated after a fixed number of responses. This is to minimize learning during the test session, which might confuse the subjects. Furthermore, the subjects should only be tested every third or fourth day (after they have demonstrated reliable treatment appropriate responding in the prior two or three training sessions). Training doses, test doses, and pretreatment times are usually based on reports of pharmacological effects of the drug in question found in the literature.

Drug discrimination is a remarkably simple, yet elegant, technique. Using this paradigm, investigators can often gain insight into the mechanism of action of a given agent. The results of these studies can then be correlated with other studies, such as receptor binding studies and second messenger assays.

Like other techniques, drug discrimination does have its shortcomings. Because the interoceptive cue is what is being evaluated, other drug effects and their specific mechanisms may not be accounted for. No technique is perfect. Nonetheless, for studying drugs with psychotropic effects, drug discrimination remains a powerful weapon in the arsenal of the behavioral pharmacologist.

II. Ibogaine in Drug Discrimination Studies

A. Ibogaine as a Discriminative Stimulus

Before there was any evidence supporting the antiaddictive effects of ibogaine, this agent was known first and foremost as a hallucinogen. Because of this, drug discrimination seems well suited to the study of ibogaine. Knowledge of those receptors involved in the ibogaine discriminative cue could contribute significantly to our understanding of its mechanism of action, both as a hallucinogen and possibly as a therapy for substance abuse conditions.

Figure 1a shows the dose-response effects ibogaine (●), harmaline (▲), and noribogaine (10-hydroxyibogamine) (■) in rats trained with 10.0 mg/kg ibogaine as a discriminative stimulus. All drugs were administered i.p. 60 minutes before testing. Each point represents one determination in each of 10 subjects unless otherwise noted by the number of subjects completing the test over the number of subjects tested. The ED_50 for ibogaine was 4.6 mg/kg.

Figure 1b shows the time course for the ibogaine-trained stimulus. Maximal substitution was observed at a pretreatment time of 60 minutes (94%). Following this, a time-dependent decrease in ibogaine-appropriate responding was observed. (*Modified from reference 3 with permission.*)

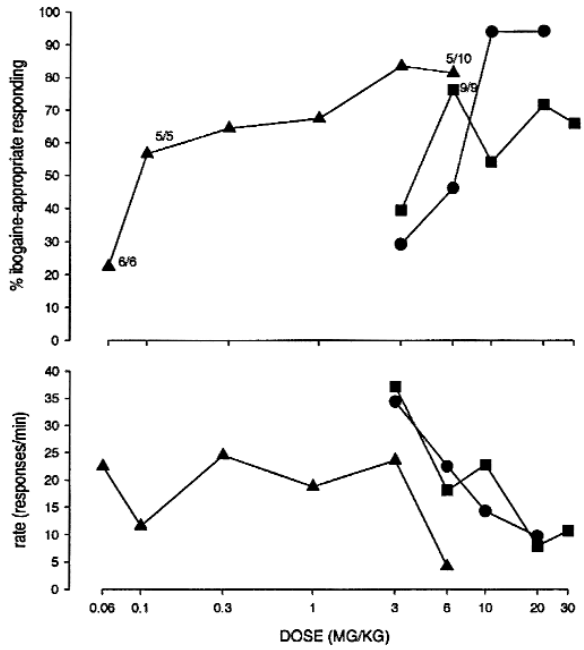


FIGURE 1A. Dose response for ibogaine ●, harmaline ▲, and noribogaine (10-hydroxyibogamine) ■.

B. Serotonergic Agents in Ibogaine-Trained Rats

The structural similarity between ibogaine and serotonin taken together with the fact that the 5-HT_{2A} receptor is the primary mediator of the discriminative stimulus effects of the classical hallucinogens lysergic acid diethylamide (LSD) and (-)-2,5-dimethoxy-4-methyl-amphetamine (DOM) (*4-6*) makes serotonergic agents a natural starting point in the study of ibogaine.

Palumbo and Winter (*7*) were the first to look at ibogaine in drug discrimination studies. They found that ibogaine produced an intermediate level of substitution in both LSD and DOM-trained subjects. This effect was blocked by the 5-HT_2 antagonist pizotylene. The first report in which ibogaine was trained as a discriminative stimulus was by Schecter and Gordon (*8*). These authors observed an intermediate level of substitution by the 5-HT releasing agent fenfluramine. This evidence suggested a possible role for serotonergic receptors in the stimulus effects of ibogaine. Further investigations have revealed that the 5-HT_{2A} receptor plays a role, although this does not appear to be essential to the ibogaine-induced discriminative stimulus. This is evidenced by the observation

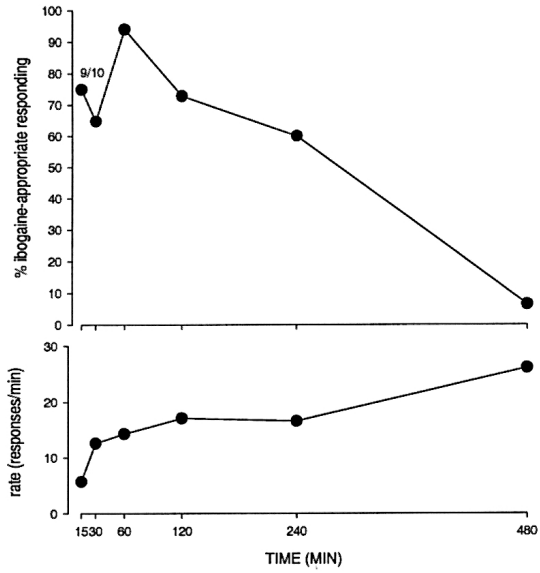
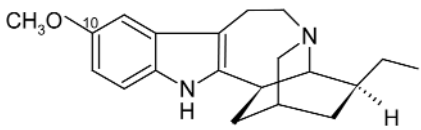


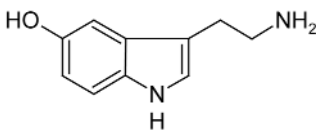
FIGURE 1B. Ibogaine time course.

that both DOM and LSD produced intermediate levels of substitution for ibogaine that was blocked by the 5-HT_{2A} antagonist pirenpirone (*9*). The conclusion that this component is nonessential stems from the fact that while pirenpirone blocked the ibogaine-appropriate responding produced by LSD and DOM, it did not affect the ibogaine-appropriate responding produced by ibogaine itself (*9*) (Figure 3). For a detailed discussion of nonessential stimulus components, see reference *10*.

A possible explanation for the differences in ibogaine-appropriate responding produced by LSD illustrated above, compared to the work of Schecter and Gordon (34.5% substitution) (*8*), could be accounted for by rat strain differences and/or pretreatment time differences for ibogaine training (60 minutes vs. 30



Ibogaine



Serotonin

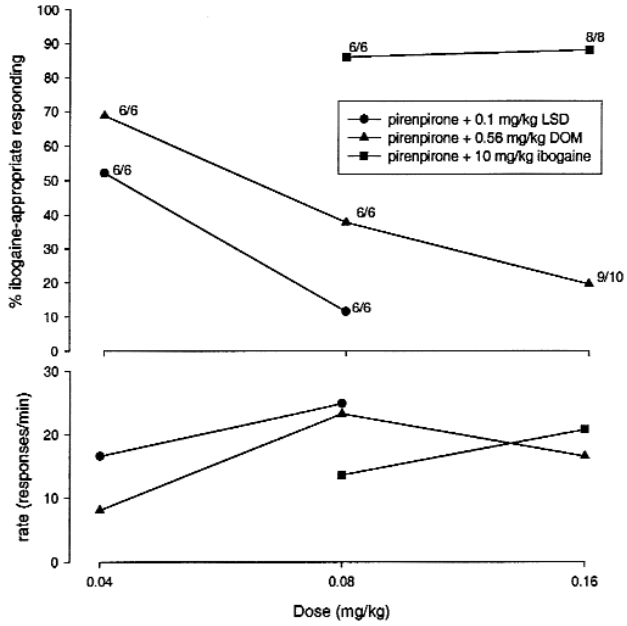


FIGURE 2. The dose response relationships for pirenpirone (75 minutes presession) in the presence of LSD (●), DOM (▲), and ibogaine (■) in rats trained to discriminate ibogaine (10.0 mg/kg, i.p., 60 minutes presession) from vehicle. The ratio adjacent to each of the points represents the number of subjects completing the test session over the number of subjects participating in each test session. *From reference 9 with permission.*

minutes, respectively).

In addition to 5-HT_{2A} receptors, there is evidence for the involvement of the 5-HT_{2C} receptor. In contrast, the 5-HT_{1A} and 5-HT_3 subtypes do not appear to play a major role in the ibogaine-mediated discriminative stimulus (*11*). Interestingly, the phenomenon observed with the 5-HT_{2A} component is also seen with the 5-HT_{2C} component of the ibogaine cue. That is, involvement of the 5-HT_{2C} receptor in the ibogaine-trained discriminative stimulus appears to be nonessential. As illustrated in Table I, the 5-HT_{2C} agonists MK 212 and mCPP both produced intermediate levels of substitution, which were blocked by metergoline, an agent that has antagonist properties at 5-HT_{2C} receptors. In contrast, the ibogaine-appropriate responding produced by ibogaine itself was not affected by mesulergine (*10*) or metergoline (*11*).

These studies have demonstrated a role for 5-HT_{2A} and 5-HT_{2C} receptors in the ibogaine discriminative cue. A role for the 5-HT_{2A} receptor is further supported by biochemical studies, which provided evidence for *in vivo* occupancy of these

TABLE I.

Drug treatment	% ibogaine-appropriate Responses	Rate (Responses/min)	n/N
Ibogaine	94.0	14.3	10/10
Ibogaine (10 mg/kg) + Metergoline (1.0 mg/kg)	100.0	36.4	4/4
MK 212 (0.3 mg/kg) + Metergoline (1.0 mg/kg)**	10.0 [79.6]*	16.1	7/8
mCPP (0.8 mg/kg) Metergoline (1.0 mg/kg)**	23.8 [76.4]*	13.0	6/8

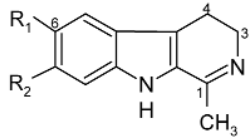
The ratio n/N represents the number of animals responding (n) out of the number of animals tested (N). The % ibogaine-appropriate responding produced by both mCPP and MK-212 alone is enclosed in brackets. Treatment sessions were compared to immediately preceding ibogaine training sessions using Wilcoxon's signed ranks test.

*Reflects significant differences from the ibogaine-treatment condition ($p<0.05$).

**Reflects significant differences between the drug alone and the drug + antagonist conditions as determined by the Mann-Whitney Rank Sum test. *Modified from reference 11 with permission.*

receptors by ibogaine (*10*). Although these receptor interactions are not essential to the ibogaine stimulus, they provide a link between ibogaine and classical hallucinogens such as LSD and DOM. This is further supported by a recent study investigating the effects of monoamine reuptake inhibitors on the stimulus effects of hallucinogens. Specifically, the DOM, LSD, and ibogaine discriminative cues were all potentiated by the monoamine reuptake inhibitors fluoxetine, venlafaxine, and fluvoxamine (*12*). The exact mechanism for this is unknown at present. Certainly, further insights into this area of study will enhance our knowledge both of hallucinogens and of antidepressant medications, which are commonplace in psychiatric practice.

C. Beta-Carboline Agents In Ibogaine-Trained Rats



6-Methoxyharmalan	$R_1 = OCH_3$, $R_2 = H$
Harmaline	$R_1 = H$, $R_2 = OCH_3$
Harmine	$R_1 = H$, $R_2 = OCH_3$, $\Delta^{3,4}$
THBC	$R_1 = H$, $R_2 = H$, 1,2-H_2

One group of hallucinogens that has received little attention is the beta-carboline (or Harmala) alkaloids group. Interestingly, these agents bear a strong structural resemblance to ibogaine. Anecdotal reports suggest that the tremorigenic and subjective effects of agents, such as harmaline and harmine, are not unlike those of ibogaine (*13*). Several of these alkaloids were tested in ibogaine-trained rats (*10*). The results are shown in Figure 3. Full generalization was observed with 6-methoxyharmalan and harmaline, while partial generalization was seen with harmine, harmane, harmalol, and THBC (tetrahydro-beta-carboline). No generalization was seen to 6,7-dimethoxy-4-ethyl-β-carboline-3-carboxylate (DMCM) or norharmane.

Unfortunately, the mechanism of action of the harmala alkaloids remains unknown. However, this is not the case for other beta-carbolines like DMCM. This agent has inverse agonist properties at benzodiazepine sites (*14*). We found

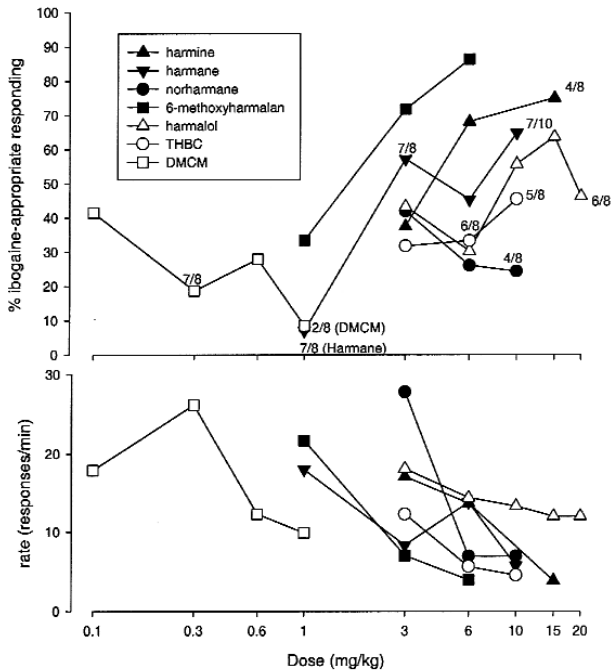


FIGURE 3. Dose-response relationships for beta-carbolines in rats trained with 10.0 mg/kg ibogaine as a discriminative stimulus. All agents were administered i.p., 60 minutes presession. The ratio adjacent to each of the points is the number of subjects completing the test session over the number of subjects participating in each test session. Where no ratio is shown, a ratio of 8/8 is implied. *Modified from reference 19 with permission.*

it interesting that the *iboga* alkaloid, tabernanthine, is reported to have benzodiazepine inverse agonist effects in rats (*15*). Nonetheless, as shown above, ibogaine itself did not generalize to DMCM. Likewise, *in vitro* work by Deecher and colleagues (*16*) showed ibogaine, as well as harmaline, to be without effect on GABA-stimulated chloride uptake in the mouse brain.

The results of these studies with beta carbolines have implications regarding the potential antiaddictive effects of ibogaine. In morphine self-administration studies, Glick *et al*. (*17*) showed that, unlike ibogaine, harmaline did not produce a sustained decrease in morphine consumption by rats. If the self-administration paradigm used by these researchers is an accurate model of substance abuse in humans, then it appears that mimicry of the ibogaine discriminative stimulus is not effective in predicting antiaddictive activity in light of the fact that harmaline fully mimics ibogaine (*3*). Furthermore, norharmane, an agent that did not substitute for ibogaine in the present study, attenuates naloxone-precipitated withdrawal from morphine, as does ibogaine (*18*). For further information on the effects of beta carbolines in ibogaine-trained subjects, see reference *19*.

Interestingly, recent work by Grella and colleagues (*20*) shows significant harmaline-appropriate responding by the hallucinogen DOM (76%). These observations, taken together with our findings (*10*), support a role for the 5-HT_{2A} receptor subtype in the stimulus effects of ibogaine and harmaline.

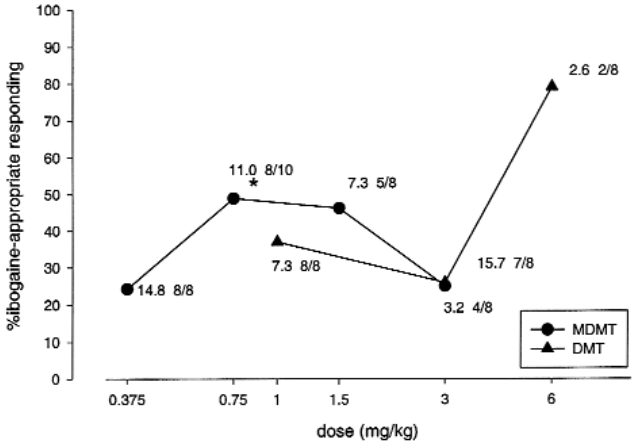


FIGURE 4. Dose response relationships for DMT and MDMT in rats trained with ibogaine. Note that * refers to statistically significant difference from vehicle condition ($p<0.05$) (Helsley, *et al*., previously unpublished data).

D. Tryptamine Hallucinogens in Ibogaine-Trained Rats

The tryptamines form another subgroup of indoleamine hallucinogens. As shown in Figure 4, these agents appear to be less like ibogaine in terms of the stimulus cues compared to the beta-carboline, indoleamine, and phenethylamine hallucinogens, although weak partial generalization is seen with MDMT. A possible explanation for this finding lies in the observation that the stimulus effects of the tryptaminergic hallucinogen MDMT are mediated chiefly through interactions with 5-HT_{1A} receptors (*21, 22*). These receptors do not appear to be involved in the ibogaine stimulus (*11*).

Figure 4 also shows dose response relationships for DMT and MDMT in rats trained with ibogaine (10 mg/kg) as a discriminative stimulus. All agents were administered i.p., 15 minutes presession. The ratio adjacent to each of the points is the number of subjects completing the test session over the number of subjects participating in each test session. Also next to each point is the response rate in responses per minute.

E. NMDA Antagonists in Ibogaine-Trained Subjects

NMDA antagonists are often classified as hallucinogens because of their psychotomimetic effects. These agents occupy a binding site within a calcium channel; in so doing they occlude the channel. This calcium channel is normally gated by the excitatory neurotransmitter glutamate (for review of NMDA antagonists, see reference *23*). The best known of these agents is phencyclidine (angel dust, PCP). This agent was originally marketed as an anesthetic agent, but it was quickly removed from the market because of extreme psychotic reactions. Interestingly, ketamine, another NMDA antagonist, is still used today as an anesthetic. Emergence reactions are significantly milder than those seen with phencyclidine and are usually easily controlled with benzodiazepines.

A possible role for ibogaine acting at NMDA receptors is supported by the observation that ibogaine has appreciable affinity for this binding site (*24,25*). Popik and associates investigated the effects of ibogaine on MK 801 (dizocilpine)-trained mice in a T-maze. These authors observed approximately 70% dizocilpine-appropriate responding at an ibogaine dose of 100 mg/kg (*26*). Subsequent studies suggest that this interaction does not play a major role in the stimulus effects of ibogaine at lower doses, as neither phencyclidine nor MK 801 produced significant substitution in ibogaine-trained subjects (*27*). Correspondingly, ibogaine failed to substitute for phencyclidine in phencylidine-trained rats and monkeys (*28*) and MK 801-trained rats (*29*). The most plausible explanation for the contrast between these results and those of Popik, *et al.* would be dose and species differences.

F. Opioids in Ibogaine-Trained Subjects

Ibogaine's effects on addiction and withdrawal phenomena naturally lead to questions regarding its effects on opiate systems. The results of drug discrimination studies with opioids in ibogaine-trained subjects are quite interesting. Specifically neither mu- nor kappa-agonists substituted for ibogaine. No substitution, but weak partial antagonism, was seen with the pure antagonist naloxone. An intermediate level of substitution, but no significant antagonism, was observed with naltrexone (55.6%) (*27*). Also, in rats trained with the kappa-agonist U50,488, no substitution was seen with ibogaine (*29*). However, significant generalization (60-70%) was observed with the mixed agonist/antagonist compounds pentazocine, diprenorphine, and nalorphine (*27*).

Interestingly, the intermediate substitution produced by diprenorphine and nalorphine was antagonized by naloxone (*27*). Although the implications of these

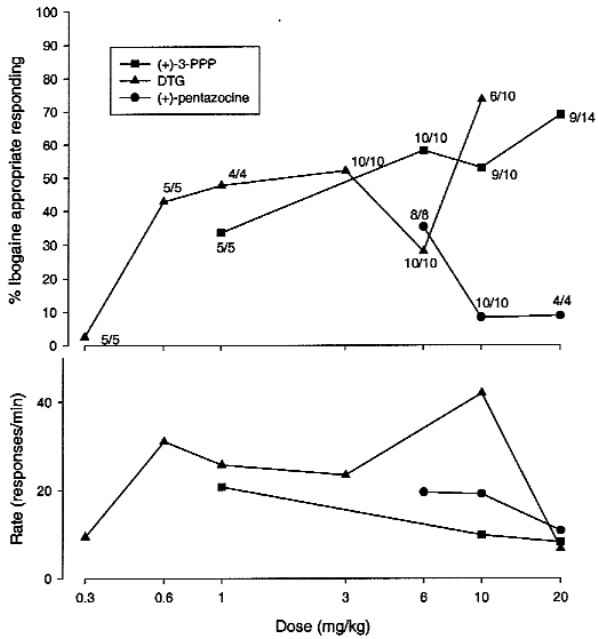


FIGURE 5. The dose response relationships for s ligands in rats trained to discriminate ibogaine (10.0 mg/kg, i.p., 60 minutes presession) from water. All agents were administered i.p., 30 minutes presession. The ratio adjacent to each of the points represents the number of subjects completing the test session over the number of subjects participating in each test session. *Taken from reference 27 with permission.*

results are not clear, they do suggest a role for opiate receptors in the mechanism of action of ibogaine. Further studies will be necessary to clarify this.

G. Sigma Ligands in Ibogaine-Trained Rats

In keeping with its unusual pharmacological profile, ibogaine has appreciable affinity for sigma (σ) receptors of the σ_2 subtype (*30,31*). Sigma receptors are a relatively new discovery, and hence, compared to other receptors, little is known about them. Thus, we are only beginning to characterize pharmacological agents as agonists or antagonists at these receptors. Nonetheless, ibogaine appears relatively selective for the σ_2 subtype. Several sigma ligands were tested in ibogaine-trained rats, and it was observed that nonselective sigma ligands (DTG, (+)-3-PPP) produced intermediate levels of substitution (Figure *5*), while the σ_1 selective agents (+)-SKF 10,047 and (+)-pentazocine failed to substitute (*27*).

Unfortunately no σ_2-selective agents were available at the time of these studies. Because we are still in the early stages in the study of the pharmacology of these receptors, all that can be concluded from these studies is that sigma receptors of the σ_2 subtype play a role in the ibogaine discriminative stimulus. As more selective sigma ligands are discovered, the exact role of these receptors in ibogaine's mechanism of action will hopefully become more clear.

H. Noribogaine

In radioligand binding assays, ibogaine shows remarkably low affinity for most known receptors (micromolar vs. nanomolar) (*32*). This, taken together with the observation that ibogaine's pharmacological activity is relatively long lived, suggests the possibility that a long-acting metabolite may mediate many of ibogaine's pharmacological effects; noribogaine (10-hydroxyibogamine) is thought to be such an agent (*33*).

10-Hydroxyibogamine appears to be similar to ibogaine in its stimulus properties, but it does not substitute completely for the parent compound, as illustrated in Figure 1 (*3*). Zubaran and colleagues (*29*) observed similar results. These authors also looked at brain levels of ibogaine and its metabolite. Interestingly, they found the metabolite to be more potent than the parent compound in eliciting ibogaine-appropriate responding with ED_{50} values of 1.98 and 4.51 mg/kg, respectively. Brain levels of noribogaine were similar at behaviorally equi-effective doses of both agents (1.11 µg/g after administration of the ED_{50} of 10-hydroxyibogamine and 1.23 µg/g after the ED_{50} of ibogaine). These results suggest that the stimulus effects of ibogaine are mediated mainly by 10-hydroxyibogamine (*29*). Further studies will be necessary to confirm this.

III. Summary

The results of the studies described here support the hypothesis that ibogaine produces its effects via selective interactions with multiple receptors. It appears that 5-HT_{2A}, 5-HT_{2C}, and σ_2 receptors are involved in mediating the stimulus effects of ibogaine. In addition, opiate receptors may also be involved. In contrast, σ_1, PCP/MK-801, 5-HT_3, and 5-HT_{1A} receptors do not appear to play a major role.

Ibogaine's hallucinogenic effects may be explained by its interactions with 5-HT_{2A} and 5-HT_{2C} receptors, while its putative antiaddictive properties may result from its interactions with σ_2 and opiate receptors. Alternatively, the possibility that ibogaine's hallucinogenic properties underlie its antiaddictive effects, as previously suggested (*34*), would support a role for 5-HT_2 receptors in mediating the reported therapeutic effects of ibogaine.

Certainly many questions remain regarding ibogaine's mechanism of action. Although drug discrimination will be useful for answering some of those questions, the true potential of this technique is realized when it is combined with other techniques. The next few years promise to be fruitful with respect to our understanding of this agent. Reasons supporting this belief include advances in the study of sigma receptors, interest in ibogaine's effects on second messenger systems, and the development of ibogaine congeners such as 18-methoxycoronaridine (*35*).

In conclusion, the aforementioned studies should serve to guide further endeavors. Pertinent questions have been generated: What is the role of sigma receptors in the effects of ibogaine, especially with regard to addiction? How does ibogaine affect opiate neurotransmission? What effects, if any, do the Harmala alkaloids have on addiction phenomena? What is the mechanism of action of harmaline? Can 10-hydroxyibogamine serve as a discriminative stimulus and, if so, what receptor interactions mediate its stimulus effects? Does the ibogaine-trained stimulus generalize to novel agents, including 18-methoxycoronaridine?

Acknowledgments

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References

1. J.C. Winter, *NIDA Res. Monograph* **146,** 157 (1994).
2. R.T. Kelleher and L.H. Morse, *in* "Reviews of Physiology, Biochemistry, and Behavior," Volume 60, pp. 2-56. Springer-Verlag, New York, 1968.
3. S. Helsley, R.A.Rabin, and J.C. Winter, *Life Sci.* **60,** PL147 (1997).
4. D. Fiorella, R.A. Rabin, and J.C. Winter, *Psychopharmacology* **121,** 347 (1995).
5. D. Fiorella, R.A. Rabin, and J.C. Winter, *Psychopharmacology* **121,** 357 (1995).
6. D. Fiorella, S. Helsley, D.S. Lorrain, R.A. Rabin, and J.C. Winter, *Psychopharmacology* **121,** 364 (1995).
7. P.A. Palumbo and J.C. Winter, *Pharmacol. Biochem. Behav.* **43,** 1221 (1992).
8. M.D. Schechter and T.L. Gordon, *Eur. J. Pharmacol.* **249,** 79 (1993).
9. S. Helsley, D. Fiorella, R.A. Rabin, and J.C. Winter, *Pharmacol. Biochem. Behav.* **59,** 419 (1998).
10. J.C. Winter, *Pharmacol. Biochem. Behav.* **20,** 201 (1984).
11. S. Helsley, R.A. Rabin, and J.C. Winter, *Prog. Neuro-Psychopharmacol. Biol. Psych.* **23,** 317 (1999).
12. J.C. Winter, S. Helsley, D. Fiorella, and R.A. Rabin, *Pharmacol. Biochem. Behav.* **63,** 507 (1999).
13. C. Naranjo, *Clin. Toxicol.* **2,** 209 (1969).
14. E.N. Petersen, *Eur. J. Pharmacol.* **94,** 117 (1983).
15. J.-H. Trouvin, P. Jacqmin, C. Rouch, M. Lesne, and C. Jacquot, *Eur. J. Pharmacol.* **140,** 303 (1987).
16. D.C. Deecher, M. Teitler, D.M. Soderlund, W.G. Bornmann, M.E. Kuehne, and S.D. Glick, *Brain Res.* **571,** 242 (1992).
17. S.D. Glick, M.E. Kuehne, J. Raucci, T.E. Wilson, D. Larson, R.W. Keller, Jr., and J.N. Carlson, *Brain Res.* **657,** 14 (1994).
18. S.L.T. Cappendijk, D. Fekkes, and M.R. Dzoljic, *Behav. Brain Res.* **65,** 117 (1994).
19. S. Helsley, R.A. Rabin, and J.C. Winter, *Eur. J. Pharmacol.* **345,**139 (1998).
20. B. Grella, M. Dukat, R. Young, M. Teitler, K. Herrick-Davis, C.B. Gauthier, and R.A. Glennon, *Drug Alc. Dep.* **50,** 99 (1998).
21. D.G. Spencer, T. Glaser, and J. Traber, *Psychopharmacology* **93,** 158 (1987).
22. J.C. Winter, R.A. Fillipink, D.M. Timineri, S. Helsley, and R.A. Rabin, *Pharmacol. Biochem. Behav.* **65,** 75 (2000).
23. J. Willetts, R.L. Balster, and J.D. Leander, *Trends Pharmacol. Sci.* **11,** 423 (1990).
24. P. Popik, R.T. Layer, and P. Skolnick, *Psychopharmacology* **114,** 672 (1994).
25. R.T. Layer, P. Skolnick, C.M. Bertha, U.K. Bandarage, M.E. Kuehne, and P. Popik, *Eur. J. Pharmacol.* **309,** 159 (1996).
26. P. Popik, R.T. Layer, L.H. Fossom, M. Benveniste, B. Geter-Douglass, J.M. Witkin, and P. Skolnick, *J. Pharmacol. Exp. Ther.* **275,** 753 (1995).
27. S. Helsley, R. Filipink, W.D. Bowen, R.A. Rabin, and J.C. Winter, *Pharmacol. Biochem. Behav.* **59,** 495 (1998).
28. H.E. Jones, H. Li, and R. Balster, *Pharmacol. Biochem. Behav.* **59,** 413 (1998).
29. Zubaran, M. Shoaib, I.P. Stolerman, J. Pablo, and D.C. Mash, *Neuropsychopharmacol.* **21,** 119 (1999).
30. R.H. Mach, C.R. Smith, and S.R. Childers, *Life Sci.* **57,** PL 57 (1995).
31. W.D. Bowen, B.J. Vilner, W. Williams, C.M. Bertha, M.E. Kuehne, and A.E. Jacobson, *Eur. J. Pharmacol.* **279,** R1 (1995).
32. P.M. Sweetnam, J. Lancaster, A. Snowman, J.L. Collins, S. Perschke, C. Bauer, and J. Ferkany, *Psychopharmacology* **118,** 369 (1995).
33. D.C. Mash, J.K. Staley, M.H. Baumann, R.B. Rothman, and W.L. Hearn, *Life Sci.* **57,** PL 45

(1995).
34. J.H. Halpern, *Addiction Res*. **4,**177 (1996).
35. S.D. Glick, M.E. Kuehne, I.M. Maisonneuve, U.K. Bandarage, and H.H. Molinari, *Brain Res.* **719,** 29 (1996).