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Stimulus Effects of Ibogaine in Rats Trained With Yohimbine, DOM, or LSD

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PALUMBO, P. A. AND J. C. WINTER. *Stimulus effects of ibogaine in rats trained with yohimbine, DOM, or LSD.* PHARMACOL BIOCHEM BEHAV 43(4) 1221–1226, 1992.—The stimulus effects of ibogaine were compared with those of yohimbine, an α_2-adrenoceptor antagonist, 2,5-dimethoxy-4-methylamphetamine (DOM), a 5-hydroxytryptamine$_2$ (5-HT$_2$) agonist, and lysergic acid diethylamide (LSD), a nonspecific 5-HT agonist. Rats were trained with either yohimbine (6 mg/kg), DOM (0.6 mg/kg), or LSD (0.1 mg/kg) vs. no treatment in a two-lever discrimination task. Tests of generalization were then conducted with ibogaine. In yohimbine-trained animals, 39.7% of responses following ibogaine (15 mg/kg) were on the drug-appropriate lever, but this response level was not significantly different from no treatment-appropriate responding. A response distribution that was significantly different from responding under both drug and no treatment training conditions was observed in DOM-trained rats after administration of 15 mg/kg ibogaine. Pizotyline (BC-105) blocked all DOM-appropriate responding produced by ibogaine. In LSD-trained animals, 20 mg/kg ibogaine mimicked LSD. Pizotyline blocked LSD-appropriate responding produced by ibogaine in five of six animals. The present data suggest the involvement of 5-HT$_2$ receptor activity, and the possibility of a 5-HT$_{1A}$ contribution, in the stimulus properties of ibogaine.

Ibogaine Yohimbine DOM LSD Stimulus control Rats Serotonin receptors

IBOGAINE, an indolealkylamine derivative, produces central stimulatory and anxiogenic effects in animals (5,25). Anxiogenic effects were inferred from observations that cats became markedly excited and attempted to hide or escape after ibogaine administration (25), while dogs became more tense and alert (5). In man, ibogaine has central stimulatory effects and has been reported to be hallucinogenic (24,25). Ibogaine appears to influence multiple neurotransmitter systems in the brain. Thus, head and body tremors characteristically produced by serotonergic stimulation occur in rats after ibogaine administration (29), while the central stimulatory effects of ibogaine are blocked by atropine (25), and ibogaine actively displaces the dopamine antagonist haloperidol from binding sites in calf brain (32).

In the 1960s, claims were made that ibogaine could disrupt addiction to heroin and cocaine (19). Two U.S. patents have been awarded in which ibogaine is presented as an effective treatment for narcotic addiction (4,499,096, Feb. 12, 1985) and for cocaine and amphetamine abuse (4,587,243, May 6, 1986). In rats, ibogaine was recently shown to produce a persistent decrease in morphine self-administration (12). Because ibogaine is known to depress levels of the dopamine metabolites 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) in certain brain areas for at least 19 h after administration (21), Glick and coworkers (12) suggested that dopaminergic systems may be involved in this ibogaine effect.

The purpose of the present study was to characterize the stimulus effects of ibogaine by comparison with those of 2,5-dimethoxy-4-methylamphetamine (DOM), yohimbine, and lysergic acid diethylamide (LSD). DOM was chosen as a reference compound because of its efficacy as a discriminative stimulus (30), its known hallucinogenic activity (27), and its highly selective affinity for the 5-hydroxytryptamine$_2$ (5-HT$_2$) receptor (7,11,26). Mimickry of the stimulus effects of DOM by those of ibogaine was predicted on the basis of ibogaine's hallucinogenic activity in man (24) and the presence of a 5-methoxy-*N*,*N*-dimethyltryptamine (MDMT) moiety within its structure. Glennon and coworkers (9) found that the stimulus effects of MDMT mimicked those of DOM. Yohimbine, like ibogaine, is an indolealkylamine derivative with central stimulatory and anxiogenic effects that have been observed in man (16) and animals (3,5). Anxiogenic effects in animals have been inferred from results in which yohimbine increased alertness and tenseness in dogs (5) and acted as a "stress inoculation" in rats (3). Although yohimbine is in general regarded as a selective α_2-adrenoceptor antagonist, behavioral (35,37,38) and biochemical (38) evidence suggests that yohimbine may also act at the 5-HT$_{1A}$ receptor. Thus, the stimulus effects of yohimbine provide a useful reference point for the activity of ibogaine at both adrenergic and serotonergic receptor sites. The nonspecific serotonin agonist LSD was chosen as a third reference compound. LSD is an indoleakyalamine compound

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that has high affinity for 5-HT_{1A}, 5-HT_{1B}, and 5-HT_2 receptor sites (36). This drug is well known to be hallucinogenic (15) and serves as an effective discriminative stimulus (14). We anticipated that ibogaine generalization tests in LSD-trained rats would complement test data from DOM- and yohimbine-trained animals in an investigation of the relative roles of different serotonin receptor types in the stimulus effects of ibogaine.

In the event that ibogaine would produce DOM-appropriate and/or LSD-appropriate responding, we intended to attempt blockade of these effects with 10 mg/kg pizotyline (BC-105). It has been reported that pizotyline binds with high affinity at 5-HT_2 receptor sites and with lesser affinity at 5-HT_1 sites (18,36). Winter and Rabin (36) used 10 mg/kg pizotyline vs. 1 mg/kg DOM and 0.1 mg/kg LSD. Both DOM and LSD are believed to produce their stimulus effects primarily by 5-HT_2 actions (10,11). Antagonism of the stimulus effects of both DOM and LSD was observed, and all animals tested completed their test sessions (36). Colpaert and coworkers (2) used 10 and 40 mg/kg pizotyline vs. 0.16 mg/kg LSD. Although 40% reductions in response rates as compared to control response rates were observed at both doses of pizotyline, antagonism of LSD stimulus effects was also observed at both doses.

METHOD

Animals

Male Fischer-344 rats were obtained from Harlan-Sprague-Dawley (Indianapolis, IN). They were housed in pairs under a natural light-dark cycle and allowed free access to water in the home cage. Subjects were food deprived and maintained at weights ranging from 234 to 323 g.

Apparatus

Two small-animal test chambers (Colbourn Instruments, Lehigh Valley, PA; model E 10-10) were used for all experiments. These were housed in larger light-proof, sound-insulated boxes, which contained a houselight and an exhaust fan. Chambers contained two levers mounted at opposite ends of one wall. Centered between the levers was a dipper, which delivered 0.1 ml sweetened condensed milk diluted 2 : 1 with tapwater.

Procedure

Training. After learning to drink from the dipper, subjects were trained to depress first one and then the other of the two levers. The number of responses required before reinforcement was given was gradually increased from 1 to 10, and all subsequent training and testing involved a fixed-ratio 10 (FR 10) schedule of reinforcement. Subjects were then assigned to one of three groups and discrimination training was begun. Prior to a 10-min training session, animals received either an IP drug injection or no treatment. Following drug administration, every 10th response on the lever designated as drug appropriate was reinforced. Similarly, responses on the opposite lever were reinforced in the absence of treatment. For one half the subjects in each group, the left lever was designated as the drug-appropriate lever. The right lever was drug appropriate for the remaining animals. Each rat was subjected to one training session per day for 5 consecutive days per week. Training conditions were alternated on this basis: no treatment on Monday, Wednesday, and Friday and drug treatment on Tuesday and Thursday. Drug-induced stimulus control was assumed to be present when 83% or more of all responses prior to delivery of the first reinforcer were on the appropriate lever for five consecutive sessions. For groups I, II, and III, the training drugs were yohimbine (6 mg/kg), DOM (0.6 mg/kg), and LSD (0.1 mg/kg), respectively. Drug injections were given 15 min before drug training sessions.

Tests of generalization. After drug-induced stimulus control was established, generalization tests or tests of antagonism were conducted in groups I, II, and III. Tests were conducted once per week (on Thursday or Friday) in each animal so long as performance during the preceding training sessions did not fall below a criterion of 83% correct responding. Thus, a minimum of three training sessions separated test sessions. If an animal did not perform according to the 83% correct criterion, testing was resumed only after responses were 83% correct before the first reinforcement for five consecutive training sessions. In general, tests with a given dose of ibogaine or ibogaine plus antagonist were balanced between Thursdays (following no treatment training sessions) and Fridays (following drug training sessions). During test sessions, no responses were reinforced, and the session was terminated after the emission of 10 responses on either lever. The distribution of responses between the two levers was expressed as the percentage of the total responses emitted on the drug-appropriate lever.

To ascertain that the injection procedure itself was not the basis for the observed discrimination, animals received vehicle generalization tests. Animals were injected with the appropriate vehicle and tested 15 min later. For ibogaine generalization tests, animals were injected with ibogaine 15 min prior to test sessions. When animals were tested with a combination of ibogaine and pizotyline, the latter drug was injected 60 min before and ibogaine 15 min before the test session.

Drugs

Yohimbine HCl and ibogaine HCl were purchased from Aldrich Chemical Co. (Milwaukee, WI). These were dissolved in distilled water and a minimal amount of absolute ethanol. Racemic DOM and LSD were provided by the National Institute on Drug Abuse (Rockville, MD). Pizotyline (pizotifen maleate) was obtained from Sandoz Pharmaceuticals (East Hanover, NJ). These were dissolved in 0.9% saline solution.

Statistics

Comparisons were made between data from test sessions and data from immediately preceding training sessions. Paired *t*-tests were used to determine the statistical significance of observed differences in response distribution (13). A difference was considered significant when the calculated value of *t* exceeded the tabulated value of *t* at the 5% level.

RESULTS

Figure 1 shows that rats trained to discriminate the stimulus effects of yohimbine did not generalize to those of ibogaine. At ibogaine doses of 1, 3, 10, and 20 mg/kg, responding was clearly similar to no treatment-appropriate responding. At 15 mg/kg, a moderate degree of drug-appropriate responding was observed (39.7%), but this was not statistically significantly different from responding after no treatment. Only 2 of 10 animals completed the test at 20 mg/kg, and the response rate fell to 0.7/min.

The results of tests of generalization in rats trained with

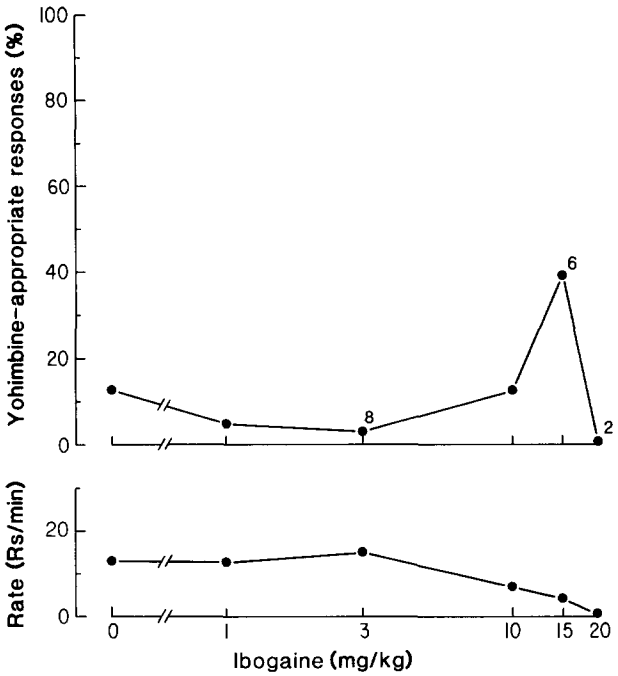

FIG. 1. Effects of ibogaine in 10 rats trained with yohimbine (6 mg/kg) as a discriminative stimulus. The number of animals completing the test at a given dose, if fewer than 10, is indicated next to that point. Each point is the mean of one determination in each of the animals that completed the test. Ordinate, upper panel; Mean percentage of responses on the yohimbine-appropriate lever; ordinate, lower panel; Number of responses per minute; abcissa; dose plotted on a log scale.

DOM are shown in Fig. 2. Animals gave responses that did not differ from no treatment-appropriate responding at doses of 3 and 10 mg/kg ibogaine. At 15 mg/kg, intermediate responding was observed, that is, responding was significantly different from both DOM-appropriate and no treatment-appropriate responding. Because 20 mg/kg completely suppressed responding in the first three animals tested, no further tests were carried out at this dose. In those animals that responded at least in part on the DOM-appropriate lever when tested with 10 or 15 mg/kg ibogaine, an attempt was made to block this responding with the serotonin receptor antagonist pizotyline at a dose of 10 mg/kg. If responding was suppressed at this dose, a further attempt at antagonism was made with 3 mg/kg pizotyline. Table 1 shows that DOM-appropriate responding following ibogaine was completely blocked by pizotyline.

As shown in Fig. 3, a dose of 10 mg/kg ibogaine produced 47% LSD-appropriate responding in LSD-trained rats, an intermediate result. At 20 mg/kg ibogaine, animals emitted 82.3% of their responses on the LSD-appropriate lever. This was significantly different from no treatment-appropriate responding and no different from responding under the LSD training condition. Thus, 20 mg/kg ibogaine occasioned the LSD response, although it must be noted that only three of eight animals were able to complete the test. In animals that responded at least in part on the LSD-appropriate lever after 10 or 20 mg/kg ibogaine, 10 mg/kg pizotyline was used in an attempt to antagonize this effect. If responding was suppressed, the antagonistic dose of pizotyline was lowered to 3 mg/kg. Pizotyline blocked LSD-appropriate responding produced by ibogaine in five of six animals (Table 2).

Administration of water-ethanol vehicle alone in yohimbine-trained rats, or saline alone in DOM- and LSD-trained rats, produced responding appropriate for the no-treatment training conditions (Figs. 1-3).

DISCUSSION

Because ibogaine and yohimbine have anxiogenic effects in common (16,25), and because both are reported to produce central effects that are mediated by serotonin (29,35), we predicted at least some similarity between the stimulus properties of the two drugs. At the 15-mg/kg dose of ibogaine, 6 of 10 yohimbine-trained animals completed generalization tests. Yohimbine-appropriate response percentages for these animals were 100, 100, 29, 9, 0, and 0, with a mean of 39.7%. Although this mean does not differ statistically from no treatment-appropriate responding in the paired t-test, it is moderately higher than our training criterion for no treatment responding (no more than 17% of responses on the yohimbine-appropriate lever). These data seem to suggest that the stimulus properties of ibogaine and yohimbine may have a shared component. This component might be due to 5-HT_{1A} receptor stimulation because yohimbine seems to have 5-HT_{1A} activity (37,38) and ibogaine can induce forepaw treading and flat body posture (29), two behaviors typical of 5-HT_{1A} receptor activation (31). However, it must be added that ibogaine appears to have negligible affinity for the 5-HT_{1A} receptor; the K_i value for ibogaine at 5-HT_{1A} is greater than 10,000 nM (Rabin and Winter, unpublished).

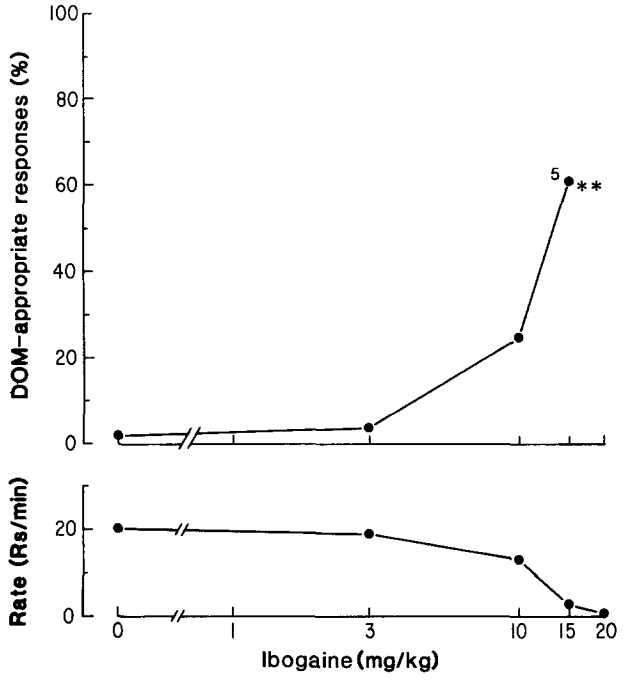

FIG. 2. Effects of ibogaine in nine rats trained with 2,5-dimethoxy-4-methylamphetamine (DOM) (0.6 mg/kg) as a discriminative stimulus. The number of animals completing the test at a given dose, if fewer than nine, is indicated next to that point. **Significant difference from both drug-appropriate and no treatment-appropriate responding ($p < 0.05$). All other details are as in Fig. 1.

TABLE 1

PIZOTYLINE ANTAGONISM OF DOM-APPROPRIATE RESPONDING PRODUCED BY IBOGAINE

Animal	10 mg/kg Ibogaine	15 mg/kg Ibogaine	10 mg/kg Ibogaine + 10 mg/kg Pizotyline	15 mg/kg Ibogaine + 10 mg/kg Pizotyline	15 mg/kg Ibogaine + 3 mg/kg Pizotyline
22 (13)	47 (18)	0 (6)	0 (20)		
23 (16)	0 (6)	100 (2)		0 (7)	
24 (15)	0 (33)	77 (2)		–	–
25 (16)	0 (11)	38 (6)		0 (15)	
26 (38)	0 (13)	91 (6)		–	0 (8)
30 (16)	91 (6)	–	0 (12)		

Each value is the percentage of responses emitted on the DOM-appropriate lever before the first reinforcement. –, the animal did not complete the test. The response rate for each test session is given in parentheses. Numbers in parentheses in the first column are response rates for vehicle generalization tests.

When ibogaine generalization tests were carried out in DOM-trained animals, a bona fide intermediate result was observed. Thus, the 15-mg/kg dose of ibogaine produced a response level of 61.2% on the drug-appropriate lever, a value significantly different from responding under each of the training conditions. Because the unique stimulus properties of a particular drug probably result from the stimulation of more than one pharmacological receptor type (1,34), intermediate responding may indicate partial similarity between the test drug and the training drug (4,33). Therefore, partial similarity between the stimulus properties of DOM and ibogaine is suggested by the 61.2% response level on the DOM-appropriate lever after 15 mg/kg ibogaine.

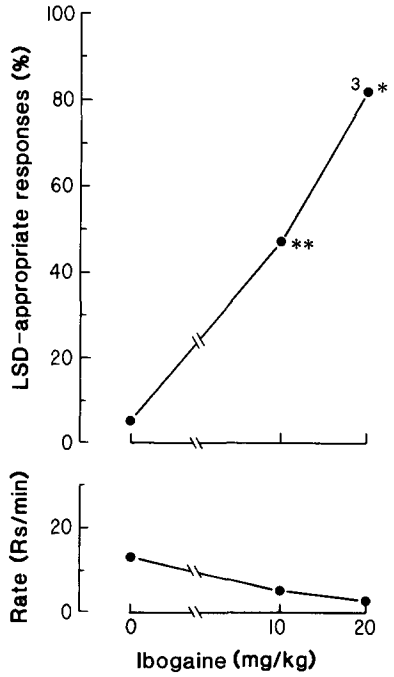

FIG. 3. Effects of ibogaine in eight rats trained with lysergic acid diethylamide (LSD) (0.1 mg/kg) as a discriminative stimulus. The number of animals completing the test at a given dose, if fewer than eight, is indicated next to that point. **Significant difference from both drug-appropriate and no treatment-appropriate responding ($p < 0.05$). *Significant difference from no treatment-appropriate responding ($p < 0.05$) and no difference from LSD-appropriate responding. All other details are as in Fig. 1.

Common activity at the 5-HT_2 receptor may be responsible for this partial similarity. It is highly probable that DOM stimulus control is primarily mediated by activity at the 5-HT_2 receptor. DOM stimulus effects mimic those of the nonspecific 5-HT agonists LSD, quipazine, and MDMT (10,28), while the stimulus effects of the specific 5-HT_{1A} and 5-HT_{1B} agonists 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) and 1-(*m*-trifluoromethylphenyl)piperazine (TFMPP), respectively, do not mimic those of DOM (6,8). Results of tests with specific antagonists at 5-HT_2 receptors also support a prominent role for 5-HT_2. Thus, ketanserin and pirenpirone block the stimulus effects of DOM (11,36). Our observations a) that rats trained to discriminate the stimulus effects of DOM partially generalize to those of ibogaine and b) that the 5-HT_2 antagonist pizotyline blocks all DOM-appropriate responding produced by ibogaine support a common 5-HT_2 component in the actions of both drugs.

Our interpretation of the pizotyline antagonism results must be tempered with a word of caution. Pizotyline has been reported to bind with high affinity at both 5-HT_2 receptor sites and histamine (H_1) receptor sites and with moderately high affinity at muscarinic, dopaminergic, and α_1-adrenergic receptor sites (18). Minnema and coworkers (23) found that the stimulus effects of pizotyline were only partially similar to those of the putative 5-HT antagonists methysergide and metergoline, while the stimulus effects of the phenothiazine antihistamine promethazine mimicked those of pizotyline. A dose of 1 mg/kg pizotyline has been shown to attenuate MDMT-appropriate responding produced by 1.5 mg/kg MDMT but not that produced by 3.0 mg/kg MDMT (39). Doses of pizotyline up to 10 mg/kg did not antagonize responding produced by 3.0 mg/kg MDMT (39). Citing these results, and also unpublished work in which promethazine failed to antagonize the stimulus effects of both 1.5 and 3.0 mg/kg MDMT, Young and coworkers (40) suggested that pizotyline may have predominantly antiserotonergic effects at low doses and predominantly antihistaminergic effects at high doses. Thus, there is a possibility that the antagonistic effects of pizotyline may be mediated, at least in part, by its actions at other, especially histaminergic, receptor types.

Our results in yohimbine-trained and DOM-trained rats strongly implicate 5-HT_2 involvement in the stimulus properties of ibogaine and suggest the possibility of a 5-HT_{1A} contribution. On this basis, we expected that ibogaine would mimic

TABLE 2

PIZOTYLINE ANTAGONISM OF LSD-APPROPRIATE RESPONDING PRODUCED BY IBOGAINE

Animal	10 mg/kg Ibogaine	20 mg/kg Ibogaine	10 mg/kg Ibogaine + 10 mg/kg Pizotyline	10 mg/kg Ibogaine + 3 mg/kg Pizotyline	20 mg/kg Ibogaine + 10 mg/kg Pizotyline
24 (15)	77 (5)	–	–	0 (14)	
30 (7)	100 (4)	–	–	0 (16)	
43 (11)	83 (3)	–	0 (6)		
45 (10)	23 (5)	100 (15)			0 (19)
46 (15)	67 (5)	100 (2)	0 (5)		13 (14)
47 (14)	*	47 (2)			63 (2)

Details are as in Table 1.

*Animal 47 was not tested at 10 mg/kg. The eighth animal tested at this dose subsequently died.

LSD in LSD-trained animals because LSD binds with high affinity at both 5-HT_{1A} and 5-HT_2 receptors (36). The intermediate result in LSD-trained animals with a dose of 10 mg/kg ibogaine, and the stimulus generalization that occurred between LSD and 20 mg/kg ibogaine, indeed indicate similarity between the stimulus effects of ibogaine and LSD. Further, pizotyline blocked LSD-appropriate responding produced by ibogaine in five of six animals. These results are consistent with 5-HT_{1A} and 5-HT_2 involvement in the stimulus effects of ibogaine.

Another explanation for the observation that complete stimulus generalization was observed between LSD and ibogaine, while only partial stimulus generalization was observed between DOM and ibogaine, besides that provided by the possibility of a 5-HT_{1A}-mediated component in the stimulus effects of ibogaine, involves dopaminergic systems. In a recent report, Meert and coworkers (22) found that the dopaminergic (D_2) antagonist haloperidol potentiated antagonism by ritanserin (a 5-HT_2 antagonist) of the LSD discriminative cue and concluded that LSD discriminative stimulus effects may partly involve a catacholiminergic mechanism. Ibogaine also seems to affect dopaminergic systems in the brain (20,21,32). Therefore, the greater similarity between the stimulus effects of LSD and ibogaine may be due to common dopaminergic effects.

Glennon and coworkers (10) observed a correlation between ED_{50} values of $5HT_2$ agonists for generalization to DOM and doses of those agonists that produce hallucinations in man and concluded that $5HT_2$ receptor stimulation may be responsible for hallucinogenic activity. Consequently, our results give credence to anecdotal clinical evidence of ibogaine's hallucinogenic properties presented by Naranjo (24). Hallucinogenic drugs were widely abused in the United States in the mid-1960s (17). Although ibogaine never achieved the notoriety of drugs such as LSD and DOM, it is designated as a controlled substance in the United States and Belgium. The possible abuse potential of ibogaine must be considered in assessment of benefit vs. risk with regard to its purported value in the treatment of drug addiction.

This work just begins to elucidate the mechanism by which ibogaine produces its stimulus effects. Further investigation of the relative roles of the different serotonin receptor types in ibogaine stimulus effects must include: a) a comparison of the stimulus properties of ibogaine with those of other nonspecific serotonin agonists and with those of specific 5-HT_{1A} and 5-HT_2 agonists; b) attempts to block ibogaine stimulus effects with more specific 5-HT_{1A} and 5-HT_2 antagonists; and c) receptor binding studies with ibogaine involving the various serotonin receptor types and perhaps even α_2-adrenoceptors.

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