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Comparison of the behavioral effects of ibogaine from three sources: mediation of discriminative activity

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Ibogaine is an alkaloid employed for its hallucinatory properties in West Central Africa which has been the subject of alleged efficacy as an aid in the interruption and treatment of chemical dependency. The major sources of the Schedule I agent are: Sigma Chemical Co., the National Institute on Drug Abuse and as NDA International Inc.'s Endabuse. The intent of the present study was to, for the first time, train rats to discriminate the interoceptive stimuli produced by (10 mg/kg, intraperitoneally administered) ibogaine. Once trained, these rats were used to investigate the dose-response effects to ibogaine from each of the three suppliers. In addition, stimulus generalization to the dopamine antagonist CGS 10476B, as well as to the serotonergically active compounds fenfluramine, TFMPP (1-(m-trifluoromethylphenyl)piperazine, DOI (1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane), MDMA (3,4-methylenedioxymethamphetamine), quipazine and LSD, was tested. The results indicate that ibogaine is readily discriminable from its vehicle and that ibogaine from each of the three supplies produced statistically similar discrimination with ED_{50} values ranging from 2.5 to 3.4 mg/kg. In addition, various doses of the novel drugs tested produced, at best, intermediate ibogaine-appropriate responding and, thus, no drug tested can be considered to generalize to ibogaine-like stimuli. Discussion concerns the multiple actions of ibogaine that have been cited in the scientific literature. The similarity in potency of ibogaine from three potential suppliers should allow for pre-clinical work using any of these research samples to be comparable.

Ibogaine; Stimulus properties of drugs; 5-HT (5-hydroxytryptamine, serotonin)

1. Introduction

Ibogaine is the major alkaloid found in the cortex of the root of the *Iboga tabernanthe* shrub indigenous to West Central Africa, where it is used by hunters to remain motionless and combat fatigue, hunger and thirst while stalking their prey. At higher doses, iboga is employed for its hallucinatory properties in religious rituals of the Bwiti (male members) and Mbiri (female members) tribes (Stafford, 1983). Outside of these cultures, ibogaine has been shown to be stimulatory (Gershon and Lang, 1962), anxiogenic (Schneider and Sigg, 1957), as well as hallucinatory (Clineschmidt et al., 1978). Probably because of this latter effect, ibogaine appeared on the illicit drug market in the 1960's and was, subsequently (1970), assigned by the Food and Drug Administration to the Schedule I classification which indicated that it had no research/therapeutic usefulness and was a potentially addictive agent. In spite of this rather checkered history, ibogaine has been the subject of four U.S. patents which have been issued in anticipation of its proven efficacy in treating drug addiction (patent No. 4,499,096 for opiate treatment in 1985; No. 4,587,243 for stimulant abuse in 1986; No. 4,857,523 for alcoholism in 1989 and No. 5,026,697 for cigarette addiction in 1991; all issued to Mr. Howard S. Lotsof). Since ibogaine has been alleged to be useful in several anecdotal reports by heroin addicts, this has led to various U.S.-based (NDA International, Inc.) treatment collectives in Europe; nonetheless, the effectiveness of ibogaine as a treatment for drug addictions is still to be determined. The major source of ibogaine to (Schedule I license holding) research scientists doing pre-clinical studies has been the Sigma Chemical Co., St. Louis, MO. Most recently, all available ibogaine has been purchased from this source and recrystallized from ethanol to ensure purity by the Medications Development Division at NIDA (Dr. J. Biswas, personal communication). The third potential source is a synthetic product from Mr. Lotsof's NDA International Inc. where it holds the trade name Endabuse.

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The behavioral paradigm known as drug discrimination employs the interoceptive cueing effects of psychoactive drugs to produce differential operant responding and it has been shown to be stable, sensitive and specific in determining the mechanism of drug action (Glennon and Rosecrans, 1981; Schechter et al., 1989). Employing this procedure, the purpose of the present experimentation was twofold: (1) to train rats to discriminate 10 mg/kg ibogaine from its vehicle and, if successful, to test generalization to other serotonergically and dopaminergically active drugs; and (2) to test the discriminative potency of different doses of ibogaine using supplies from three different sources, viz., Sigma Chemical Co., St. Louis, MO; the Medication Development Division at NIDA and Endabuse from NDA International Inc. Determination of ED_{50} values for each of these compounds in animals trained to discriminate ibogaine at 10 mg/kg would act as a viable behavioral bioassay to correlate past (Sigma compound in animals; Endabuse in humans) and future (recrystallized Sigma compound from NIDA) preclinical experimentation employing this compound.

2. Materials and methods

2.1. Subjects

Twelve male Sprague-Dawley rats weighing 390–500 g at the onset of discriminative training were individually housed and their weights were adjusted by daily rationing of commercial rat chow to approximately 80–85% of their free feeding weights. Water was continuously available in the home cages which were kept at a regulated temperature (20–22°C) and maintained on a 12 h (06:00–18:00) light/12 h dark cycle.

2.2. Apparatus

Twelve standard rodent operant chambers (Lafayette, Instrument Corp., Lafayette, IN) each containing two levers situated 7 cm apart and 7 cm above a metal grid floor were used. Equidistant between the levers was placed a food receptacle that received delivery of a 45 mg Noyes food pellet. Each operant chamber was enclosed in a sound-attenuated cubicle with an exhaust fan and a 9 W house light. Solid-state programming equipment (Med Associates, Inc., St. Albans, VT) was located in an adjacent room and was used to control and record discrimination sessions.

2.3. Discriminative training

Drug discrimination training was based upon procedures described in detail elsewhere (Schechter, 1986; 1989). In all cases, there were two training phases. In the first phase, the food-deprived rat learned to press the lever indicating saline administration and received a food presentation for each correct response on a fixed ratio 1 (FR1) schedule. This schedule was made progressively more difficult, in daily 15 min sessions over 10 days, until an FR10 schedule was achieved, i.e., the rat had to press the lever 10 times to receive food. Throughout lever-press training, all rats received daily intraperitoneal (i.p.) injections of saline (0.9% sodium chloride, 1 ml/kg) 30 min prior to being placed into the two-lever operant chamber. Immediately following saline-lever training, the opposite lever was activated and rats received food for each correct response (FR1 schedule) after the i.p. administration of an equal volume of saline containing 10 mg/ml ibogaine. Daily sessions of 15 min duration with drug administration were conducted over 8 days until an FR10 schedule was attained. In order to minimize the effects due to any position preference, half of the rats ($n = 6$) responded on the left lever for food pellets in sessions following ibogaine injection, whereas the other half were given food after responding on the right lever following ibogaine injection. Responses on the opposite lever produced food pellets only after saline administration.

The second phase of drug discrimination training then began. The rats were trained 5 days per week with reinforcement on an FR10 schedule in a repeating biweekly sequence with ibogaine (I) and saline (S) administered according to the pattern: I,S,S,I,I; S,I,I,S,S. The rats had to respond on the appropriate lever to receive food reinforcement. Which lever was appropriate was dependent upon whether the ibogaine or saline was administered 30 min prior to the start of the session. Responses upon the inappropriate lever were recorded but produced no programmed consequence. The training criterion was reached when the animals selected the appropriate lever, according the drug injected at the onset of each training session (first ten responses accumulated on the state-appropriate lever), on at least eight of ten consecutive daily sessions.

2.4. Dose-response relationship to ibogaine

After the rats attained the discriminative training criterion, testing and training sessions of 15 min duration with alternating administrations of either ibogaine or its vehicle were continued on every second day. The procedure had the intent of maintaining and ensuring discrimination to the ibogaine vs. saline conditions. On alternate days, the rats received injections of doses of ibogaine different from the 10 mg/kg dose used in their training. The first series of dose-response experiments were conducted with the ibogaine from Sigma Chemical Co. The second and third dose-response experiments were conducted using the NIDA com-

pound and NDA, Inc.'s compound Endabuse, respectively. In the case of the latter two suppliers, ibogaine at each dose of 10.0, 7.5, 5.0 and 2.5 mg/kg was tested. With the originally trained Sigma Chemical Co. compound (since maintenance day sessions with the training 10 mg/kg were performed on interspersed days), it was the first lever pressed during these maintenance sessions that was used in calculating the dose-response experiments with ibogaine from this source. Each dose of ibogaine, from whichever source, was tested twice, once following a drug (10 mg/kg ibogaine from Sigma Chemical Co.) maintenance session and once following vehicle maintenance session. This counterbalancing was used to control for any possible residual influence from the previous maintenance session. If at any time during testing, a rat's maintenance discrimination fell below the 80% criterion (i.e., choosing the state-appropriate lever on less than eight of ten consecutive maintenance sessions), data on that animal was to be dropped from the results. This, however, did not occur during the entire experimentation.

2.5. *Stimulus generalization studies*

Tests of stimulus generalization were conducted after all of the rats had undergone dose-response determinations with the ibogaine from the three sources. In these generalization test sessions, the ibogaine-trained rats were challenged with various doses of other agents in order to determine whether or not they would recognize the challenge agent as producing stimulus effects similar or dissimilar to those produced by 10 mg/kg ibogaine. Maintenance of the ibogaine vs. saline discrimination was ensured by continuation of training sessions throughout this phase of the study. Interspersed between maintenance sessions were days used to test the effects of other drug and by employing this pattern, each novel test drug/dose was preceded by one ibogaine and one maintenance saline session. It was the first ten presses ('selected' lever) on these maintenance sessions which were used to judge if the animal was maintaining its discriminative performance to the training conditions. On days that novel drugs/doses were tested, the rats were immediately removed from the test chamber upon making ten responses on either of the two levers. This precluded any continued training with a drug or ibogaine dose that was not used for initial training, i.e., a drug/dose different from 10 mg/kg ibogaine. Stimulus generalization (transfer) from ibogaine to a test drug was said to occur when 80% of the rats, after being administered a given dose of a novel drug, made their first choice responses on the ibogaine-correct lever. This seemed appropriate as the original criterion to judge ibogaine-appropriate responding was, indeed, 80% of rats selecting the ibogaine-appropriate lever.

Each test drug was administered in a random order in at least two doses with the initial dose and post-administration time course for testing chosen from the literature (see section *2.7. Drugs*, below) available on that agent. Doses higher then those used were often tested but results were precluded by the appearance of behavioral disruption, i.e., long onset to lever pressing at the highest dose used. Drugs chosen for use and the rationale behind their choice were: CGS 10476B, a drug that has been shown to reduce the release of dopamine without any binding affinity to postsynaptic dopamine receptors (Altar et al., 1986; 1988); indirect (fenfluramine) and direct (putatively specific) 5-HT receptor agonists TFMPP (1-(m-trifluoromethylphenyl)piperazine) acting upon 5-HT_{1B} receptors; DOI (1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane) acting upon 5-HT_2 receptors; Glennon, 1987], as well as drugs thought to work on both serotonin and dopamine release and regarded as being hallucinatory (MDMA (3,4-methylenedioxymethamphetamine), quipazine and LSD; Glennon and Rosecrans, 1981).

2.6. *Measurements and statistics*

The lever pressed ten times first was designated as the 'selected' lever. The percentage of rats selecting the lever appropriate for ibogaine was the quantal measurement of discrimination and quantal data are presented as percent correct first choice responses on the ibogaine-correct lever. In addition, the number of responses on the ibogaine-correct lever divided by the total responses on both levers made prior to ten responses (including the ten on the ibogaine-correct lever) $\times$ 100, constitutes the quantitative measurement. This latter measurement was used to analyze data on both levers and to incorporate counts on the 'unselected' lever in the statistical analysis. The advantage in using both measurements has been previously discussed (Stolerman and D'Mello, 1981). The quantal data for the dose-response experiments were analyzed by a computer-based program (Tallarida and Murray, 1986) of the method of Litchfield and Wilcoxon (1949) which employs probit vs. log-dose effects and generates ED_{50} values.

2.7. *Drugs*

The following drugs (source; post-injection test interval) were used in this study: CGS 10476B (Ciba-Geigy; 30 min), *d,l*-fenfluramine hydrochloride (A.H. Robins; 30 min), TFMPP hydrochloride (Research Biochemicals Inc.; 15 min), DOI hydrochloride (Research Biochemicals Inc.; 30 min), MDMA hydrochloride (National Institute on Drug Abuse; 20 min), quipazine dimaleate (Research Biochemicals Inc.; 15 min) and lysergic acid diethylamide (National Institute on Drug

TABLE 1

Drug discriminative performance after novel drug tests (generalization) in rats trained to discriminate ibogaine from saline.

Drug	Dose (mg/kg)	Quantal	Quantitative (S.D.)
CGS 10476B	30	20.8	25.0 (19.3)
	20	41.7	38.0 (11.7)
	10	12.5	18.3 (7.9)
Fenfluramine	2.5	58.3	56.3 (8.4)
	2.0	70.8	60.0 (3.6)
	1.0	37.5	39.9 (1.2)
MDMA	2.5	41.7	41.3 (0.2)
	2.0	41.7	45.9 (2.4)
	1.5	45.8	47.4 (3.8)
Quipazine	2.5	29.2	40.3 (8.4)
	2.0	41.7	45.8 (15.3)
DOI	1.0	33.3	41.1 (5.8)
	0.5	33.3	37.5 (9.2)
TFMPP	2.5	45.8	52.2 (2.1)
	2.0	45.8	49.7 (7.4)
	1.0	33.3	38.4 (6.7)
LSD	0.12	33.3	33.3 (NA)
	0.06	25.0	34.5 (NA)

Abuse; 15 min). All drugs were dissolved in 0.9% saline and were injected i.p. in a volume of 1 ml/kg. All doses are calculated as the salt.

3. Results

The twelve rats learned to discriminate 10 mg/kg ibogaine (from Sigma Chemical Co.) from its saline vehicle in a mean (±S.D.) of 16.9 (3.0) sessions with a range of 12–25 sessions. Thus, by the 26th session (13 sessions with each of ibogaine and saline), all twelve rats were considered able to discriminate ibogaine from its vehicle; this makes ibogaine a reliable and readily discriminable psychoactive drug. Testing other drugs for generalization in these animals produced results represented in table 1. During all of these experiments with drugs other than 10 mg/kg ibogaine dose used for training, there was a consistent and reliable 80% criterion level performance during interspersed maintenance sessions with both 10 mg/kg ibogaine and saline. At no dose of any of these novel drugs did ibogaine-trained rats choose the ibogaine-correct lever on 80% or greater first-choice selections. In the case of quipazine and DOI, doses higher than those used produced behavioral disruption and in the case of LSD, inadequate quantities precluded a second trial at each dose. The greatest generalization was seen to occur with 2.0 mg/kg fenfluramine. This may be considered an intermediate result since this value is significantly different from responding under each of the two training conditions, i.e., $P < 0.05$ in Student's t-tests of quantitative data after 2.0 mg/kg fenfluramine (60.0 ± 3.6) and these measurements after either 10 mg/kg ibogaine or saline.

In contrast to these negative results, the dose-response experiments using commercially available (from Sigma Chemical Co.) vs. recrystallized (from ethanol by NIDA) vs. patented (Endabuse) ibogaine are detailed in table 2. The ED_{50} values (i.e., the dose calculated to allow for 50% of rats making first lever selections on the ibogaine-correct lever) of each of the dose-response curves using 2.5, 5.0, 7.5 and 10.0 mg/kg ibogaine in test sessions are not significantly different from each other.

4. Discussion

The present results constitute the first published indication that ibogaine is capable of controlling differential responding in a drug discrimination task. In fact, the rapid acquisition, as indicated by all rats learning to discriminate between ibogaine at 10 mg/kg by the 26th session, would indicate that the essential psychoactive properties of this drug are present and ibogaine is highly discriminable at the dose employed. The training dose of 10 mg/kg ibogaine is, in itself, within

TABLE 2

Commercial (Sigma) vs. recrystallized (NIDA) vs. patented (Endabuse) ibogaine: dose-response discrimination in rats ($n = 12$) trained to discriminate 10 mg/kg ibogaine (Sigma) from saline.

Dose (mg/kg)	Sigma		NIDA		Endabuse	
	Quantal	Quantitative (SD)	Quantal	Quantitative (SD)	Quantal	Quantitative (SD)
10.0	91.7	88.7 (0.9)	97.2	90.0 (7.5)	91.7	82.8 (1.4)
7.5	87.5	73.6 (10.7)	79.2	77.6 (5.0)	79.2	80.1 (18.2)
5.0	75.0	72.9 (13.5)	70.8	66.7 (12.9)	75.0	70.2 (0.9)
2.5	50.0	51.8 (20.7)	41.7	46.0 (0.6)	33.3	36.4 (18.7)
0.0 (Sal)	5.6	11.8 (17.0)	0.0	9.7 (6.5)	0.0	5.9 (0.8)
ED_{50} (95% CL)	2.51 (1.69–3.71)		3.14 (2.30–4.29)		3.37 (2.59–4.39)	

the range used in human abusers, i.e., 4–5 mg/kg ibogaine with behavioral alteration that last for 6 h (Naranjo, 1967) and is slightly lower than the therapeutic dose used by the International Coalition for Addict Self-Help, viz., 15–25 mg/kg to treat heroin addicts (H. Lotsof, personal communication).

The pharmacokinetic half-life of ibogaine has been estimated at approximately 1 h in both rats (Dharir, 1971)) and mice (Zetler et al., 1972). Interestingly, recent reports suggest that ibogaine (in higher doses than used here) has effects upon both morphine and amphetamine when administered 19 h prior to testing (Maisonneuve et al., 1991; Sershen et al., 1992a,b). If ibogaine had effects that persisted for 24 h, the ability of animals to be trained during the ibogaine, saline, saline, ibogaine, ibogaine (I,S,S,I,I; see section *2.3.*) sequence would have been precluded, in that, when ibogaine is followed by saline, any residual behavioral effects, or presence of an active metabolites, would have obscured the animals' ability to learn the non-drug, i.e. saline, discrimination. If ibogaine had worked by whatever mechanism of action, for example, in releasing a neurotransmitter or depleting a neurotransmitter for a long period of time, the next day administration of saline or, indeed, a second day administration of ibogaine (in the I,I training sequence) would occur during the time of neurotransmitter activity. Either case would, thus, produce a negative effect upon next day discriminative learning. This phenomenon has been shown to occur in that rats become acutely tolerant to the metabolite cathine when it is administered 24 h after cathinone, the parent compound, had been injected (Schechter, 1990).

As most of the pre-clinical experimentation with ibogaine has been reported by laboratories that acquired it from Sigma Chemical Co. compound No. I-7003 (Deecher et al., 1992; Glick et al., 1991; Maisonneuve et al., 1991; Schneider and Sigg, 1957; Sershen et al., 1992a,b; Sloviter et al., 1980), future research will permit acquisition of ibogaine solely from the National Institute of Drug Abuse. In addition, the use of ibogaine in the form of Endabuse, the trademarked procedure to synthesize ibogaine for use in human drug abusers, provides another source for the compound. Ibogaine was herein tested for its discriminative dose-response effects conducted in rats trained to the Sigma compound and tested with both the NIDA and Endabuse ibogaine. Results indicate that the drugs were equipotent. This result should preclude any potential difficulties in continued pre-clinical work (Sigma vs. NIDA), as well as mg/kg determinations and comparisons by NDA Inc. or other agencies using ibogaine in human addictive studies.

Unfortunately, the use of serotonergic and dopaminergic agents tested in ibogaine-trained rats did not provide a clear generalization and, therefore, no mechanism of ibogaine action is apparent from these results. The information from human abusers that ibogaine is hallucinatory (Naranjo, 1967) and the presence of the indole nucleus in ibogaine would suggest that the central effects are mediated by serotonin (Clineschmidt et al., 1978). At best, an intermediate result was seen with fenfluramine (70.8%, table 1) and this suggests partial similarity between ibogaine and this test drug, in that, a partial generalization occurred. Fenfluramine, however, is a serotonergic releaser (Sershen et al., 1992a) and the testing of more specific 5-HT receptor agonists, such as the 5-HT_{1B} ligand TFMPP and the 5-HT_2 agonist DOI, produced lesser discriminative generalization. Testing of the hallucinogens LSD and MDMA, likewise, produced less than 50% responding on the ibogaine-appropriate lever at the doses employed. These results, therefore, cannot clearly elucidate the mechanism of action by which ibogaine produces its discriminative stimulus effects. This result is not unexpected since the literature is replete with evidence as to the possibility that ibogaine works upon numerous neurotransmitters. For example, ibogaine has been seen to block the increase in dopamine release found in the limbic and striatal brain neurons and to attenuate the increased locomotor activity induced by both morphine (Maisonneuve et al., 1991) and cocaine (Broderick et al., 1992). It was on the basis of these results that CGS 10746B was thought to be a potential agonist. In addition, ibogaine (5–40 mg/kg, i.p.) was shown to dose-responsively increase the occurrence of the 'serotonin syndrome' in rats (which includes forepaw padding, splayed hind limbs and side-to-side head weaving) considered to be LSD-like and mediated by serotonergic mechanisms (Sloviter et al., 1980). In addition, the observation that atropine blocks ibogaine action has lead to the suggestion that the mechanism of ibogaine action is muscarinic (Dhahir et al., 1990), that it has affinity to benzodiazepine receptors as a causative mechanism in its ability to produce tremor (Trouvin et al., 1987) and that it has binding affinity to specific opiate sites (Deecher et al., 1992) have all allowed for the multiplicity of actions of ibogaine in preclinical research. In light of the multiple nature of its anti-addictive properties as indicated by the four patents that involve opiates, stimulants, ethanol and nicotine (see 1. Introduction), it is no wonder that the neurochemical mechanism of ibogaine action is so difficult to determine. Only additional pre-clinical work will allow for elucidation of the mechanism by which ibogaine acts in the brain by itself and as a drug that may alter the effects of other (abused) drugs.

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