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Failure of Ibogaine to Produce Phencyclidine-Like Discriminative Stimulus Effects in Rats and Monkeys

HENDRÉE E. JONES, HUA LI AND ROBERT L. BALSTER

Department of Pharmacology and Toxicology, Medical College of Virginia, Virginia Commonwealth University, Richmond, VA 23298-0310

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JONES, H. E., H. LI AND R. L. BALSTER. *Failure of ibogaine to produce phencyclidine-like discriminative stimulus effects in rats and monkeys.* PHARMACOL BIOCHEM BEHAV **59**(2) 413–418, 1998.—The discriminative stimulus properties of ibogaine were investigated in rats trained to discriminate phencyclidine (PCP; 2.0 mg/kg, IP) from saline under a two-lever fixed-ratio (FR) 32 schedule of food reinforcement. Ibogaine (5.6–17.6 mg/kg, IP) showed a complete lack of substitution. Ibogaine (0.5–4.0 mg/kg, IM) also failed to generalize in rhesus monkeys trained to discriminate PCP (0.1 mg/kg, IM) from sham injection. Lysergic acid diethylamide (LSD), tested as a reference compound, produced partial substitution for PCP in rats and occasioned little responding on the PCP-associated lever in monkeys. These results demonstrate important differences between the behavioral effects of PCP and other types of hallucinogenic drugs such as LSD and ibogaine and do not support the hypothesis that the affinity of ibogaine for the PCP site on *N*-methyl-D-aspartate (NMDA) receptors plays a major role in its acute behavioral effects. © 1998 Elsevier Science Inc.

Drug discrimination Ibogaine Lysergic acid diethylamide LSD Phencyclidine PCP *N*-methyl-D-aspartate NMDA

THE use of ibogaine (Endabuse™) in the treatment of drug addiction has been suggested based on the evidence that it may affect phenomena such as drug self-administration and withdrawal. In rodents, ibogaine administration has been shown to decrease morphine (8), heroin and cocaine (4,7,26) self-administration. Pretreatment with ibogaine has been observed to antagonize cocaine (25) and amphetamine induced locomotor activity in mice (24), although in rats, ibogaine increases amphetamine's effect on locomotor activity (15,24). In general, these animal results are in accordance with clinical reports of beneficial effects on heroin (12), cocaine, or amphetamine (13) abuse following ibogaine treatment in humans. Although the effectiveness of ibogaine as a treatment for drug abuse remains under study, other research has been focused on determination of the mechanisms responsible for the drug's actions.

Ibogaine appears to have complex cellular mechanisms of action with effects on multiple neurotransmitter systems (31). 5-HT receptors (30), dopamine receptors (16,24,25), and κ-opioid receptors (6) have all been implicated in mediating the actions of ibogaine. Although ibogaine has been reported to produce lysergic acid diethylamide (LSD)-like discriminative stimulus effects in rats (19), substitution testing of serotonergic and dopaminergic drugs in ibogaine-trained rats failed to provide a clear picture of its profile of acute behavioral effects or possible mechanisms of action (23).

One focus of recent attention is the evidence that ibogaine interacts with the channel site on the *N*-methyl-D-aspartate (NMDA) receptor as shown in vitro by displacement of [^{3}H]dizocilpine binding (17,21,31). The K_i values for ibogaine to inhibit [^{3}H]dizocilpine binding have ranged from 1.01 μm (21) to 3.2 μm (31). The possibility that ibogaine's ability to

Requests for reprints should be addressed to Robert L. Balster, Department of Pharmacology & Toxicology, Medical College of Virginia, Virginia Commonwealth University, Richmond, VA 23298–0310.

function as an NMDA receptor antagonist plays a role in its potential use as a medication for drug abuse is attractive because of the substantial evidence that NMDA receptors may be involved in drug tolerance, sensitization, and dependence (11,32).

Because the nature of the acute behavioral effects of ibogaine is not well understood and because it may function as a phencyclidine (PCP)-like NMDA receptor antagonist in vitro, we decided to test it for PCP-like discriminative stimulus effects in rats and monkeys. Positive results would help support the proposal that ibogaine has NMDA receptor antagonist effects in vivo but also suggest that PCP-like side effects such as impairment in motor function, perception, and proprioception (10,20,22) could be a limiting factor in its clinical use. Many studies have shown that nearly all NMDA receptor antagonists that act at the PCP site in the channel produce full substitution for PCP using drug discrimination procedures in animals (1,34,35).

LSD was also tested for substitution in PCP-trained animals. LSD was chosen as a reference compound because it is an established hallucinogen, with which ibogaine shares some discriminative stimulus effects (19), but without known actions on NMDA receptors.

METHOD

PCP Discrimination in Rats

Six male albino rats (COBS CD, Charles River, Wilmington, MA) were trained to lever press under a fixed ratio (FR)-32 schedule of food reinforcement in a standard two-lever operant conditioning chamber, as previously described (33). They were housed in individual wire cages with free access to water and given restricted postsession feedings (10–15 g per day) to motivate lever pressing for food reinforcement. All animals were maintained on a 12 L:12 D cycle; training and testing occurred during the light phase. Rats were placed in operant conditioning chambers 15 min postinjection, and session commencement was signaled by illumination of a house light centrally located approximately 20 cm above a food trough positioned between the response levers. Responses on one lever were reinforced following PCP administration (2 mg/kg, IP); responses on the other lever were reinforced following saline (0.9% NaCl in 1.0 ml/kg, IP) administration. Training sessions were 30 min in duration and conducted 5 days a week under a double alternation schedule continuing until the following criteria were met on four consecutive sessions (two PCP and two saline): 1) first FR completed on the correct lever, 2) 85% or more correct-lever responding throughout the session, and 3) response rate greater than 1.0 response per second. Following PCP–saline discrimination acquisition (approximately 35 training sessions), generalization tests to PCP (0.5–8.0 mg/kg), ibogaine (5.6–17.6 mg/kg), and LSD (0.01–0.04 mg/kg) were conducted. At least 2 weeks of continued training intervened between testing each drug. All rats were tested to obtain a full dose–effect curve for PCP, followed by the entire dose–effect curve for ibogaine, and finally LSD. All doses were tested in ascending order. Control tests were conducted on Tuesdays and Fridays with the training dose of PCP and saline before testing each drug. Animals were never given more than one injection of a substance on any one day.

Test sessions were conducted on Tuesdays and Fridays if the above criteria were met on the preceding training day. Test sessions differed from training in that responses on either lever were reinforced. All injections were administered IP 15 min before the session began. Pretreatment times for the drugs were selected based on previous reports using rats (8,19). Between injections and the onset of training/test sessions subjects were returned to their home cages. The percentage of PCP lever responding and rate of responding (responses/s) were collected for test sessions and averaged (±SEM) for the group. When the response rate was ≤0.05 response/s the lever selection data for that subject was omitted from the group data.

PCP Discrimination in Rhesus Monkeys

Four adult rhesus monkeys (9.8–11.1 kg) with considerable experience in PCP discrimination studies [e.g., (2)] served as subjects. Monkeys were individually housed in stainless steel cages in an American Association for the Accreditation of Laboratory Animal Care approved animal facility. All monkeys were maintained on a 12 L:12 D cycle in a temperature-controlled vivarium with water available ad lib. Food (Purina monkey chow) was provided twice a day (a.m. and p.m.) in an amount sufficient to maintain constant body weight. The first daily feeding (between 0900 and 1000 h) was provided to the animals following their behavioral session to facilitate food-reinforced responding. All training and testing occurred during the light phase. Monkeys were placed in standard primate restraint chairs using the pole-and-collar technique. The monkeys had been trained to discriminate IM injections of 0.1 mg/kg PCP (0.08 mg/kg for monkey M1146) from sham injections under a FR-50 schedule of food reinforcement. For sham injections, a syringe with no needle was pressed against the site of injection. Training sessions (20 min duration) were conducted under a double alternation schedule (PCP, PCP, sham, sham, etc.) throughout the testing period. Test sessions were scheduled for Tuesday and Friday when the following criteria were met on the four most recent training sessions (two PCP and two sham): 1) first FR completed on appropriate lever; and 2) ≥90% correct-lever responding. Test sessions were distinct from training sessions in that, during the 20-min test sessions, FRs completed on either lever were reinforced. Monkeys were first tested with the full dose–effect curve for PCP, followed by LSD and then with ibogaine. All doses were tested in ascending order. Testing of each drug was separated by a minimum of 1 week. Control tests were conducted with the training dose of PCP, 0.05 ml/kg saline and vehicle (when appropriate) prior to each dose–effect curve determination.

Monkeys were tested with PCP (0.02, 0.04, 0.08, 0.10, 0.12, 0.16, and 0.18 mg/kg, IM; 0.02 to 0.12 mg/kg for M1146) administered 10 min prior to the session. LSD (0.0006, 0.001, 0.0017, 0.003, and 0.006 mg/kg, IM; 0.0006 to 0.003 mg/kg for M999) was injected 30 min before the session commenced; and ibogaine (0.5, 1.0, 2.0, and 4.0 mg/kg, IM) was given 15 min prior to the session. Pretreatment times for ibogaine and LSD were based on results from previous operant behavioral investigations using these administration times with rats (8,19) and monkeys (18). Individual subject results from test sessions are presented for both PCP lever selection and rate of responding except that lever selection data are not shown when response rate was ≤0.15 response/s.

Drugs

PCP HCl, LSD [lysergic acid diethylamide tartrate (2:1)], and ibogaine HCl were provided by the National Institute on Drug Abuse (Rockville, MD). PCP was dissolved in physiological saline (0.9%). Ibogaine was dissolved in sterile water and 5% ethanol (by volume). LSD was dissolved in sterile water.

RESULTS

Lever selection in rats was under excellent stimulus control by PCP and saline injections as shown by the control test data obtained before the determination of each of the three dose–effect curves (Fig. 1). Response rates on PCP control test sessions were not different from rates on saline control tests. PCP was generalized in a dose-dependent manner from the training dose of 2 mg/kg (Fig. 1). Doses of 2 and 4 mg/kg produced 100% PCP lever responding with no response-rate decreasing effects. In contrast, ibogaine completely failed to produce PCP lever responding at all the doses tested (5.6–17.6 mg/kg) in all subjects (Fig. 1). At the highest ibogaine dose tested (17.6 mg/kg), only one rat failed to meet the response rate criteria needed for inclusion in the percentage of drug lever responding (%DLR); therefore, the %DLR for 17.6 mg/kg ibogaine was based on data from five of the six subjects. Ibogaine did produce dose-dependent decreases in response rates, with the 17.6 mg/kg dose suppressing rates to 34% of the corresponding saline control rates. LSD produced partial substitution for PCP (Fig. 1); however, the maximal level of PCP lever responding (56%) occurred at a dose of LSD (0.04 mg/kg) that also suppressed rates of responding to 35% of rates during saline control tests. Two rats responded less than 0.05 responses/s; thus, data from four of six rats was included for the lever selection average at the 0.04 mg/kg dose. Of these rats, two responded predominantly on the PCP lever and two responded predominantly on the saline lever.

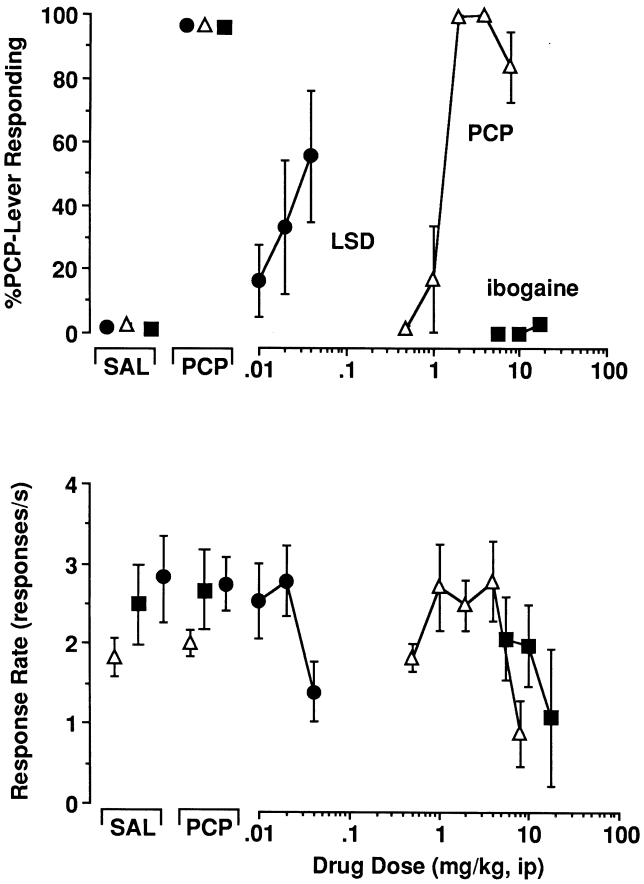
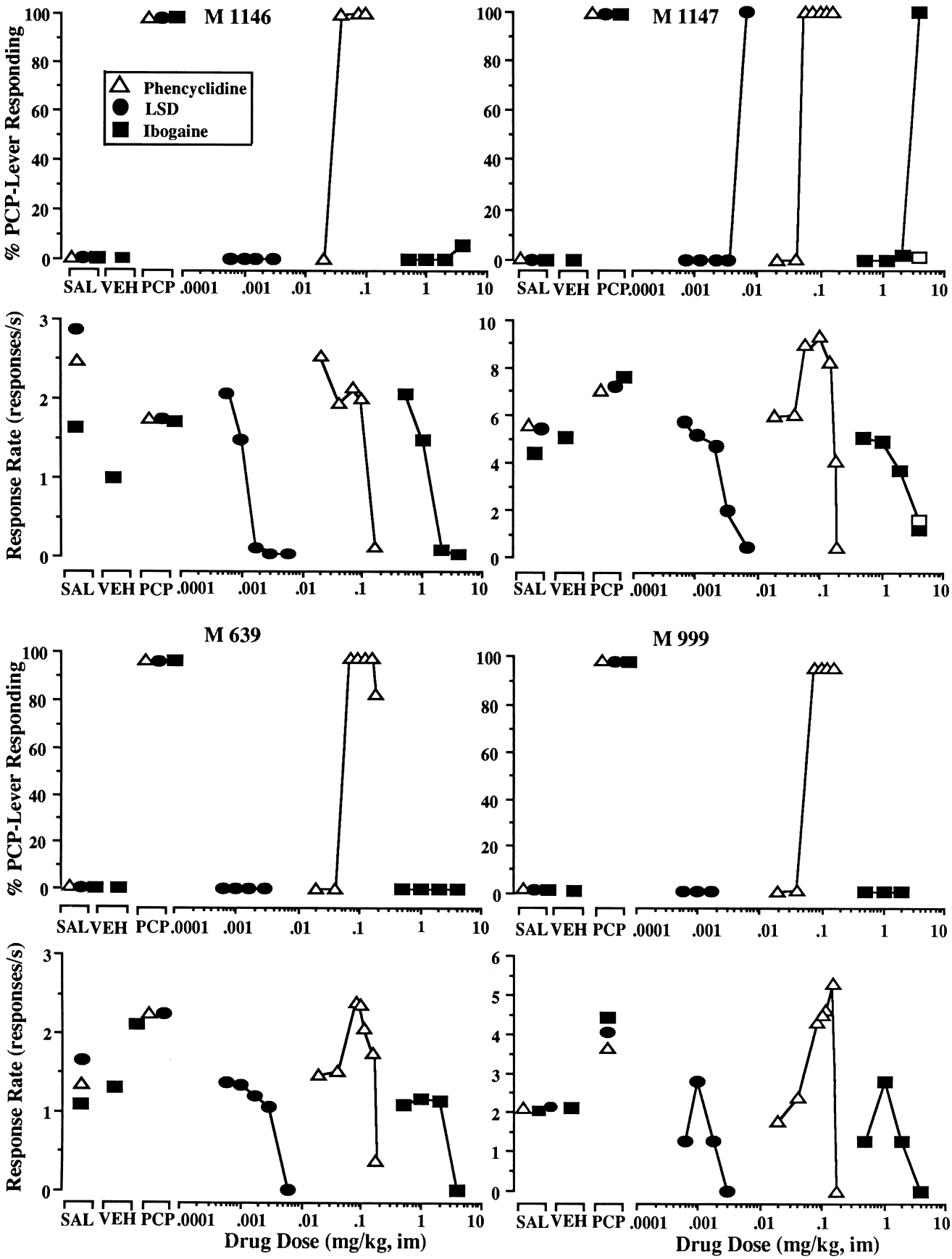


FIG. 1. Effects of IP administration of various doses of phencyclidine (PCP), LSD, and ibogaine in rats trained to discriminate 2 mg/kg PCP from saline ($n = 6$). Mean (±SEM) percentage of PCP-lever responding (upper panel) and mean (±SEM) rates of responding (lower panel) following PCP (△), LSD (●), and ibogaine (■) injection are shown. Points above SAL and PCP represent results of control tests with saline and 2 mg/kg PCP conducted in association with each dose–effect curve determination.

Lever selection in monkeys was under excellent stimulus control by PCP and saline injections as shown by the control test results in Fig. 2. Neither saline nor the low ethanol concentration vehicle injections produced any PCP lever responding whereas tests with the training dose of PCP produced near 100% PCP lever responding. In three of the monkeys (M1147, M639, and M999), control tests with PCP resulted in faster rates of responding than on saline and vehicle control tests. Substitution tests conducted with various doses of PCP produced full dose-dependent substitution for the training dose in all four subjects (Fig. 2). The response rate increasing effects of PCP in monkeys M1147, M639, and M999 were also evident at intermediate doses in the PCP dose–response determination, with decreases in responding in all four monkeys at doses higher than those needed to produce full substitution. Ibogaine produced predominantly saline lever responding in all four monkeys except for M1147 where one test dose produced PCP lever responding accompanied by severe response rate suppression (Fig. 2). To clarify this result, 9 months later M1147 was again tested with the highest dose of ibogaine. The second administration of 4.0 mg/kg ibogaine, under similar conditions as the previous test, produced only 2% PCP lever responding accompanied by a reduced level of responding similar to that observed with the first test (open squares in Fig. 2). In all monkeys, clear response rate decreasing effects were obtained with the highest doses (2.0–4.0 mg/kg) tested. Similar to results with ibogaine, LSD also produced saline lever responding in all subjects except at the highest dose in one monkey (M1147), where the PCP lever was selected accompanied by marked behavioral disruption in the form of response rate suppression. With the possible exception of M999, neither ibogaine nor LSD produced increases in rates of responding as did PCP at intermediate doses.

DISCUSSION

The main finding of the present study is that ibogaine lacks PCP-like discriminative stimulus effects in both rats and rhesus monkeys. Although one monkey, M1147, responded on the PCP lever following administration of the highest dose of 4.0 mg/kg, upon retesting at a much later date, only 2% PCP lever responding was obtained. Because both administrations of this dose of ibogaine produced greater than 50% decreases in response rates relative to rates during control test sessions, and all other monkeys showed response rate decreasing effects without PCP lever selection, it is clear that ibogaine has acute discriminative stimulus effects that are not PCP-like. Furthermore, ibogaine did not produce response-rate increasing effects as did PCP in three of the four monkeys. Taken together, the data from both rats and monkeys do not lend support to an hypothesis based on in vitro results which suggests that the acute effects of ibogaine are mediated by its affinity for the channel site on the NMDA receptor complex (17,21). It is also consistent with information which suggests that the nature of the acute intoxication produced by ibogaine (29) and PCP (10) are different in humans. Although the acute effects of PCP and ibogaine have not been directly compared in humans, ibogaine is reported to produce de-


M 1146
M 1147
M 639
M 999
Phencyclidine
LSD
Ibogaine
% PCP-Lever Responding
Response Rate (responses/s)
SAL VEH PCP .0001 .001 .01 .1 1 10
Drug Dose (mg/kg, im)

creased muscular coordination, increased light sensitivity, nausea, vomiting, and an hallucinogenic state lasting from 4–8 h in heroin addicts (29). In contrast, in normals, acute PCP administration often produces behavioral toxicity similar to psychiatric syndromes with impaired recent memory and judgment, confusion, and disorientation, depersonalization, perceptual changes, catatonia, and catalepsy (5,10,22). Because NMDA receptor antagonists with PCP-like discriminative stimulus effects in animals produce a PCP-like intoxication in humans (1), it seems unlikely that PCP-like effects could contribute to the side-effect profile were ibogaine to be developed as a pharmacotherapy.

The lack of PCP-like effects with ibogaine are not because ibogaine completely lacks discriminative stimulus effects. Rats have been trained to discriminate 10 mg/kg ibogaine from saline in less than 30 sessions (23). It has also been shown to substitute for LSD in a drug discrimination study (19). Based on that result, it could be tentatively concluded that ibogaine's acute effects are more similar to LSD than to PCP. Therefore, ibogaine and LSD may also share common mechanisms for their discriminative stimulus effects (19). It may not be surprising that ibogaine, despite having some affinity for the NMDA receptor, lacks PCP-like effects. In vitro, ibogaine has affinity for many neural sites in the central nervous system including μ and κ-opioid, 5-HT, α-adrenoceptor, and muscarinic acetylcholine receptors and uptake sites for dopamine and serotonin (6,9,27,31). It also binds to a Na^+ channel (31). Its affinities for these sites are in the same low micromolar range as its affinity for NMDA receptors. Thus, at present, there is little basis to speculate which of these, or other, cellular sites are most important in determining ibogaine's acute effects on behavior. Possibly, it is these multiple actions that are most important (31). In vivo studies showing that ibogaine's effects can involve dopaminergic (4,9,14–16), serotonergic (19,30), and opioid (14,15) systems is also evidence for its multiplicity of actions.

Because ibogaine binds to the PCP site on the NMDA receptor yet lacks PCP-like discriminative stimulus effects, the possibility could be considered that ibogaine would serve as an antagoinist of PCP. This is unlikely for several reasons. First, it is not easy to conceptualize how a competitive antagoinist to a channel blocker could work, because binding to the site should occupy space in the channel and interfere with ion flux. Second, ibogaine has 30–50-fold lower affinity than PCP for the PCP site (17,21). Thus, one might expect that doses very substantially higher than PCP would need to be administered in vivo to occupy sufficient PCP sites in the channel to compete with PCP for binding. Such doses would have been impossible to administer in the present study because ibogaine was only about twofold less potent than PCP in rats for response rate decreasing effects and 10-fold less potent for this effect in monkeys. Even higher test doses of ibogaine would have certainly resulted in behavioral toxicity and lethality.

In rats, ibogaine produced even less PCP-like effects than did LSD in our studies because LSD produced partial substitution. In monkeys, there was very little evidence for PCP-like effects of LSD because only one subject showed substitution and only at a dose that substantially decreased response rates. Although LSD and PCP are commonly used compounds in drug discrimination research, there have been few studies directly comparing their effects. Furthermore, to the best of our knowledge, we are the first to examine LSD in PCP-trained monkeys. In rodents, it has been reported that a range of LSD doses failed to generalize from PCP in rats trained to discriminate PCP (3.0 mg/kg) from saline in a two-lever drug discrimination task (28). LSD also failed to generalize from PCP in another study in PCP-trained (3.2 mg/kg) rats (3). In humans, direct comparisons of LSD and PCP have revealed clear differences between the subjective effects of the two drugs (20).

Taken together with the results of the previous studies showing both behavioral and biochemical differences in the acute effects of PCP and LSD, the lack of full cross generalization between these two drugs in our studies provides further support for classifying these drugs as representatives of distinct types of hallucinogens. Although the present study adds to the growing body of literature about the acute behavioral effects of ibogaine, further investigations are needed to reveal its still elusive mechanism of action.

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FIG. 2. Effects of phencyclidine (PCP) (△), LSD (●), and ibogaine (■) in four rhesus monkeys trained to discriminate 0.1 mg/kg PCP (0.08 mg/kg for M1146) from sham injection. Individual subject data are shown with percentage PCP lever responding in the upper panels and effects on rates of responding in the lower panels for each monkey. Shown above PCP and SAL are the results of control tests with the PCP training dose and saline (0.05 ml/kg) conducted before each dose–effect curve determination. Shown above VEH is the result of a control test with the ibogaine vehicle. Monkey M1147 was tested a second time with 4.0 mg/kg of ibogaine (□). Note that response rate scales for M1147 and M999 are different than those of M639 and M1146.

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