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Effects of Ibogaine on Performance in the 8-Arm Radial Maze

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HELSLEY, S., D. FIORELLA, R. A. RABIN AND J. C. WINTER. *Effects of ibogaine on performance in the 8-arm radial maze*. PHARMACOL BIOCHEM BEHAV **58**(1) 37–41, 1997.—The effects of ibogaine were studied in 12 rats trained to perform in an 8-arm radial maze. In Phase I, the mean number of sessions to criterion and cumulative errors to criterion, as well as mean response rate, were determined for two groups of six animals in a task where only four arms were baited. Group 1 received a potentially neurotoxic dose of ibogaine (50 mg/kg IP administered twice, with approximately 8 h between injections), and group 2 received vehicle. Both groups had similar levels of performance, but ibogaine-treated subjects had a significantly lower rate of responding in the maze. During Phase II, subjects were given a range of doses of ibogaine 20 min prior to working in the maze. Ibogaine produced a dose-dependent decrease in response rate, but efficiency (% arms correct) was not affected. In Phase III, subjects were divided into the same groups as they had been in Phase I. Ibogaine (30 mg/kg, IP) or vehicle was administered immediately following daily sessions in the maze. Ibogaine-treated rats committed significantly fewer errors than those in the vehicle treated group. Thus, in the present study, ibogaine failed to produce any deleterious effects on either acquisition of a novel task or efficiency in a previously learned task. © 1997 Elsevier Science Inc.

Ibogaine Radial maze Learning and memory

IBOGAINE is one of several indole alkaloids found in the root of *Tabernanthe iboga*, a shrub indigenous to Africa. Iboga has been used for an unknown period of time by African tribesmen for both its stimulant and hallucinogenic effects.

Recent studies in both human and nonhuman subjects suggest a beneficial effect of ibogaine in the treatment of substance abuse. In rats, ibogaine blocks self-administration of morphine (3,4), heroin (2), cocaine (1,2,3), and ethanol (14). Although clinical data in support of ibogaine's anti-addictive effects are limited (15), patents have been issued for its use in the treatment of opiate (6), cocaine (7), amphetamine (7), ethanol (8), and nicotine abuse (9).

In previous studies in the rat, ibogaine caused degeneration of Purkinje cells in the cerebellar vermis (10,11). Behavioral studies in rats are suggestive of an acute disruption of sensory-motor performance, as well as deficits in learning after a single injection of ibogaine. Unlike the sensory-motor effects, the memory deficits persist for several days (5). Indeed, it has been suggested that ibogaine's putative anti-addictive effects arise from an interference with learning and memory processes (5).

The radial maze has been used to assess the effects of drugs and of brain lesions, induced either electrically or chemically, on learning and memory (12). Most relevant to the present investigation is the observation by Kesner et al. (5) of "a significant disruptive effect on spatial learning 1–3 days after the ibogaine injection, but no long-term consequence 7–9 days later." These investigators also reported that ibogaine caused an acute disruption of sensory-motor performance (5). In the present study, the effects of ibogaine on acquisition of a new task and on performance of an already learned task in the 8-arm radial maze were examined.

METHOD

Subjects

Twelve male Fischer-344 rats obtained from Harlan Sprague–Dawley (Indianapolis, IN) were housed in pairs under a nor-

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mal light-dark cycle with unrestricted access to water. Standard rat chow was given immediately postsession. Caloric intake was restricted to maintain body weight around 250 g. Animals used in this study were maintained in accordance with the "Guide for Care and Use of Laboratory Animals" of the Institute of Laboratory Animal Resources, National Research Council.

Apparatus

All sessions were conducted in a radial maze, which consists of a central hub 34-cm in diameter, with 8 arms 86-cm long and 9-cm wide, with 10-cm side walls. The maze is elevated 46-cm above the floor. The maze is composed of aluminum except for the plastic food cups at the end of each arm.

Training

Subjects were acclimated to the maze during 10-min sessions in which pieces of Post Fruity Pebbles cereal (avg. weight per piece = 40 mg) were placed at the beginning, middle, and food cup of each arm. The number of reinforcers was reduced gradually until only the food cups were baited.

After it was firmly established that the subjects were entering all arms and eating the food, they were presented with a task in which all eight arms were baited. Criterion-level performance was achieved when, in three consecutive sessions, one or less reentry occurred per session. Entry or reentry was considered to have occurred when a subject had advanced at least three-fourths of the way down an arm. Sessions were terminated either when the subject visited all eight arms, or 10 min had elapsed. All subjects were trained to criterion.

Testing Procedure

The same 12 subjects were used for all phases of this study. Radial maze sessions were run daily (M–F).

Phase I. The effects of a single high dose of ibogaine on acquisition of a 4-arm task was determined as follows. Rats were divided into two groups, to be tested with either ibogaine (n = 6) or vehicle (n = 6). Group assignments were based on cumulative sessions to criterion in the initial 8-arm task. No significant differences existed between groups at the outset of the study. Ibogaine (50 mg/kg) or vehicle (5 ml/kg) was administered twice, with 8 h between the injections; an identical interval was used by O'Hearn and Molliver (11) in demonstrating ibogaine-induced neurotoxicity. In this task, only arms 1–4 were baited. Errors were defined as either entry into a nonbaited arm (i.e., arms 5–8) or reentry into any arm. Upon achieving criterion performance for this task (three consecutive sessions during which one or fewer errors occurred), subjects were switched to a task where all eight arms were baited. These drug-free sessions were run for a period of 1 week before entry into Phase II. Because there were no significant differences between the ibogaine and vehicle treatment groups, it was concluded that no residual drug effects were present.

TABLE 1

AVERAGE SESSIONS TO CRITERION, CUMULATIVE ERRORS TO CRITERION, AND RESPONSE RATE IN AN INITIAL 8-ARM TASK

Group 1				Group 2			
I.D. #	STC	ETC	RATE	I.D. #	STC	ETC	RATE
103	11	18	1.8	101	8	11	2.4
104	3	2	1.5	102	4	2	1.9
105	8	12	2.4	107	4	4	1.9
106	8	16	2.0	108	10	10	4.4
110	9	12	2.4	109	8	12	5.3
111	8	6	2.2	112	14	17	1.6
Avg.	7.8	11.0	2.0	Avg.	8.0	9.3	3.0

STC = sessions to criterion, ETC = errors to criterion. Group 1 became the ibogaine-treated group and Group 2 became the vehicle-treated group.

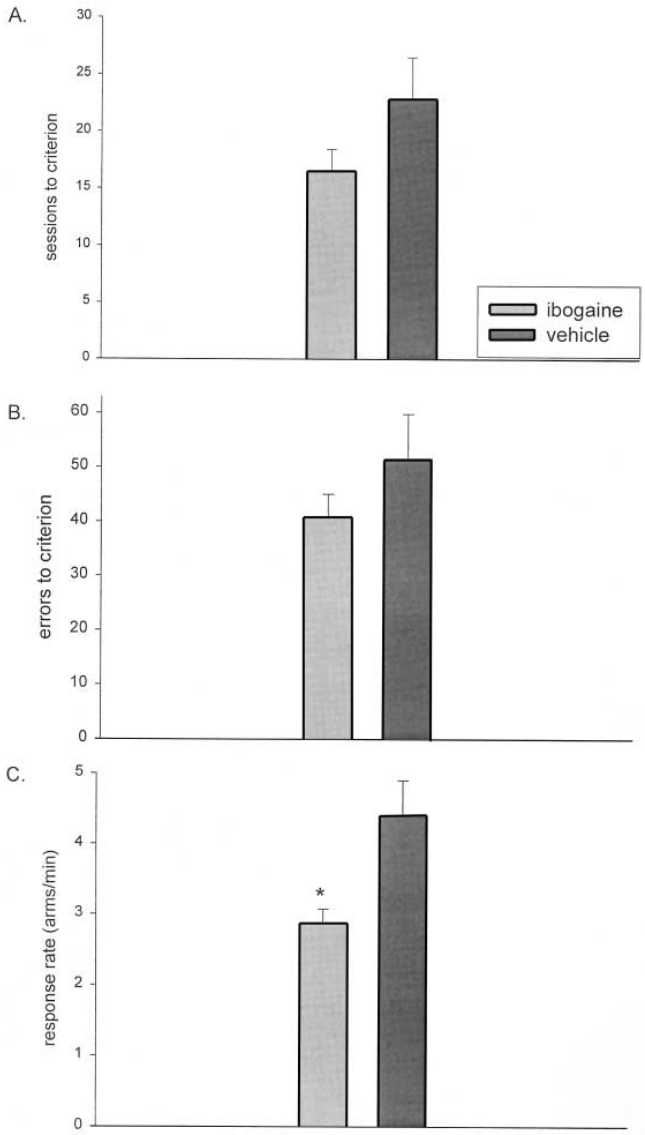

FIG. 1. Effects of ibogaine on sessions to criterion (A), errors to criterion (B), and response rate (C) on the acquisition of a task in an 8-arm radial maze in which only four arms were baited. Ibogaine (n = 6; dark bars) was injected IP at a dose of 50 mg/kg administered twice over an 8-h period. Vehicle was injected IP at a volume of 5 ml/kg twice over an 8-h period (n = 6; light bars). Testing began 48 h after treatment. Ordinate: sessions to criterion (A); errors to criterion (B); response rate (C). * reflects a statistically significant difference from control [$p < 0.05$].

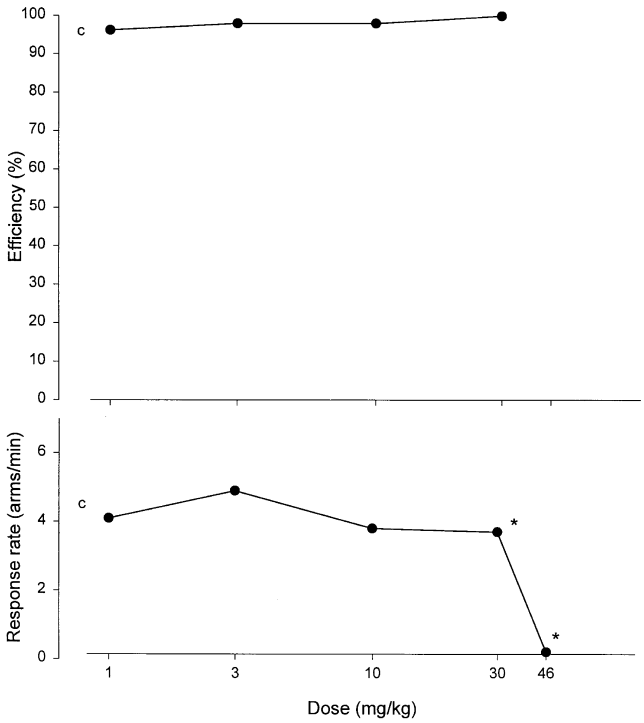

FIG. 2. Effects of ibogaine administered IP 20 min prior to performance testing in the radial maze. Each point represents mean values from six subjects. At the 46 mg/kg dose, none of the six subjects tested completed the task, thus only values for response rate are shown. "C" denotes the control value. * reflects a statistically significant difference from control [$p < 0.05$].

Phase II. The effects of presession ibogaine administration on performance of a previously learned 8-arm task were determined as follows. Ibogaine (1, 3, 10, 30, or 46 mg/kg) was administered 20 min prior to testing. Six rats were tested at each dose. Doses were tested in random order. Not every rat was tested at every dose. In this task, the subjects served as their own controls. Test sessions were only conducted in those subjects who committed one or fewer errors in the training session conducted the previous day. Because each rat served as its own control, all rats received ibogaine during this phase of the study. Following these studies, subjects were again observed for a 1 week period (M–F) in a task where all eight arms were baited. All subjects performed at criterion level.

Phase III. The effects of postsession ibogaine administration on acquisition of a 4-arm task were determined as follows. Individual rats were assigned to the same group, either ibogaine or vehicle, as they had been in Phase I. Ibogaine (30 mg/kg) or vehicle (3 ml/kg) was administered immediately following each session. In this task, only arms 5–8 were baited. Sessions were conducted until criterion performance was achieved.

Data Collection

During each session, arm entries were scored visually and recorded. In phases I and III, sessions to criterion and errors to criterion were noted for each subject. During phase II, efficiency (number of correct entries divided by the total number of arms entered) was calculated. Response rates (arms entered per minute) were recorded during all phases.

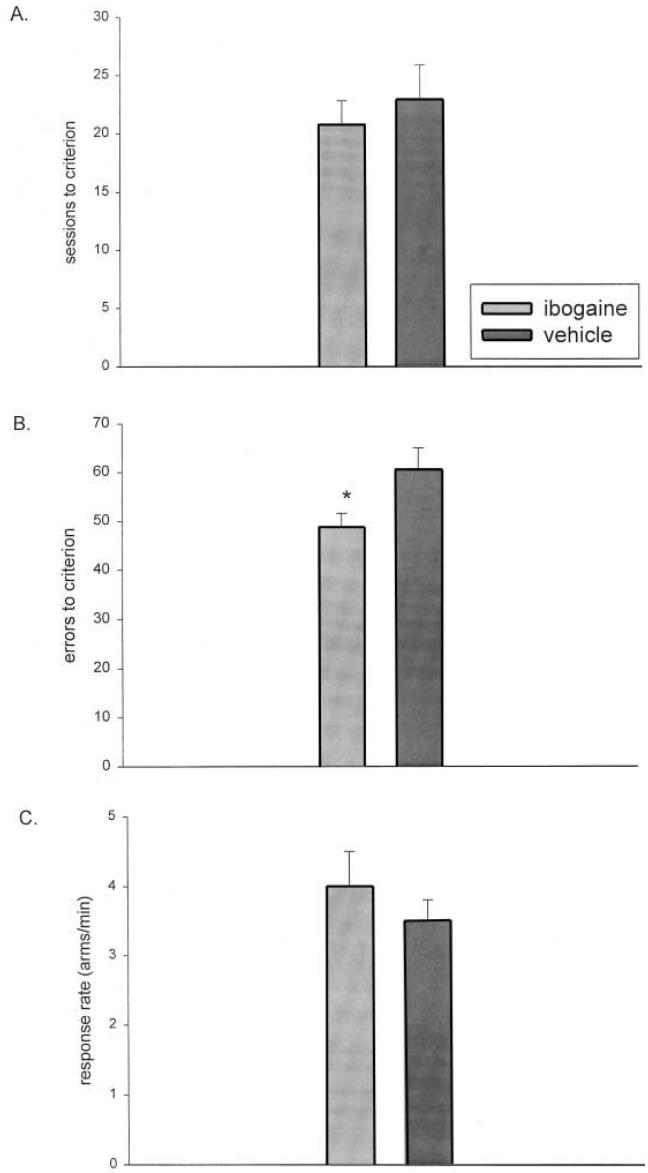

FIG. 3. Effects of postsession ibogaine on sessions to criterion (A), errors to criterion (B), and response rate (C) on the acquisition of a task in an 8-arm radial maze in which only four arms were baited. Ibogaine ($n = 6$; dark bars) was injected IP at a dose of 30 mg/kg immediately following each session. Vehicle was injected IP at a volume of 3 ml/kg ($n = 6$; light bars). Ordinate: sessions to criterion (A); errors to criterion (B); response rate (C). * reflects a statistically significant difference from control [$p < 0.05$].

Drugs

Ibogaine HCl was provided by the National Institute on Drug Abuse (Rockville, MD). Solutions were made with distilled water and injected IP.

Statistics

In Phases I and III, comparisons between groups were made by individual applications of the Mann–Whitney *U*-test.

In Phase II, efficiency and response rate were compared using Wilcoxon's signed ranks test with control values averaged from a block of four consecutive sessions conducted at the end of the phase. Differences were considered significant if the probability that they occurred by chance alone was less than 5% ($p < 0.05$).

RESULTS

Table 1 shows average sessions to criterion, cumulative errors to criterion, and response rate in an initial 8-arm task, the results of which were used to form two groups of animals. No significant differences were observed between the vehicle and ibogaine groups at the beginning of the study.

Figure 1 depicts the effect of ibogaine on sessions to criterion (Fig. 1A), cumulative errors to criterion (Fig. 1B), and response rate (Fig. 1C) in a 4-arm task. Rats were injected with two 50-mg/kg doses separated by 8 h. The ibogaine-treated group showed a significantly lower response rate than the vehicle group ($p = 0.015$), but ibogaine was without effect on either errors or sessions to criterion.

Figure 2 illustrates the effect of varying doses of ibogaine administered 20 min prior to testing in an 8-arm task. No effect on accuracy was observed, but ibogaine significantly reduced response rates at higher doses (30 and 46 mg/kg).

Figure 3 displays group means for subjects given ibogaine (30 mg/kg) or vehicle immediately following sessions in the maze in a 4-arm task. Ibogaine-treated rats committed significantly fewer errors than those treated with vehicle ($p = 0.041$). No other significant differences were observed.

DISCUSSION

In the present study, ibogaine failed to produce any detrimental effect on either acquisition of a novel task or performance in a previously learned task in the radial maze. Indeed, ibogaine-treated animals committed significantly fewer errors than control subjects in Phase III of the present study. In contrast, Kesner et al. (5) observed inhibitory effects of ibogaine on learning and memory persisting up to three days after administration of a 40 mg/kg dose. It is possible that the conflicting results between the present study and that of Kesner et al. (5) arose because of different experimental procedures (these authors used a dry land version of the Morris water-maze) or because of differences in the response to ibogaine by Fischer-344 rats in the present study and the Long–Evans rats used by Kesner and his colleagues.

In rats pretreated with ibogaine, a dose-dependent suppression of rate of responding was observed. This reached statistical significance at 30 mg/kg. Similar rate suppressing effects of ibogaine have been reported by others (5,13). Ibogaine has shown a tendency to reduce responding maintained by a variety of reinforcing stimuli including morphine (3,4), heroin (2), cocaine (1,2,3), ethanol (14), and food (2). These effects may result from ibogaine's interaction with sensory or motor systems. Consistent with this hypothesis, a low-amplitude whole-body tremor, which appeared within 10 min of administering ibogaine, was observed in subjects at doses as low as 10 mg/kg. This may explain why, in Phase 1 of the present study, a large dose of ibogaine resulted in a significantly lower response rate compared with vehicle. However, response rates were nearly identical between rats given ibogaine (30 mg/kg) and those given vehicle postsession during Phase III.

Because the same 12 subjects were used in all three phases, there exists the possibility of carryover of ibogaine's effects from one phase to the next. To assess this possibility, subjects were observed at the conclusion of each phase for four consecutive sessions, during which all eight arms were baited; no differences during these interphase control sessions were observed. In addition, no deleterious effects of ibogaine were observed either in Phase II or in Phase III, suggesting that there was no cumulative toxic effect.

When dealing with a putative neurotoxic agent, the main concern regarding carryover is that it may result in an overestimation of the toxic effects of the substance in question. If ibogaine had a deleterious effect on maze performance, carryover could only enhance this effect. The failure of ibogaine to elicit such effects, together with the fact that the ibogaine-treated group committed significantly fewer errors in Phase III, strongly suggests that ibogaine does not have a detrimental effect on performance in the radial maze. Whether the results presented in Fig. 3 reflect an ibogaine-induced enhancement of learning and memory is not clear at present.

In conclusion, the present investigation failed to demonstrate any deleterious effects by ibogaine on either acquisition of a novel task or efficiency in the performance of a previously learned task.

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