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Effects of Ibogaine on Sensory-Motor Function, Activity, and Spatial Learning in Rats

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KESNER, R. P., P. JACKSON-SMITH, C. HENRY AND K. AMANN. *Effects of ibogaine on sensory-motor function, activity, and spatial learning in rats.* PHARMACOL BIOCHEM BEHAV 51(1) 103-109, 1995. — Ibogaine, a naturally occurring alkaloid, has been shown to reduce naloxone-precipitated withdrawal symptoms from morphine. Given the clinical possibilities, it is important to determine ibogaine's effects on sensory-motor function, activity, learning, and memory. Long-Evans rats injected with doses of 20-60 mg/kg of ibogaine displayed slower response times on sensory and sensory-motor tests and were impaired in performing specific motor reflexes at doses of 40-60 mg/kg. Furthermore, these rats showed a marked reduction in locomotor and nonlocomotor activity, as well as emotionality at doses ranging from 10-40 mg/kg. At the higher doses the rats appeared to be virtually inactive. There were also deficits in learning a spatial location task (a dry-land version of the Morris water-maze). The deficits, however, were probably due to a reduction in locomotor activity and reduction in detection of sensory information. In a final experiment, a single injection of 40 mg/kg of ibogaine had marked deleterious effects on the acquisition of the spatial location task 1 but not 7 days after the injection, even though in this case there were no effects on sensory motor function 1 or 7 days after the injection. Thus, there are severe sensory-motor activity and learning problems while the animal is under the influence of ibogaine (acute effect) as well as long-term consequences on learning without concomitant changes in sensory-motor function.

Ibogaine Sensory-motor function Spatial learning Morphine Withdrawal Water maze

IBOGAINE is a drug produced by extraction from the roots of *Tabernanthe iboga*, a plant commonly found in Africa. There is anecdotal evidence that one injection of ibogaine eliminates addiction to drugs such as heroin, morphine, and cocaine. There has not been a large number of animal studies with ibogaine. In one study, ibogaine was given to rats that had been trained to bar press for morphine, and was found to produce a dose-related decrease in bar pressing (4). This effect was observed for up to several days after a single administration.

In a different study, a single injection of ibogaine decreased cocaine self-administration for several days, and with repeated ibogaine injections cocaine intake was significantly decreased for weeks (1). Ibogaine also has been shown to reduce the effects of naloxone-precipitated withdrawal symptoms from morphine (5).

It has been shown that development of drug tolerance, drug addiction, withdrawal from drug addiction, and drug

craving are influenced not only by mechanisms of reward and incentive motivation, but also by mechanisms of learning and memory. Current theories have proposed that operant and classical conditioning, habituation, and sensitization play a very important role in determining the level of drug tolerance, drug addiction, drug withdrawal, and drug craving (7,12,14,16). It is therefore possible that the inhibitory effects of ibogaine on drug addiction and drug craving might be due to a general interference with learning and memory processes. The hippocampus is known to play an important role in learning and memory (3,6,17). It was therefore of real interest to discover that rats will self-administer dynorphin A (opiate agonist) injected directly into the CA₃ region of the hippocampus (18). The authors suggest that craving and compulsive drug seeking may depend on memory for past drug reinforcements, and because the hippocampus is important in learning and memory, it may play a critical role in drug addiction and drug craving. The possibility exists that ibogaine's blockade of

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drug addiction is due in part to its actions on the hippocampus, and therefore on learning and memory processes. The purpose of the present study was to test this idea by selection of a spatial navigation learning task that is known to be sensitive to hippocampal dysfunction (9). However, before we could examine the effects of ibogaine on spatial navigation learning, it was necessary to determine the effects of different doses of ibogaine on sensory motor function as well as general activity level, so that the appropriate doses could be selected for the learning study.

EXPERIMENT I: NEUROLOGIC TESTS

Methods

The subjects consisted of eight naive male Long-Evans rats, approximately 100 days old. Each animal was given the entire battery of neurologic tests, once per day for a block of 4 consecutive days. Following a 3-day interval, the rats were again given a block of four consecutive sessions. Each animal was injected with either 10, 20, 30, 40, 50, or 60 mg/kg [intraperitoneally (IP)] of ibogaine or vehicle (sterile water) 30 min before testing each day. Ibogaine was supplied by NIDA. Every animal was tested once with each drug dose and twice with vehicle. Half of the rats received low doses of ibogaine (0, 10, 20, and 30 mg/kg) on the first block of four sessions, and the higher doses (0, 40, 50, and 60 mg/kg) on the second block of four sessions. For purposes of counterbalancing the effects of ibogaine, the other four rats received the higher doses on the first block and the lower doses on the second block of four sessions using a Latin square design. The animals were placed in a small box (30 × 45 × 10 cm) and allowed 10 s to adjust to the surroundings before each of the neurologic tests was administered.

Sensory Tests

Visual stimulus orienting test. A 5 × 5-cm cardboard square with a checkered pattern of black and white, 2.5-cm squares attached to a wooden stick was used. This square was held in the peripheral field of vision on either side of the animal's head. A response was defined as orienting to the checkered square, and the latency to respond was measured by a second experimenter using a stopwatch. A maximum score of 60 s was given when the animal failed to respond. Two measurements were taken one from the right and the other from the left of the rat. The average of the two latencies was used as a measure of visual detection.

Whisker touch orienting test. A cotton swab was brought from behind the animal's head and put in contact with the vibrissae. The vibrissae were continually stimulated while the swab was held outside the rat's field of vision until a response occurred or a maximum of 60 s was reached. The test was given successively on each of the rat's right and left sides. The latency to respond (orient toward the swab) was measured. The average latency of the two responses was used as a measure of whisker touch detection.

Olfactory orienting test. Twenty-one different distinctive scents, including, for example, mint, lemon, and root beer, were used in this test. To decrease the possibility of tolerance, the odors were randomly chosen for each test with no repetition within a 4-day block. A cotton swab was moistened with the preselected scent and brought from behind the animal's head, so that it remained out of the field of vision and did not touch the animal. Each of the rats was exposed to two scents, both of which were presented from its right and left sides. The

latency to orient was recorded and the average of the four tests was used as a measure of olfactory detection.

Somatosensory orienting test. A thin wire (30 cm long) was applied to and held against the animal's shoulders, midsection, and hind quarters (with gentle pressure) on both right and left sides. The animal's latency to orient to each touch was recorded, and the average of the six response times was used as a measure of somatosensory detection.

Sensory-Motor Tests

Placing reflex test. The rat was first suspended by the tail and then brought to the edge of a table. Normal animals reach for the edge of a table by forelimb extension when brought within reach of it. When the animal responded using only the sight of the table, the animal was given a score of 1; when it required touch of the vibrissae to the table, the score was 0.75; when it required touch of the snout, the score was 0.50; and when it required additional touching of the snout to the table, the score was 0.25. When no response was elicited, the score given was 0.

Tilted platform test. Each animal was placed at the center of a 30 × 30-cm plywood platform covered with carpet. The platform was tilted at 30° and the animal was placed with its head pointing toward the low end. Normal animals respond by turning uphill facing the high end of the platform. The latency to turn around and face uphill perpendicular to the front end was measured, and a maximum score of 60 s was used.

Motor Tests

Grasping reflex. Each animal was suspended by the nape of the neck, and both front feet were touched by a single piece of thin wire. The rating scale used was a score of 1 for grasping the wire and 0 for no response. A normal animal will flex its digits around the wire, grasping tightly.

Righting reflex (back). For this test each animal was placed on its back and released. When the animal righted itself, a score of 1 was given. When the animal failed to right itself, a score of 0 was given.

Righting reflex (free fall). Each animal was held upside down 20 cm above a foam pad and released. When the animal righted itself in midair, landing on its feet, a score of 1 was given. When the animal failed to right itself completely, a score of 0 was given.

RESULTS

The effect of ibogaine injections on mean latency to respond to the visual stimulus is shown in Table 1. As doses of ibogaine increased from 0–60 mg/kg there was a corresponding increase in latency to respond to the visual stimulus. A one-way within-subject analysis of variance (ANOVA) indicated that there was a significant drug dose effect [$F(6, 114) = 16.7, p < 0.0001$]. Further Newman-Keuls tests revealed that doses of 30, 40, 50, and 60 mg/kg of ibogaine resulted in significantly ($p < 0.01$) longer latencies in comparison with vehicle control (0 mg/kg).

Table 1 also shows the effect of ibogaine injections on latency to respond to the olfactory stimulus. As the table indicates, as doses of ibogaine increased there was a corresponding increase in latency to respond to the olfactory stimulus. A one-way within-subject ANOVA indicated that there was a significant drug dose effect [$F(6, 114) = 25.4, p < 0.0001$]. Further Newman-Keuls tests revealed that doses of 20, 30, 40,

TABLE 1
EFFECTS OF IBOGAINE INJECTION ON PERFORMANCE OF SPECIFIC MEMORY TASKS

Tests	Latency to Respond (s)						
	0	10	20	30	40	50	60
Visual stimulus	1.4/0.6	3.0/2.2	2.8/0.7	4.7/1.2	9.2/2.0	10.2/3.0	12.6/2.8
Olfactory stimulus	3.0/0.6	4.6/1.9	10.4/1.6	9.4/1.3	17.5/2.1	12.2/1.2	14.0/2.3
Somatosensory stimulus	1.5/0.3	2.0/0.9	2.3/0.7	3.2/0.6	3.7/0.8	7.1/2.0	5.9/1.9
Whisker-touch stimulus	0.7/0.2	3.6/1.3	6.4/1.5	4.6/1.0	16.3/2.5	10.6/3.1	11.0/3.6
Tilted platform	13.5/3.6	32.1/15.0	28.7/7.2	23.9/5.2	33.0/5.2	18.3/4.4	31.7/9.0

Data are means/SE (mg/kg).

50, and 60 mg/kg of ibogaine resulted in significantly ($p < 0.01$) longer latencies in comparison with vehicle control.

The effect of ibogaine injections on mean latency to respond to the somatosensory stimulus is also shown in Table 1. As doses of ibogaine increased there was a corresponding increase in latency to respond to the somatosensory stimuli. A one-way within-subject ANOVA indicated that there was a significant drug dose effect [$F(6, 114) = 14.2, p < 0.0001$]. Further Newman-Keuls tests revealed that doses of 30, 40, 50, and 60 mg/kg of ibogaine resulted in significantly ($p < 0.05$) longer latencies in comparison with vehicle control.

Table 1 also shows the effect of ibogaine injections on mean latency to respond to whisker touch. As doses of ibogaine increased, there was a corresponding increase in latency to respond to the whisker touch stimulus. A one-way within-subject ANOVA indicated that there was a significant drug dose effect [$F(6, 114) = 20.3, p < 0.0001$]. Further Newman-Keuls tests revealed that doses of 20, 30, 40, 50, and 60 mg/kg of ibogaine resulted in significantly ($p < 0.01$) longer latencies in comparison with vehicle control.

Finally, the effect of ibogaine injections on mean latency to respond to the tilted platform is shown in Table 1. The table indicates that ibogaine produced an increase in latency to respond compared to the vehicle control condition. A one-way within-subject ANOVA revealed that there was a significant drug dose effect [$F(6, 114) = 4.36, p < 0.0005$]. Further Newman-Keuls tests revealed that at all doses but the 50 mg/kg dose of ibogaine the rats had significantly ($p < 0.05$) longer latencies in comparison with vehicle control rats.

The effect of ibogaine injections on the mean placing reflex score is shown in Table 2. Ibogaine disrupted the appropriate execution of the placing reflex only at the 50-mg/kg ibogaine dose. A one-way within-subject ANOVA revealed that there was a significant drug dose effect [$F(6, 114) = 12.1, p <$

0.001]. Further Newman-Keuls tests indicated that the dose of 50 mg/kg of ibogaine resulted in a significantly lower score compared to all the other doses ($p < 0.01$).

The effect of ibogaine injections on the mean grasping reflex score is also shown in Table 2. Ibogaine disrupted the appropriate execution of the grasping reflex only at the 40- and 50-mg/kg ibogaine doses. A one-way within-subject ANOVA revealed that there was a significant drug dose effect [$F(6, 114) = 3.4, p < 0.004$]. Further Newman-Keuls tests indicated that doses of 40 and 50 mg/kg ibogaine resulted in significant lower scores compared to the other doses ($p < 0.01$).

Table 2 shows the effect of ibogaine injections on the mean righting reflex (back) score. Ibogaine disrupted the execution of the righting reflex starting at doses of 40 mg/kg ibogaine and above. A one-way within-subject ANOVA revealed that there was a significant drug dose effect [$F(6, 114) = 11.4, p < 0.0001$]. Further Newman-Keuls tests indicated that doses of 40, 50, and 60 mg/kg of ibogaine resulted in significantly lower scores compared to the other doses ($p < 0.01$).

Finally, the effect of ibogaine injections on mean free fall righting reflex score is shown in Table 2. Ibogaine disrupted the execution of the righting reflex (free fall) starting at doses of 30 mg/kg ibogaine and above. A one-way within-subject ANOVA revealed that there was a significant drug dose effect [$F(6, 114) = 5.1, p < 0.0001$]. Further Newman-Keuls tests indicated that doses of 30, 40, 50, and 60 mg/kg of ibogaine resulted in significantly lower scores compared to 0, 10 and 20 mg/kg ibogaine ($p < 0.05$).

Discussion

The results point to a reduction in detection of sensory information as indicated by longer latencies to respond. This

TABLE 2
EFFECTS OF IBOGAINE INJECTION ON PERFORMANCE OF SPECIFIC MOTOR TASKS

Tests	Performance Score						
	0	10	20	30	40	50	60
Placing reflex	1.0/1.0	1.0/1.0	1.0/1.0	1.0/1.0	1.0/1.0	0.8/0.1	1.0/1.0
Grasping reflex	1.0/1.0	1.0/1.0	1.0/1.0	1.0/1.0	0.9/0.1	0.9/0.1	1.0/1.0
Righting reflex (back)	1.0/1.0	1.0/1.0	1.0/1.0	1.0/1.0	0.8/0.1	0.9/0.1	0.6/0.2
Righting reflex (fall)	1.0/1.0	1.0/1.0	1.0/1.0	0.1/0.1	0.9/0.1	0.9/0.1	0.8/0.2

Data are means/SE (mg/kg).

reduction in sensory responsiveness was already evident at doses of 20 mg/kg of ibogaine for the olfactory and whisker-touch orienting tests. At doses of 40 mg/kg ibogaine, reduction in detection of sensory information was observed in all of the sensory assessment tests. Furthermore, in general, the higher the dose of ibogaine the greater the sensory impairment. Thus, ibogaine has a marked disruptive effect on detection of sensory input.

With respect to sensory-motor function, ibogaine disrupted performance on the tilted platform test at the lowest dose (10 mg/kg). This test is sensitive to vestibular and cerebellar function and is consistent with a recent report that ibogaine has deleterious actions on cerebellar function (13). With respect to tests of motor function, in general, problems did not appear until doses of 40–50 mg/kg ibogaine.

Thus, ibogaine appears to have its greatest effects on tests of vestibular and cerebellar function, followed by effects on sensory function, and then motor functions.

EXPERIMENT 2: ACTIVITY AND EMOTIONALITY

The rats under the influence of ibogaine were not very active. It was thus important to employ a standard test of activity to quantify the effects of ibogaine on the level of activity.

The effect of ibogaine (0, 10, 20, 30, or 40 mg/kg) on activity and emotionality was assessed in an open field. Because doses of 50 and 60 mg/kg ibogaine severely impaired motor responses, these dose levels were not used in the activity experiment.

Methods

The apparatus used was a large, open wooden box (120 × 120 cm) with 30-cm-high walls. The floor of the box was painted white and divided by black lines forming 64 square sections (15 × 15 cm). The subjects were 40 Long-Evans rats, deprived to and maintained at 80–85% of free-feeding body weight. For the open field experiment, eight rats in each group were assigned a dose (0, 10, 20, 30, or 40 mg/kg) of ibogaine, which remained consistent throughout the testing period. Thirty minutes after IP injection, each animal was placed in the center of the open field for 10 min. The mean number of squares entered was used as a measure of locomotor activity. Grooming, scratching, righting, and washing behaviors were recorded and combined into a single nonlocomotor activity score. Emotionality was measured by the occurrence of urination and defecations, and these were combined for an emotionality score. Testing was conducted on each of 3 consecutive days.

Results

The effect of ibogaine injections on locomotor activity (mean squares traversed) as a function of days of testing is shown in Fig. 1. Ibogaine produced a dose-dependent decrease in locomotor activity compared to the vehicle control. A two-way ANOVA with dose level as the between factor and days as the within factor revealed a significant drug effect [$F(4, 20) = 8.1, p < 0.0005$] and a significant days effect [$F(2, 40) = 3.27, p < 0.05$]. A subsequent Newman-Keuls test revealed that all ibogaine groups displayed significantly ($p < 0.05$) lower locomotor activity compared to the vehicle control.

The effect of ibogaine injections on nonlocomotor activity (grooming, scratching, washing, and righting) as a function of days of testing is shown in Fig. 2. Ibogaine produced a

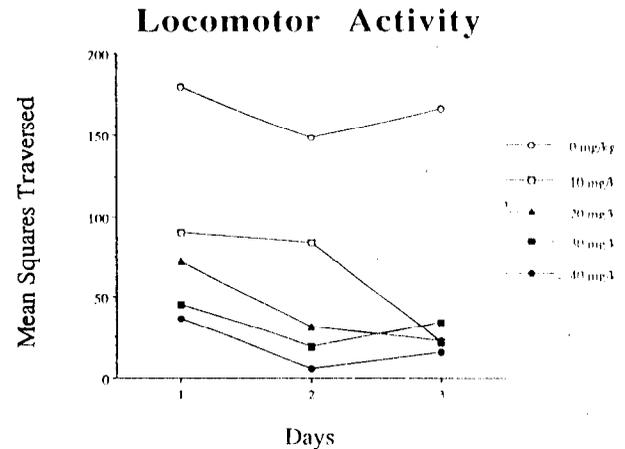


FIG. 1. The effect of ibogaine (mg/kg) on mean number of squares traversed as an index of locomotor activity as a function of days.

dose-dependent decrease in nonlocomotor activity compared to the vehicle control. A two-way ANOVA with dose level as the between factor and days as the within factor revealed significant drug effect [$F(4, 20) = 13.5, p < 0.0001$] and significant days effect [$F(2, 40) = 5.29, p < 0.009$]. A subsequent Newman-Keuls test revealed that all ibogaine groups displayed significantly ($p < 0.05$) lower nonlocomotor activity compared to the vehicle control.

The effect of ibogaine injections on urination and defecation as a function of days of testing is shown in Fig. 3. Ibogaine produced a decrease in urination and defecation (emotionality) compared to the vehicle control. A two-way ANOVA with dose level as the between factor and days as the within factor revealed a significant drug effect [$F(4, 20) = 7.5, p < 0.025$].

Discussion

The results indicate that ibogaine produces a dose-dependent reduction in locomotor activity and nonlocomotor activity as well as urination and defecation. The rats receiving

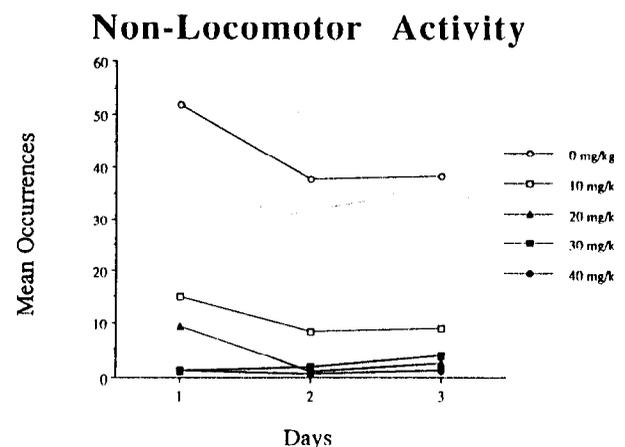


FIG. 2. The effect of ibogaine (mg/kg) on the mean number of occurrences of washing, righting, scratching, and grooming as an index of nonlocomotor activity as a function of days.

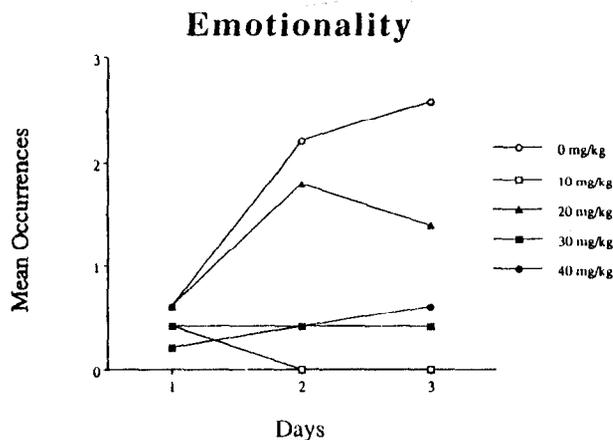


FIG. 3. The effect of ibogaine (mg/kg) on the mean number of occurrences of urination and defecation as an index of emotionality as a function of days.

the higher doses (30–40 mg/kg) of ibogaine were very inactive and appeared to be in a state of suspension. These results are consistent with the observation of reduced locomotor activity in mice injected with 80 mg/kg of ibogaine (15). It has been shown that ibogaine produces immediate and delayed changes in dopamine metabolism in nucleus accumbens, striatum, and prefrontal cortex and that these changes relate to decreases in morphine-induced locomotor activity (11). Thus, it is likely that changes in locomotor activity are due to ibogaine action on dopaminergic brain systems. The enhanced efficacy in reducing activity levels for the 10-mg/kg group with repeated treatments could have been due to cumulative effects of the drug. Furthermore, the ibogaine-injected rats were less emotional compared to the vehicle-injected rats. This is significant because it indicates or suggests that the reduced activity of ibogaine-injected rats was not a result of an enhanced fear response to the open field. It is not clear why the 20-mg/kg ibogaine-injected rats showed greater emotionality compared to the 10-mg/kg group.

EXPERIMENT 3: LEARNING TASKS

Even though ibogaine has marked effects on detection of sensory stimuli and reduces activity level, it was still important to determine whether these effects would lead to learning and memory problems. To measure the effects of ibogaine on learning and memory, rats were trained on a spatial location memory task in a dry-land version of a water maze. This task has been shown to be sensitive to hippocampal dysfunction.

Methods

Apparatus. The apparatus (cheeseboard) was made of 3.3-cm-thick wood, painted white and elevated 26 cm from the floor. It was circular with a diameter of 119 cm. It contained 177 evenly spaced, round holes (2 cm in diameter and 1.5 cm deep) spaced 4 cm apart. The walls of the room contained pictures as extramaze visual cues. The trials were monitored by a video camera positioned directly above the maze, which fed into a tracking system consisting of an image analyzer (HVS Ltd. VP 110) coupled to an Apple IIe computer. A light-emitting diode attached to Velcro tape was placed onto the rat's body for tracking purposes.

Behavioral procedures. Pretraining involved attaching Velcro tape to an animal and allowing it to explore the apparatus with food (Froot Loop cereal) in half of the food wells. This enabled the rats to habituate to the cheeseboard environment. The animals were familiarized with the apparatus for 6 days. After the 2nd day the number of food wells containing Froot Loops was reduced to 35, and on the 5th day to 25.

On the 7th day the animals were assigned a specific food location (one food well containing once piece of Froot Loop cereal) in one of the four quadrants of the apparatus; this location remained consistent throughout testing. Thirty minutes before testing the animals were injected with 0, 10, 20, or 30 mg/kg of ibogaine; each drug-dose group contained eight subjects. The animals were given eight trials per day with two trials at each of the four starting locations. The intertrial interval was a minimum of 5 s. Each trial consisted of placing an animal on the edge of the apparatus facing the wall at one of the four starting locations. The animal was allowed to search for the food well containing the Froot Loop cereal until it found the correct hole and ate the food, or until 120 s had transpired. The latency to find the correct food well was used as the dependent measure. On the following 2 days each animal received the same drug treatment 30 min before testing and was given an additional eight trials using the same procedure previously described.

Results

The results are shown in Fig. 4. In the spatial location learning task, rats with 10, 20, or 30 mg/kg ibogaine injections could not learn the task, as indicated by long latencies to find the food location.

An ANOVA of the latency data with drug dose as the between-subject variable and blocks of trials as the within-subject variable revealed a significant effect of drug dose [$F(3, 28) = 25.2, p < 0.001$] and a significant effect of blocks of trials [$F(5, 140) = 3.2, p < 0.009$]. The observation of a significant effect of blocks without a significant interaction of drug dose and blocks indicates that all the rats improved across trials. Based on subsequent Newman-Keuls tests, rats that received ibogaine were significantly different from saline-injected rats ($p < 0.01$), but not from each other.

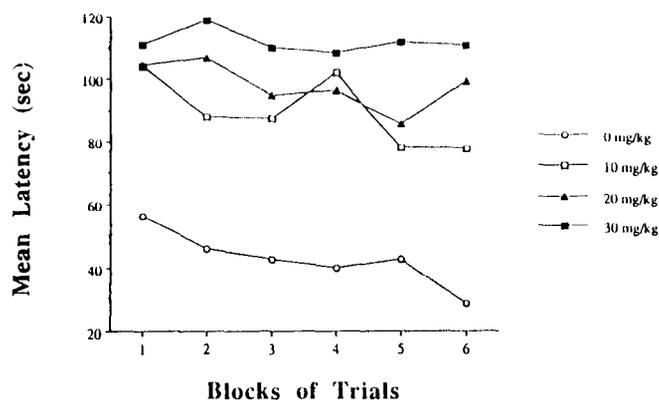


FIG. 4. The effect of ibogaine (mg/kg) on the mean latency (s) to find the correct food location in the spatial location task as a function of blocks of four trials (two per day).

Discussion

The results indicate that rats with 10, 20, or 30 mg/kg ibogaine injections could not learn the spatial location task, although there was a slight improvement across trials. This could be due in part to the reduction in locomotor activity, and thus, difficulties in searching for the location of the food. This inability to learn could also be due to a reduction in the ability to detect visual stimuli.

Therefore, one cannot clearly assess the effects of ibogaine on learning and memory in this task, because of its marked effects on activity level and sensory-motor functions.

EXPERIMENT 4: LONG-TERM EFFECTS OF IBOGAINE

Even though the acute effects of ibogaine on sensory-motor function, activity, and learning are rather profound, we needed to determine whether a single dose of ibogaine would have long-term consequences on sensory-motor function and learning of a spatial location task.

Methods

Thus, new rats ($n = 30$) were injected (IP) with either the vehicle ($n = 14$) or ibogaine ($n = 16$) (40 mg/kg) and subsequently tested for learning of the spatial location task 1 day [vehicle ($n = 9$), ibogaine ($n = 10$)] or 7 days [vehicle ($n = 5$) and ibogaine ($n = 6$)] later using the same procedure described in Experiment 3, the spatial location task.

In addition, of the 19 rats that were tested in the spatial location task 1 day later, eight (four vehicle and four ibogaine) were tested for sensory-motor function using the same procedures described in Experiment 1 before the 1st day of testing in the spatial location task, and 11 (five vehicle and six ibogaine) were tested for sensory-motor function immediately after the last day of testing (day 3) in the spatial location task. Of the 11 rats that were tested in the spatial location task 7 days later, all 11 (five vehicle and six ibogaine) were tested for sensory-motor function immediately after the last day of testing (day 9) in the spatial location task.

Results

After a single 40-mg/kg ibogaine injection, there were no neurologic problems on the 1-, 3-, or 10-day neurologic tests for visual and somatosensory information or motor tests (placing, grasping, and righting reflexes). Even though this was not assessed formally, the rats were not inactive 1-11 days after the ibogaine injection. As an illustration of the lack of effect of ibogaine, results are shown for the olfactory and whisker-touch sensory tests, and the tilted platform test for the vehicle and 40-mg/kg ibogaine groups tested 30 min after injection (from Experiment 1) and vehicle or 40-mg/kg ibogaine groups tested 24 h after injection (Table 3). Relative to the 30-min ibogaine-injection test, there were no problems 24 h following an ibogaine injection.

A two-way ANOVA with dose (0 or 40 mg/kg ibogaine) and test interval (30 min vs. 24 h) as the two factors was performed on latency to respond to olfactory stimuli, and revealed a significant dose effect [$F(1, 41) = 10.6, p < 0.003$], a significant interval effect [$F(1, 41) = 11.2, p < 0.002$], and a significant dose \times interval interaction [$F(1, 41) = 9.5, p < 0.004$]. A similar analysis on latency to respond to whisker touch revealed a significant dose effect [$F(1, 41) = 11.8, p < 0.002$], a significant interval effect [$F(1, 41) = 5.4, p < 0.03$], and a significant dose by interval interaction [$F(1, 41) = 6.5, p < 0.02$]. A final analysis on latency to respond

TABLE 3
MEMORY FUNCTION 30 min OR 24 h FOLLOWING
IBOGAINE INJECTION

Tests	Latency to Respond (s)			
	30 minutes		24 hours	
	0	40	0	40
Olfactory stimulus	3.2/0.7	15.7/3.3	2.4/0.5	2.8/0.7
Whisker-touch stimulus	0.9/0.4	11.6/4.1	1.3/0.6	3.6/2.0
Tilted platform	21.5/9.7	31.6/11.5	5.3/1.1	12.1/6.8

Data are means/SE (mg/kg).

to the tilted platform revealed primarily a significant interval effect [$F(1, 41) = 4.5, p < 0.04$] with a dose effect almost reaching significance [$F(1, 41) = 3.7, p < 0.06$].

The results of a single injection of 0 or 40 mg/kg of ibogaine 1 or 7 days before testing on mean latency to find the correct food location are shown in Figs. 5 and 6, and indicate that there was a significant disruptive effect on spatial learning 1-3 days after the ibogaine injection, but no long-term consequence 7-9 days later. An ANOVA of the latency data 1 day after injection with drug dose as the between-subject variable and blocks of trials as the within-subject variable revealed a significant dose effect [$F(1, 17) = 4.5, p < 0.05$], but no significant trials or significant dose \times trials interaction effect. Thus, a single injection of ibogaine produced a disruption in learning the spatial location task. A similar ANOVA on the latency data 7 days after injection revealed only a significant block of trials effect [$F(5, 45) = 4.3, p < 0.003$], but no significant dose or significant dose \times trial interaction effect, indicating that both groups learned the task.

Discussion

The results of this last experiment suggest that even though ibogaine has no long-term consequences on sensory-motor function, there are significant effects on the acquisition of a spatial navigation task 1-3 days after a single injection of 40

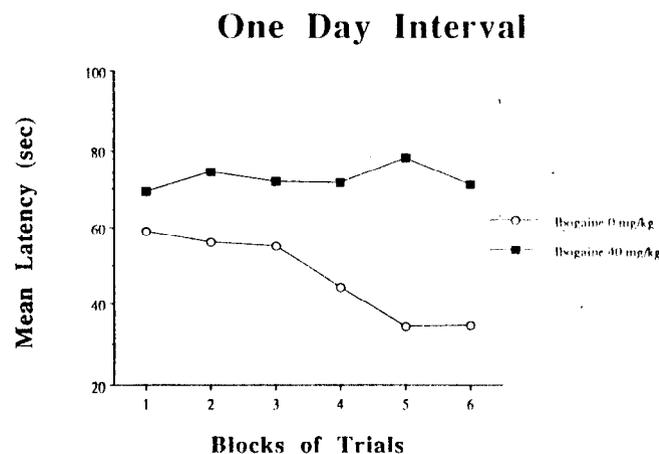


FIG. 5. Mean latency (s) to find the correct food location as a function of blocks of four trials (two per day) starting 1 day after a single injection of 0 or 40 mg/kg ibogaine.

Seven Day Interval

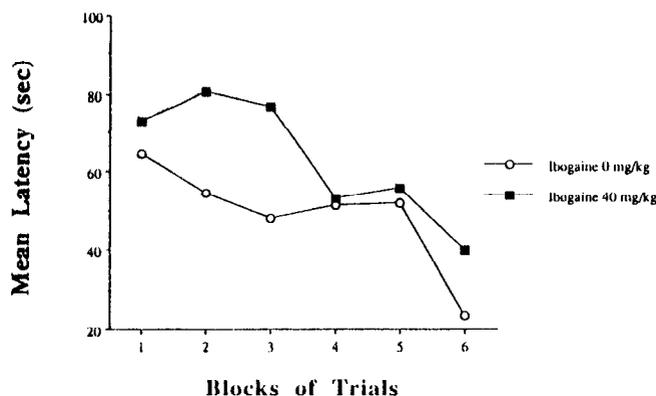


FIG. 6. Mean latency (s) to find the correct food location as a function of blocks of four trials (two per day) starting 7 days after a single injection of 0 or 40 mg/kg ibogaine.

mg/kg of ibogaine. This long-term effect appears to be time limited, because only a small nonsignificant effect on learning was found 7-9 days after a single injection of 40 mg/kg of ibogaine.

Thus, ibogaine at doses of 10-40 mg/kg can produce marked impairments on activity, sensory-motor function, and learning while the subject is under the influence of the drug, as well as a long-term effect on learning that cannot be due to

deficits in sensory-motor function or marked changes in activity level. It is not clear how ibogaine can produce long-term effects on learning ability, especially because the half-life of ibogaine in rats is about 1 h (2). Similar long-term effects of ibogaine on behavior have been described elsewhere (4,11). It is not known whether a metabolite of ibogaine has a long half-life or whether ibogaine produces long-term changes in specific neural transmitter systems. It has been shown that ibogaine can decrease the levels of dopamine metabolites at least for 19 h after an ibogaine injection (11).

The long-term deficits of ibogaine on the dry-land version of the water maze spatial navigation task are similar to what has been reported for rats with hippocampal lesions (9), suggesting the possibility that long-term effects of ibogaine could be based on its influence on hippocampal learning and memory function. It should be noted that ibogaine also has effects on the dopaminergic system within nucleus accumbens, prefrontal cortex, and striatum (10,11), and thus could alter reward mechanisms as well. However, lesions of the striatum or medial prefrontal cortex do not produce marked deficits in spatial navigation tasks (8,9). It is a possibility that ibogaine has effects on addiction via a dual action on reward as well as learning and memory mechanisms. The present study indicates that ibogaine has effects on learning and memory. Whether ibogaine affects learning and memory processes associated with tolerance development, addiction, withdrawal from addiction, and craving needs to be assessed.

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