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Attenuation of Alcohol Intake by Ibogaine in Three Strains of Alcohol-Preferring Rats

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REZVANI, A. H., D. H. OVERSTREET AND Y.-W. LEE. *Attenuation of alcohol intake by Ibogaine in three strains of alcohol-preferring rats.* PHARMACOL BIOCHEM BEHAV 52(3) 615–620, 1995.—Alcohol-preferring (P), Fawn-Hooded (FH) and alcohol-accepting (AA) rats were injected intraperitoneally (IP) or subcutaneously (SC) with different doses (10, 30, and 60 mg/kg) of Ibogaine or vehicle. In a separate experiment, FH rats were administered intragastrically (IG) with either 60 mg/kg of Ibogaine or vehicle for 5 days. In addition, the effects of Ibogaine on blood alcohol concentrations were measured. Our data show that, contrary to the SC administration of Ibogaine, IP administration of the agent significantly and dose-dependently reduced alcohol intake in these rats. Subchronic IG administration of 60 mg/kg of Ibogaine into FH rats significantly reduced alcohol intake without the development of tolerance or a significant effect on food or water intake. A single IP injection of 60 mg/kg Ibogaine into FH rats did not affect the blood alcohol levels. These results show that Ibogaine when injected IP or IG, but not SC, can significantly reduce alcohol intake without an effect on blood alcohol concentrations or food intake. These findings may suggest the involvement of Ibogaine's metabolite(s) in reducing alcohol intake. Although the neuronal mechanism(s) of action of Ibogaine on the regulation of alcohol intake is not fully understood, it is speculated that Ibogaine or its metabolite(s) exerts its attenuating effect on alcohol intake by modulating neurotransmitters/neuromodulators proposed to be involved in regulation of alcohol consumption.

Fawn-Hooded rats Alcohol-preferring rats Alcohol drinking Blood alcohol Ibogaine
Alcohol seeking behavior Herbal medicine Alternative medicine

ALCOHOL dependency and alcohol related diseases are threatening human health at an alarming rate and are posing major social and economic problems. Thus, the development of suitable therapeutic agents for the treatment of this disease should be one of the major objectives of alcohol research. Several pharmacological agents including fluoxetine (19,25), naltrexone (50), thyrotropine releasing hormone analog (17, 31), and several neuronal calcium channel antagonists (29,32, 34,39) have been shown to reduce alcohol intake.

Herbal preparations have been used over many centuries to treat a variety of ailments effectively. Recently, extracts from several medicinal herbs have been demonstrated to reduce alcohol consumption in two strains of alcohol-preferring rats (26,35). Ibogaine (NIH 10567, Endabuse™) is the principal indole alkaloid found in the root bark of *Tabernanthe iboga* (*Apocynaceae* family), a shrub found in West Central Africa. This herb is used primarily as a stimulant to combat thirst, hunger, and fatigue by the natives. It has been reported that the crude extracts of *Tabernanthe iboga* cause a feeling of excitement, drunkenness, mental confusion, and possibly hallucinations when taken in high enough doses (42). Efficacy of Ibogaine in the treatment of drug addiction has been suggested (US Patent 4,857,523). Recent animal studies indicate that Ibogaine may significantly affect drug withdrawal and intake of addictive drugs. It has been shown in rats that pretreatment with Ibogaine significantly decreases morphine self-administration for several days along with preventing withdrawal symptoms (8). Similarly, antiwithdrawal effects have been observed in Ibogaine-treated morphine-dependent monkeys (1). In addition, it has been demonstrated that Ibogaine produces a marked decrease in cocaine intake in rats (3) and C57BL/6By mice (44).

Rewarding properties of addictive drugs such as alcohol have been shown to be associated with their ability to stimulate both dopaminergic (40) and serotonergic (19,22,23) systems in the brain. Although not conclusive yet, it has been proposed that Ibogaine exerts its anticraving effects by stimulating dopaminergic systems (8,14). As an initial step towards isolating active chemicals from Ibogaine, which may have potential applications in the treatment of alcohol dependency,

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we have tested the alcohol-attenuating effects of Ibogaine in three different strains of alcohol-preferring rats. All three strains exhibit a high preference for alcohol and drink significant amounts of alcohol in a free choice situation.

MATERIALS AND METHODS

Animals

Adult male alcohol-preferring (P), Fawn-Hooded (FH) and alcohol-accepting (AA) rats were used for these experiments. At the beginning of the experiments P, FH, and AA rats weighed 0.55 ± 0.02, 0.46 ± 0.02, and 0.47 ± 0.02 kg, respectively. Rats were housed individually in stainless steel wire mesh cages (26 × 34 × 20 cm) under constant temperature of 21° ± 1°C and a reversed 12 D : 12 L cycle (1000–2200 h dark). P rats were obtained from the Indiana University School of Medicine (Indianapolis, IN), FH rats were obtained from a viral-free colony established at the University of North Carolina School of Medicine (Chapel Hill, NC), and AA rats were provided by Alko Lab Inc. (Helsinki, Finland).

Screening for Alcohol Preference

Rats were screened for alcohol preference using the standard two-bottle method (33,51). They were first given free access to tap water for 1 day in a graduated Richter tube. Then they were given free access to a solution of 10% (v/v) ethanol as a sole source of fluid for 3 consecutive days. Food was available ad lib throughout. This procedure allowed them to become accustomed to drinking from the Richter tubes and to the novel taste of alcohol. Further, 3-day forced alcohol exposure allowed them to experience the pharmacological properties of alcohol. After 3 days of forced alcohol exposure, rats were given free access to tap water and a solution of 10% ethanol for at least 2 weeks. Food, water, and alcohol intake and body weight were recorded every day between 0900 and 0930 h.

Preparation of Drugs

Solutions of ethanol were prepared daily from 95% reagent grade ethanol and distilled water. Ibogaine HCl was obtained from the National Institute of Drug Abuse (Bethesda, MD). Solutions of Ibogaine was prepared daily in pyrogen free glassware with distilled water. Three different doses of Ibogaine (10, 30, and 60 mg/kg) were used.

Experimental Protocol

Acute effects of Ibogaine on alcohol, water, and food intake. After establishing a stable baseline for alcohol and water intake in FH rats, at approximately 0930 h a single SC injection of distilled water or one of the doses of Ibogaine (10, 30, and 60 mg/kg) was given to each rat (n = 8). All animals in this group received all of the treatments (i.e., distilled water and three doses of Ibogaine in a counterbalanced design) with a 1-day interval between the drug and the vehicle administration. Water, alcohol, and food intake as well as animal's body weight were measured every day between 0900 and 0930 h during the course of the experiment.

In the second series of experiments, the effect of acute intragastric administration of Ibogaine and control vehicle in FH rats was investigated. The same FH rats (n = 8) used for the above experiments were given either a dose of 60 mg/kg Ibogaine or an equal volume of distilled water by gavage at approximately 0930 h for 1 day. Three days were allowed between injections. Water, alcohol, and food intake were measured for the proceeding 24 h.

In the third study, the acute effects of intraperitoneal (IP) administration of the same doses of Ibogaine were determined in all three different strains, FH (n = 8), P (n = 20), and AA (n = 7) rats. After establishment of a stable baseline for alcohol and water intake, rats were injected either with the control vehicle or one of the three doses of Ibogaine in a random order design. The intervals between the injections were at least 3 days. All of the FH and AA rats received all of the treatments. P rats were divided into three groups: one group (n = 7) received vehicle and 10 mg/kg of Ibogaine; another group (n = 7) received vehicle and 30 mg/kg of Ibogaine; and the third group (n = 6) received vehicle and 60 mg/kg of Ibogaine. Thus, each rat in each group received two injections with a 5-day interval between injections. Throughout the study water, food, and alcohol intake were measured every morning between 0900 and 0930 h.

Subchronic effects of Ibogaine on ethanol, water, and food intake. In the same group of FH rats (n = 8), after recovery from previous experiments and reestablishment of a stable baseline for alcohol and water intake, all animals were given a dose of 60 mg/kg Ibogaine at approximately 0930 h and 4 weeks later an equal volume (on the basis of ml/kg B.W.) of distilled water by gavage for 5 consecutive days. Alcohol, food, and water intake were measured throughout.

Effects of Ibogaine on blood alcohol levels. A group of six alcohol-naive adult male FH rats were used to measure the effects of Ibogaine on blood alcohol concentrations. Rats were injected IP with either 60 mg/kg Ibogaine or an equal volume of distilled water and 15 min later with a dose of 2.5 g/kg ethanol (16% v/v) following a cross-over design with a 1-week interval. In this design, half of the rats received Ibogaine + alcohol and the other half received distilled water + alcohol. One week later the order was reversed (i.e., the first group received distilled water + alcohol and the second group received Ibogaine + alcohol). Blood samples were drawn from the tip of the tail at 1, 3, and 5 hours after alcohol injection for determination of blood alcohol levels. The detail of the chromatography technique for the blood alcohol analysis has been fully described elsewhere (33).

Statistical analysis of data. The data are expressed as means ± standard error of means (SEM), and statistical differences between Ibogaine-treated groups and control groups were determined by using ANOVA with repeated measures and Tukey's protected t-test for multiple comparisons.

RESULTS

Acute Effects of Ibogaine

AA, FH, and P rats drink significant amounts of alcohol in a free choice situation. When given free access to food, water, and a solution of 10% (v/v) ethanol, FH, P, and AA rats consumed an average of 5.6 ± 0.3, 6.7 ± 0.2, and 5.9 ± 0.4 SEM g/kg/day of ethanol, respectively. Compared with control vehicle, a single SC administration of different doses of Ibogaine did not exert a significant effect on either food, water, or alcohol intake in FH rats (data not shown). However, when Ibogaine was injected IP it significantly attenuated alcohol intake in FH, P, and AA rats in a dose-dependent manner (Fig. 1). IP administration of Ibogaine also suppressed alcohol preference dose dependently. Administration of 10, 30, and 60 mg/kg Ibogaine (IP) induced 8%, 13%, and 25% ($p < 0.05$) reduction in alcohol preference in AA rats. The corresponding values for FH and P rats were 20%, 26%,

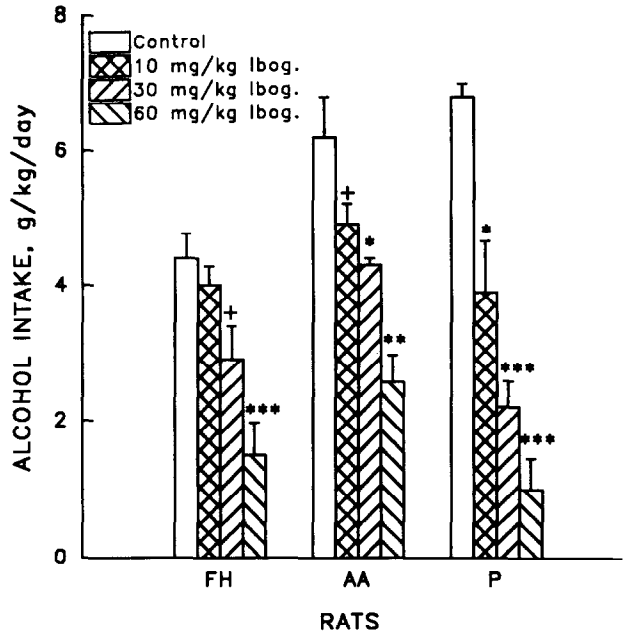

FIG. 1. Effects of different doses of Ibogaine (Ibog) and control vehicle on alcohol intake in FH, AA, and P rats. Data are means ± SEM. *$p < 0.05$, **$p < 0.002$, and ***$p < 0.001$ compared with the corresponding control vehicle.

and 51% ($p < 0.01$) and 22%, 39%, ($p < 0.01$), and 63% ($p < 0.001$), respectively. As can be seen from these data, the high dose of 60 mg/kg Ibogaine administered IP exerted a significant effect on all three strains but P rats were more affected.

IP administration of three different doses of Ibogaine did not significantly influence food intake in either FH or AA rats. However, the administration of the same doses of Ibogaine into P rats produced mixed results (Table 1). Overall, there was a nonsignificant trend for the water intake to be elevated in all three strains after Ibogaine administration (Table 1). Among the three doses tested, the 30 mg/kg dose significantly increased water intake and the high dose of 60 mg/kg significantly decreased the food intake (Table 1). Similar to IP injections, a single IG administration of 60 mg/kg Ibogaine into FH rats significantly ($p < 0.01$) reduced (60%) alcohol intake and alcohol preference ($p < 0.05$). The corresponding values of alcohol intake after a single IG administration of 60 mg/kg Ibogaine and distilled water were 2.29 ± 1.3 and 5.73 ± 0.6, respectively. Both IP and IG administrations of Ibogaine were significantly more effective than the SC administration of the drug (Table 2).

TABLE 2

EFFECTS OF ROUTE OF ADMINISTRATION ON THE SUPPRESSING EFFECT OF IBOGAINE (60 mg/kg B.W.) ON ALCOHOL INTAKE IN FH RATS

Route of Administration	Alcohol Intake (g/kg/day)
Subcutaneous	3.9 ± 0.7 (+8%)
Intragastric	1.7 ± 0.5 (−55%)*
Intraperitoneal	1.5 ± 0.5 (−65%)**

The numbers in parentheses are percent change in alcohol intake from the corresponding control values. *$p < 0.05$ compared with the subcutaneous administration; **$p < 0.02$ compared with the subcutaneous administration.

Subchronic Effects of Ibogaine

Subchronic administration of 60 mg/kg Ibogaine into FH rats by gavage for 5 consecutive days significantly [$F(1, 8) = 29.4$, $p < 0.0001$] and consistently reduced alcohol intake without the development of tolerance (Fig. 2) and a significant effect on food [$F(1, 8) = 0.0003$, $p > 0.9$] and water [$F(1, 8) = 0.02$, $p > 0.9$) intake (data not shown).

Effects of Ibogaine on Blood Alcohol Levels

Compared with control vehicle, a single injection (IP) of a high dose of Ibogaine into FH rats 15 min before ethanol (2.5 g/kg, 16% v/v) administration (IP) did not significantly affect the level of alcohol in the blood. As Fig. 3 demonstrates, blood alcohol curves for both control vehicle and Ibogaine followed identical patterns and peaked and descended with the same slope.

DISCUSSION

The present findings demonstrate, for the first time, that Ibogaine significantly reduced alcohol intake in three different strains of alcohol-preferring rats in a dose-dependent fashion. In contrast to IG and IP routes, SC administration of different doses of Ibogaine failed to influence alcohol intake. This

TABLE 1

EFFECTS OF INTRAPERITONEAL ADMINISTRATION OF DIFFERENT DOSES OF IBOGAINE AND CONTROL VEHICLE ON WATER AND FOOD INTAKE (g/kg/day) IN P, FH AND AA RATS

	P		FH		AA	
Treatment	Water	Food	Water	Food	Water	Food
Vehicle	7.5 ± 2.5	31.0 ± 1.6	61.7 ± 4.0	53.0 ± 2.7	9.6 ± 10.0	44.5 ± 3.0
Ibogaine (mg/kg)						
10	15.0 ± 6.2	39.5 ± 4.3*	57.4 ± 6.6	52.5 ± 2.6	15.5 ± 7.8	45.0 ± 1.5
30	20.7 ± 4.6*	29.6 ± 1.0	68.0 ± 6.9	51.6 ± 2.0	15.3 ± 6.3	47.5 ± 3.0
60	19.0 ± 4.3	24.0 ± 2.4*	65.0 ± 7.0	47.5 ± 2.9	15.6 ± 5.0	35.0 ± 5.0

*$p < 0.05$ compared with corresponding vehicle values.

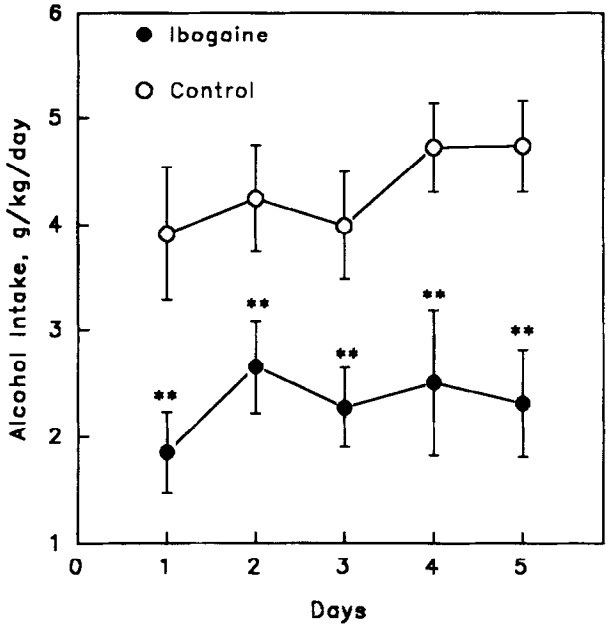

FIG. 2. Effects of subchronic administration of 60 mg/kg Ibogaine and control vehicle by gavage on alcohol intake in Fawn-Hooded rats. Data are means ± SEM. $^{**}p < 0.002$ compared with corresponding control vehicle.

may indicate that Ibogaine itself is not effective in reducing alcohol intake and one or more of its metabolites is responsible for this action. This is supported by the fact that the elimination half-life of Ibogaine for plasma is about 53 min (48). The involvement of one or several active metabolites of Ibogaine in reducing cocaine intake has been also suggested (3). Another possible reason for the lack of effect of Ibogaine when it is injected SC is the formation of local depots. It is also possible that Ibogaine is poorly absorbed into the circulation when it is injected SC, either due to the formation of depots or by some other mechanism.

In contrast to the SC administration of Ibogaine, both IG and IP routes of administration were effective in significantly reducing alcohol intake (Table 1). Since drugs administered by gavage and by IP usually undergo first pass metabolism, it is conceivable that Ibogaine requires metabolic activation by the liver to exert its action on alcohol intake. Indeed, recently, a single principal metabolite of Ibogaine with neuronal activity has been identified and isolated from blood and urine samples of rats, primates, and humans (11). We have shown that this primary metabolite of Ibogaine, when it is injected SC or IP, significantly attenuates alcohol intake in P rats (36). The effect of this metabolite on the intake of other drugs of abuse has not yet been determined. To fully characterize this lack of effect with SC injection, the profile of blood levels of Ibogaine following both SC and IP adminstration of the drug needs to be determined.

Although the neuronal mechanisms underlying the suppression of alcohol drinking by Ibogaine are not yet fully understood, there may be several possible mechanisms. One possible mechanism is the interaction between Ibogaine and the dopaminergic systems in the brain. Numerous studies indicate that brain dopamine plays a role in the rewarding properties of alcohol (2,40,41). The dopamine agonist bromocriptine (17) and dopamine uptake inhibitors (22) reduce alcohol intake in alcohol-preferring rats. Further, it has been reported that ethanol enhances the release of dopamine in the nucleus accumbens (5) and activates the firing of dopamine neurons in the ventral tegmental area of the rat brain (7). It has also been shown that the number of dopamine D_2 receptor sites and the content of DA are lower in several central nervous regions of selectively bred alcohol-preferring rats compared to alcohol nonpreferring rats (18,21,47).

Ibogaine has been reported to interact with dopaminergic system in the brain (14). Ibogaine enhances the dopaminergic response to *d*-amphetamine. Pretreatment with Ibogaine potentiates the effect of *d*-amphetamine on dopamine release in both striatum and nucleus accumbens (15). Ibogaine pretreatment has been shown to enhance the stimulatory motor effects induced by *d*-amphetamine in rats (16) but reduce this effect in C57BL/6By mice (42). However, Ibogaine treatment has been demonstrated to stimulate locomotor activities in rats (43). Furthermore, Ibogaine has been demonstrated to significantly (39% above control) increase the brain dopamine levels in rats (46) or to decrease the extracellular dopamine in striatum and nucleus accumbens (9). Recently, it has been demonstrated that Ibogaine can block the releasing effects of CGS-12066A, a 5-HT agonist, on DA efflux (45).

There is some evidence that Ibogaine also interacts with serotonergic mechanisms. Ibogaine has been reported to act as a direct serotonin receptor agonist causing the same 5-HT behavioral syndromes as LSD (43). Further, involvement of 5-HT_2 receptor activity and the possibility of a 5-HT_{1A} contribution in the stimulus properties of Ibogaine have been suggested (27). Because both clinical and animal studies suggest the involvement of the serotonergic system in the regulation of alcohol consumption (12,13,22,25,38), Ibogaine may exert its attenuating effects on alcohol intake by influencing this system in the brain. The subsensitivity of FH rats to Ibogaine in relation to P rats would be consistent with this model be-

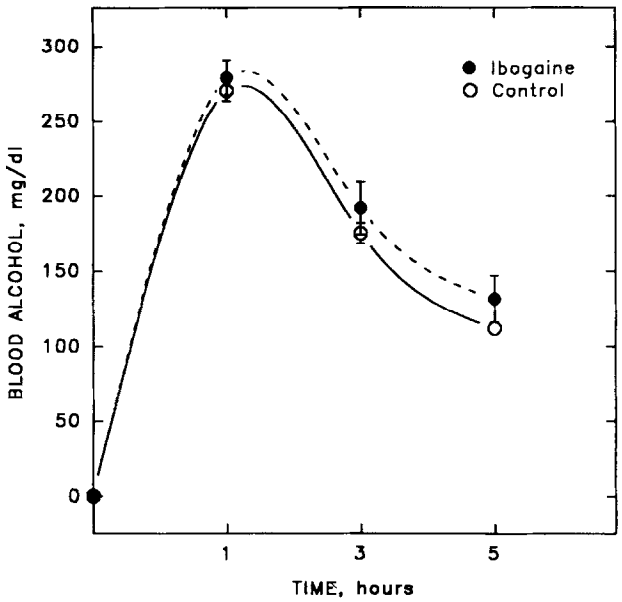

FIG. 3. Effects of 60 mg/kg Ibogaine and an equal volume of control vehicle on blood alcohol levels in Fawn-Hooded rats injected (IP) with 2.5 g/kg alcohol. Data are means ± SEM.

cause it has been previously reported that FH rats are less affected by serotonergic agents (37).

Ibogaine also has been reported to possess opioid properties. Ibogaine congeners have been demonstrated to have affinity for opiate receptors. In a radiolabled receptor survey, Deecher et al. (4) demonstrated that Ibogaine interacts at the κ-opiate receptor. Recently, it has been shown that Ibogaine can inhibit κ-mediated dopamine release in rats (30). There are several reports supporting the involvement of the endogenous opioid systems in the regulation of alcohol intake in rats (6), monkeys (24), and humans (50). Thus, considering the reported opioid property of Ibogaine, it is possible that it exerts its attenuating effects on alcohol intake by interferring with the endogenous opioid systems.

Another possible mechanism is the interaction of Ibogaine with neuronal calcium channels. There is evidence that neuronal calcium channels regulate alcohol intake. Administration of calcium channel inhibitors significantly attenuates alcohol intake in rats (29,32,39) and monkeys (34). A calcium blocking action has been proposed for the iboga alkaloid tabernanthine, an indole alkaloid similar to Ibogaine, in peripheral tissues (10,20). Thus, it is likely that Ibogaine, similar to calcium antagonists, exerts its reducing effect on alcohol intake by blocking calcium entry into neuronal cells.

Recently, another possible mechanism for the actions of Ibogaine has been proposed. It has been shown that Ibogaine is a competitive inhibitor of MK-801 binding to *N*-methyl-D-asparate (NMDA) receptor coupled cation channels (28). Because MK-801 attenuates the development of tolerance to morphine (49) and alcohol (52), the antiaddictive property of Ibogaine has been suggested to be attributed to the blockade of NMDA receptor coupled cation channels (28).

Overall, Ibogaine when it is injected IG or IP, but not SC, significantly reduces alcohol intake in different strains of alcohol-preferring rats without a significant effect on food consumption and blood alcohol levels. The involvement of active metabolite(s) of Ibogaine in reducing alcohol intake is suggested by our data. Although the true mechanisms of action of Ibogaine in reducing alcohol consumption are not fully understood, it may exert its attenuating effects on alcohol consumption by interferring with dopamine, serotonin, and/or other neurotransmitters and neuromodulators in the brain. Experiments are in progress in our laboratory to further explore these possibilities.

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