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Attenuation of Alcohol Consumption by a Novel Nontoxic Ibogaine Analogue (18-Methoxycoronaridine) in Alcohol-Preferring Rats

AMIR H. REZVANI,* DAVID H. OVERSTREET,* YING YANG,* ISABELLE M. MAISONNEUVE,† UPUL K. BANDARAGE,‡ MARTIN E. KUEHNE‡ AND STANLEY D. GLICK†

*Skipper Bowles Center for Alcohol Studies and Department of Psychiatry, The University of North Carolina School of Medicine at Chapel Hill, Chapel Hill, North Carolina 27599-7178,
†Departments of Pharmacology and Neuroscience, Albany Medical College, Albany, New York 12208
‡Department of Chemistry, University of Vermont, Burlington, Vermont 05405

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REZVANI, A. H., D. H. OVERSTREET, Y. YANG, I. M. MAISONNEUVE, U. K. BANDARAGE, M. E. KUEHNE AND S. D. GLICK. *Attenuation of alcohol consumption by a novel nontoxic ibogaine analogue (18-methoxycoronaridine) in alcohol-preferring rats.* PHARMACOL BIOCHEM BEHAV **58**(2) 615–619, 1997.—We previously reported that single administration of ibogaine, an indol alkaloid with antiaddictive properties, dose dependently reduced alcohol intake in three strains of alcohol-preferring rats. The present study examined the effect of different doses of a newly developed nontoxic ibogaine analogue, 18-methoxycoronaridine (18-MC), on alcohol intake. Selectively bred alcohol-preferring rats received a single intraperitoneal injection of vehicle or 5, 20 and 40 mg/kg of 18-MC at 9:30 AM, and their consumption of alcohol, water and food was measured for 24 h. Our results demonstrate that a single injection of 18-MC significantly and dose dependently attenuated alcohol consumption and preference and commensurately increased water intake. Only the highest dose of 18-MC significantly decreased food intake. Although the true mechanism of action of 18-MC in suppressing alcohol intake is not yet fully understood, it may, like ibogaine, exert its attenuating effects on alcohol consumption by modulating neurotransmitters believed to be involved in the regulation of alcohol intake. © 1997 Elsevier Science Inc.

Ibogaine Ibogaine analogue Alcohol drinking Drug abuse Pharmacotherapy

ALCOHOL abuse and alcoholism cause major health, economic and social problems throughout the world. Despite the greater effort devoted to treatment research in recent years, remediation of alcohol dependence remains a challenging goal. Thus, the development of suitable medications for the treatment of alcohol dependency should be a major objective of alcohol research. Several pharmacological agents including naltrexone (42), calcium channel antagonists (27), a TRH analogue (17,18,34), a Chinese herbal medicine (24) and the ergot bromocriptine (1) significantly attenuate alcohol intake.

Animal studies also have shown that pretreatment with ibogaine (Endabuse™; NIH 15067), an indole alkaloid in the root bark of the West Central African shrub *Tabernanthe iboga*, with an antiaddictive property, can significantly reduce morphine and cocaine self-administration (3,10,41). Recently, we have shown that ibogaine and its primary metabolite noribogaine (15) can significantly reduce alcohol intake in several strains of alcohol-preferring rats in a dose-dependent manner (31,36). However, at high doses, ibogaine can cause side effects (9) that may limit its therapeutic application. Thus, an attempt was made to design an ibogaine analogue with no toxicity but with the same inhibitory action on reinforcing drugs. 18-Methoxycoronaridine (18-MC) appears to be such a newly designed analogue (8).

Requests for reprints should be addressed to A. Rezvani, Center for Alcohol Studies, CB 7178, University of North Carolina School of Medicine, Chapel Hill, NC 27599-7178.. E-mail: azadi@med.unc.edu

18-MC is a novel *iboga* alkaloid congener that mimics the suppressant effects of ibogaine on both morphine and cocaine self-administration in Sprague–Dawley rats (8). The drug is nontremorigenic and produces no cerebllar neurotoxicity (8). Because all drugs of abuse may share a common neuronal circuitry within the reward pathways and 18-MC suppresses morphine and cocaine self-administration, presumably by influencing dopamine in the nucleus accumbens (8), we examined the suppressant effects of this novel analogue on intake of another drug, alcohol, in a strain of selectively bred alcohol-preferring rats that show a high preference for alcohol when given a free choice between water and alcohol (30,34,35).

MATERIALS AND METHODS

Animals

Eight adult male alcohol-preferring rats were used for this project. Rats were obtained from a colony of selectively bred alcohol-preferring rats established at the Indiana University. When given a choice between water and a solution of 10% alcohol, these rats show a high preference for alcohol (34–36). This strain has been used extensively in the field of alcohol research (6,19,21,31,32,34–36).

Animals were housed individually in suspended stainless steel wire-mesh cages (26 × 34 × 20 cm) under a constant temperature of 22 ± 1°C and a 12-h light–dark reversed cycle (lights on at 10 PM). Animals were fed Agway Prolab Rat/Mouse/Hamster 3000 formula (Agway, Syracuse, NY) and water ad libitum.

Baseline Alcohol Preference

Rats were screened for alcohol preference following the standard method of the two-bottle choice employed in our laboratory for many years (24,30,31,34). One week after their arrival to the laboratory, rats were first given free access to tap water in a Richter tube for 1 day. The next day, they were given free access to a solution of 10% (v/v) alcohol in a Richter tube as a sole source of fluid for 3 consecutive days. This procedure allowed them to become accustomed to drinking from the Richter tube and to the taste and possible pharmacological effects of alcohol. Thereafter, rats were given free access to two Richter tubes, one containing tap water and the other containing a solution of 10% ethanol for at least 3 weeks. Food was available throughout. The intake of water and alcohol were measured every day between 0900 and 1000 h. The body weights and food intakes were measured on Mondays, Wednesdays and Fridays except for the days of experiments, when all parameters were recorded at 24 h after each injection.

Drug Preparation

18-MC was synthesized by Martin Kuehne and Upul Bandarage, University of Vermont, Burlington. Solutions of 18-MC were prepared daily in a 0.004 M solution of sodium phosphate. A solution of 0.004 M sodium phosphate was used as control vehicle. A solution of 10% ethanol was prepared daily from 95% reagent grade alcohol and distilled water. All injections were made intraperitoneally (IP). The volume of control vehicle or drug injected was 4 ml/kg body weight. All solutions for injections were prepared in pyrogen-free glassware with deionized water.

Experimental Protocol

Following the standard procedure of the two-bottle choice (24,30,36) and after establishment of a stable baseline for alcohol and water intake, rats were injected IP with the control vehicle or one of the doses of 18-MC (5, 20 and 40 mg/kg) in a random order design at approximately 0930 h. All animals received all of the treatments, i.e., control vehicle and three doses of 18-MC. At least 4 days were allowed between injections. Alcohol, water and food intake were measured every morning between 0900 and 1000 h for the next 24 h.

Statistical Analysis of Data

The results are expressed as means ± SEM. Alcohol intake (g/kg) was calculated by multiplying the volume of alcohol consumed in 24 h by 10% and 0.7893 (ethanol density)/body weight (kg). Statistical differences between vehicle-treated and drug-treated groups were determined by using an analysis of variance with repeated measures and Newman-Keuls protected *t*-test. All measurements were standardized by converting them into grams per kilogram per day or milliliters per kilogram per day. Alcohol preference was calculated as follows: volume (ml) of alcohol consumed in 24 h/total fluid intake (ml) × 100 (36).

RESULTS

When given free access to alcohol, water and food, alcohol-preferring rats consumed an average of 81.6 ± 5.7 ml/kg (6.4 ± 0.4 g/kg) alcohol, 6.4 ± 0.4 ml/kg water and 54 ± 3 g/kg food per day. Compared with control vehicle, a single injection of 5, 20 or 40 mg/kg 18-MC significantly reduced alcohol intake in a dose-dependent fashion [$F(3, 18) = 10.57$, $p < 0.01$] (Fig. 1A). The proportion of alcohol intake to total fluid intake, which has been used as a reliable index of alcohol preference in other studies (19,24,30,36), was significantly lower following administration of different doses of 18-MC [$F(3, 28) = 9.56$, $p < 0.01$] (Fig. 1B). Administration of 18-MC resulted in an overall increase in water intake [$F(3, 28) = 6.79$, $p < 0.01$] (Fig 1C). Although a single dose of 5 or 20 mg/kg 18-MC did not exert a significant effect on food intake, a single injection of 40 mg/kg 18-MC significantly reduced food consumption ($p < 0.01$) (Fig. 1D). Overall, the suppressant effect of 18-MC lasted at least 24 h, and it had vanished the day following drug administration.

DISCUSSION

The present data show, for the first time, that 18-MC, a novel nontoxic ibogaine analogue, when injected acutely can significantly reduce alcohol intake and alcohol preference in a dose-dependent manner in a strain of alcohol-preferring rats. The specificity of this compound for suppressing alcohol intake is highlighted by the fact that, at doses that significantly suppressed alcohol intake and preference, there was a commensurate increase in water intake. Further, food intake was not significantly influenced by 20 mg/kg, which significantly reduced alcohol intake. However, the higher dose of 40 mg/kg significantly reduced food intake.

Several neuronal mechanisms may be involved in the suppressant effects of 18-MC on alcohol intake and preference. The reinforcing properties of alcohol and other drugs of abuse may be partly related to their interactions with dopamine, serotonin, gamma-aimnobutyric acid (GABA), glutamate and the endogenous opiate systems in the brain (5,9,12,28,33,37). In rats, ethanol increases dopamine in the mesolimbic system

(4). In alcohol-preferring rats, ethanol rapidly increases the levels of dihydroxyphenylalanine (DOPAC) and homovanillic acid (HVA) in both nucleus accumbens and frontal cortex, suggesting increased activity of the dopaminergic system projecting from the ventral tegmental area (VTA) to these forebrain regions (7). Concordantly, alcohol-preferring rats will self-administer alcohol into the VTA (6). Drugs such as bromocriptine (19) and TA-0910, a centrally potent TRH analogue that activates central dopaminergic systems, reduce alcohol intake in alcohol-preferring rats (18,34) and alcohol-preferring monkeys (29). Thus, the involvement of the dopamine mesolimbic pathway, especially the nucleus accumbens, is widely accepted as being involved in the reinforcing property of alcohol.

Ibogaine administration to rodents alters the levels of dopamine and its metabolites. Ibogaine, among its actions on neurotransmitters (26), induces prolonged (at least 19 h) decreases in the extracellular levels of dopamine metabolites (DOPAC and HVA) in the nucleus accumbens, striatum and prefrontal cortex (13), and its anticraving properties may be the result, at least in part, of its actions on dopaminergic systems in the brain (8,11,14). Interestingly, similar to ibogaine, systemic administration of 18-MC decreases extracellular levels of dopamine in the nucleus accumbens in rats (8). Thus, 18-MC may exert its suppressant effects on alcohol intake by the same mechanism as ibogaine. However, this compound has no apparent tremorigenic effect, and even at a high dose (100 mg/kg) does not produce any cerebellar toxicity (8). Therefore, 18-MC appears to exert comparable suppressant effects on alcohol intake but with no apparent side effects or neurotoxicity that have been reported for a high dose (100 mg/kg) of ibogaine (20,22).

With the present data, however, other possible neuronal mechanisms cannot be ruled out. Ibogaine interacts with the neuronal serotonin systems believed to be involved in alcohol-seeking behavior (19,21,23,25,32,33,38,40). Ibogaine increases serotonin concentrations in rat nucleus accumbens (2) and decreases levels of the serotonin metabolite 5-HIAA in mouse frontal cortex, hippocampus and olfactory tubercle (39). Thus, the antiaddictive properties of ibogaine (16,36) and its analogue 18-MC may be related in part to their actions on serotonergic systems in the brain.

Because other neurotransmitter systems, such as glutamate, GABA and endogenous opioid, have been implicated in alcohol-

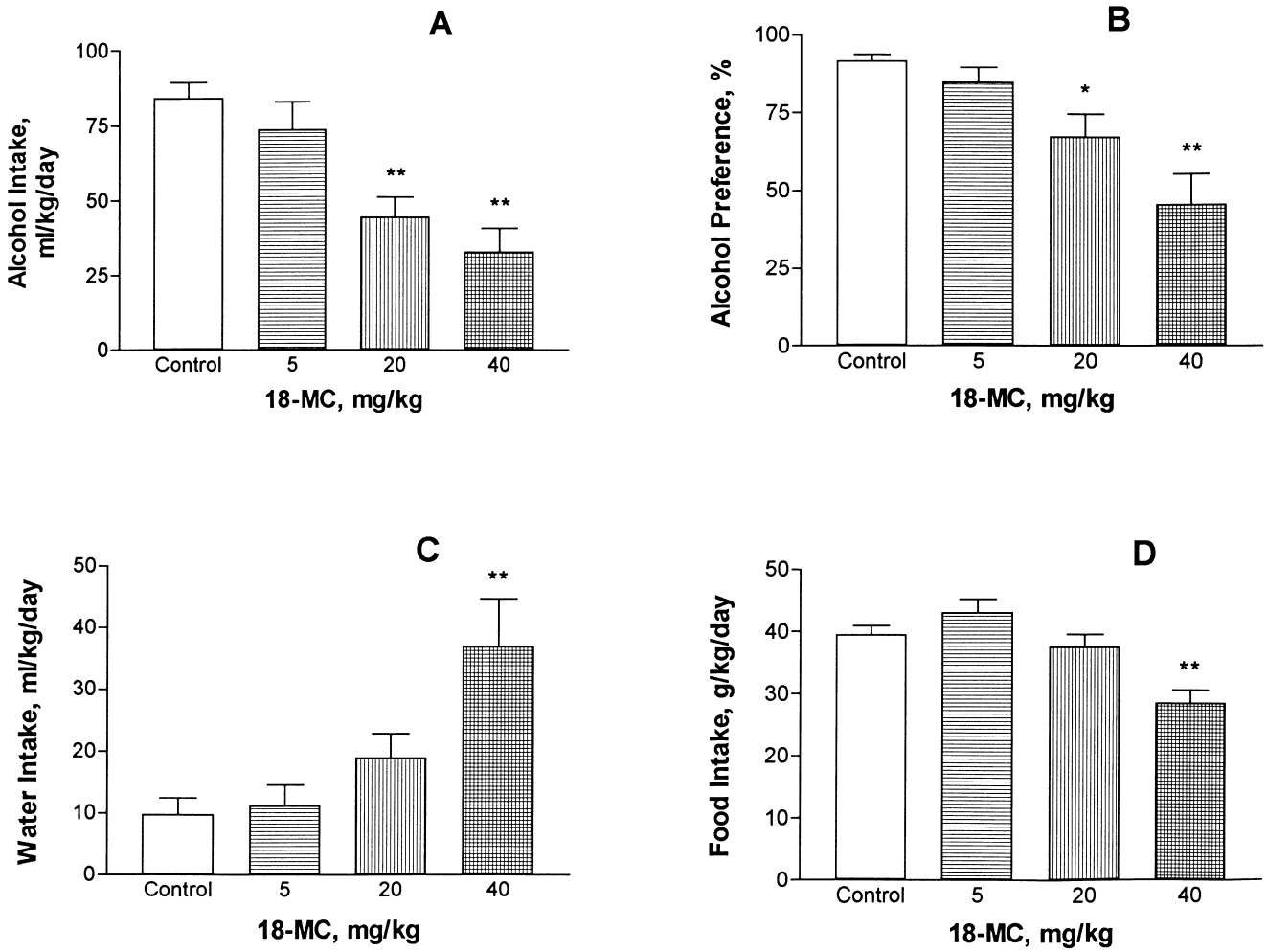

FIG. 1. Effects of acute administration of vehicle and different doses of 18-MC on the daily intake of 10% (v/v) alcohol (A), alcohol preference (B), and intake of water (C) and food (D) by alcohol-preferring rats. Data are mean ± SEM ($n = 8$). *$p < 0.05$, **$p < 0.01$ vs. controls.

seeking behavior, 18-MC may exert its attenuating effect on alcohol intake by interfering with one or more of these systems.

In summary, administration of the newly developed ibogaine analogue 18-MC can significantly attenuate alcohol intake and preference in selectively bred alcohol preferring rats without apparent side effects. Although the true mechanism of its action in suppressing alcohol intake is not yet fully understood, it may exert its attenuating effects on alcohol consumption by reducing extracellular dopamine. However, a firm conclusion about the mechanism of action awaits further pharmacological and behavioral studies of this newly developed compound.

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REFERENCES

1. Borg, V.: Bromocriptine in the prevention of alcohol abuse. Acta Psychiatr. Scand. 68:100–110; 1983.
2. Broderick, P. A.; Phelan, F. T.; Berger, S. P.: Ibogaine alters cocaine-induced biogenic amine and psychostimulant dysfunction but not [^{3}H]GBR–1235 binding to the dopamine transporter protein. NIDA Res. Monogr. Ser. 119:285; 1992.
3. Cappendijk, S. L. T.; Dzoljic, M. R.: Inhibitory effects of Ibogaine on cocaine self-administration in rats. Eur. J. Pharmacol. 241:261–265; 1993.
4. DiChiara, G.; Imperato, A.: Ethanol preferentially stimulates dopamine release in the nucleus accumbens of freely moving rats. Eur. J. Pharmacol. 115:131–132; 1985.
5. Froehlich, J. C.: Harts, J.; Lumeng, L.; Li, T.-K.: Naloxone attenuates voluntary ethanol intake in rats selectively bred for high ethanol preference. Pharmacol. Biochem. Behav. 35:385–390; 1990.
6. Gatto, G. J.; McBride, W. J.; Murphy, J. M.; Lumeng, L.; Li, T. K.: Ethanol self-infusion into the ventral tegmental area by alcohol-preferring rats. Alcohol 11:557–564; 1994.
7. Gessa, G. L.; Muntoni, F.; Collu, M.; Vargin, L.; Mereu, G.: Low doses of ethanol activate dopaminergic neurons in the ventral tegmental area. Brain Res. 348:201–203; 1985.
8. Glick, S. D.; Kuehne, M. E.; Maisonneuve, I. M.; Bandarage, U. K.; Molinari, H. H.: 18-Methoxycoronaridine, a non-toxic *iboga* alkaloid congener: Effects on morphine and cocaine self-administration and on mesolimbic dopamine release in rats. Brain Res. 719:29–35; 1996.
9. Glick, S. D.; Kuehne, M. E.; Raucci; J.; Wilson T. E.; Larson, T. D.; Keller, R. W.; Carlson, J. N.: Effects of *iboga* alkaloids on morphine and cocaine self-administration in rats: Relationship to tremorigenic effects and to effects on dopamine release in nucleus accumbens and striatum. Brain Res. 657:14–22; 1994.
10. Glick, S. D.; Rossman, K.; Steindorf. S.; Maisonneuve, I. M.; Carlson, J. N.: Effects and after effects of Ibogaine on morphine self-administration in rats. Eur. J. Pharmacol. 195:341; 1991.
11. Glick, S. D.; Rossman, K.; Wang. S.; Dong. N.; Keller, R. W. Jr.: Local effects of Ibogaine on extracellular levels of dopamine and its metabolites in nucleus accumbens and striatum: Interactions with *d*-amphetamine. Brain Res. 628:201–208; 1993.
12. Koob, G. F.; Rassnick, S.; Heinrichs, S.; Weiss, F.: Alcohol, the reward system and dependence. EXS 71:103–104; 1994.
13. Maisonneuve, I. M.; Keller, R. W.; Glick, S. D.: Interactions between ibogaine, a potential anti-addictive agent, and morphine: An in vivo microdialysis study. Eur. J. Pharmacol. 199:35–42; 1991.
14. Maisonneuve, I. M.; Rossman, K. L.; Keller, R. W., Jr.; Glick, S. D.: Acute and prolonged effects of Ibogaine on brain dopamine metabolism and morphine-induced locomotor activity in rats. Brain Res. 575:69–73; 1992.
15. Mash, D. C.; Staley, J. K.; Pablo, J. P.; Holohean, A. M.; Hackman, J. C.; Davidoff, R. A.: Properties of ibogaine and its principal metabolite (12-hydroxyibogamine) at the MK-801 binding site of the NMDA receptor complex. Neurosci. Lett. 192:53–56; 1995.
16. Mash, D. C.; Staley , J. K.; Bauman, M. H.; Rothman, R. B.; Hearn, W. L.: Identification of primary metabolite of ibogaine that targets serotonin transporters and elevated serotonin. Life Sci. 57:Pl45–Pl50; 1995.
17. Mason, G. A.; Rezvani, A. H.; Overstreet, D. H.; Garbutt, J. C.: The thyrotropin releasing hormone analog TA–0910 reduces voluntary alcohol intake of P rats subchronically in a limited scheduled access paradigm. Alcohol Clin. Exp. Res. 20:1000–1003; 1996.
18. Mason, G. A.; Rezvani, A. H.; Grady, D. R.; Garbutt, J. C.: The sub-chronic effects of the TRH analog TA–0910 and bromocriptine on alcohol preference in alcohol preferring (P) rats: Development of tolerance and cross tolerance. Alcohol Clin. Exp. Res. 18:1196–1201; 1994.
19. McBride, W. J.; Murphy, J. M.; Lumeng, L.; Li, T.-K.: Serotonin, dopamine and GABA involvement in alcohol drinking of selectively bred rats. Alcohol 7:199–205; 1990.
20. Molinari, H. H.; Maisonneuve, I. M.; Glick S. D.: Ibogaine neurotoxicity: A reevaluation. Brain Res.; in press.
21. Murphy, J. M.; McBride, W. J.; Lumeng, L.; Li, T.-K.: Effects of serotonin and dopamine agents on ethanol intake of alcohol-preferring (P) rats. Alcohol Clin. Exp. Res. 12:306; 1988.
22. O'Hearn, E.; Molliver, M. E.: Degeneration of Purkinje cells in parasagital zones of the cerebellar vermis after ibogaine or harmaline. Neuroscience 55:303–310; 1993.
23. Overstreet, D. H.; Rezvani, A. H.; Pucilowski, O.; Janowsky, D. S.: 5-HT receptors: Implications for the neuropharmacology of alcohol and alcoholism. Alcohol Alcohol. suppl. 2:207–212; 1994.
24. Overstreet, D. H.; Lee, Y. W.; Rezvani, A. H.: Suppression of alcohol intake after administration of the Chinese herbal medicinein, NPI-028, and its derivatives. Alcohol Clin. Exp. Res. 20: 221–227; 1996.
25. Overstreet, D. H.; Rezvani, A. H.; Janowsky, D. S.: Genetic animal models of depression and ethanol preference provide support for cholinergic and serotonergic involvement in depression and alcoholism. Biol. Psychiatr. 31:919–936; 1992.
26. Popik, P.; Layer, R. T.; Skolnick, P.: 100 Years of ibogaine: Neurochemical and pharmacological actions of a putative anti-addictive drug. Pharmacol. Rev. 47:235–253; 1995.
27. Pucilowski, O.; Rezvani, A. H.; Overstreet, D. H.; Janowsky, D. S.: Calcium channel inhibitors attenuate consumption of ethanol, sucrose and saccharin solutions in rats. Behav. Pharmacol. 5:494–501; 1994.
28. Reid, L. D.; Delconte, J. D.; Nichols, M. L.; Bilsky, E. J.; Hubbell, C. L.: Tests of opioid deficiency hypotheses of alcoholism. Alcohol 8:247–257; 1991.
29. Rezvani, A. H.; Garbutt, J. C.; Overstreet, D. H.; Li, L.; Walker, C. H.; Mason, G. A.: Thyrotropin releasing hormone analog TA–0910 suppresses alcohol intake in alcohol drinking African green monkeys. Alcohol Clin. Exp. Res. 21:261–266; 1997.
30. Rezvani, A. H.; Grady, D. R.: Suppression of alcohol consumption by fenfluramine in Fawn-Hooded rats with serotonin dysfunction. Pharmacol. Biochem. Behav. 48:105–110; 1994.
31. Rezvani, A. H.; Mash, D. C.; Hearn, W. L.; Lee, Y. W.; Overstreet, D. H.: Noribogaine, a primary ibogaine metabolite, reduces alcohol intake in P and Fawn-Hooded rats. Alcohol Clin. Exp. Res. 19:15A; 1995.
32. Rezvani, A. H.; Overstreet, D. H.; Janowsky, D. S.: Drug-induced reductions in ethanol intake in alcohol preferring and fawn-hooded rats. Alcohol Alcohol. suppl. 1:433–437; 1991.

33. Rezvani, A. H.; Overstreet, D. H.; Janowsky, D. S.: Genetic serotonin deficiency and alcohol preference in the Fawn-Hooded rats. Alcohol Alcohol. 25:573–575; 1990.
34. Rezvani, A. H.; Garbutt, J. C.; Shimoda, K.; Garges, P. L.; Janowsky, D. S.; Mason, G. A.: Attenuation of alcohol preference in alcohol preferring rats by a novel TRH analogue TA-0910. Alcohol Clin. Exp. Res. 16:326–330; 1992.
35. Rezvani, A. H.; Garges, P. L.; Miller, D.; Gordon, C. J.: Attenuation of alcohol consumption by MDMA in two strains of alcohol drinking rats. Pharmacol. Biochem. Behav. 43:103–107; 1992.
36. Rezvani, A. H.; Overstreet, D. H.; Lee, Y. W.: Attenuation of alcohol intake by Ibogaine in three starins of alcohol preferring rats. Pharmacol. Biochem. Behav. 52:615–620; 1995.
37. Samson, H. H.; Tolliver, G. A.; Haraguchi, M.; Hodge, C. W.: Alcohol self-administration: Role of mesolimbic dopamine. Ann. N.Y. Acad. Sci. 654:242–253; 1992.
38. Sellers, E. M.; Higgins, G. A.; Sobell, M. B.: 5-HT and alcohol abuse. Trends Pharmacol. Sci. 13:69–75; 1992.
39. Sershen, H.; Harsing, L. G., Jr.; Hashim, A.; Lajtha, A.: Ibogaine reduces amphetamine-induced locomotor stimulation in C57BL/6By mice, but stimulates locomotor activity in rats. Life Sci. 51:1003–1011; 1992.
40. Sershen, H.; Hashim, A.; Lajtha, A.: Effect of Ibogaine on serotonergic and dopaminergic interactions in striatum from mice and rats. Neurochem. Res. 19:1463–1466; 1994.
41. Sershen, H.; Hashim, A.; Lajtha, A.: Ibogaine reduces preference for cocaine consumption in C57BL/6By mice. Pharmacol. Biochem. Behav. 47:13–19; 1994.
42. Volpicelli, J. R.; Alterman, A. I.; Hayashida, M.; O'Brien, C. P.: Naltrexone in the treatment of alcohol dependence. Arch. Gen. Psychiatr. 49:876–880; 1992.