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Selective Reduction by the 5-HT Antagonist Amperozide of Alcohol Preference Induced in Rats by Systemic Cyanamide

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MYERS, R. D., M. LANKFORD AND A. BJÖRK. *Selective reduction by the 5-HT antagonist amperozide of alcohol preference induced in rats by systemic cyanamide.* PHARMACOL BIOCHEM BEHAV 43(3) 661–667, 1992.—This investigation was undertaken to determine the effect of a unique psychotropic agent on the volitional drinking of alcohol induced pharmacologically in the rat by an inhibitor of aldehyde dehydrogenase. Following administration of cyanamide in a dose of 10 mg/kg twice daily for 3 days, the pattern of drinking of ethyl alcohol was determined in each of 12 Sprague-Dawley rats by means of a standard preference test for 3–30% alcohol vs. water. Then, each rat was offered water and its maximally preferred concentration of alcohol, which ranged from 7–15%. After a 4-day predrug test, either the saline control vehicle or the diphenylbutylpiperazinecarboxamide derivative, amperozide, was administered subcutaneously. The injections of amperozide were given b.i.d. at 1600 and 2200 h over 3 days in a dose of 0.5, 1.0, or 2.5 mg/kg. The intake of alcohol during the sequence of amperozide injections was significantly reduced in a dose-dependent manner in terms of both absolute g/kg and proportion of alcohol to water intake, whereas the saline control vehicle was without any effect on alcohol consumption. Although the highest dose of amperozide reduced the total intake of fluid due to the sharp decline in alcohol drinking, neither the consumption of food nor level of body weight was affected by any dose of the drug either during or after its administration. Because amperozide acts centrally on the synaptic activity of dopaminergic and serotonergic neurons in limbic system structures, it is envisaged that the drug ameliorates the aberrant drinking of alcohol by virtue of a direct effect on either one or both of these classes of neurons. As a consequence, amperozide thus counteracts by its central action those functional mechanisms underlying the behavioral craving for alcohol, its potent reinforcing property, or both phenomena.

Alcohol drinking Amperozide Serotonin receptors Ethanol Alcohol preference Dopaminergic systems
Mesolimbic system structures Alcoholism Therapeutic treatment Aberrant drinking

CONSIDERABLE scientific information has accumulated over the last two decades on the neurochemical basis underpinning the pathogenesis of alcohol drinking. A role for specific endogenous neurohumoral factors in the brain has been proposed in relation to the etiology of alcoholism (18,24). Although an animal analogue for the alcoholic syndrome is still being refined (21), new observations on the biochemical, pharmacological, and behavioral properties of aldehyde-amine metabolites have provided a reliable and well-characterized animal model for volitional alcohol drinking to the point of physical dependence (25). The clinical significance of such a model to the alcoholic patient is of importance to the development of pharmacological strategies in the treatment of alcoholism.

Recently, the diphenylbutylpiperazinecarboxamide derivative, amperozide (FG5606), has been shown to possess a unique profile of pharmacological properties that make it a possible candidate for the treatment of alcoholism. To illustrate, amperozide ameliorates the typical aggression observed in isolated mice and is a potent antagonist of muricidal behavior (16). Moreover, it exhibits anxiolytic and antidepressant effects while impairing neither motor coordination nor the animal's level of arousal (16). Behaviorally, amperozide given in low doses exhibits a pronounced anticonflict effect in the rat indicative of an anxiolytic-like action (9), and thus acts possibly through the GABA-benzodiazepine-Cl^- ion complex (33). In addition, the intense aggressive behavior following mixing of previously unacquainted pigs is markedly reduced by their treatment with amperozide (3,13). When amperozide is given to the newly weaned piglet, the typical gastrointestinal disturbances and inanition are reversed (2) so that its weight gain proceeds normally and mortality is reduced significantly.

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The pig that is incapable of adapting to a new situation after mixing develops a chronic stress syndrome, the so-called wasting pig, but recovers after treatment with amperozide, which implies that amperozide can readjust social function (19,33).

Therefore, in view of the unique pharmacological attributes of amperozide this project was undertaken to determine whether this drug would attenuate or otherwise affect the aberrant intake of alcohol in the rat. Amperozide exerts an action on homologous structures of the limbic system (15) within which an aldehyde adduct such as tetrahydropapaveroline (THP) or a tetrahydro-β-carboline acts to induce aberrant drinking of alcohol (18,31,35). Moreover, amperozide exerts an action within central serotonergic synapses that are now thought to be involved in the volitional selection of alcohol (21,24,32). In the present experiments, Sprague-Dawley rats, which do not prefer alcohol, were induced to drink the fluid by the systemic administration of the aldehyde dehydrogenase inhibitor, cyanamide (1,8). Then, amperozide was administered in one of three doses over 3 days in the midpoint of an 11-day test interval wherein the maximally preferred solution of alcohol was offered in a self-selection paradigm.

METHOD

Animals

Male or female Sprague-Dawley rats (n = 26), 30 days old at the beginning of the experiments, were housed in stainless steel wire cages and kept on a 12L : 12D cycle with lights on at 0700 h. Each rat was maintained on a daily regimen of 50 g Purina rat chow and 50 ml water per day with respective intakes of food and water as well as body weights recorded at 0830 h on each day.

Cyanamide Treatment

Each rat was given a series of subcutaneous injections of cyanamide (Sigma, St. Louis, MO) according to experimental procedures described previously (8). A dose of 10 mg/kg cyanamide was selected based upon previous dose-response data to induce an elevated and stable preference for alcohol (8). The solution of cyanamide was prepared daily in sterile distilled water and kept in a closed container on ice. Injections of cyanamide or the control vehicle were given twice daily at 1000 h and 1600 h on each of 3 consecutive days. Intakes of food and water and body weight were recorded daily.

Alcohol Preference Tests

At 60 days of age, each rat was tested for its pattern of alcohol drinking by means of a standard 3–30% alcohol preference screen. Three 100-ml Kimax tubes were placed equidistantly on the front of the cage and randomly repositioned daily to avoid the animal's development of a position habit (24). Water was placed in one tube, the second was empty, and the third contained alcohol, which was increased in concentration on each day over a 10-day interval as follows: 3, 4, 5, 7, 9, 11, 13, 15, 20, and 30% (18). The optimally preferred test concentration, derived from the animal's maximum intake of a given test solution (7,20), was then offered together with water for a 4 to 6-day period while the intake of alcohol stabilized. Each individual test concentration was the highest concentration at which the largest volume of alcohol was consumed prior to a shift below the 50% level in the proportion of alcohol intake to the total amount of fluids consumed.

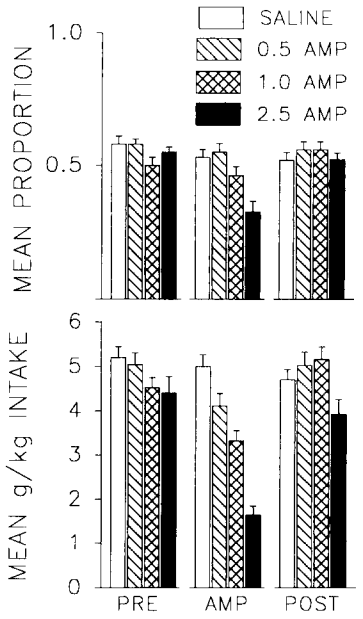

FIG. 1. Mean ± SE intakes of alcohol in proportion of alcohol to total fluid (top) and absolute g/kg (bottom). Preference was tested for 4 control days before (PRE), 3 days during (AMP), and 4 control days after (POST) amperozide injections b.i.d. of 0.5 mg/kg (n = 9), 1.0 mg/kg (n = 15), and 2.5 mg/kg (n = 11).

Amperozide Treatment

Following a 4-day predrug control interval, rats were given amperozide (Kabi Pharmacia Therapeutics, Malmö, Sweden) or saline control vehicle on 3 consecutive days. The solution of amperozide HCl was prepared daily in sterilized 0.9% saline at pH 4.5–5.0. The drug or vehicle was administered subcutaneously, according to a randomized sequence, twice daily at 1600 and 2200 h in one of three dose as based upon the findings of Gustafsson and Christensson (15,16): saline (n = 13), 0.5 mg/kg (n = 9), 1.0 mg/kg (n = 15), and 2.5 mg/kg (n = 11). Treatments with the two lower doses of amperozide and saline were randomized within a group of 15 rats; the specific number of rats used for each condition was determined by the single factor of stability of intake over the 4-day predrug preference test. A second group of 11 rats was given the highest dose only after their intakes of preferred concentrations of alcohol had stabilized. During the 3-day period of injections of amperozide or control vehicle, the tests of alcohol preference continued uninterruptedly. At the end of this interval, the preference testing was maintained for another 4-day postdrug control period.

The data were analyzed using the Stat-Mate software program using a one-way analysis of variance (ANOVA) followed by posthoc Student–Newman–Keuls test when appropriate. A p value of <0.05 was considered statistically significant.

RESULTS

Amperozide given subcutaneously in doses of 0.5, 1.0, and 2.5 mg/kg twice daily over a 3-day interval markedly altered the volitional consumption of alcohol of the rats. Although significant differences were found in all groups of test animals, those in which 2.5 mg/kg amperozide was injected twice daily exerted the maximum and most sustained effect on the intake of alcohol.

TABLE 1

MEAN ± SE FOOD, WATER, ETHANOL, AND TOTAL FLUID INTAKES AND BODY WEIGHT OF MALE (M) AND FEMALE (F) RATS IN WHICH 0.5, 1.0, OR 2.5 mg/kg AMPEROZIDE OR SALINE VEHICLE WAS ADMINISTERED SUBCUTANEOUSLY TWICE DAILY

	Food (g)	Water (ml)	Ethanol (ml)	Total (ml)	Weight (g)
Low dose (n = 9)					
Pre	15.0 ± .54	20.6 ± .18	28.7 ± 1.6	47.0 ± 1.9	492.2 ± 6.3 (M) 281.7 ± 5.4 (F)
0.5 mg	15.6 ± .51	20.6 ± 2.2	23.5 ± 1.5	44.3 ± 2.6	489.0 ± 7.5 (M) 284.1 ± 2.1 (F)
Post	17.6 ± .65	27.6 ± 3.0	28.5 ± 1.5	52.1 ± 2.6	497.3 ± 7.0 (M) 290.1 ± 3.8 (F)
Intermediate dose (n = 15)					
Pre	15.3 ± .51	21.0 ± .16	25.9 ± 1.7	46.5 ± 1.9	499.0 ± 6.5 (M) 285.2 ± 2.7 (F)
1.0 mg	15.3 ± .54	20.4 ± 1.7	19.4 ± 1.7	40.4 ± 2.1	495.3 ± 7.7 (M) 277.2 ± 8.4 (F)
Post	15.7 ± .49	20.7 ± 1.3	29.8 ± 1.9	50.3 ± 2.0	503.4 ± 7.4 (M) 276.4 ± 2.6 (F)
High dose (n = 11)					
Pre	16.7 ± .70	16.0 ± .70	21.9 ± 1.2	37.7 ± 1.0	485.3 ± 5.1 (M) 281.4 ± 6.1 (F)
2.5 mg	16.2 ± .65	15.8 ± 1.3	8.5 ± 1.1	26.7 ± 1.8	485.0 ± 5.3 (M) 278.2 ± 8.4 (F)
Post	18.0 ± .64	19.3 ± .86	21.7 ± .80	39.9 ± 1.1	490.5 ± 5.2 (M) 275.3 ± 6.1 (F)
Saline control (n = 13)					
Pre	16.1 ± .47	22.7 ± 1.7	32.5 ± 1.7	55.2 ± 2.0	498.8 ± 7.2 (M) 267.7 ± 1.2 (F)
Saline	17.4 ± .60	24.0 ± 2.0	31.8 ± 2.3	55.8 ± 2.6	493.3 ± 9.4 (M) 267.4 ± 3.0 (F)
Post	15.8 ± .45	25.0 ± 1.8	28.7 ± 1.9	53.7 ± 2.1	493.0 ± 7.3 (M) 273.2 ± 3.1 (F)

Precontrol for 4 days, injections for 3 days, and postcontrol for 4 days. n, number of rats.

As shown in Fig. 1 (top), the proportions of alcohol to total fluid consumed were similarly reduced from the precontrol levels by the intermediate as well as highest dose of amperozide given, $F(1, 104) = 117.32$, $p < 0.01$, and $F(1, 76) = 83.76$, $p < 0.01$, respectively; however, no significant difference in the proportional measure of preference was produced by the lowest dose of the drug (Fig. 1, top).

As presented in Fig. 1 (bottom), the lowest dose (0.5 mg/kg given twice daily) had a small but nevertheless significant effect in attenuating the g/kg intake of alcohol from the precontrol mean level of 5.0 mg/kg to a mean of 4.1 mg/kg, $F(1, 62) = 5.62$, $p < 0.01$. The intermediate dose of 1.0 mg/kg given similarly also reduced overall the daily g/kg intake of alcohol from the mean precontrol amount of 4.5 mg/kg to a mean of 3.3 mg/kg, $F(1, 104) = 12.5$, $p < 0.01$. The highest dose of amperozide (2.5 mg/kg) exerted the greatest effect on the absolute value of alcohol ingested. The g/kg intake was reduced by over twofold from the mean precontrol level of 4.4 g/kg to a mean of 1.6 g/kg alcohol (Fig. 1, bottom) during administration of this dose, $F(1, 76) = 132.7$, $p < 0.01$. As shown in Table 1, the saline control vehicle was without any significant effects on the intake of alcohol.

The consumption of alcohol over 11 days expressed as the mean proportional and g/kg intakes is presented in Fig. 2 top and bottom, respectively, for the pre- and postcontrol and treatment intervals. During injections of the lowest dose of amperozide, the decline in alcohol drinking from the precontrol baseline was not evident until the second day; however, an immediate effect of the drug occurred following administration of the intermediate and highest doses of amperozide (Fig. 2, top and bottom). As can be seen in Fig. 2 bottom, the highest dose of amperozide exerted overall the most potent effect on the daily g/kg intakes of alcohol.

A composite analysis of the mean effects of the three doses of amperozide on the intakes of food, water, and alcohol and on body weights of treated rats are presented in Table 1. Both during and after the course of the drug treatment, no significant effects were produced by any of the doses of amperozide in terms of a change in body weight nor in the amounts of food and water consumed by rats. However, in the high-dose (2.5 mg/kg) group, the total amount of fluid consumed during administration of amperozide was significantly lower than that of the pre-, $F(1, 76) = 28.44$, $p < 0.01$, and posttests, $F(1, 76) = 45.17$, $p < 0.01$. This reduction reflected the sharp decline in the intake of alcohol produced by administration of amperozide. During the 4-day postdrug test, however, the total fluid value was comparable to that of the predrug intake.

Individual Responses to Amperozide

To evaluate the effects of amperozide on individual rats, the mean percent change from the 4-day predrug baseline in g/kg and proportion of alcohol to a total fluid consumed was

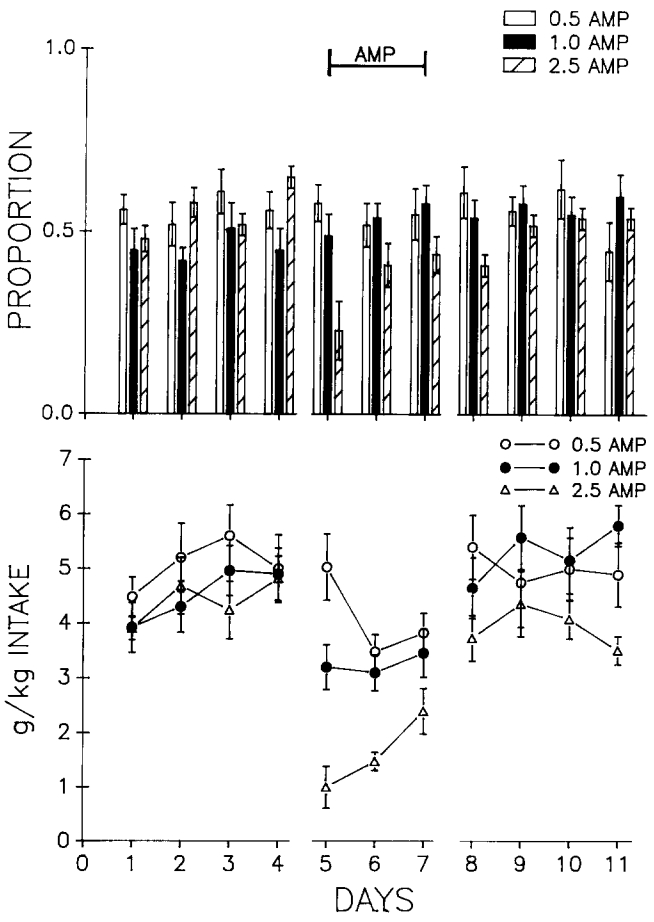

FIG. 2. Mean ± SE intakes of alcohol over 11 days in proportion of alcohol to total fluid (top) and absolute g/kg (bottom). Preference was tested over control days 1-4 before (PRE), days 5-7 during (AMP), and control days 8-11 after (POST) amperozide injections b.i.d. of 0.5 mg/kg (n = 9), 1.0 mg/kg (n = 15), or 2.5 mg/kg (n = 11).

calculated for the 3 days of amperozide injections and 4 days postdrug. Table 2 presents a composite analysis of the percent decline for the three doses of amperozide. The mean percent reduction in absolute g/kg and proportional intakes of alcohol during amperozide essentially was dose related (Table 2). The mean percent change in proportional values was virtually identical following the low (18.2 ± 9.3) and intermediate (20.8 ± 5.8) doses. Following injections (post), the percent decline in alcohol drinking was virtually unrelated to the doses of amperozide (Table 2). However, the large variance in alcohol intakes in both g/kg and proportion measures denoted both increases and decreases in alcohol drinking of individual rats, respectively.

As shown in Fig. 3 left, the 0.5-mg/kg dose of amperozide given b.i.d. evoked a moderate decrease or small percent change in the absolute intake of alcohol offered to individual rats in concentrations of 7% (△) and 11% (○). In three rats, the percent change in g/kg consumption of alcohol (Fig. 3, left) declined further following treatment with the drug (post). The percent change in proportional intakes declined in six of nine rats but rose above basal levels in two rats (Fig. 3, right).

The percent decline in the consumption of alcohol produced by the intermediate dose of amperozide also varied with the animal. As presented in Fig. 4 left, the percent change in the absolute intakes of alcohol in concentrations of 7% (△) and 11% (○) was in general greater than that of the lowest dose of the drug. Similarly, the proportional intakes were lower in 12 of 15 rats tested (Fig. 4, right). As shown in Fig. 5 the 2.5-mg/kg dose of amperozide evoked a consistent percent decline in the preference for alcohol in concentrations of 7% (△), 9% (▲), 11% (○), 13% (●), and 15% (□) in virtually all animals. Following injections of amperozide (post), the percent values in terms of both g/kg (Fig. 5, left) and proportion (Fig. 5, right) returned to basal intake levels in essentially half the rats.

DISCUSSION

Selected drugs have been evaluated in our laboratory that can reduce alcohol drinking evoked centrally by neuroactive substances including an aldehyde adduct, an inhibitor of aldehyde dehydrogenase, or the neurotoxin 6-hydroxydopamine (6,7,36). Opiate receptor antagonists and compounds affecting both the reuptake of 5-hydroxytryptamine (5-HT) can attenuate transiently alcohol drinking in a self-selection situation in the presence of water. For example, naloxone or naltrexone reduces alcohol drinking induced in the rat by ICV infusions of THP (7,28). Similarly, in the macaque monkey, which preferred alcohol following ICV injections of human cerebrospinal fluid (30), naltrexone or buspirone decreases the intake of alcohol (6,27). In the rat with a neurotoxic lesion of the nucleus accumbens, sertraline temporarily reduces the preference for alcohol (32). However, a concomitant reduc-

TABLE 2

MEAN ± SE % DECLINE FROM BASELINE INTAKES OF ALCOHOL (g/kg) AND PROPORTION OF ALCOHOL TO TOTAL FLUID DURING 0.5, 1.0, AND 2.5 mg/kg AMPEROZIDE GIVEN BID FOR 3 DAYS (INJECTION) AND 4 DAYS FOLLOWING (POST) ADMINISTRATION

	g/kg		Proportion	
Dose of amperozide	Injection	Post	Injection	Post
0.5 mg (n = 9)	21.6 ± 4.5%	18.8 ± 5.7%	18.2 ± 9.3%	10.7 ± 9.5%
1.0 mg (n = 15)	29.5 ± 5.5%	6.7 ± 8.2%	20.8 ± 5.8%	1.9 ± 4.7%
2.5 mg (n = 11)	60.2 ± 5.2%	9.7 ± 5.2%	35.4 ± 6.1%	4.6 ± 2.6%

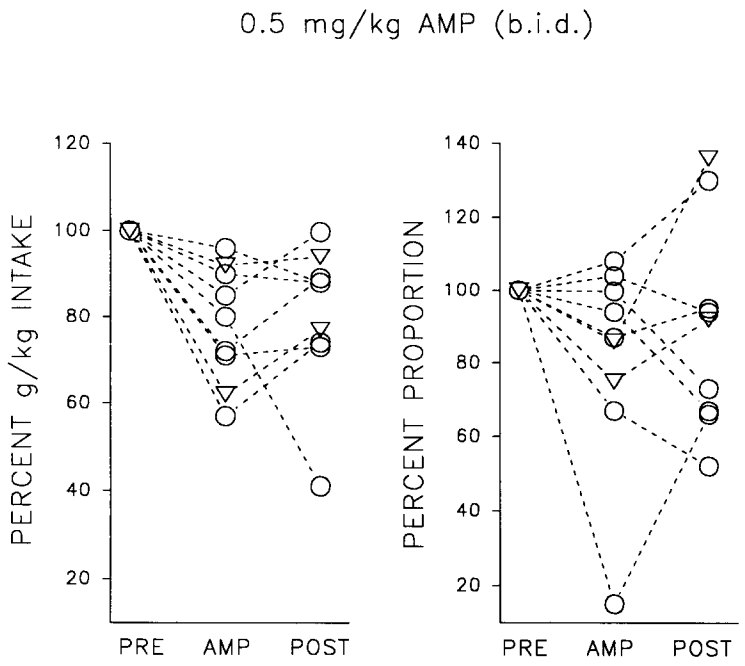

FIG. 3. Percent changes in g/kg (left) and proportion of alcohol to total fluid (right) from basal intakes (PRE) of alcohol in individual rats (n = 9). Each value is mean percent of 3 days during 0.5 mg/kg amperozide (AMP) b.i.d. injection and for 4 days after (POST). Concentration of alcohol offered was 7% (△) and 11% (○, ▽).

tion in the normal intake of food occurs during the administration of this inhibitor of 5-HT reuptake (32). This finding raises a critical question pertaining to the specificity of action of this and other agents on alcohol consumption per se (12,32). That is, if the drug impairs the central mechanism governing caloric intake, a reduction in the drinking of a high-caloric fluid such as alcohol could simply result from a secondary effect of the drug.

In the present experiments, amperozide administered twice daily exerted an ameliorative effect on alcohol intake that was clearly dose dependent. Of special importance is the fact that amperozide exhibited no significant effect on the amount of food and water consumed either during or following its administration. This finding is notable because drugs that attenuate the preference for alcohol consumed in a concentration of pharmacological consequence typically impair the ingestion of food (7,12,24,28,35,36). Thus, in the doses given amperozide apparently exerts a specific action on the unique mechanisms proposed to exist in the brain that are responsible for the aberrant selection of alcohol (21,25). The fact that in many animals the effect of the drug on drinking persisted after cessation of injection suggests that amperozide could induce a more prolonged action on neuronal processes responsible for alcohol preference.

Presently, it is conceivable that two neurotransmitter systems underlie the functional mechanisms whereby amperozide interacts with alcohol and its reinforcing attributes: the serotonergic and dopaminergic systems. First, amperozide in vitro exhibits a high affinity for cerebral 5-HT_2 receptors, a relatively low affinity for cortical α_1- and α_2-adrenoreceptors as well as D_2 receptors in the corpus striatum and other structures

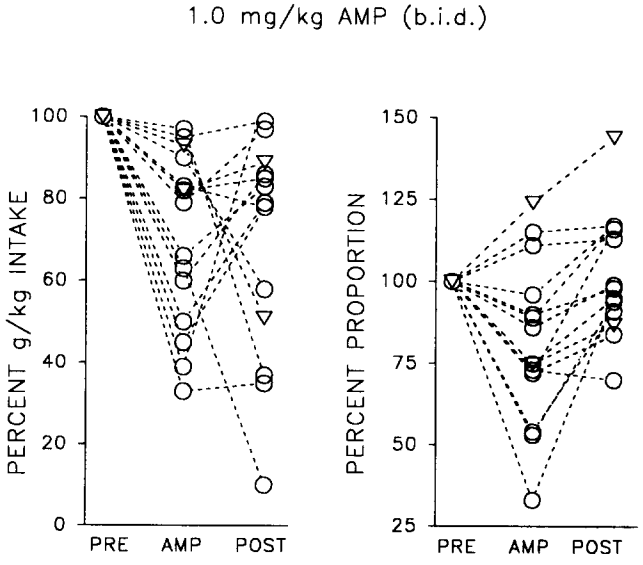

FIG. 4. Percent changes in g/kg (left) and proportion of alcohol to total fluid (right) from basal intakes (PRE) of alcohol in individual rats (n = 15). Each value is mean percent of 3 days during 1.0 mg/kg amperozide (AMP) b.i.d. injection and for 4 days after (POST). Concentration of alcohol offered was 7% (▽) and 11% (○).

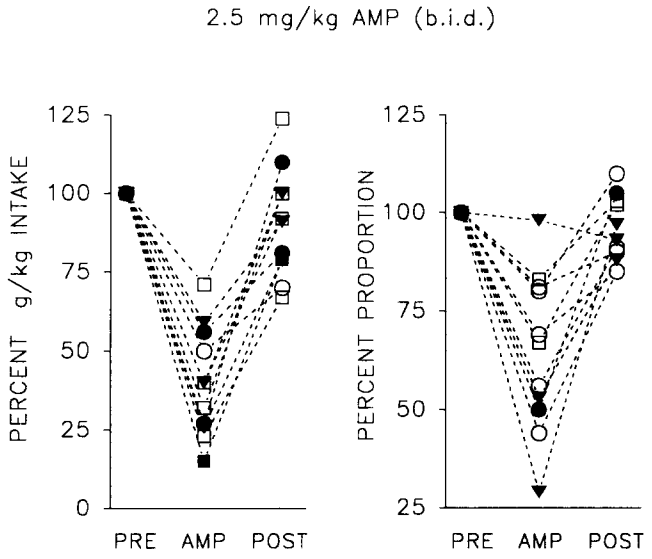

FIG. 5. Percent changes in g/kg (left) and proportion of alcohol to total fluid (right) from basal intakes (PRE) of alcohol in individual rats (n = 11). Each value is mean percent of 3 days during 2.5 mg/kg amperozide (AMP) b.i.d. injection and for 4 days after (POST). Concentration of alcohol offered was 9% (▼), 11% (○), 13% (●), and 15% (□).

in the limbic system (38). Amperozide in vitro also possesses a high affinity for the 5-HT_2 receptor but far lower affinity for 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1C} receptor subtypes (17). Although amperozide given acutely does not reduce the density of 5-HT_2 receptors in the cerebral cortex of the rat (22), the number of 5-HT_2 binding sites, however, is decreased by chronic treatment with amperozide (37). Further, amperozide exhibits inhibitory properties in terms of the in vitro reuptake of 5-HT in the rat (10). Increased 5-HT release in the face of selective blockade of 5-HT_2 receptors may lead to an increased stimulation of 5-HT_{1A} receptors that also may be involved in the self-administration of a drug such as alcohol.

Second, dopaminergic synapses in the mesolimbic–mesocortical system have been implicated previously in the rewarding attributes of alcohol (25,26). In relation to this, it is notable that amperozide inhibits the uptake of [^{3}H]dopamine (DA) in the corpus striatum of the rat in vitro and enhances the release of this catecholamine from perfused limbic and striatal tissue in vitro (11). Further, amperozide reduces the amphetamine-stimulated release of [^{3}H]DA (11) and enhances the accumulation of dihydroxyphenylalanine (DOPA) and dihydroxyphenylacetic acid (DOPAC) within the limbic system and the cortex of the rat (34); however, amperozide exerts no effect on the rate of synthesis of DA in these structures (39). When tested on single, identified dopaminergic neurons in the ventral tegmental area (VTA), amperozide either augments the firing rate and burst firing or stabilizes the pattern of neuronal firing (14). Amperozide also blocks the pacemaker-like activity of DA neurons within the VTA induced by cooling of the medial prefrontal cortex (14).

Overall, amperozide affects the serotonergic, dopaminergic, or both systems in limbic system structures (4,5) now postulated to underpin the neuronal mechanism responsible for the craving or reinforcing property of alcohol (25,26,36). Amperozide exerts a profound effect within the same structures of the limbic system in which an aldehyde adduct such as THP or a β-carboline acts to induce intense alcohol drinking (25,26). These sites comprise the limbic–midbrain and limbic–forebrain pathways encompassing both serotonergic and dopaminergic structures including the nucleus accumbens, medial forebrain bundle, and VTA (31). Based upon a large number of genetic and pharmacological studies, 5-HT-containing neurons in these pathways are seemingly involved, in part, in the fundamental mechanisms underlying alcohol drinking (23,36). Inhibitors of the reuptake of 5-HT and other compounds such as 5-HTP, which augment levels of 5-HT within central serotonergic synapses, tend to attenuate the volitional selection of alcohol (21,24,29). Because amperozide clearly affects 5-HT_2 receptors pharmacologically, it may exert its principal central action on alcohol preference through this subtype of serotonergic receptor (22).

In the present investigation, the experimental protocol involved a metabolic accumulation of biogenic aldehydes by virtue of the pharmacological inhibition of aldehyde dehydrogenase by cyanamide. Such a buildup of the metabolites of alcohol favors the formation of the dopamine and tryptamine classes of aldehyde adduct (8,25). Consequently, in a strain of rat that ordinarily rejects alcohol the preference for relatively high and gustatorily aversive concentrations of alcohol was subsequently induced. Therefore, further research would appear to be essential to examine amperozide in animals whose predilection for alcohol is based etiologically upon a genetic irregularity rather than upon a perturbation of an aldehyde dehydrogenase isozyme. In addition, its clinical application would require a more long-term experimental regimen of administration to assess its therapeutic potential in the treatment of the disease of alcoholism.

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