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RAPID COMMUNICATION

5-HT_2 Receptor Blockade by Amperozide Suppresses Ethanol Drinking in Genetically Preferring Rats

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MYERS, R. D., M. F. LANKFORD AND A. BJÖRK. *5-HT_2 Receptor blockade by amperozide suppresses ethanol drinking in genetically preferring rats.* PHARMACOL BIOCHEM BEHAV **45**(3) 741–747, 1993.—Previously, it was shown that the unique diphenylbutylpiperazinecarboxamide derivative, amperozide (FG 5606), inhibits the volitional drinking of ethanol induced in the rat by the inhibitor of aldehyde dehydrogenase, cyanamide. In this study, the efficacy of this long-acting psychotropic agent and potent 5-hydroxytryptamine$_2$ (5-HT_2) receptor antagonist was examined in the genetic line of ethanol-preferring (P) and -nonpreferring (NP) rats. In both lines, the pattern of drinking of ethyl alcohol was determined by a standard preference test for 3–30% ethanol vs. water. Then, the maximally preferred concentration of ethanol was determined for each individual, which ranged from 9–15% for P rats and 9–13% for NP animals. After a 4-day predrug test, either the saline control vehicle or amperozide was administered SC b.i.d. at 1600 and 2200 h. The drug was given over a 3-day period in one of three doses: 0.5, 1.0, or 2.5 mg/kg. The intake of ethanol of P rats was reduced significantly in a dose-dependent manner in terms of both absolute g/kg and proportion of ethanol to water during injections of amperozide. The same doses of amperozide had no effect on the low intake of ethanol in NP rats. The saline control vehicle also did not alter the consumption of ethanol of P or NP rats. Further, neither the consumption of food nor level of body weight was affected by amperozide either during or after its administration. These results demonstrate that in the individual predisposed genetically to drink ethanol amperozide exerts a palliative effect on the aberrant preference for ethanol consumed in a pharmacologically significant amount. Presently, dopaminergic and serotonergic synapses in the brain are implicated in the genetic differences in the patterns of ethanol consumption that distinguish the P from the NP line of rats. Because amperozide influences the functional activity of both dopaminergic and serotonergic neurons in the mesolimbic system, it is envisaged that the drug attenuates ethanol drinking by way of its direct action on these neurons.

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

PREVIOUSLY, it was shown that amperozide (FG 5606), a diphenylbutylpiperazinecarboxamide derivative, possesses a unique profile of pharmacological properties that relate to the alcoholic syndrome (1,2,7). Amperozide exerts an action on structures of the limbic system (6) that are homologous to those that have been implicated pathologically in the aberrant drinking of ethanol to the point of physical dependence and addiction (15). Recently, we found that amperozide administered acutely reduces the intake of ethanol significantly in a dose-dependent manner in terms of both absolute g/kg and proportion of ethanol to water intake (16). Further, when amperozide is delivered continuously by osmotic minipump over 7 days the consumption of ethanol not only declines significantly but the preference for ethanol continues to decrease over retests at 30-, 70-, 110-, and 140-day intervals. Of special significance is the fact that during both its acute and chronic treatment amperozide does not produce any side effects, including alterations in the consumption of food, level of body weight, or water drinking (16,17).

Because central 5-hydroxytryptamine (5-HT) synapses have

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been implicated historically in the volitional selection of ethanol (11,18), it has been proposed that the drug acts, therefore, through mesolimbic 5-HT_2 receptors to modify in an irreversible manner serotonergic pathways in the brain (16,17). In this connection, drugs that affect cerebral aminergic synapses can influence the uncommon preference for ethanol of the genetically bred drinking (P) rat (12), which coincides with the proposed role of central monoamines underlying the pathogenesis of aberrant drinking (13,14,19). Although there is no uniform agreement on an animal model to simulate the etiology of alcoholism (11), the genetically bred P line of rats (10) most closely approximates the human syndrome for two reasons. First, the concentrations of ethanol preferred maximally by individual P rats are much higher than the 10% solution typically used as a test concentration (9). Second, large volumes of ethanol are consumed even in the presence of far more palatable and highly nutritious solutions offered as alternative choices (9). Because of its clinical significance to the patient with an inherent predilection to alcohol imbibition, the genetic drinking animal would seem an essential component of a model for the development of the pharmacological treatment of alcoholism (12,16).

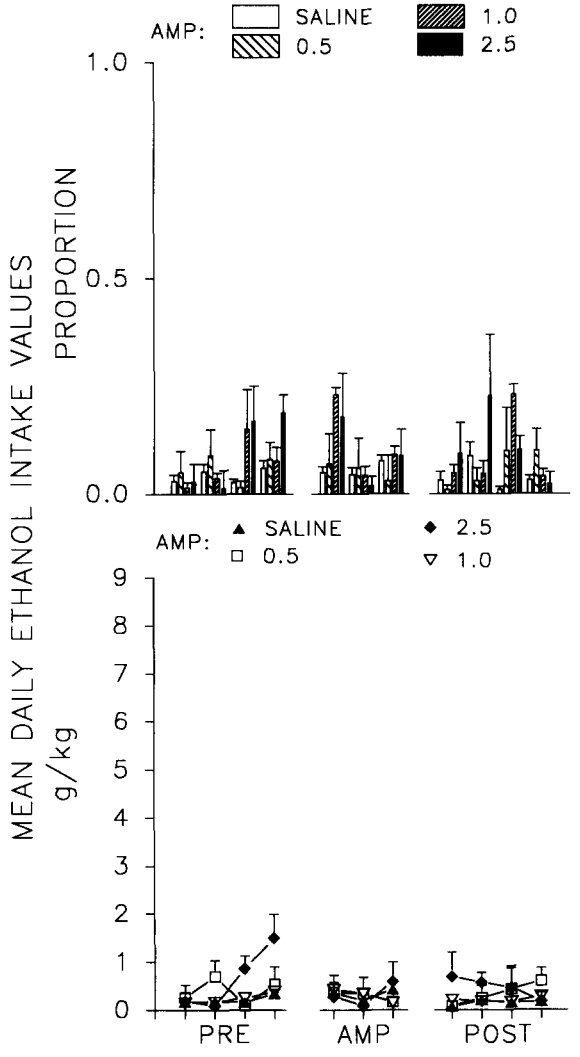

FIG. 1. Mean ± SE daily intakes of ethanol in terms of proportion of ethanol to total fluid (top) and absolute g/kg (bottom) in nonpreferring (NP) rats (n = 6) tested for 4 control days before (PRE), 3 days during (AMP), and 4 control days after (POST) SC injections of amperozide given in doses of 0.5, 1.0, and 2.5 mg/kg b.i.d.

The purpose of this project, therefore, was to determine whether amperozide also would reduce the atypical intake of ethanol in the genetically bred, ethanol-drinking animal. Because the P line of rat exhibits lower levels of cerebral 5-HT and also reacts to drugs that alter the activity of 5-HT in the brain (11), this study examined the efficacy of amperozide, which has a selective affinity for 5-HT_2 receptors in the brain (21). In the present experiments, the nonpreferring (NP) rat, which avoids ethanol, was tested in parallel with P rats. In this case, amperozide was administered in one of three doses over 3 days in the midpoint of an 11-day test interval in which the solution of ethanol maximally preferred by each individual was offered in a self-selection paradigm.

METHOD

Male rats of the P and NP lines weighing 200–250 g were provided by the Alcohol Research Center of Indiana University (Indianapolis, IN). Each rat was housed individually in a wire mesh cage and maintained in a temperature-controlled environment at 22–24°C under a 12 L : 12 D cycle with lights on at 0700 h. Water and Purina Rat Chow were available ad lib to each animal throughout the experiments. At 0830–0930 h, daily measures of intakes of food and fluids as well as body weight were recorded.

Determinations of Ethanol Preference

Initially, each rat was tested for its preference for ethanol against water by means of a standard 3–30% ethanol test (9). Three calibrated 100-ml Kimax drinking tubes were affixed equidistantly to the front of each animal's cage. One contained a v/v solution of ethanol, the second was filled with water, and the third served as a "dummy" tube and remained empty. A 3% concentration of ethanol was offered to each animal on the first day and then on each successive day increased in concentration to 30% over the next 11 days as follows: 4, 5, 6, 7, 9, 11, 13, 15, 20, 25, and 30%. The tubes were rotated daily according to a predetermined random schedule, thereby preventing the development of a position habit (13).

The maximally preferred concentration of ethanol was determined individually for each animal as based upon the highest intake of a given test solution (9) offered together with water. After the intake of ethanol stabilized over a period of 4–6 days, a test solution was then selected for each individual rat at which the greatest intake of ethanol in absolute g/kg was consumed prior to a downward shift below the 50% level in the proportion of ethanol to the total amount of fluid ingested (9,16).

Treatment With Amperozide

Following a 4-day predrug control interval, amperozide (Kabi Pharmacia AB, Business Unit CNS, Malmö, Sweden) or saline control vehicle was given to both P and NP rats over 3 consecutive days. The solution of amperozide HCl was prepared daily in sterilized 0.9% saline at pH 4.5–5.0. The saline vehicle or amperozide was administered SC b.i.d. at 1600 and 2200 h according to a randomized sequence in one

of three doses, based upon previous findings (6,16,17): 0.5, 1.0, and 2.5 mg/kg. During the 3-day period of injections as well as for another 4-day postdrug control period, preference testing for ethanol vs. water continued with the same test concentrations of ethanol continuously available to each rat.

Statistical Analysis

The data were analyzed by the In-Stat software program, in which one-way analyses of variance (ANOVAs) were performed and followed by posthoc Student-Newman-Keuls tests when appropriate. A p value of <0.05 was considered statistically significant.

RESULTS

Amperozide given acutely in doses of 0.5, 1.0, and 2.5 mg/kg b.i.d. over a 3-day interval resulted in contrasting effects on P and NP lines of rats.

Ethanol Drinking of NP Rats

As shown in Fig. 1, SC injection of the three doses of amperozide exerted differential but insignificant effects on ethanol consumption by NP rats. To illustrate, during administration of the 0.5-mg/kg dose of amperozide the mean absolute ethanol intake and proportion of ethanol to total fluid

TABLE 1

MEAN ± SE FOOD, WATER, ETOH AND TOTAL FLUID INTAKES AND BODY WEIGHT OF P AND NP RATS GIVEN SALINE VEHICLE OR 0.5, 1.0, OR 2.5 mg/kg AMPEROZIDE SC bid

	Food (g)	Water (ml)	ETOH (ml)	Total (ml)	Weight (g)
Low Dose (n = 6)					
Pre					
P	30.9 ± .71	2.6 ± .53	35.0 ± 2.1	37.6 ± 2.6	582.1 ± 11.4
NP	19.0 ± .49	33.0 ± 1.6	2.4 ± .41	35.4 ± 2.0	610.0 ± 7.3
0.5 mg					
P	26.8 ± 1.7	8.5 ± 1.7	21.6 ± 2.7	30.1 ± 4.4	575.9 ± 12.3
NP	19.4 ± 1.2	28.8 ± 2.5	1.7 ± .38	30.5 ± 2.8	608.1 ± 7.6
Post					
P	30.5 ± .48	5.8 ± 1.1	36.4 ± 2.3	42.2 ± 3.5	587.0 ± 11.3
NP	20.6 ± .78	33.8 ± 1.3	1.3 ± .32	35.5 ± 1.6	623.0 ± 6.4
Intermediate dose (n = 6)					
Pre					
P	31.1 ± 7.1	9.0 ± 2.8	34.4 ± 7.0	43.4 ± 9.8	575.2 ± 8.0
NP	21.5 ± .73	32.0 ± 1.7	1.7 ± 4.2	33.7 ± 5.9	599.2 ± 9.2
1.0 mg					
P	25.6 ± 1.0	13.7 ± 2.7	19.9 ± 3.6	33.6 ± 6.3	568.6 ± 8.0
NP	22.2 ± 1.4	25.6 ± 2.6	2.7 ± .47	28.3 ± 3.1	599.6 ± 9.1
Post					
P	30.4 ± 1.0	12.4 ± 3.1	27.8 ± 2.3	28.3 ± 5.4	579.8 ± 8.2
NP	22.9 ± .92	31.3 ± .86	1.1 ± .34	32.2 ± 1.2	613.0 ± 7.6
High dose (n = 6)					
Pre					
P	31.8 ± .95	5.3 ± 1.0	35.8 ± 2.5	41.1 ± 5.5	591.1 ± 8.0
NP	22.5 ± 8.6	29.0 ± 1.7	2.3 ± .56	33.3 ± 2.2	603.9 ± 27.2
2.5 mg					
P	26.0 ± 1.2	12.8 ± 1.9	13.7 ± 2.4	26.5 ± 4.3	589.1 ± 9.5
NP	21.1 ± .96	20.8 ± 1.5	2.8 ± .85	23.6 ± 2.3	617.3 ± 16.4
Post					
P	29.7 ± 1.2	7.2 ± 2.0	35.6 ± 3.7	42.8 ± 5.7	600.0 ± 7.7
NP	24.8 ± 1.2	31.3 ± 1.3	2.2 ± .40	33.5 ± 1.7	622.2 ± 14.2
Saline control (n = 6)					
Pre					
P	27.8 ± 1.2	4.8 ± 1.1	34.9 ± 2.2	39.7 ± 3.3	604.0 ± 7.9
NP	20.7 ± .56	33.7 ± 2.1	1.6 ± .25	35.3 ± 2.3	641.8 ± 9.9
Saline					
P	31.5 ± 1.6	4.0 ± .99	36.7 ± 2.6	42.7 ± 3.6	611.0 ± 9.0
NP	21.9 ± 1.0	32.0 ± .95	1.9 ± .29	33.9 ± 1.2	647.8 ± 11.9
Post					
P	30.7 ± 1.0	5.2 ± 1.1	30.8 ± 2.8	36.0 ± 3.9	617.8 ± 7.7
NP	19.3 ± .61	30.1 ± 1.0	1.9 ± .76	32.0 ± 1.8	656.7 ± 11.0

Precontrol period was 4 days, injection period was 3 days, and postcontrol period was 4 days. (n = number of rats.)

consumed on each day declined from 0.4 ± 0.07 predrug to 0.3 ± 0.06 g/kg/day and from 0.06 ± 0.01 to 0.05 ± 0.01, respectively. After the 1.0-mg/kg dose, consumption of ethanol increased from 0.3 ± 0.07 to 0.38 ± 0.07 g/kg/day rose in terms of proportional values from 0.07 ± 0.03 to 0.11 ± 0.04. Following administration of the 2.5-mg/kg dose of amperozide, the absolute ethanol intakes fell from 0.40 ± 0.1 to 0.30 ± 0.1 g/kg/day, whereas the proportional values increased from 0.09 ± 0.04 to 0.1 ± 0.02 (Fig. 1).

As shown in Table 1, the 0.5-mg/kg dose of amperozide reduced the mean volume of ethanol consumed from 2.4 ± 0.4 ml before treatment to 1.7 ± 0.4 ml/day during its administration. During injections of the intermediate dose of amperozide, the volume of ethanol consumed by NP rats rose slightly from 1.7 ± 0.4 ml to 2.7 ± 0.5 ml (Table 1). Amperozide given in the highest dose increased the mean volume of ethanol consumed from 2.3 ± 0.6 ml to 2.8 ± 0.8 ml. Again, however, none of the fluctuations following amperozide treatment was statistically significant.

P Rats

As presented in Fig. 2, the 0.5-mg/kg dose of amperozide injected b.i.d. suppressed the mean daily intakes of absolute ethanol significantly from 5.65 ± 0.35 to 3.5 ± 0.46 g/kg/day, $F(1, 41) = 13.80$, $p < 0.01$, as well as the proportional values from 0.84 ± 0.03 preadminstration to 0.70 ± 0.05, $F(1, 41) = 5.30$, $p < 0.05$. Similarly, the 1.0-mg/kg dose of amperozide b.i.d. reduced both g/kg and proportional values (Fig. 2) significantly from 5.4 ± 0.32 to 3.4 ± 0.55, $F(1, 41) = 11.05$, $p < 0.01$, and from 0.81 ± 0.4 to 0.58 ± 0.7, $F(1, 41) = 8.67$, $p < 0.01$, respectively. The 2.5-mg/kg dose of amperozide caused the greatest suppression of ethanol drinking in P rats, diminishing the g/kg intake (Fig. 2, bottom) of 5.6 ± 0.33 to 2.2 ± 0.36, $F(1, 41) = 45.80$, $p < 0.01$, accompanied by a decrease in proportional intake (Fig. 2, top) from 0.85 ± 0.03 to 0.48 ± 0.06, $F(1, 41) = 27.50$, $p < 0.01$.

Table 1 shows that 0.5 mg/kg amperozide caused a significant decline in mean volume of ethanol consumed by P rats from a prelevel of 35.0 ± 2.2 ml/day to 21.6 ± 2.7 ml/day during amperozide, $F(1, 41) = 15.06$, $p < 0.01$, and returning to 36.4 ± 2.3 ml/day after amperozide. The mean volume of ethanol ingested (Table 1) declined from 34.2 ± 2.0 to 19.9 ± 3.6, $F(1, 41) = 13.62$, $p < 0.01$, during injections of the 1.0-mg/kg dose, whereas during administration of the highest dose of amperozide the volume of ethanol consumed fell from 35.0 ± 2.5 to 13.7 ± 2.4 ml/day, $F(1, 41) = 35.80$, $p < 0.01$. As shown in Table 1, the saline control vehicle was without any significant effects on the intake of ethanol on either P or NP animals.

Individual Responses To Amperozide

Because each of the doses of amperozide exerted differential effects on individual rats, the mean percent change from the 4-day predrug baseline intake of ethanol in absolute g/kg and proportional value was calculated for the 3 days of amperozide injections and 4 days posttreatment. As shown in Fig. 3 (left), the 0.5-mg/kg dose of amperozide given b.i.d. evoked a moderate percent change in the range of 80% to a substantial decline below 40% in g/kg intake of ethanol offered to individual rats in concentrations of 9, 11, 13, and 15%. In one rat, the percent change in g/kg consumption of ethanol (Fig. 3, left) persisted (POST). Although the percent

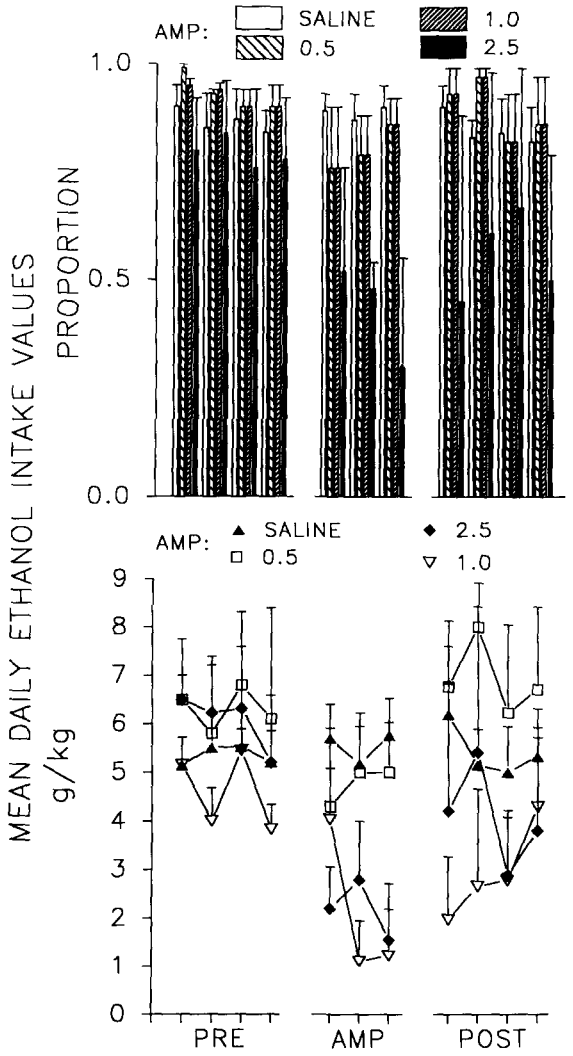

FIG. 2. Mean ± SE daily intakes of ethanol over 11 days in terms of proportion of ethanol to total fluid (top) and absolute g/kg (bottom) in preferring (P) rats ($n = 6$) tested for 4 control days before (PRE), 3 days during (AMP), and 4 control days after (POST) SC injections of amperozide given in doses of 0.5, 1.0, and 2.5 mg/kg b.i.d.

decline in ethanol consumed during the 1.0-mg/kg b.i.d. dose of amperozide varied among P rats, the percent change in the absolute intakes of ethanol in concentrations ranging from 9–15 % (Fig. 3, middle) exceeded that of the lowest dose of the drug. Further, in three rats the decline in g/kg consumption of ethanol persisted during the 4-day posttest. As presented in Fig. 3 (right), the 2.5-mg/kg dose of amperozide evoked a consistent percent decline in the g/kg intake of ethanol across the same concentrations of 9–15 % in all P rats.

The percent changes in proportional intakes of ethanol of individual P rats (Fig. 4, left) showed a decline from baseline levels following the 0.5-mg/kg dose of amperozide. Similarly, the decline in proportional intakes of P animals following the 1.0-mg/kg dose was greater than that following the lower dose (Fig. 4, middle). Following injections of amperozide in the highest dose (POST), the percent changes in the proportional

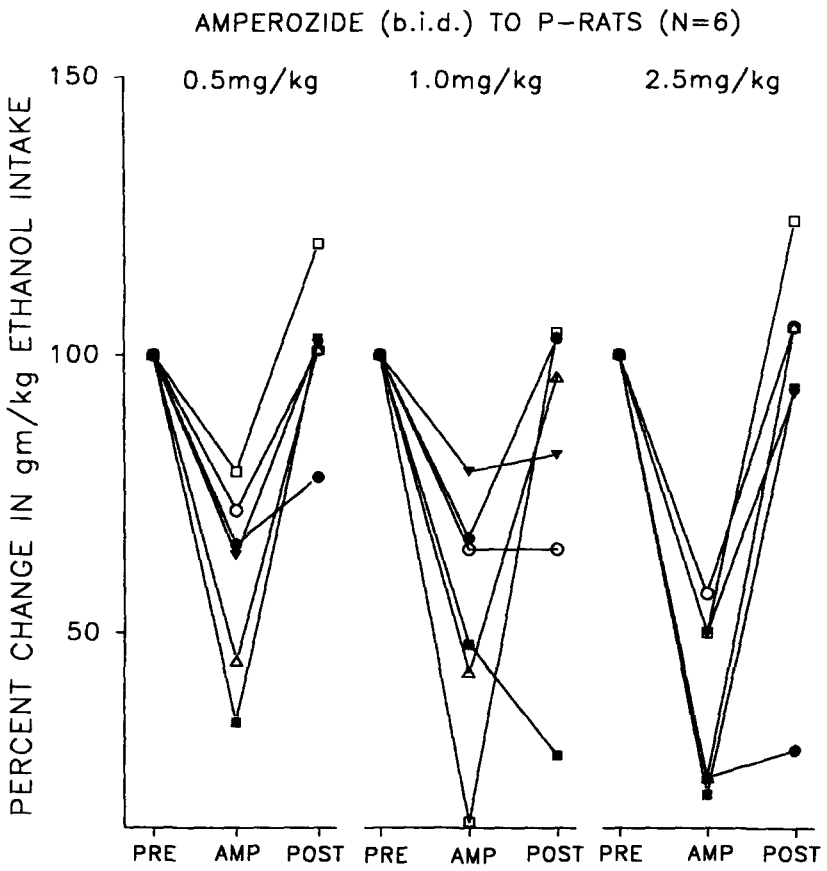

FIG. 3. Percent changes in absolute consumption of ethanol (ETOH) in g/kg/day from basal intakes (PRE) of ethanol in individual preferring (P) rats (n = 6). Each value represents the mean percent change for the 3 days during injections b.i.d. of 0.5 mg/kg (left), 1.0 mg/kg (middle), and 2.5 mg/kg (right) amperozide (AMP) and for the 4 control days after treatment (POST). The individual preferred concentrations of ethanol offered to P rats were: 9% (△); 11% (▲ and □); 13% (■ and ○); 15% (●).

values (Fig. 4, right) essentially mimicked that of the g/kg consumption of ethanol and were greater than either of the two lower doses of the drug.

DISCUSSION

The present results show that amperozide is efficacious in ameliorating the excessive drinking of ethanol in genetically bred P rats predisposed to prefer ethanol. Previously, it was shown that amperozide suppresses ethanol preference, in a dose-dependent manner, of the rat induced to drink following systemic administration of the aldehyde dehydrogenase inhibitor cyanamide (16). It is notable that the present results show that the magnitude of reduction and, therefore, characteristics of the palliative action of amperozide on ethanol preference are concordant with those observed in the cyanamide-treated rat (17). Because the P rat develops a persistent tolerance to the sedative hypnotic effect of ethanol more readily than the NP rat (22), amperozide may act to diminish the tolerance to the fluid and thereby reduce the craving for the fluid.

Acting as an antipsychotic and antidepressant, amperozide could serve to assuage withdrawal symptoms as the intake of ethanol of P rats diminishes. The enhanced release of dopamine produced by amperozide also could lead to a short-term potentiation of firing of dopaminergic neurons in anatomical structures within the mesolimbic system of the P rat now thought to comprise a neuronal "circuit" for ethanol drinking (15). Although such a release of the catecholamine may lead eventually to a downregulation of dopamine receptors in the longer term, chronic treatment with amperozide does not produce a downregulation of dopamine receptors within the limbic forebrain (Svartengren, personal communication). However, because dopaminergic pathways may influence their anatomical areas of innervation, amperozide may excite mesencephalic dopaminergic neurons by way of the blockade of a tonic inhibitory firing of serotonergic neurons due to the 5-HT_2 receptor blocking property of the drug (5).

In terms of the mechanism of action of amperozide on preference of the P rat, amperozide has a high affinity for the 5-HT_2 receptor and acts also to release dopamine from the mesolimbic system of the rat (8). In this connection, P rats possess lower levels of 5-HT in brain than the nonpreferring NP rats (4) and recent data show that the P rat also apparently has fewer numbers of serotonergic neurons in the brain (23). Therefore, the occupation of central 5-HT_2 receptors by amperozide would enable residual 5-HT, upon its presynaptic re-

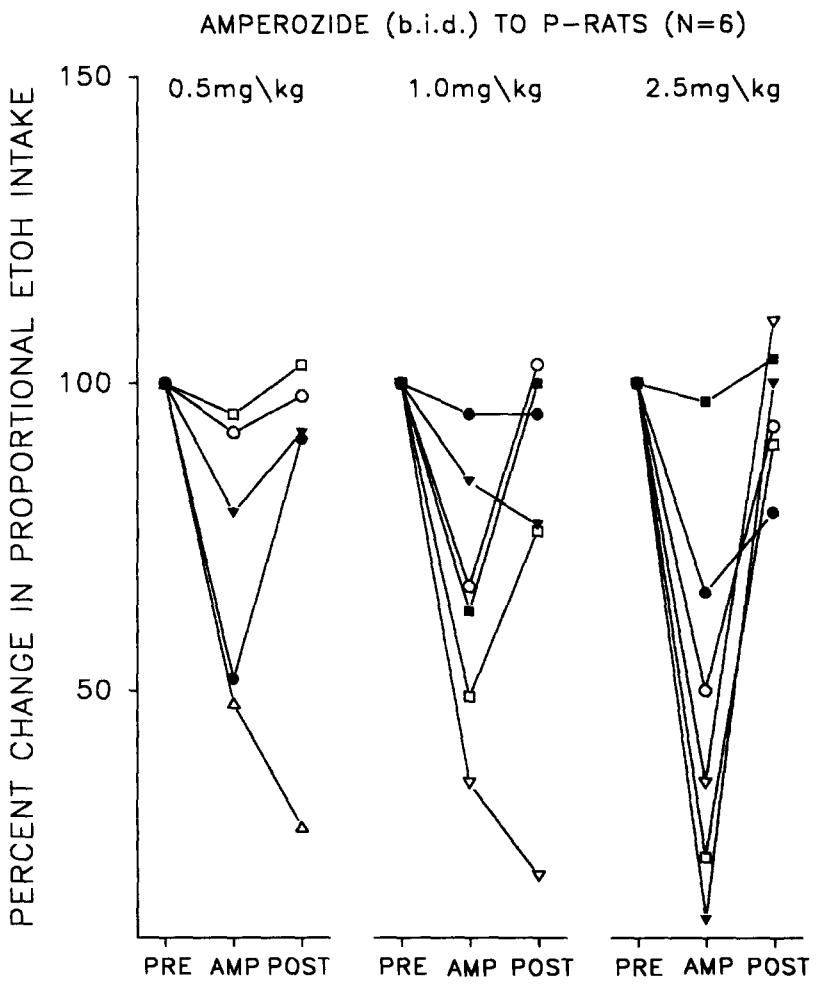

FIG. 4. Percent changes in the proportion of ethanol (ETOH) to total fluid consumed from basal proportional intakes (PRE) of ethanol in individual preferring (P) rats (n = 6). Each value represents the mean percent change for the 3 days during injections of amperozide (AMP) b.i.d. of 0.5 mg/kg (left), 1.0 mg/kg (middle), and 2.5 mg/kg (right) and for the 4 control days after treatment (POST). The individual preferred concentrations of ethanol offered to P rats were: 9% (△); 11% (▲ and □); 13% (○ and ■); 15% (●). Proportion data was not included for one rat given 13% ethanol during the 0.5-mg/kg dose because of a defective water tube.

lease, to bind reciprocally to other subtypes of the serotonergic receptor. Alternatively, the levels of the indoleamine could be enhanced within the synaptic cleft.

In this connection, drugs that can inhibit the reuptake of 5-HT presynaptically have been shown to reduce the volitional intake of ethanol (3,12,20). However, this potentially important observation is impugned by the substantial side effects of this class of drug, particularly on caloric regulation as reflected by significant impairments in food intake (3,20). In comparison with sertraline, fluoxitine, and drugs that affect serotonergic systems, the action of amperozide differs not only in relation to side effects on caloric regulation but also in terms of preference for maximally preferred concentrations of ethanol that possess pharmacological significance.

Finally, the absence of side effects of amperozide as well as its apparent irreversibility comprise a relatively unique profile of action on ethanol preference not reported previously for other drugs. Thus, for those individuals who possess an inherent liability toward alcohol addiction this finding in itself is of clinical significance in terms of therapeutic strategies for the future.

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