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The 5-HT_4 Receptor Antagonist, GR113808, Reduces Ethanol Intake in Alcohol-Preferring Rats

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PANOCKA I., R. CICCOCIOPPO, C. POLIDORI, P. POMPEI AND M. MASSI. *The 5-HT_4 receptor antagonist, GR113808, reduces ethanol intake in alcohol-preferring rats.* PHARMACOL BIOCHEM BEHAV **52**(2) 255–259, 1995.— The present study evaluated the effect of the selective 5-HT_4 receptor antagonist, GR113808, on ethanol intake in alcohol-preferring rats. Rats were offered 10% ethanol 2 h/day. In the first experiment, rats had food and water ad lib and 10% ethanol was offered from 1800 to 2000 h. In the second experiment, food was freely available, 10% ethanol was offered 2 h/day, from 1800 to 2000 h, and water was offered for 4 h, from 1800 to 2200 h. In both experiments GR113808 was subcutaneously injected at doses of 1, 3, or 10 mg/kg for 4 consecutive days, 5 min before access to ethanol. From the first day of administration, GR113808 significantly reduced the volitional ethanol intake in water sated rats at the three doses tested. In water-deprived rats, it reduced ethanol intake at 3 and 10 mg/kg, without modifying total fluid and food intake. In both experiments the effect of GR113808 remained rather stable during the 4 days of administration. The present findings, showing that the 5-HT_4 receptor antagonist, GR113808, selectively reduces ethanol intake in alcohol-preferring rats, suggest that 5-HT_4 receptors may play a role in alcohol intake control.

Ethanol intake GR113808 5-HT_4 receptors 5-HT_4 receptor antagonists

FUNCTIONAL and binding studies have shown that 5-HT_4 receptors, positively coupled to adenylate cyclase (4,11,22), are widely distributed in the central nervous system, gastroenteric apparatus, adrenal glands, bladder, atria, and blood vessels (3,7,8,12,16,19).

High densities of 5-HT_4 receptors have been identified in various regions of the limbic system of the rodent brain, such as the islands of Calleja, olfactory tubercle, fundus striati, nucleus accumbens, ventral pallidum, septal region, hippocampus, and amygdala (15,28,36,37). Moreover, high densities of 5-HT_4 receptors have been demonstrated in the hippocampo-habenulo-interpeduncular pathway and in the striato-nigro-tectal pathway (37).

Not much is known about the functional role of 5-HT_4 receptors in the central nervous system. Up to now, they have been shown to mediate 5-HT-induced increase in pyramidal cells discharge in the hippocampus (1,6,28), suggesting a role in memory and learning processes (12). Furthermore, recent studies indicate that 5-HT_4 receptor agonists stimulate dopamine release from rat striatal slices (32,33), and results obtained in the conditioned place preference paradigm suggest that they play a role in the brain reward mechanisms (2). Interestingly, high densities of 5-HT_4 receptors are found in the nucleus accumbens (15,36), a brain area that is strongly related to reward processes and drug self-administration behavior (17).

Based on these observations, and also taking into account that 5-HT has been implicated in alcohol intake control (24,30), that 5-HT mechanisms are involved in the discriminative stimulus properties of ethanol (14,31), and that ethanol stimulates 5-HT release in the nucleus accumbens (20,23,38), the question may be raised whether pharmacological manipu-

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lation of 5-HT_4 receptors might influence the central effects of ethanol and eventually its intake.

Our study was carried out in genetically selected alcohol-preferring rats bred from Sardinian alcohol-preferring rats (9,10). The 5-HT_4 receptor antagonist, GR113808, was employed. The drug shows approximately 3000-fold selectivity between 5-HT_4 and 5-HT_3 receptors, and negligible affinity for other 5-HT receptor subtypes and for non-5-HT receptors (5,13,15).

METHOD

Animals

Adult male alcohol-preferring rats were used. They were bred for 12 generations in the Institute of Pharmacology of the University of Camerino, starting from Sardinian alcohol-preferring rats of the 13th generation provided by the Department of Neurosciences of the University of Cagliari (Italy). Rats were individually housed on a 12L : 12D cycle (light 0600–1800 h) in a temperature-controlled room. Food pellets (diet No. 4RF18, Mucedola, Milano) were available ad lib. Before experiments rats were offered free access to tap water and 10% ethanol in graduaded drinking tubes. The position of drinking tubes for water and ethanol was changed every day to avoid development of place preference.

Drug Administration

GR113808 was dissolved in distilled water and subcutaneously (SC) injected in a volume of 1 ml/kg body weight, 5 min before access to ethanol solution.

Experiment 1: Effect of GR113808 on 10% Ethanol Intake in Water-Sated Rats

The rats selected for the experimental groups showed a percent alcohol preference [defined as alcohol intake (ml/rat)/total fluid intake (ml/rat) × 100] above 80%, corresponding to daily ethanol intake of 5–7 g/kg of body weight.

After selection rats had free access to water and food 24 h/day, but only 2 h/day access to 10% ethanol solution, from 1800 to 2000 h. Before the beginning of the experiment, rats were familiarized with this schedule of access to ethanol and with the injection procedure for 15 days. Six groups of six rats were employed. Three groups were treated with either 1, 3, or 10 mg/kg of GR113808; each group was matched with a control group receiving SC injection of vehicle. Alcohol and water intake were measured at 15, 30, 60, and 120 min after access to ethanol. Food consumption was measured at the beginning of the access to ethanol and after 120 min. The same drug treatment was repeated for 4 consecutive days. Body weight of rats was measured just before the beginning of treatment and 4 days later, at 1800 h.

In Experiment 1, ethanol intake occurred essentially in the absence of water and food intake, thus not allowing the evaluation of the behavioral selectivity of the drug effect.

Experiment 2: Effect of GR113808 on 10% Ethanol Intake in Fluid-Deprived Rats

The aim of Experiment 2 was to evaluate simultaneously the effect of GR113808 on ethanol and water drinking and on food intake, which occurs consistently in fluid-deprived rats as soon as fluids are made available.

Again, rats with a percent alcohol preference above 80% were employed. During the experiment, rats were fluid deprived for 20 h, from 2200 h to 1800 h of the following day. At 1800 h they were given free choice between water and 10% ethanol until 2000 h. At 2000 h ethanol was removed and water was still available for another 2 h. Rats were familiarized with the schedule of access to fluids and with the injection procedure for 15 days before the experiment began. Six groups of six rats were employed. Three groups were treated with either 1, 3, or 10 mg/kg of GR113808; each group was matched with a control group receiving SC injection of vehicle. Fluid intake was measured at 15, 30, 60, and 120 min. Food consumption was measured at 120 min after rats were given access to water and 10% ethanol. Drug treatment was repeated for 4 consecutive days.

Statistical Analysis

Data were analysed by means of split-plot analysis of variance (ANOVA) with between-group comparisons for drug treatment and within-group comparisons for time. Food intake data were analysed by one-way ANOVA. Planned pairwise comparisons were made by means of *t*-test. Difference in body weight between treated rats and controls was determined at the beginning and at the end of treatment by means of *t*-tests. Statistical significance was set at $p < 0.05$.

RESULTS

Experiment 1: Effect of GR113808 on 10% Ethanol Intake in Water-Sated Rats

On the first treatment day, GR113808 reduced ethanol intake at each of the three doses tested (Fig. 1). ANOVA revealed a statistically significant effect [$F(1, 10) = 6.36$, $p < 0.05$, $F(1, 10) = 16.42$, $p < 0.01$, and $F(1, 10) = 21.52$, $p < 0.01$] in response to 1, 3, and 10 mg/kg, respectively. At the dose of 10 mg/kg, the ANOVA also revealed a significant treatment/time interaction, $F(3, 30) = 7.99$, $p < 0.001$.

The inhibitory effect observed in the first treatment day remained rather stable during the 3 subsequent days of treatment (Table 1).

During the 2-h access to ethanol, water and food intake occurred only occasionally and were negligible both in treated and control rats (data not shown).

Following GR113808 administration in the range of doses tested, the behavior of treated rats was essentially normal, and no general behavioral alteration was observed.

Experiment 2: Effect of GR113808 on 10% Ethanol Intake in Fluid-Deprived Rats

Ethanol intake in controls was similar to that of control water-sated rats in Experiment 1. GR113808 also reduced ethanol consumption in fluid-deprived animals on the first treatment day (Fig. 2). At the lowest dose of GR113808, ANOVA revealed neither a significant drug effect, $F(1, 9) = 2.17$, $p > 0.05$, nor a significant drug/time interaction. In response to 3 mg/kg, ANOVA revealed a not significant drug effect, $F(1, 9) = 3.71$, $p > 0.05$, but a significant drug/time interaction, $F(3, 27) = 2.97$, $p < 0.05$. Planned pairwise comparison showed a significant difference from controls at 60 and 120 min. In response to 10 mg/kg a significant drug effect was observed, $F(1, 10) = 7.74$, $p < 0.01$, in the absence of drug/time interaction.

The inhibitory effect observed in the first treatment day

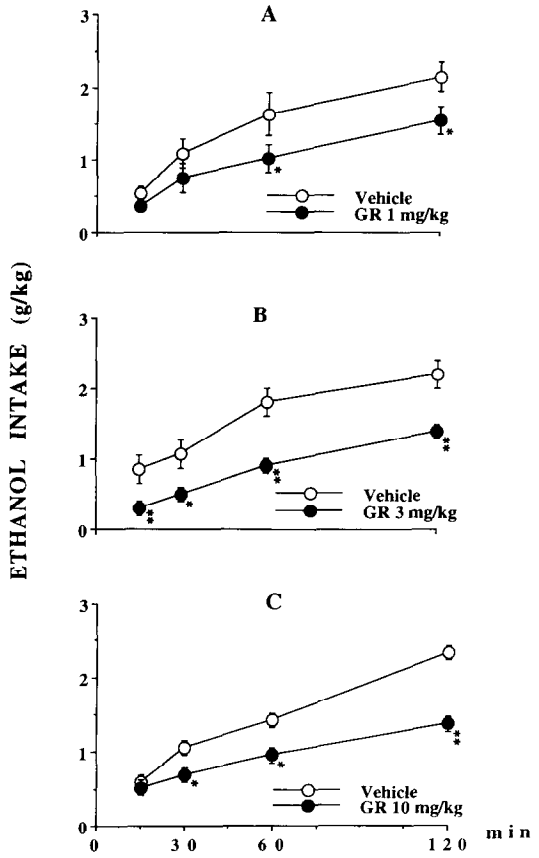

FIG. 1. Effect of SC injection of: (A) 1 mg/kg, (B) 3 mg/kg, or (C) 10 mg/kg of GR113808 (GR) or vehicle on 10% ethanol intake during 120 min of free choice between water and 10% ethanol in water-sated rats. Each point is the mean ± SEM of data from six animals. Statistical difference from controls (vehicle): $*p < 0.05$, $**p < 0.01$; where not indicated, difference from controls was not statistically significant.

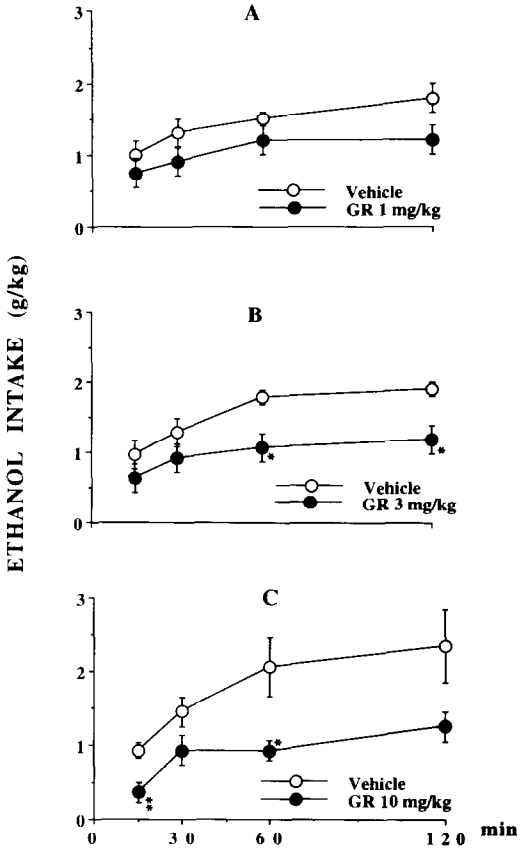

FIG. 2. Effect of SC injection of: (A) 1 mg/kg, (B) 3 mg/kg, or (C) 10 mg/kg of GR113808 (GR) or vehicle on 10% ethanol intake during 120 min of free choice between water and 10% ethanol, in fluid-deprived rats. Each point is the mean ± SEM of data from five animals, vehicle groups in (A) and (B), and from six animals for the other groups. Statistical difference as in Fig. 1.

remained rather stable during the 3 subsequent days of treatment (Table 1).

The reduction in ethanol intake induced by GR113808 was accompanied by an increase in water intake, so that each of the three groups, receiving different drug doses, showed a total fluid intake not significantly different from that of controls (Fig. 3).

TABLE 1

INHIBITION OF 2-h ETHANOL INTAKE IN WATER-SATED AND IN WATER-DEPRIVED RATS TREATED WITH GR113808 FOR 4 CONSECUTIVE DAYS

	Day 1	Day 2	Day 3	Day 4
Water sated				
GR 1 mg/kg	71.8 ± 9.3*	85.7 ± 13.8	69.8 ± 9.0*	82.7 ± 6.9*
GR 3 mg/kg	62.9 ± 3.9†	61.6 ± 8.3*	67.1 ± 12.0	68.7 ± 4.8*
GR 10 mg/kg	61.8 ± 5.3†	76.6 ± 8.1*	75.9 ± 8.7*	74.0 ± 7.2*
Water deprived				
GR 1 mg/kg	76.7 ± 14.8	76.2 ± 17.0	67.0 ± 12.2	68.1 ± 13.8
GR 3 mg/kg	68.7 ± 4.0†	81.6 ± 4.9	55.5 ± 8.5*	61.8 ± 8.8†
GR 10 mg/kg	61.4 ± 6.8*	70.4 ± 4.8†	60.6 ± 8.1†	77.7 ± 6.4*

Data are mean ethanol intake (expressed as percent of controls) ± SEM. Statistical difference from controls (determined on the g/kg data): $*p < 0.05$; $†p < 0.01$; where not indicated, difference from controls was not statistically significant.

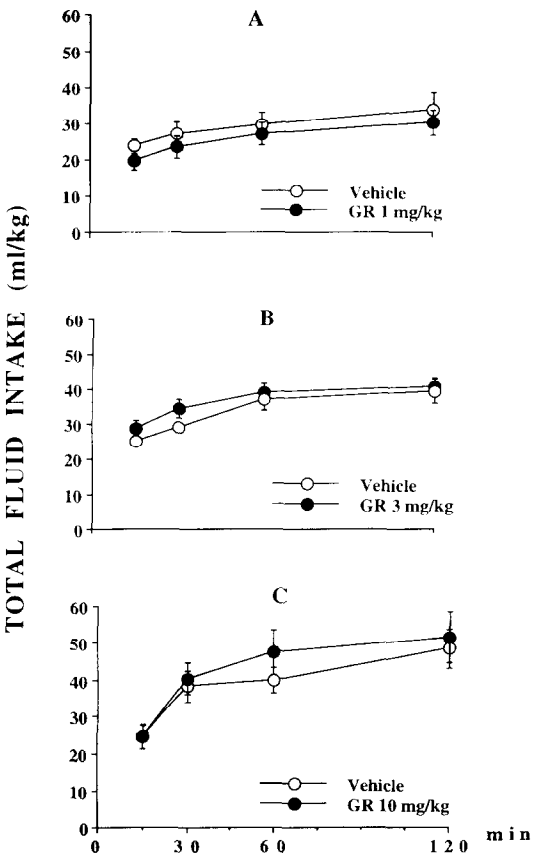

FIG. 3. Effect of SC injection of: (A) 1 mg/kg, (B) 3 mg/kg, or (C) 10 mg/kg of GR113808 (GR) or vehicle on total fluid intake during 120 min of free choice between water and 10% ethanol, in fluid-deprived rats. Each point is the mean ± SEM of data from five animals, vehicle groups in (A) and (B), and from six animals for the other groups. Difference from controls (vehicle) was never statistically significant.

The 2-h food intake following 1, 3, or 10 mg/kg of GR113808 was 14.4 ± 1.5, 9.9 ± 0.6, or 11.5 ± 0.6 g/rat, respectively. Food intake of treated rats was statistically indistinguishable from that of controls: 14.6 ± 2.9, 9.9 ± 0.8, or 11.4 ± 1.5 g/rat, respectively.

Body weight of the treated rats at the beginning and at the end of the 4-day treatment in both experiments was essentially identical to that of controls.

DISCUSSION

The results of the present study show that GR113808 reduces ethanol intake, both in water-sated (Experiment 1) and in water-deprived rats (Experiment 2).

Interestingly, the inhibition of ethanol intake observed in our study was statistically significant up to 2 h after drug injection, even though GR113808 has been reported to have a very short half-life in plasma (5). However, because the elimination half-life of GR113808 has not been determined yet in the rat central nervous system, it is not known whether the duration of the effect is related to the pharmacokinetics of the drug or whether the effect lasts beyond the drug half-life.

In water-deprived rats, GR113808 reduced ethanol intake but did not modify food or total fluid intake. These findings provide clear evidence that its inhibitory effect on ethanol consumption was behaviorally selective.

Total fluid intake was maintained similar to that of controls, because water consumption was increased. Because the drug never stimulated water drinking in water-sated rats, the increase in water intake observed in Experiment 2 was likely a compensatory event to maintain total fluid intake.

It is well known that ethanol consumption can be reduced by compounds selective for other 5-HT receptor subtypes, such as 5-HT_2 or 5-HT_3 antagonists (19,21,25,26) and 5-HT_{1A} agonists (18,27,29,34,35). However, binding studies have shown that GR113808 has only weak affinity for 5-HT_3 receptors (about 3000 times lower than for 5-HT_4 receptors) and negligible affinity for the other 5-HT receptors, including 5-HT_2 and 5-HT_1 receptors (5,13,15).

Finally, it is well known that ethanol consumption can be reduced by drugs that increase central 5-HT availability by inducing 5-HT release or by blocking 5-HT uptake (30); however, no evidence has been provided suggesting that GR113808 may possess these pharmacological properties.

Not much is known about the neuropharmacology of 5-HT_4 receptors. Autoradiographic studies have shown high densities of this receptor subtype in the nucleus accumbens and in other mesolimbic-cortical areas (15,36), which are related to reward processes and drug self-administration behaviors (17). Accordingly, results obtained in the conditioned place preference paradigm suggest that 5-HT_4 receptors are involved in the brain reward mechanisms (2).

Voluntary ethanol ingestion, as well as parenteral ethanol injection, is known to stimulate 5-HT release in mesolimbic areas, including the nucleus accumbens (20,23,38). Because 5-HT is likely involved in the rewarding effect of ethanol (30), it might be speculated that 5-HT_4 receptors mediate, at least in part, this effect of 5-HT. Thus, blockade of 5-HT_4 receptors might reduce the reinforcing properties of ethanol.

Recently, it has been demonstrated that 5-HT_4 and 5-HT_{1A} receptors are colocalized on hippocampal cells, where they exert opposite effects on 5-HT neuronal activity (28). In this regard, it will be interesting to evaluate whether 5-HT_4 antagonists and 5-HT_{1A} agonists may synergistically act to suppress ethanol consumption.

In conclusion, the results of the present study suggest that in addition to other 5-HT receptor subtypes the 5-HT_4 also may be involved in the control of voluntary ethanol intake in rats. The high densities of these receptors in the nucleus accumbens and in other mesolimbic areas suggests that they might influence ethanol intake by interfering with its reinforcing properties.

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