Pharmacology Biochemistry & Behavior, Vol. 30, pp. 823–827. © Pergamon Press plc, 1988. Printed in the U.S.A. 0091-3057/88 $3.00 + .00

Attenuation of Alcohol Intake by a Serotonin Uptake Inhibitor: Evidence for Mediation Through the Renin-Angiotensin System

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Received 1 December 1987

GRUPP, L. A., E. PERLANSKI AND R. B. STEWART. *Attenuation of alcohol intake by a serotonin uptake inhibitor: Evidence for mediation through the renin-angiotensin system.* PHARMACOL BIOCHEM BEHAV **30**(4) 823–827, 1988.—Although the serotonin uptake inhibitors have been shown to reduce alcohol intake in both animals and man, the mechanism of this effect is unclear. It is known that enhanced serotonergic activity can stimulate activity in the renin-angiotensin system and that elevated activity in the renin-angiotensin system can reduce voluntary alcohol intake. Therefore, serotonin uptake inhibitors such as fluoxetine might exert their effect on alcohol intake, in part, through the renin-angiotensin system. The present experiment assesses this possibility by examining the effect of the angiotensin converting enzyme inhibitor, enalapril, on the fluoxetine-induced decrease in alcohol intake. Four groups of rats were offered limited access to alcohol for 1 hr each day. When intake stabilized each group was injected with 2.5, 5.0 or 10.0 mg/kg of fluoxetine or the saline vehicle 1 hr prior to the access to alcohol. Fluoxetine produced a dose-dependent decrease in alcohol intake. Following this, all groups received injections of 1 mg/kg of the angiotensin converting enzyme inhibitor, enalapril, 40 min prior to the fluoxetine. Enalapril had no effect on alcohol intake in the saline group, but reversed the suppression in alcohol intake produced by the 2.5 mg/kg and 5.0 mg/kg doses of fluoxetine and partially reversed the effect of the 10.0 mg/kg dose. These findings indicate that the fluoxetine-induced reduction in alcohol intake may, in part, be mediated through the renin-angiotensin system.

Alcohol intake Renin-angiotensin system Serotonin uptake inhibitor
Angiotensin converting enzyme inhibitor Fluoxetine Enalapril

OVER the past 10–15 years a large body of experimental evidence has accumulated which implicates serotonin (5-hydroxytryptamine, 5-HT) in the regulation of voluntary alcohol intake. Among the first reports was that of Myers and Martin [22] who showed that the administration of the 5-HT precursor, 5-hydroxytryptophan (5-HTP), could reduce alcohol intake in rodents. Since then, the role of 5-HT in alcohol intake has been investigated by a variety of experimental approaches. Serotonergic activity can be pharmacologically enhanced in various ways: by adrenergic agonists such as fenfluramine which release 5-HT into the synaptic cleft, by direct 5-HT-receptor agonists such as quipazine, by l-tryptophan, the initial precursor in the synthesis of 5-HT, or by 5-HT uptake inhibitors such as zimelidine or fluoxetine which increase the available pool of 5-HT in the synapse by preventing its neuronal uptake. Experiments which have applied each of these 5-HT "enhancing" manipulations have clearly shown that all are capable of producing a significant reduction in voluntary alcohol intake [24–26, 32].

A somewhat different approach has been to examine brain 5-HT levels in a number of rodent lines bred for differences in their preference for alcohol. Although some of the early studies did not find significant differences in whole brain 5-HT content between C57BL alcohol-preferring mice and DBA alcohol-nonpreferring mice (e.g., [12]) or between alcohol-accepting AA and alcohol-nonaccepting ANA lines

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of rats [1], more recent studies selectively analyzing specific brain regions have shown that a relationship between alcohol preference and correlates of serotonergic activity does indeed exist. For example, Murphy *et al.* [19] have found that 5-HT level in the cortex, striatum, hippocampus and hypothalamus of the alcohol-preferring P rat is significantly lower than that found in the same regions of the alcohol nonpreferring NP rat. A similar relationship was obtained in studies with the N/NIH rats [20] or other inbred strains of mice [31].

This broad-based support for the role of 5-HT in modulating alcohol drinking has led a number of investigators to evaluate the ability of the 5-HT uptake inhibitors to curtail intake in human heavy drinkers. Amit *et al.* [2] using zimelidine found a significant reduction in alcohol intake among their sample of heavy drinkers, and more recently Naranjo *et al.* [23] using citalopram, a specific 5-HT uptake inhibitor, also found a small but significant decrease in intake as measured by the number of drinks consumed and the number of abstinent days. Taken together, the results of both the rat and human work suggest that serotonin plays a role in the control of alcohol consumption. However, the mechanism by which enhanced serotonergic activity translates into a reduction in alcohol intake is not known.

The present experiment tests the hypothesis that enhanced serotonergic activity may reduce alcohol intake through the renin-angiotensin (R-A) system. This hypothesis is based on the synthesis of two lines of research. The first line refers to the literature showing that 5-HT can enhance activity in the R-A system by releasing renin. For example, Meyer *et al.* [17] showed that the injection of 5-HT produced a rapid five-fold increase in plasma renin activity (PRA) which could be blocked by the administration of the 5-HT antagonist methysergide. Ganong *et al.* [3] showed that the 5-HT precursor 5-HTP could also stimulate PRA and that this increase could be blocked by methergoline, a specific 5-HT receptor antagonist. Finally, Modlinger *et al.* [18] have shown that the oral administration of the 5-HT precursor, tryptophan, to normal human volunteers resulted in a large and significant rise in PRA, thereby demonstrating that a serotonergically mediated rise in PRA also occurs in man.

The second line refers to the research showing that elevated activity in the R-A system reduces voluntary alcohol intake. For example, when a low salt diet is combined with a diuretic [10,11], when angiotensin II is injected subcutaneously [5], when renin-dependent (Two-Kidney, One-Clip) hypertensive rats are tested [6,7], or when the beta-adrenergic agonist, isoproterenol, is given (Sneddon, Solway, Perlanski, Stewart and Grupp, unpublished observations), rats consume significantly less alcohol than placebo-treated counterparts. Most of these manipulations are known to enhance PRA and all lead to an increase in the activity of the R-A system.

Therefore, since enhanced serotonergic activity can stimulate acitivity in the R-A system and since elevated activity in the R-A system reduces voluntary alcohol intake, it is possible that drugs such as the 5-HT uptake inhibitor, fluoxetine, which enhance serotonergic activity, might reduce alcohol intake, at least in part, through the R-A system. The following experiment tests this hypothesis by examining the effect of the angiotensin converting enzyme inhibitor, enalapril, on the fluoxetine-induced reduction in alcohol intake. If fluoxetine indeed exerts its effect on alcohol intake by elevating R-A activity, then enalapril, which reduces the conversion of angiotensin I (AI) to the bioactive angiotensin II (AII) would be expected to attenuate the fluoxetine-induced decrease in alcohol intake.

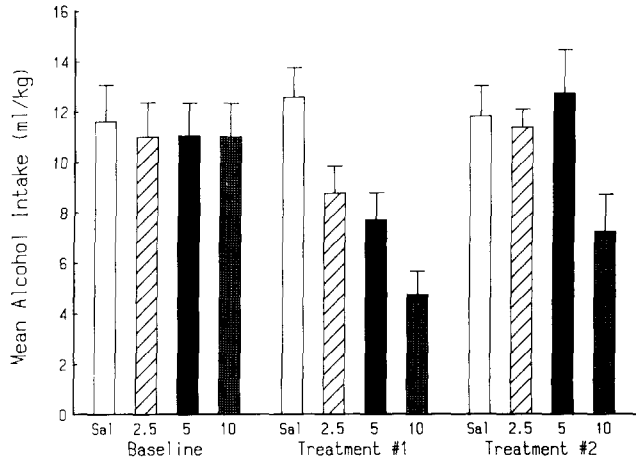

FIG. 1. Mean 6% (w/v) alcohol intake for the three fluoxetine groups and the saline group during the three phases of the experiment: Baseline—no drugs administered, animals offered alcohol and water using the limited access procedure. Treatment 1—the three doses of fluoxetine (2.5, 5 and 10 mg/kg) and saline were administered 1 hr prior to the limited access period. Treatment 2—the 1 mg/kg dose of enalapril was administered 40 min prior to the administration of fluoxetine or saline. Bars represent ± standard error of the mean.

METHOD

Subjects

The subjects were 35 naive male Wistar rats weighing 330–400 g. They were individually housed in cages equipped with a water bottle and food hopper and kept on a reverse 12-hr/12-hr light/dark cycle with lights off at 7:00 a.m. The animals were always run during the dark cycle.

Procedure

A limited access drinking procedure was used [13,16]. Each day during the dark cycle the animals were removed from their home cages, weighed, and then placed for 40 min in individual "drinking cages" which had two graduated drinking tubes at the front, one containing a solution of alcohol and water, the other containing water. No food was available in the drinking cage. After the 40 min had elapsed, the amounts of water and alcohol consumed were recorded and the animals were returned to their home cages where water and Purina rat chow were always available. The positions of the fluids in the drinking cages were alternated daily to control for position preferences. For two weeks a 3% (w/v) alcohol solution was offered followed by a 6% (w/v) solution for a further 34 days. The data to be reported are based on the experimental manipulations that were carried out during the 34 day period when the 6% alcohol solution was available. The experiment consisted of three phases: a Baseline phase followed by two Treatment phases—Treatment 1 and Treatment 2.

Baseline. This phase lasted 8 days at the end of which the animals were divided into 4 groups matched for alcohol intake and designated to receive either the saline vehicle

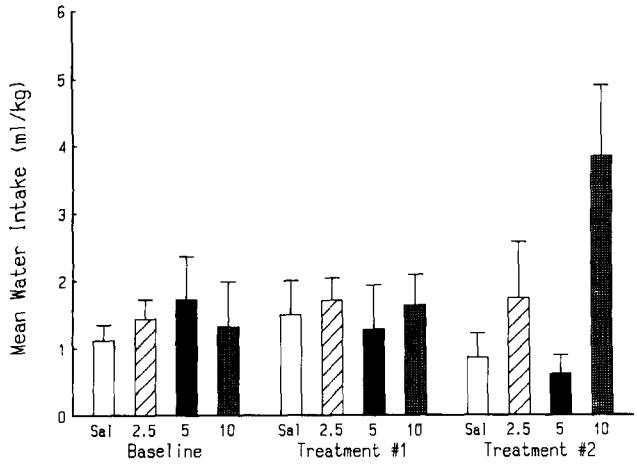

FIG. 2. Mean water intake for the three fluoxetine groups and the saline group during the three phases of the experiment. Baseline—no drugs administered, animals offered alcohol and water using the limited access procedure. Treatment 1—the three doses of fluoxetine (as in Fig. 1) and saline were administered 1 hr prior to the limited access period. Treatment 2—the 1 mg/kg dose of enalapril was administered 40 min prior to the administration of fluoxetine or saline. Bars represent ± standard error of the mean.

(n=8), 2.5 mg/kg fluoxetine (n=9), 5 mg/kg fluoxetine (n=9), or 10 mg/kg fluoxetine (n=9) in the following two phases.

Treatment 1. This phase lasted 13 days during which each group received its respective daily dose of fluoxetine or saline by the intraperitoneal (IP) route 1 hr prior to the 40 min access period to 6% alcohol and water. No pretreatment was given.

Treatment 2. This phase also lasted 13 days during which each group continued to receive its respective daily dose of either fluoxetine or saline 1 hr prior to the alcohol access period. In addition, however, all four groups were pretreated IP with 1 mg/kg of the angiotensin converting enzyme inhibitor, enalapril, 40 min prior to the administration of fluoxetine or saline (i.e., 100 min prior to the availability of alcohol).

RESULTS

Alcohol Intake

Figure 1 shows the mean alcohol intake for the three fluoxetine groups and the saline control group during the Baseline and two Treatment phases. The drinking for each animal was averaged across the 8 days of the Baseline phase and across the 13 days of each of the two Treatment phases. A two-way analysis of variance of these means with Drug as the between-subjects factor and Treatment phase as the within-subjects factor yielded significant effects of Drug, $F(3,31)=2.95$, $p<0.05$, Phase, $F(2,62)=11.57$, $p<0.001$, and the interaction of Drug with Phase, $F(6,62)=4.48$, $p<0.001$. One-way analyses of variance comparing the three phases for each of the four groups showed that alcohol intake was significantly altered in the 2.5 mg/kg, $F(2,16)=4.5$, $p<0.03$, 5 mg/kg, $F(2,16)=12.5$, $p<0.001$, and 10 mg/kg, $F(2,16)=10.59$, $p<0.001$, fluoxetine groups. Alcohol intake in the saline group did not change across the three phases of the experiment, $F(2,14)=0.23$, n.s.

Post hoc tests for simple effects examined the effect of fluoxetine on alcohol intake (comparing Baseline with Treatment 1) and the effect of enalapril pretreatment on fluoxetine-induced changes in alcohol intake (comparing Treatment 1 to Treatment 2). Compared to Baseline, all three groups receiving the different doses of fluoxetine significantly reduced their alcohol intake during Treatment 1 [2.5 mg/kg: $t(8)=2.84$, $p<0.05$; 5.0 mg/kg: $t(8)=5.05$, $p<0.01$; 10.0 mg/kg, $t(8)=7.02$, $p<0.01$]. This reduction appeared to be dose-related. Pretreatment with 1 mg/kg of enalapril during Treatment 2 reversed the suppressive effect of fluoxetine on alcohol intake. The groups receiving 2.5 and 5.0 mg/kg fluoxetine drank significantly greater amounts of alcohol in Treatment 2 compared to their intake during Treatment 1 [2.5 mg/kg: $t(8)=3.02$, $p<0.05$; 5.0 mg/kg: $t(8)=4.29$, $p<0.01$] and these levels of intake were virtually equivalent to those of the Baseline. The 10 mg/kg fluoxetine group pretreated with enalapril also showed a clear tendency to return toward baseline levels of intake, but the increase was not great enough to be significant, $t(8)=1.76$, n.s. It is possible that a higher dose of enalapril would reverse the effects of the highest dose of fluoxetine.

TABLE 1

EFFECT OF FLUOXETINE AND FLUOXETINE + ENALAPRIL ON BODY WEIGHT

	Body Weight (g)		
Group	Baseline	Treatment 1	Treatment 2
Saline	372.4 ± 3.8	404.7 ± 4.9	435.2 ± 6.4
2.5 mg/kg	380.3 ± 7.1	409.7 ± 9.0	436.9 ± 9.6
5.0 mg/kg	379.4 ± 4.3	402.3 ± 5.4	422.0 ± 7.8
10.0 mg/kg	374.5 ± 8.5	382.6 ± 9.7	378.6 ± 11.5

Values are mean ± SEM in grams. The saline control group and the 2.5 and 5 mg/kg fluoxetine groups all gained weight and had statistically similar weights across the three phases of the experiment. The 10 mg/kg fluoxetine group failed to gain weight (see text for details).

Water Intake

Figure 2 shows the mean water intake for the three fluoxetine groups and the saline group during the Baseline and two Treatment phases. As was the case for alcohol, water drinking for each animal was averaged across the 8 days of the Baseline phase and across the 13 days of each of the two Treatment phases. A two-way analysis of variance of these means with Drug as the between-subjects factor and Treatment phase as the within-subjects factor yielded a nonsignificant effect of Drug, $F(3,31)=1.6$, n.s., and Phase, $F(2,62)=1.19$, n.s., and a significant Drug × Phase interaction, $F(6,62)=6.4$, $p<0.02$. One-way analyses of variance for each of the four groups showed that only the 10 mg/kg group increased its water intake significantly, $F(2,16)=17.05$, $p<0.05$, and this occurred in Treatment 2 during the concurrent administration of fluoxetine and enalapril. However, this increase, while significant, was rather small and clearly not a major effect of the manipulation.

Animal Weight

Table 1 shows the mean animal weights for the three

fluoxetine groups and the saline control group during the Baseline and two Treatment phases. The weight of each animal was averaged across the 8 days of the Baseline phase and across the 13 days of each of the two Treatment phases. A two-way analysis of variance of these means with Drug as the between-subjects factor and Treatment phase as the within-subjects factor yielded significant effects of Drug, $F(3,31)=3.18$, $p<0.05$, Phase, $F(2,62)=250.78$, $p<0.001$, and the interaction of Drug with Phase, $F(6,62)=25.48$, $p<0.001$. One-way analyses of variance for each of the four groups showed that weight was significantly increased in the saline, $F(2,14)=162.08$, $p<0.001$, 2.5 mg/kg, $F(2,16)=180.83$, $p<0.001$, and 5 mg/kg, $F(2,16)=56.99$, $p<0.001$, fluoxetine groups. Weight of the 10 mg/kg fluoxetine group did not increase across the three phases of the experiment, $F(2,16)=1.84$, n.s. Post hoc tests indicated that, compared to Baseline, the saline, 2.5 and 5 mg/kg groups showed significant increases in body weight during Treatment 1 [saline—$t(7)=10.23$, $p<0.01$; 2.5 mg/kg—$t(8)=9.95$, $p<0.01$; 5.0 mg/kg—$t(8)=8.66$, $p<0.01$]. Pretreatment with 1 mg/kg of enalapril during Treatment 2 did not alter the effects of fluoxetine on weight gain as the groups receiving saline, 2.5 and 5 mg/kg fluoxetine continued to show significant increases in weight during this phase [saline—$t(7)=12.87$, $p<0.01$; 2.5 mg/kg—$t(8)=15.03$, $p<0.01$; 5.0 mg/kg —$t(8)=5.73$, $p<0.01$].

DISCUSSION

Although there is considerable clinical and experimental interest in the role of serotonin in the control of alcohol intake, and solid evidence demonstrating that enhanced serotonergic activity can attenuate alcohol intake (e.g., [2, 21, 23, 25, 26, 32]), the mechanism of this effect has not been delineated. The present experiment attempted to address this issue by examining the hypothesis that the R-A system plays a role in mediating the effect of the 5-HT uptake inhibitor, fluoxetine, on voluntary alcohol intake. This hypothesis is based on experimental findings showing that an increase in serotonergic activity stimulates the R-A system (e.g., [3, 14, 17, 18]), and that when the R-A system is stimulated, alcohol intake is attenuated [4–7, 10, 11, 27]. The present experiment tested this hypothesis by administering the angiotensin converting enzyme inhibitor, enalapril, to animals whose alcohol intake was reduced by the 5-HT uptake inhibitor, fluoxetine. If fluoxetine's suppressive effect on alcohol intake is exerted, in part, by stimulating R-A activity, then enalapril, which reduces R-A activity by preventing the conversion of AI to AII, would be expected to counteract this effect of fluoxetine.

The results support the hypothesis that the R-A system plays a role in mediating the effect of fluoxetine on alcohol intake. In particular, the present experiment is the first to show that fluoxetine can reduce alcohol consumption in a dose dependent manner using a procedure which fosters alcohol drinking in a bout [16]. Virtually all of the previous studies have used the continuous access two-bottle 24-hr choice procedure to assess the ability of fluoxetine to reduce alcohol intake. The present findings of a reduction of alcohol intake in Treatment 1 extend this property of fluoxetine to a procedure whose validity in terms of inducing sufficient alcohol intake to achieve a pharmacologically relevant central nervous system (CNS) effect is confirmed by the fact that detectable blood alcohol levels have been obtained using this procedure [13]. The results from Treatment 2 in which the angiotensin converting enzyme inhibitor, enalapril, was administered 40 min prior to fluoxetine clearly indicate that enalapril can reverse the reduction in alcohol drinking produced by the 2.5 and 5.0 mg/kg doses of fluoxetine, restoring the intake in each of these groups to baseline levels, and also produce a suggestive tendency to restore alcohol intake in the group receiving the highest (10 mg/kg) dose of fluoxetine. Although the angiotensin converting enzyme inhibitors can reduce alcohol intake under certain conditions [27], in the present experiment the 1 mg/kg dose of enalapril was without any effect of its own on alcohol intake. Taken together these findings support the hypothesis that the reduction in alcohol intake brought about by agents such as fluoxetine which enhance serotonergic activity might, in part, be mediated through their ability to stimulate activity in the R-A system.

Chronic fluoxetine administration produced a decrease in alcohol intake regardless of whether there was (i.e., the 10 mg/kg group) or was not (i.e., the saline, 2.5 and 5 mg/kg groups) a concomitant effect on weight gain. Furthermore, enalapril reversed the effect of fluoxetine on alcohol intake without altering any of its effects on weight gain. These findings provide a preliminary indication that the processes involved in the fluoxetine-induced reduction in alcohol intake and those responsible for its anorexigenic actions might not completely overlap.

A number of investigators have attempted to determine whether different types of the 5-HT receptor selectively mediate the effect of the 5-HT uptake inhibitors on alcohol intake. Murphy *et al.* [21] found that administration of the 5-HT_2 receptor antagonists LY53857 or methysergide failed to block the attenuating effects of fluvoxamine on alcohol consumption. On the other hand, McBride *et al.* [15] have reported that the administration of the 5-HT_{1b} receptor agonist, TFMPP, reduced alcohol intake in the alcohol preferring P line of rat and Wong *et al.* [30], comparing the P and NP lines of rats, have reported significant differences in 5-HT_1 binding but not 5-HT_2 binding. These finding suggest that the 5-HT_1 receptor may mediate the attenuating effects on alcohol consumption of agents which raise serotonergic activity. The recent report that both the selective 5-HT_{1a} agonist, ipsapirone, and the nonselective 5-HT_2 agonist, MK-212, stimulate renin release [14], add indirect evidence to support the contention that agents which reduce alcohol intake by increasing serotonergic activity may be doing so through the R-A system.

Traditionally, the R-A system has been implicated in the control of fluid and electrolyte balance. However, in recent years, evidence has accumulated which implicates the R-A system in the control of alcohol intake as well ([4,29] for review). The relationship between alcohol intake and R-A activity appears to be an inverse one, such that manipulations which increase R-A activity reduce alcohol intake, while manipulations which decrease R-A activity increase alcohol intake. To date the experimental models in which decreased R-A activity has resulted in an increase in alcohol intake include: area postrema lesions [28], high salt diet [8] and Dahl salt-sensitive hypertensive rats [9]. Similarly, the manipulations which can increase R-A activity and have resulted in a reduction in alcohol consumption include the use of low salt diet/diuretic [10,11], the adrenergic agonist isoproterenol (Sneddon, Solway, Perlanski, Stewart and Grupp, unpublished observations), the peptide AII [5], Two-Kidney, One-Clip Hypertensive rats [6,7], chronic mineralocorticoid treatment [8], and under certain condi-

tions the ACE inhibitors [27]. The present experiment now adds a 5-HT uptake inhibitor to the growing list of seemingly diverse agents or manipulations which appear to exert their individual effects on alcohol intake through the R-A system. The findings support the notion [4] that the R-A system may be a common path through which alcohol consumption is normally regulated.

ACKNOWLEDGEMENTS

The authors wish to thank Mrs. V. Cabral for preparing the manuscript, Dr. S. Bandak (Eli Lilly Canada Inc.) for supplying the Fluoxetine, and Dr. R. L. Hudgin (Merck Frosst Canada Inc.) for supplying the Enalapril. Thanks are due to Dr. H. Kalant for his critical reading of the manuscript. The research was supported by the Addiction Research Foundation of Ontario.

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