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BRIEF COMMUNICATION

The Beta Adrenergic Agonist Isoproterenol Suppresses Voluntary Alcohol Intake in Rats

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GRUPP, L. A., B. SNEDDON, E. SOLWAY, E. PERLANSKI AND R. B. STEWART. *The beta adrenergic agonist isoproterenol suppresses voluntary alcohol intake in rats*. PHARMACOL BIOCHEM BEHAV 33(2) 493–495, 1989.—The effects of isoproterenol on alcohol consumption were examined to investigate whether beta adrenergic stimulation can reduce voluntary alcohol intake. Two and one-half, 5 and 10 μg/kg isoproterenol administered subcutaneously (SC) just prior to alcohol availability produced a dose-dependent reduction in alcohol intake and elevation in water intake. Blood alcohol levels measured subsequent to a SC injection of 5 μg/kg isoproterenol or vehicle followed by an intraperitoneal injection of 2.5 g/kg alcohol showed that the adrenergic agonist did not alter the distribution or metabolism of alcohol. Since beta adrenergic agonists such as isoproterenol are potent releasers of renin, these findings support previous work showing that different kinds of interventions which share the common property of elevating activity in the renin-angiotensin system (beta adrenergic stimulation in the present case) consistently result in the reduction of voluntary alcohol intake.

Alcohol intake Renin-angiotensin system Beta adrenergic agonist Isoproterenol

STIMULATION of activity in the renin-angiotensin (r-a) system by manipulations which produce thirst [e.g., angiotensin II injections (4,7); the surgical production of hypertension by unilateral renal artery stenosis (5,6); diuretic injections in combination with a low salt diet (9,10); and injections of the angiotensin converting enzyme inhibitors, captopril and enalapril (20)], or by manipulations which are not themselves dipsogenic [e.g., administration of the serotonin uptake inhibitor, fluoxetine (8); genetically selected nonpreferring lines of rats (3)] all suppress alcohol intake. One proposed mechanism for this effect on alcohol intake suggests that an increase in r-a activity of sufficient magnitude may trigger a "stop" or "satiety" signal governing alcohol intake (2). Since alcohol itself is known to stimulate r-a activity [e.g., (14, 17, 18)], this "satiety" signal would operate in the context of a negative feedback system.

Isoproterenol is a potent dipsogen that produces thirst by stimulating both peripheral (1, 11, 13) and central (12,19) r-a activity. The following experiment assesses the ability of this beta adrenergic agonist to reduce voluntary alcohol intake.

METHOD

Subjects

The subjects were 24 naive male Wistar rats weighing 300–350 g at the beginning of the experiment. 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 (15,16). Each day during the dark cycle the animals were removed from their home cages, weighed, and then placed for 1 hr in individual

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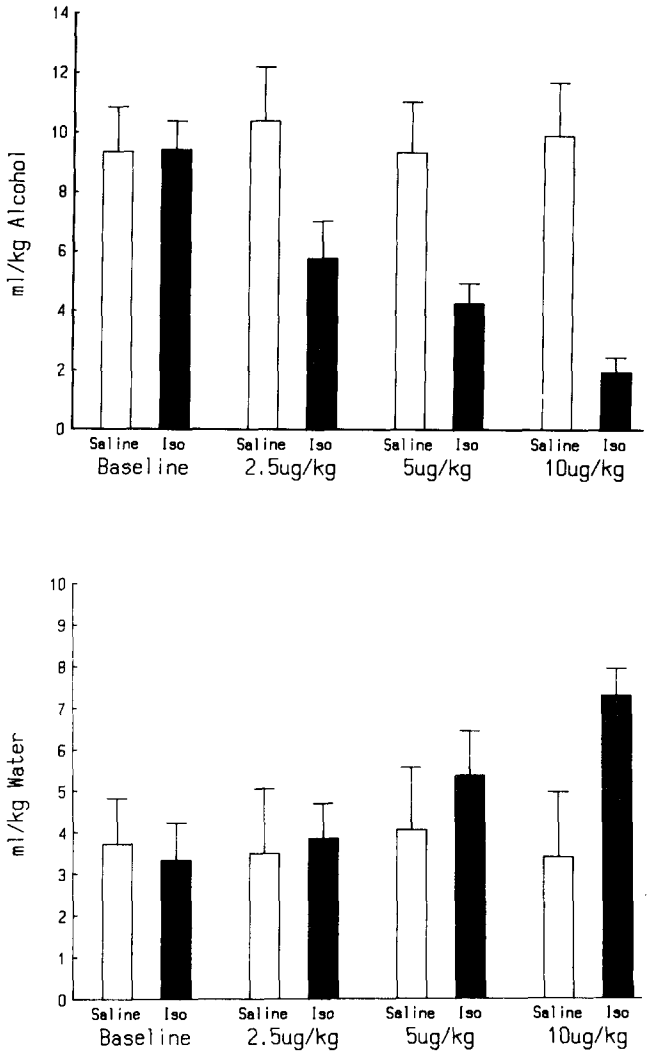

FIG. 1. Mean 6% (w/v) alcohol intake (top) and water intake (bottom) for the baseline phase when no injections were given and for the three phases during which different doses of isoproterenol, 2.5 μg/kg, 5 μg/kg and 10 μg/kg, were administered subcutaneously immediately prior to the availability of alcohol. Bars represent ± standard error of the mean.

"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 1 hr had elapsed, the amounts of water and alcohol consumed were recorded and the animals were returned to their home cages. The positions of the two 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) alcohol solution for a further 44 days. The data to be reported are based on the experimental manipulations that were carried out during this 44-day period. The first 14 days were a baseline phase at the end of which the animals were divided into 2 groups matched for alcohol intake and designated to receive either the saline vehicle ($n=12$), or isoproterenol in three sequential dose phases of 10 days each. The order of isoproterenol dosing was 5 μg/kg followed by 10 μg/kg and finally 2.5 μg/kg. Both vehicle and drug were administered subcutaneously just before placing the animals into the drinking cages.

At the conclusion of the experiment the rats were first injected with either 5 μg/kg isoproterenol or saline followed by an intraperitoneal injection of 2.5 g/kg alcohol (12.5% w/v). Blood samples were taken from the cut tip of the tail at 20-min intervals during the first hour and at hourly intervals thereafter for the next 5 hr. These samples were analyzed for alcohol levels and used to examine the effect of isoproterenol on the disposition and metabolism of alcohol.

RESULTS

Figure 1 shows the mean alcohol (top) and water (bottom) intake for the saline control group and the isoproterenol group at baseline and after administration of the three doses tested. Intake for each animal was averaged across the 14 baseline days and the 10 days of each of the three drug phases. A two-way analysis of variance of alcohol intake yielded a significant effect of Group, $F(1,22)=5.87$, $p=0.02$, indicating that isoproterenol produced a significant reduction in alcohol intake compared to the saline vehicle group. A significant Phase effect, $F(3,66)=17.28$, $p<0.001$, reflected the tendency for increasing doses of isoproterenol to produce greater reductions in alcohol intake and a significant interaction of Drug with Phase, $F(3,66)=21.0$, $p<0.001$, showed that the reduction in alcohol intake was specific to isoproterenol and did not follow the injection of the saline vehicle. A two-way analysis of variance of the water intake revealed a nonsignificant effect of Group, $F(1,22)=0.7$, n.s., but a significant Phase effect, $F(3,66)=5.8$, $p=0.001$, reflecting the tendency for isoproterenol to enhance water intake, and a significant Group × Phase interaction, $F(3,66)=6.8$, $p<0.001$, suggesting that water intake was affected to a greater extent at the higher doses of the drug.

The blood alcohol/time curves derived from samples obtained from the isoproterenol and saline injected groups were similar. The last four points on the descending portion of the curves were used to calculate the slopes which represent the rate of alcohol metabolism. The isoproterenol group did not differ significantly from the control group indicating that isoproterenol did not alter the rate of alcohol metabolism, $t(19)=0.98$, n.s. Extension of the linear portion of the curves back to the ordinate yields an estimate of the concentration at time zero from which the volume of distribution was calculated. There were no significant group differences in volume of distribution, $t(19)=0.02$, n.s. The blood alcohol level of the isoproterenol group was significantly elevated, $t(19)=1.86$, $p=0.04$, only at the first sampling time, i.e., 20 min postalcohol injection.

DISCUSSION

A considerable amount of evidence suggests that the beta adrenergic agonist, isoproterenol, stimulates thirst and water intake by releasing renin. For example, it has been shown (19) that angiotensin converting enzyme inhibitors administered both centrally and peripherally inhibited isoproterenol-induced thirst and that nephrectomy could virtually eliminate isoproterenol-induced thirst (11). The results of the present study demonstrate that the isoproterenol not only produces a dose-dependent increase in water intake, but also a dose-dependent decrease in alcohol intake. Prior to isoproterenol administration, average alcohol intake was approximately 0.5 g/kg [approximately 20–40 mg/decalitre, (21)] over a 1-hr period. This dose which exceeds that rat's metabolic capacity of 0.3–0.35 g/kg/hr would therefore produce a pharmacologically relevant effect. Pretreatment with the highest dose of isoproterenol (10 μg/kg) reduced this intake four-fold to approx. 0.12 g/kg. The effect of isoproterenol could therefore be characterized as one which decreased intake and consequently minimized the pharmacological impact of the consumed alcohol. Taken together these findings add isoproterenol, a beta adrenergic ago-

nist, to the list of quite diverse manipulations which share the common property of increasing activity in the r-a system and producing a decrease in alcohol intake [see (22) for a review].

Isoproterenol-induced thirst appears to be mediated through increased central (12,19) as well as peripheral r-a activity (1, 11, 13) and the dose-dependent increase in water intake observed in the present study clearly indicates that the r-a system was indeed stimulated. While the present results cannot comment on the relative contributions of central and peripheral r-a systems in mediating the effect of isoproterenol on alcohol intake, unpublished observations in our laboratory in which SC injections of the angiotensin antagonist Sar-1 Ala-8 angiotensin II (saralasin) failed to antagonize the effect of isoproterenol on alcohol intake, suggest an important role for the central r-a system in mediating the isoproterenol-induced reduction in alcohol consumption .

It is unlikely that isoproterenol altered alcohol intake through a change in the pharmacokinetics of alcohol. Blood alcohol levels measured after the administration of a 5 μg/kg dose of isoproterenol did not alter the volume of distribution or rate of metabolism of alcohol. There was a significantly greater blood alcohol level in the isoproterenol-treated group initially (i.e., 20 min postinjection), but it is not clear whether this in itself would necessarily lead to a reduction in alcohol intake (21).

In summary, the present findings demonstrate that isoproterenol can markedly reduce voluntary alcohol consumption. Although other actions of isoproterenol could theoretically be involved, the most parsimonious explanation is that the increased renin secretion caused by this beta adrenergic agonist increases the synthesis of angiotenin II, a peptide known to reduce alcohol drinking (4,7). Such an explanation would be congruent with other work linking a reduction in alcohol intake to increased r-a activity (22).

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