Pharmacology Biochemistry & Behavior, Vol. 36, pp. 527–530. © Pergamon Press plc, 1990. Printed in the U.S.A. 0091-3057/90 $3.00 + .00

Prostaglandin E_2 Reduces Voluntary Ethanol Consumption in the Rat

A. D. ROSS, E. PERLANSKI AND LARRY A. GRUPP[1]

Department of Pharmacology, University of Toronto
Toronto, Ontario, Canada M5S 1A8
and Neurobiology Department, Addiction Research Foundation of Ontario
33 Russell St., Toronto, Ontario, Canada M5S 2S1

Received 26 September 1989

ROSS, A. D., E. PERLANSKI AND L. A. GRUPP. *Prostaglandin E_2 reduces voluntary ethanol consumption in the rat.* PHARMACOL BIOCHEM BEHAV **36**(3) 527–530, 1990.—A number of prior studies have suggested that the prostaglandins may mediate some of the physiological effects of ethanol, and while it has been suggested that PGE_2 may be involved in regulating ethanol consumption, evidence for this has been inconclusive. In the present study, rats injected with PGE_2 at doses of 50, 100 and 200 μg/kg consumed significantly less alcohol than vehicle-treated controls. Doses of PGE_2 which were highly effective in reducing ethanol intake produced only marginal changes in the consumption of water and glucose solution. These data, together with previous studies demonstrating a link between ethanol and the prostaglandins, suggest that PGE_2 may be involved in the control of ethanol consumption.

Ethanol drinking PGE_2 Prostaglandins Renin-angiotensin system

PRIOR studies have implicated the prostaglandins (PG's) in the mediation of ethanol (ETOH) drinking behavior (3, 5, 12, 15, 20). Prostaglandin release is altered following ETOH intake (13,19) and it has been suggested that the PG's may mediate some of the physiological consequences of ETOH consumption including headaches, nausea, flushing, fever and other symptoms associated with ETOH withdrawal (7,14). Injections of PGE_2 were shown to reduce the intake of ETOH in mice (20) and treatment with PG precursor fatty acids was found to be effective in reducing ETOH intake in the hamster (5).

Research from our lab has demonstrated that the renin-angiotensin system (RAS) may also play a role in the control of ETOH drinking behavior [see (18) for review]. For example, injections of different forms of the peptide angiotensin II (ANG II), i.e., [Val^5]-ANG II (6), [Ile^5]-ANG II or [Des-Asp^1]-ANG II (ANG III) (17), have all been shown to significantly reduce ETOH consumption in rats. ANG II is known to activate the release of PG precursor fatty acids, resulting in enhanced PG biosynthesis (10,16) and to stimulate PG release from the kidney (10) and from isolated renomedullary cells (4). Since the RAS is capable of reducing ETOH intake and enhancing PG release, the possibility exists that the PG's may mediate the ability of the RAS to alter ETOH consumption. The present study explored this possibility by investigating the effect of peripheral injections of PGE_2 on voluntary ETOH consumption.

METHOD

Subjects

Thirty-five naive male Wistar rats (Charles River, Montreal) weighing between 225 to 250 g were housed individually and maintained on a reverse 12-hour light/dark cycle with lights off at 7:00 a.m. Water was always available and the rats had continuous access to food except during the daily one-hour test sessions.

Drug Preparation

ETOH solutions were prepared in tap water at concentrations of 3 and 6% (w/v). PGE_2 was dissolved in a vehicle of 95% ethanol (0.1 l/g) and 0.02% sodium carbonate (1.28 l/g) and diluted to the desired concentration in 0.9% saline at a pH of 6.5–7.0. PGE_2 solutions were prepared fresh daily and injected subcutaneously (SC) in a volume of 1 ml/kg body weight.

Training Procedure

Rats were trained to drink ETOH using a modified version of the Limited Access procedure (9,11). Each day during the dark cycle, the rats were removed from their home cages, weighed, and transferred for one hour to individual drinking cages equipped with two tubes, one containing ETOH, the other containing tap water.

[1]Requests for reprints should be addressed to Dr. Larry A. Grupp, Department of Pharmacology, University of Toronto, Toronto, Ontario, Canada M5S 1A8.

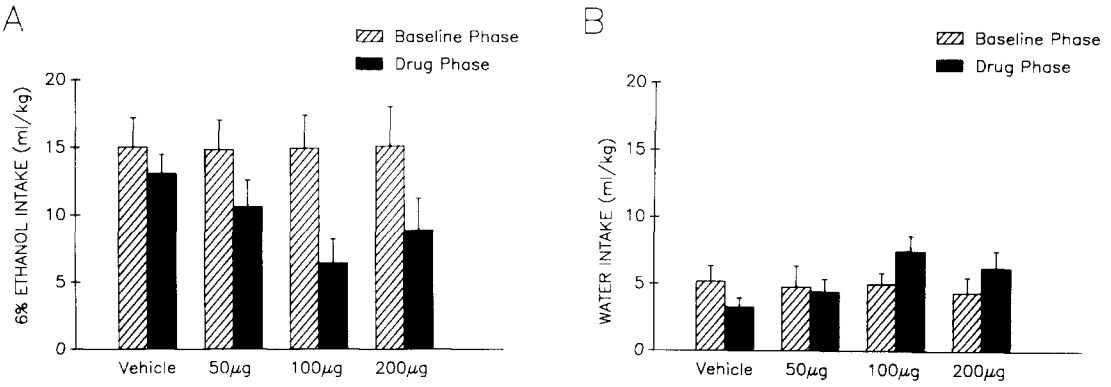

FIG. 1. Mean daily intake of 6% ethanol (A) and water (B) over one-hour drinking sessions during the Baseline Phase and during treatment with PGE_2 or vehicle (Drug Phase). Bars represent standard error of the mean.

The positions of the tubes were alternated daily to control for the development of a position preference. Drinking sessions lasted for one hour during which time food was not available.

Baseline Phase

For the first 10 days, rats were given one hour daily access to 3% (w/v) ETOH and tap water, after which 6% (w/v) ETOH was made available for 14 additional days. Baseline ETOH consumption was calculated as the mean daily consumption of ETOH during the 6% phase.

PGE_2 Treatment Phase

Rats were assigned to one of four groups, matched for baseline 6% ETOH intake. During this phase each group received daily SC injections of either vehicle (n = 8) or PGE_2 at doses of 50, 100 or 200 μg/kg (n = 9 per group) and were immediately transferred to the drinking cages. Consumption of ETOH and water was measured during 10 consecutive days of drug testing.

Glucose/Water Choice Phase

Rats that previously received injections of PGE_2 at 100 μg/kg (n = 9) or vehicle (n = 8) continued to receive their respective treatments immediately prior to the one-hour drinking sessions. During this phase a choice between a 14% (w/v) glucose solution and tap water was offered for four additional days of testing.

Statistical Analysis

An analysis of variance (ANOVA) was used to determine group differences in fluid consumption and body weight. Post hoc analyses were carried out using the Duncan's test at a significance level of $p<0.05$. Paired comparisons were made using a two-tailed t-test.

RESULTS

PGE_2 Treatment Phase

Figure 1A shows mean ETOH consumption over the 14-day baseline phase and during the 10 days of treatment with PGE_2 or vehicle. A two-way analysis of variance revealed a significant effect of Phase, $F(1,24) = 38.34$, $p<0.001$, indicating that ETOH intake was reduced following treatment with PGE_2. The effect of Dose, $F(2,24) = 0.20$, n.s., and the interaction of Dose × Phase, $F(2,24) = 1.44$, n.s., were not significant. Post hoc analysis indicated that treatment with PGE_2 significantly reduced ETOH consumption at all doses tested ($p<0.05$), with the 100 μg/kg dose being most effective, reducing ETOH intake by approximately 60%. ETOH intake was unchanged in control rats receiving injections of vehicle, $t(7) = 1.115$, n.s.

Figure 1B shows mean water consumption during the baseline and drug treatment phases. A two-way analysis of variance revealed a significant effect of Phase, $F(1,24) = 4.940$, $p<0.05$, indicating that water intake was increased following PGE_2 treatment. The effect of Dose, $F(2,24) = 0.54$, n.s., and the interaction of Dose × Phase, $F(2,24) = 1.79$, n.s., were not not significant. Post hoc analysis indicated no change in water intake in rats treated with PGE_2 at doses of 50 and 200 μg/kg, while a dose of 100 μg/kg produced a small but significant increase in water intake. Water consumption was unchanged in control rats following injections of vehicle, $t(7) = 2.209$, n.s.

Figure 2 shows the mean consumption of 14% glucose solution and water over 4 days of treatment with PGE_2 or vehicle. PGE_2 treatment produced a small but significant reduction in the intake of glucose solution, as compared to vehicle-treated controls, $t(14) = 1.856$, $p<0.05$, while water intake was not significantly altered, $t(14) = 0.175$, n.s. Thus, while 100 μg/kg of PGE_2 reduced ETOH intake by more than 50%, only a slight reduction in the intake of glucose solution was observed.

All the animals appeared healthy and robust. A one-way ANOVA of mean body weight during the PGE_2 treatment phase

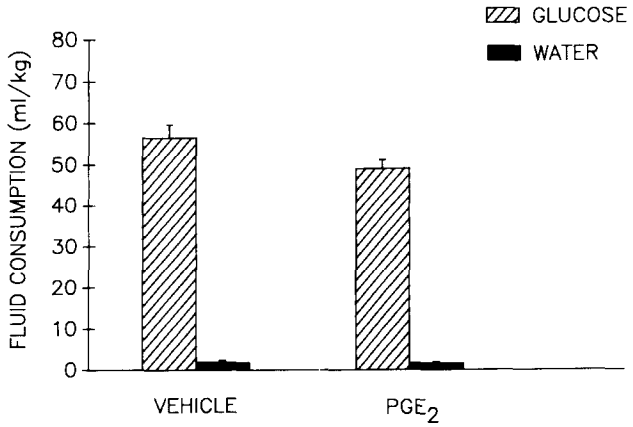

FIG. 2. Mean daily intake of water and 14% glucose solution during 4 days of treatment with 100 μg/kg PGE_2 or vehicle. Bars represent standard error of the mean.

indicated a significant difference between the four groups, $F(3,31)=4.35$, $p<0.05$. Post hoc analysis revealed that only the animals in the 200 μg/kg weighed significantly less (30–40 g) than the control group ($p<0.05$).

DISCUSSION

This experiment has shown that PGE_2 can reduce the voluntary consumption of ETOH in rats. At doses of 50–200 μg/kg, ETOH intake was reduced by up to 57% during the one-hour daily drinking sessions. These findings indicate that PGE_2 may play a role in the control of ETOH drinking behavior.

The present results are in line with previous studies indicating the ability of the PG's to modulate ETOH consumption. For example, Wallis and colleagues showed that SC injections of PGE_2 reduced the preference ratio of ETOH to water in naive-fasted C3H mice (20). While in accordance with our findings, these results are difficult to interpret since a decreased preference ratio can result from either an increase in water intake or a decrease in ETOH intake. Indirect evidence implicating the PG's in the control of ETOH drinking was reported in a study assaying PGF_{2a} levels in serum samples of human alcoholics. This study found no difference in PGF_{2a} levels between alcoholics and nonalcoholics, but did find elevated PGF_{2a} levels in those patients that completed rehabilitation therapy, while depressed PGF_{2a} levels were seen in patients who relapsed and resumed drinking ETOH (12). These results should be interpreted with some caution, however, since the measurement of prostaglandin levels in serum can be problematic (1).

Studies examining the effect of PG inhibitors are not generally supportive of a role for endogenous PG's in controlling ETOH intake. Intraperitoneal injections of indomethacin were initially reported to increase ETOH consumption in C3H/HE mice (3). However, in a follow-up study, the same authors reported that indomethacin had no effect on either naive or preestablished alcohol preference and consumption in either C3H/HE, C57/BL6 or BALB/c mice (2). In another study, daily pretreatment with indomethacin was found to produce a decrease in both ETOH/water preference ratios and in the total volume of ETOH consumed (15). In contrast with the present results, these authors proposed that high PGE levels facilitate rather than reduce ETOH drinking. Although some investigators have reported conflicting results regarding the role of PG's in modulating ETOH intake, the present study indicates that PGE_2 is capable of reducing ETOH consumption.

While all doses of PGE_2 reduced ETOH intake, only the highest dose significantly reduced body weight. This indicates that the animals were generally in good health and that the effect of this agent on ETOH consumption is independent of any untoward effects on the animals' well-being. While PGE_2 treatment greatly reduced ETOH intake, only a slight reduction in the intake of glucose solution was observed and the intake of water was either entirely unaffected or slightly increased. These findings indicate that the ability of PGE_2 to reduce ETOH consumption is, to some degree, a specific effect and is not a consequence of altered taste perception or generalized malaise, since these conditions would also be expected to produce corresponding reductions in the intake of nonalcoholic fluids. Since the consumption of ETOH is known to enhance PGE_2 release and PGE_2 is capable of reducing ETOH intake, it is tempting to speculate that endogenous PGE_2 may participate in the control of ETOH drinking behavior. Although the mechanism by which PGE_2 alters ETOH intake is not yet known, there is considerable evidence indicating that some of the deleterious effects of ETOH may be mediated by the PG's. Chlorpropamide-induced alcohol flush, alcohol intolerance, alcohol-induced sleep and hangover symptoms are effectively alleviated by the prophylactic use of PG synthetase inhibitors (7,14). Some of the physiological effects of PG treatment, which include headaches, nausea, vomiting, fever, flush/pallor, cold sweat, cramps, increased pain sensitivity, irritability, lethargy and seizures (14), closely resemble the syndrome associated with ETOH withdrawal. It is possible that PGE_2 may produce a state of discomfort which is responsible for the reduction of ETOH consumption. These properties of PGE_2 alone do not appear to be sufficient to reduce the intake of nonalcoholic fluids, but in combination with ETOH, an apparent interaction occurs which results in reduced ETOH intake.

At the present time there is no direct evidence indicating that endogenous PG's are involved in the control of ETOH drinking, however, the PG's are physiologically functionally linked to the RAS, which has been shown to play a role in the control of ETOH consumption. Since enhanced RAS activity is known to a) reduce the consumption of ETOH (6,17) and b) enhance the release of PG's (13,19), it is possible that the reduction of ETOH consumption by the RAS may occur as a result of enhanced PG release. An equally tenable hypothesis, considering that PGE_2 can stimulate the release of renin (8), is that the RAS may be responsible for the reduction of ETOH intake following treatment with PGE_2. An additional possibility is that, although a reciprocal modulation occurs between the PG's and the RAS, PGE_2 may modulate ETOH intake independently of the RAS through some of its other biologic effects on neuronal transmitter modulation, carbohydrate regulation or, because of its diuretic and natriuretic properties, altered ETOH pharmacokinetics. The mechanism of the PGE_2 effect on ETOH intake is an area rich in potential for further investigation.

ACKNOWLEDGEMENTS

The authors wish to thank Mr. Hartley Rosenthal and Mr. Roger Sunahara for their technical assistance and Mrs. Val Cabral for the preparation of this manuscript. This research was supported by the Alcoholic Beverage Medical Research Foundation.

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