Ethanol Exhibits α Receptor Blocking-Like Properties in Anesthetized Rats (42821)

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Abstract. **The ability of ethanol to reduce α-adrenergic receptor-mediated pressor responsiveness *in vivo* was investigated in chloralose-anesthetized male Sprague-Dawley rats. Catheters were inserted in the jugular vein and the femoral artery of rats for the injection of drugs and the measurement of blood pressure, respectively. Dose-response curves for phenylephrine and norepinephrine were constructed by plotting the change in mean arterial pressure following a bolus dose of the agent against the dose of the pressor agent used. Following construction of an initial dose-response curve, animals were challenged with either a 1 g/kg dose of ethanol or an equivalent volume of saline (iv) and the dose-response curves were repeated. Using a similar protocol, pressor responsiveness was evaluated in animals pretreated with either yohimbine (1 mg/kg) or prazosin (3.9 μg/kg), a dose sufficient to produce partial blockade of α receptor-mediated pressor responsiveness, and then treated with ethanol. Ethanol produced a partial blockade of α receptors when the animals were challenged with either phenylephrine or norepinephrine. This blockade produced by ethanol was shown to be similar to that produced by the receptor blocking agents used in this study. To rule out any nonspecific effects of ethanol in reducing vascular reactivity, some animals were challenged with angiotensin II both before and after treatment with ethanol, yohimbine, or prazosin and after both drugs were administered together. Ethanol, as well as the α_1- and α_2-adrenergic blocking agents tested failed to have any significant effect on angiotensin II-pressor responsiveness, ruling out any nonspecific effect of ethanol on the vasculature. It is concluded, therefore, that ethanol has α receptor blocking-like activity *in vivo*.** [P.S.E.B.M. 1989, Vol 190]

Many studies have shown a direct correlation between chronic alcohol consumption and the development of hypertension in animals (1–3) and humans (4–7). The mechanism(s) involved in the development of this ethanol-induced hypertension has not yet been elucidated, but ethanol-induced hypertension has focused new attention on the chronic and acute cardiovascular effects of ethanol ingestion. The effects of acute ethanol consumption on blood pressure are not consistent; some investigators report increases (8), others report decreases (9, 10), and others report no change (11, 12).

One effect of acute ethanol consumption is an apparent α-adrenergic receptor blocking activity. Doses of ethanol consistent with peak blood ethanol levels of approximately 140 mg/dl consistently attenuate the pressor responses to α-receptor agonists (3, 9, 10, 13, 14). Eisenhofer *et al.* (10) demonstrated that human subjects who consumed 1 g/kg of ethanol in orange juice exhibited significantly less pressor responsiveness to intravenous methoxamine than their counterparts who consumed an equivolume amount of the juice. Abdel-Rahman and co-workers (3, 9, 13, 14) have shown that the same dose of ethanol in male Sprague-Dawley rats significantly attenuated the pressor responsiveness to intravenous phenylephrine (PE), yet had no effect on the pressor responsiveness to angiotensin II (AII) (9, 13, 14), a pressor response that is nonadrenergically mediated.

In vitro studies also support the possibility of an α-blocking-like effect of ethanol. Edgarian and Altura (15) report that concentrations of 170 and 430 m*M* ethanol cause a significant rightward shift of the epinephrine dose-response curve in isolated rat portal vein strips. This was also demonstrated by Strickland (16) who showed that concentrations of 150 and 300 m*M* ethanol significantly impaired the contractile responses to PE in rat thoracic aorta. Due to the excessively high concentrations of ethanol used in these *in vitro* experiments (690–1978 mg/dl), the physiologic significance of these results must be interpreted with some caution.

Although the α-blocking-like activity of ethanol

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has been repeatedly observed (3, 9, 10, 13–16), there is, to date, no study of which we are aware that characterizes this blockade. The purpose of this study was to pharmacologically characterize the decreased pressor responsiveness to α-adrenergic receptor-mediated vasoconstrictor agents by ethanol. Alpha-adrenergic blocking agents were used either separately or in combination with ethanol. The adrenergic receptor antagonists chosen for this study were prazosin to block α_1-adrenergic receptors and yohimbine to block α_2-adrenergic receptors. Second, since only pharmacologic α-receptor agonists have been used as pressor or vasoconstrictor agents in past experiments, we wished to examine the effects of acute ethanol administration on the physiologic α receptor agonist norepinephrine (NE). Finally, to rule out a nonspecific action of ethanol on vascular reactivity, angiotensin II (AII) was used as a nonadrenergic vasopressor agent.

Materials and Methods

Male Sprague-Dawley rats weighing between 250 and 300 g were used throughout this study. All animals were anesthetized with α-chloralose (100 mg/kg ip) and supplemented intravenously as needed. A jugular vein and a femoral artery were cannulated with polyethylene tubing (PE50) to facilitate injection of drugs and measurement of blood pressure, respectively. A Statham Model P23DC pressure transducer was used to measure blood pressure which was recorded on a Grass Instruments Model 7 polygraph. Phasic blood pressure was displayed on one channel and electronically damped mean arterial pressure was displayed on another. In addition, heart rate was calculated from the blood pressure pulse using a Grass tachograph and was displayed on a third channel. Body temperature was kept at 37°C using an external warming device and a temperature controller (Thermistemp; Model 74, YSI, Yellow Springs, Ohio). Following the completion of surgery, each animal was allowed approximately 30 min to stabilize.

Dose and Administration of Ethanol. Ethanol was administered intravenously in the amount of 1 g/kg as 0.6 ml of a 16.6% (v/v) solution, given slowly over a 3-min period. Ethanol was given following construction of either the first or the second dose-response curve, depending on the experiment. More detail on when ethanol was administered is included in the protocol for each individual experiment. This dose of ethanol was chosen because it produces blood ethanol levels consistent with social drinking (100–125 mg/dl) that remain elevated for the duration of the experiment. Whenever ethanol was given to animals, they were allowed approximately 5 min to equilibrate before any other drugs were administered. Blood ethanol levels were measured according to the method of Bonnichsen (17).

Construction of Dose-Response Curves. To construct the dose-response curves, bolus doses of either PE (0.5, 1, 2, 4, 8, 16, and 32 μg/kg), NE (0.0625, 0.125, 0.250, 0.50, 1, 2, and 4 μg/kg), or AII (2.5, 5, 10, 20, 40, 80, and 160 ng/kg) were rapidly injected into the venous cannula in a volume of 0.1 ml/100 g body weight and flushed with 0.1 ml of saline. Peak responses occurred within 1–2 min and were recorded for later analysis. Animals were allowed at least 5 min to recover between successive injections. The order of the doses administered to some of the animals (i.e., lowest dose to highest dose) was randomized to prevent any systematic error due to increasing dosages. Peak changes in blood pressure were plotted against the dose of the pressor agent used to construct the dose-response curves.

Determination of the Dose of Blocking Agents. A preliminary dose-response study was performed to determine a dose of prazosin which would produce a partial blockade (20–30%) of α_1-adrenergic receptors (Fig. 3). This dose of prazosin was found to be 3.9 μg/kg and was used in all subsequent studies. Representative dose-response curves for PE following higher doses of prazosin are shown in Figure 3. The dose of the α_2-adrenergic receptor antagonist yohimbine used was 1 mg/kg, a dose that has been shown to produce a substantial rightward shift of the clonidine dose-pressor response curve (18–20).

Protocol and Experimental Groups. In order to analyze the apparent α-blocking-like activity of ethanol, this study was divided into six separate experiments. In separate experiments the ability of ethanol to block the pressor responsiveness to PE ($n = 6$) and NE ($n = 10$) was elucidated by constructing dose-response curves before and after the administration of 1 g/kg of ethanol or an equivalent volume of saline.

The effect of ethanol (1 g/kg) on pressor responsiveness to PE in rats pretreated with yohimbine was evaluated in the following way. A PE dose-response curve was constructed in 20 rats before and after 1 mg/kg of yohimbine. The rats were then divided into two subgroups of 10, one of which received 1 g/kg of ethanol and the other an equivolume of saline. The dose-response curve was then repeated for a third time.

A similar protocol was followed using prazosin (3.9 μg/kg, $n = 10$) to evaluate the ability of ethanol to alter the pressor responsiveness of rats with partial α_1-adrenergic blockade. Finally, pressor responses to PE were evaluated before and after combined pretreatment with yohimbine (1 mg/kg) and prazosin (3.9 μg/kg) and after administration of 1.0 g/kg of ethanol or equivolume saline ($n = 9$).

To establish that the effect of ethanol was selective for adrenergic receptors, the ability of ethanol to modify the pressor responsiveness to AII was evaluated. This was performed by constructing control AII dose-response curves in 12 rats. Six rats were then administered 1 g/kg of ethanol and the pressor response curve was

repeated. In the remaining six rats, yohimbine and prazosin treatment was given and the AII pressor response curve was repeated. Ethanol was then given to these rats and the pressor response curve repeated a third time.

Statistical Analysis. All values are expressed as mean ± SEM for each group. Differences in pressor response curves were compared using an analysis of variance (21); in some instances Student's t test (for unpaired samples) was used if applicable (22). The Student-Newman-Keuls test was employed for posthoc analysis of analysis of variance results (21). Significance levels were set at $P < 0.05$ for all comparisons.

Results

The effects of ethanol (1 g/kg) as well as the other treatments on baseline mean arterial blood pressure (MAP) and heart rate (HR) are summarized in Table I. Treatment with 1 g/kg of ethanol or an equivolume of saline had no effect on baseline MAP throughout the experimental period. Saline treatment did not affect baseline HR, although ethanol caused a slight (5.4%) but significant increase in rate. Yohimbine pretreatment alone or in any combination significantly reduced MAP yet had no effect on HR unless combined with prazosin pretreatment (Table I). Prazosin pretreatment alone had no effect on either HR or MAP. Combined yohimbine and prazosin pretreatment produced significant ($P < 0.05$) decreases in both parameters.

Ethanol at a dose of 1 g/kg was able to significantly diminish ($F = 4.25$, $P < 0.05$) the dose pressor responsiveness to the physiologic α receptor agonist NE (Fig. 1A). This decrease in pressor responsiveness was remarkably consistent and was 10–15 mm Hg less for any given dose of NE tested above 0.25 μg/kg. Equivolume saline had no effect on pressor responsiveness to NE. Figure 1B shows that the same dose of ethanol caused a significant ($F = 10.05$, $P < 0.05$) rightward shift of the PE pressor response curve. When saline was administered instead of ethanol, there was an increase in the pressor response to higher doses of PE (16 and 32 μg/kg) as compared with animals that received no treatment.

Table I. The Effects of Ethanol (1 g/kg), Saline, Yohimbine (1 mg/kg), and Prazosin (3.9 μg/kg) on Baseline MAP and HR

Treatment condition	N	Baseline MAP	Baseline HR
Control	24	122.3 ± 2.9	427.9 ± 8.5
After SAL	12	123.2 ± 5.3	401.2 ± 9.4
After ETOH	12	126.1 ± 5.9	450.8 ± 8.8*
Control	20	115.8 ± 4.9	416 ± 9.5
After YOH	20	93.9 ± 4.7*	400 ± 10.0
After YOH + SAL	10	85.7 ± 5.0*	395 ± 13.6
After YOH + ETOH	10	84.3 ± 4.3*	426 ± 23.2
Control	20	114.0 ± 5.8	375 ± 8.9
After PRA	20	115.4 ± 5.9	362 ± 8.5
After PRA + SAL	10	117.8 ± 8.2	357 ± 12.9
After PRA + ETOH	10	100.2 ± 8.1	388 ± 14.7
Control	9	117.4 ± 4.5	413 ± 12.6
After YOH + PRA	9	76.3 ± 6.9*	342 ± 16.9*
After YOH + PRA + ETOH	9	75.0 ± 5.0*	330 ± 32.1*

Note. Pressor agents were administered approximately 5 min after the animals were given ethanol or the blocking agent. All values reported are mean ± SEM. * indicates significantly different from appropriate control ($P < 0.05$).

[a] SAL, saline; ETOH, ethanol; YOH, yohimbine; PRA, prazosin.

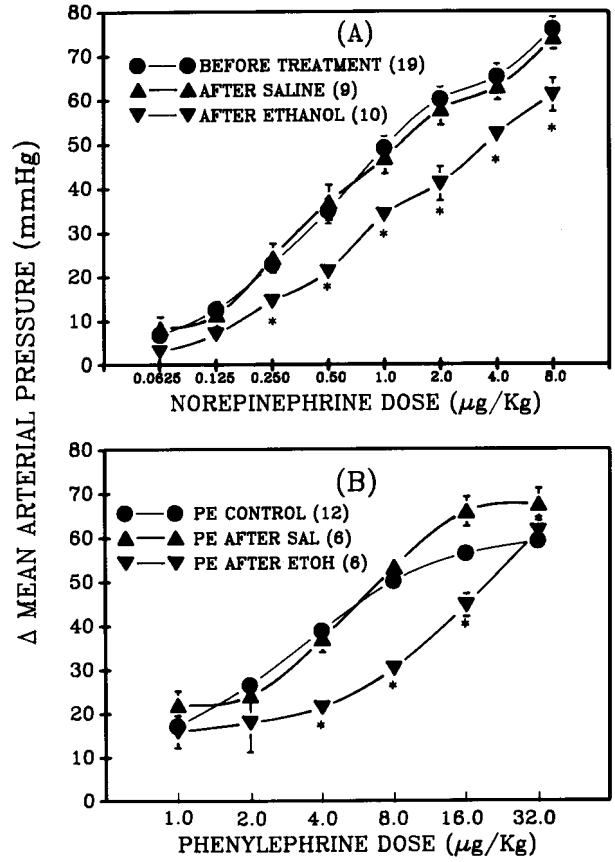

Figure 1. Effect of ethanol (1 g/kg) administration on pressor responses to NE (A) and PE (B). Total number of animals in each group is shown on parentheses. All values are mean ± SEM. * $P < 0.05$.

The administration of 1 mg/kg of yohimbine caused a marked reduction in the PE pressor response curve (Fig. 2) which is in agreement with the findings of others (15, 16, 18). Administration of equivolume saline did not alter the PE pressor response curve after yohimbine treatment, but the administration of 1 g/kg of ethanol to yohimbine-treated animals produced a significant ($F = 33.47$, $P < 0.05$) reduction in the PE pressor response curve, particularly at the higher doses of PE (Fig. 2).

Figure 3 shows the ability of various doses of prazosin to modify the pressor response to PE. As shown, doses of 1 and 0.25 mg/kg and 7.8 μg/kg not only produced a complete blockade of the PE responses but also caused significant PE-evoked decreases in blood pressure at doses of 4 μg/kg and above. When the dose of prazosin was lowered to 3.9 μg/kg, it was

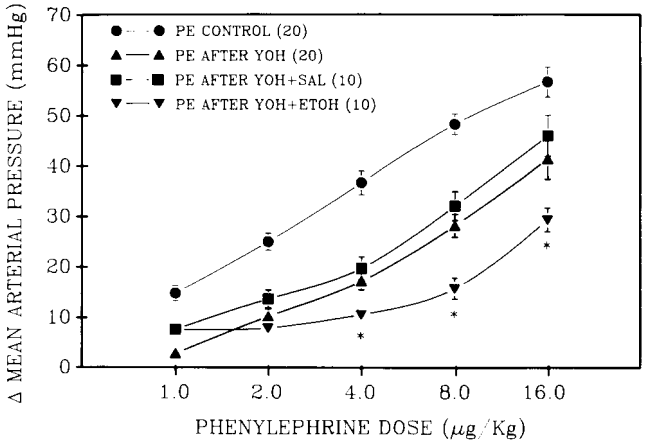

Figure 2. Effects of yohimbine (YOH) pretreatment (1 mg/kg) on pressor responsiveness to PE before and after ethanol administration (1 g/kg). Number of animals in each group is shown in parentheses. Values are mean ± SEM. * $P < 0.05$.

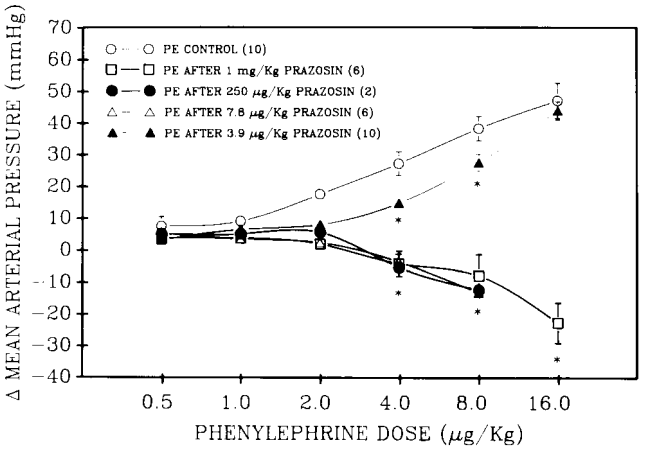

Figure 3. Effects of varying doses of prazosin on pressor responsiveness to PE. Doses of prazosin used in pretreatment are shown in key. Values are mean ± SEM. * $P < 0.05$.

no longer able to inhibit completely the pressor responsiveness to PE, but was sufficient to produce significant ($P < 0.05$) attenuation of pressor responses to 4 and 8 μg/kg doses of PE. This attenuation was overcome and full pressor responsiveness was achieved with a 16 μg/kg dose of PE. Because the blockade of α receptors by prazosin could be overcome by this dose of PE, we concluded this dose of prazosin produced a partial blockade of α receptors and this dose was used in subsequent experiments.

The administration of 1 g/kg of ethanol to prazosin-treated rats caused a significantly ($P < 0.05$) greater depression of PE pressor responsiveness to doses of 4 μg/kg and above (Fig. 4), demonstrating an additive effect of prazosin and ethanol. Equivolume saline did not affect PE pressor responsiveness after treatment with prazosin (Fig. 4).

Treatment with yohimbine and prazosin caused a reduction in baseline MAP greater than that produced by either agent alone (Table I). Similarly, the PE pressor response curve was significantly blunted ($F = 105.17$, $P < 0.05$) in rats pretreated with yohimbine and prazosin (Fig. 5). After administration of ethanol (1 g/kg), the PE pressor response was depressed further for the higher doses of PE (Fig. 5).

To determine whether this reduction in pressor responsiveness was due to a selective α receptor blockade or merely due to some nonspecific decrease in vascular reactivity, a final experiment was performed using AII as a nonadrenergic pressor agent. Administration of 1 g/kg of ethanol did not alter the pressor responsiveness to AII ($F = 1.09$) (Fig. 6). The addition of both yohimbine and prazosin had no effect on pressor responses to AII (Fig. 6). Finally, the addition of 1 g/kg of ethanol following yohimbine and prazosin pretreatment failed to produce any alteration in the pressor responsiveness to exogenously administered AII, thereby ruling out any nonspecific effect of ethanol.

Treatment with 1 g/kg of ethanol produced blood ethanol levels in the range of 200 mg/dl within 1 min of ethanol administration (Fig. 7). These high levels that resulted immediately upon dosing reflect the fact that ethanol had not had time to equilibrate between

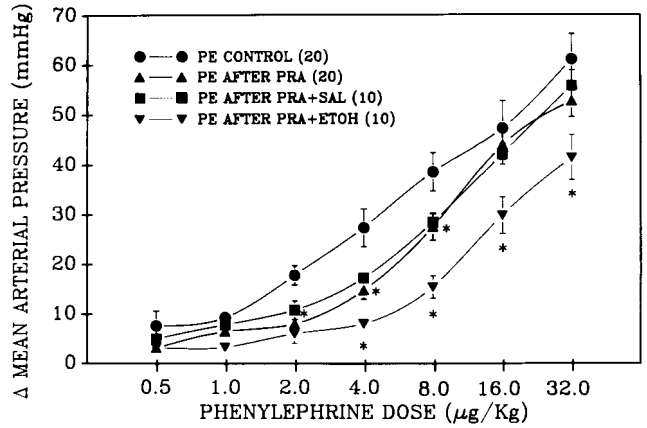

Figure 4. Effects of prazosin (PRA) pretreatment (3.9 μg/kg) on pressor responsiveness to PE before and after ethanol (1 g/kg) treatment. Number of animals in each group is shown in parentheses. Values are mean ± SEM. * $P < 0.05$ compared with control.

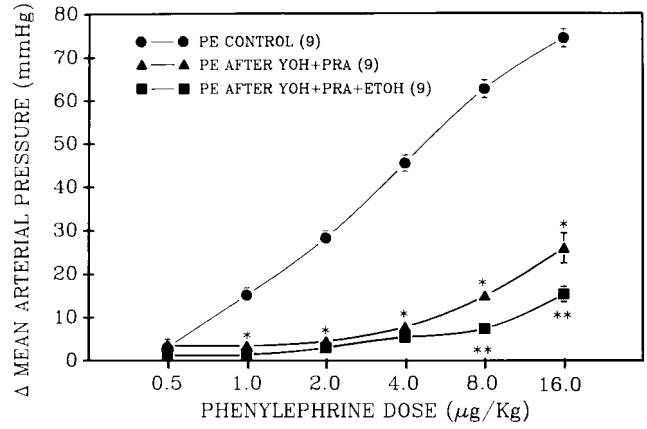

Figure 5. Combined effects of ethanol (1 g/kg) and α receptor antagonists yohimbine (YOH 1 mg/kg) and/or prazosin (PRA 3.9 μg/kg) on PE-mediated pressor responsiveness. Total number of animals in each curve is shown in parentheses. Values are mean ± SEM. * $P < 0.05$. ** indicates values significantly different from combined yohimbine and prazosin pretreatment combined ($P < 0.05$).

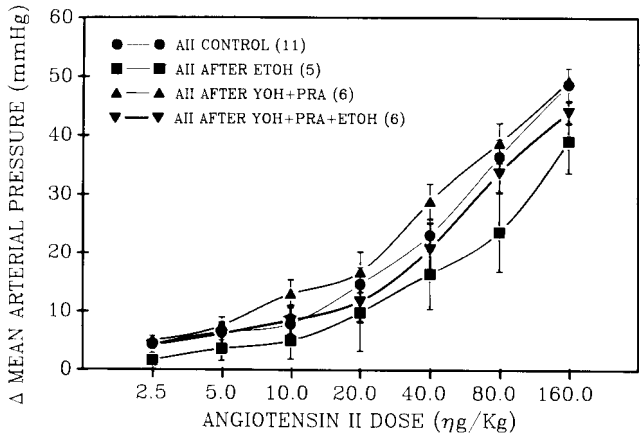

Figure 6. Effects of ethanol (1 g/kg) alone and following combined pretreatment with yohimbine (1 mg/kg) and prazosin (3.9 μg/g) (YOH + PRA) on AII-mediated pressor responsiveness. Number of animals in each curve is shown in parentheses. Values are mean ± SEM. * $P < 0.05$.

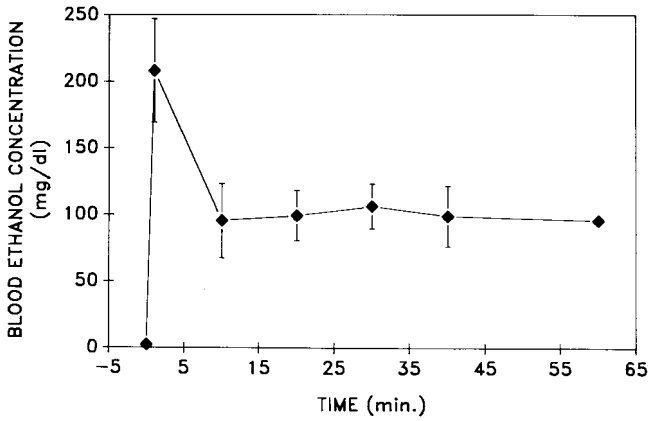

Figure 7. Time course for blood ethanol concentrations. Ethanol (1 g/kg; $n = 6$) was injected iv at time 0 and arterial blood was sampled 1 min later and then at 10-min intervals. Values are mean ± SEM.

the vascular and extravascular spaces. Ten minutes after administration, blood ethanol levels had dropped to approximately 100 mg/dl and remained at this level for the duration of the experiment (Fig. 7).

Discussion

The data showed that a 1 g/kg dose of ethanol has an α-adrenergic receptor blocking-like activity. This apparent α blockade is present whether the α receptor agonist used is the physiologic agonist NE (Fig. 1A) or the pharmacologic agent PE (Fig. 1B). These findings concerning the pharmacologic agonist PE are in agreement with published observations (3, 9, 10, 13, 14) and also agree with reports using the pharmacologic agonist methoxamine (10). More important, this apparent blockade has been shown to be present at blood ethanol concentrations that are readily attainable with social drinking (Fig. 7).

In an attempt to further examine the nature of this α blockade, we used prazosin as a selective α_1-blocking agent and yohimbine as a selective α_2 receptor blocker. Yohimbine treatment alone significantly reduced pressor responsiveness to PE. This finding agrees with the observations of others (18–20), who used the same dose of yohimbine and similar doses of PE. The reason for the decrease in MAP responses to PE observed after yohimbine is not known, but is probably due to: (i) a weak α_2-agonistic activity of PE (23) and/or (2) the dose of yohimbine used was sufficient to block both α_2- and α_1-adrenergic receptors. Earlier investigators suggested that this effect was primarily due to blockade of postsynaptic α_2 receptors (19). In either case the α-blocking effects of yohimbine were intensified with subsequent ethanol administration (Fig 2). This further rightward shift could be due to ethanol-induced blockade of α_1- and/or α_2-adrenergic receptors or to a nonspecific effect that is compounded by yohimbine pretreatment. That the effect was not related to changes in vascular volume and/or time was shown by the lack of an effect of an equivalent volume of saline.

Prazosin was used in order to compare the blockade produced by ethanol to that of a known α_1 receptor blocker. Since any α-blocking effect produced by ethanol could not be detected if total α_1 receptor blockade was produced by prazosin, it was necessary to find a dose of prazosin that would produce only a partial blockade of pressor responsiveness to PE. Doses of 1 mg/kg, 250 μg/kg, and 7.8 μg/kg not only produced a complete blockade of pressor responses to the doses of PE tested (Fig. 3), but actually caused a reversal of the pressor response and a decrease in blood pressure was seen with doses of PE greater than 2 μg/kg. The data suggest that these depressor responses are actually due to a weak β receptor-stimulating property of PE, an effect which has been previously reported (24–26). When the dose of prazosin was lowered to 3.9 μg/kg, a partial blockade of PE pressor responsiveness was achieved. Significantly ($P < 0.05$) blunted pressor responses were observed with PE doses of 4 and 8 μg/kg, but full responsiveness was restored when animals were challenged with 16 μg/kg of PE (Fig. 3). This dose of prazosin was used to pretreat animals prior to either ethanol or saline treatment. Saline failed to alter the responses to PE in animals pretreated with prazosin. Ethanol administration, however, caused a greater ($P < 0.05$) rightward shift of the PE dose-response curve. This shift can similarly be explained by a further blockade of α_1 and/or postsynaptic α_2 receptors or by a nonspecific effect of ethanol. Combined pretreatment with both of these agents substantially depressed pressor responsiveness to all doses of PE tested above 0.5 μg/kg. When 1 g/kg of ethanol was added following pretreatment with these blocking agents, there was an even greater degree of depressed pressor responsiveness at the two highest doses of PE tested. These data are consistent with our hypothesis that ethanol is acting to block α receptors, but a nonspecific effect still could not be ruled out by these findings.

That these effects were not caused by a nonspecific vascular effect of ethanol was established in the exper-

iment in which AII was used as the pressor agent. In this experiment administration of ethanol did not alter the pressor responsiveness of AII, a finding which is consistent with our earlier findings (9,13). Further treatment with both yohimbine and prazosin did not alter AII pressor responsiveness, as expected, and the addition of ethanol to rats treated with yohimbine and prazosin did not modify the AII pressor responsiveness (Fig. 6).

The results of these studies clearly show that ethanol attenuates the pressor responsiveness to physiologic and pharmacologic adrenergic agonists by α-blocking-like effect at α_1- and/or α_2-adrenergic receptors. This finding was at first surprising and would seem to be at odds with a pressor effect of chronic ethanol administration (1–7). If the decreased pressor responsiveness following acute ethanol administration persisted in the chronic situation, it would be expected that this effect would retard the development of elevated blood pressure in individuals who chronically consume ethanol. However, the important distinction here is the acute vs the chronic effects of ethanol on α receptor-mediated pressor responsiveness. We have previously reported (13) that by the time hypertension begins to develop in chronic ethanol-fed rats (about 4 weeks), partial tolerance had developed to the α-adrenergic receptor blocking-like effects of ethanol. Furthermore, with fully developed ethanol-induced hypertension, complete tolerance had developed to this property of ethanol (3). Thus, the acute α-blocking effect of ethanol has been overcome and blood pressure may become elevated.

This study clearly demonstrates an α-adrenergic receptor blocking-like property of ethanol. It cannot be determined from this type of experiment, however, if this apparent blockade resides at the level of the receptor or at some point further in the sequence of signal transduction. Because of the high degree of lipophilicity of ethanol and its well-documented membrane pertubating effects, it is possible that ethanol is acting to prevent signal transduction by acting on some integral membrane protein involved in the second messenger system. It seems just as possible that ethanol is acting to exert a weak blocking action on the receptor. Further work is required to pinpoint the precise mechanism(s) associated with this apparent α receptor blocking-like activity of ethanol.

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