Ethanol Counteraction of I\textsubscript{1}-Imidazoline but Not Alpha-2 Adrenergic Receptor-Mediated Reduction in Vascular Resistance in Conscious Spontaneously Hypertensive Rats\textsuperscript{1}

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ABSTRACT

Our recent findings have shown that ethanol selectively counteracts decreases in blood pressure (BP) evoked via activation of central I\textsubscript{1}-imidazoline receptors but not alpha-2 adrenoceptors in conscious spontaneously hypertensive rats (SHRs). This study investigated the role of sympathetic activity, cardiac output and total peripheral resistance (TPR) in the differential effect of ethanol on centrally mediated hypotension. Changes in plasma norepinephrine (NE), as index of sympathetic activity, BP, heart rate, cardiac index, stroke volume, and TPR elicited by rilmenidine or \( \alpha \)-methylnorepinephrine (selective I\textsubscript{1} and alpha-2 receptor agonists, respectively) and subsequent ethanol (0.5 or 1 g/kg) or saline, were evaluated in conscious SHRs. Intracisternal rilmenidine (25 \( \mu \)g) or \( \alpha \)-methylnorepinephrine (\( \alpha \)-MNE; 4 \( \mu \)g) elicited similar decreases in BP, TPR, and plasma NE, but cardiac index was not changed. Ethanol (0.5 g/kg i.v.) had no effect on hemodynamic responses to rilmenidine or \( \alpha \)-MNE. The higher dose (1 g/kg i.v.) of ethanol counteracted the hypotensive response to rilmenidine and significantly (\( P < .05 \)) elevated TPR and plasma NE. In contrast, ethanol (1 g/kg) had no effect on the hypotensive responses to \( \alpha \)-MNE but significantly (\( P < .05 \)) elevated plasma NE. However, this increase in NE was approximately one third of the increase evoked by ethanol when given after rilmenidine. These findings suggest that the selective counteraction by ethanol of the hypotension evoked via activation of central I\textsubscript{1} but not alpha-2 receptors may relate, at least in part, to its greater ability to reverse the sympathoinhibition and the associated decrease in vascular resistance mediated by I\textsubscript{1} receptors.

Reported findings from our laboratory have shown that ethanol counteracts the hypotensive effect of centrally acting antihypertensive agents such as clonidine and guanabenz (Abdel-Rahman, 1989; Abdel-Rahman et al., 1992; El-Mas et al., 1994b; El-Mas and Abdel-Rahman, 1997a). This adverse effect of ethanol on centrally mediated hypotensive responses is demonstrated in conscious aortic barodenervated rats (El-Mas et al., 1994b; El-Mas and Abdel-Rahman, 1997a) and spontaneously hypertensive rats (SHR) (Abdel-Rahman, 1989; Abdel-Rahman et al., 1992). In contrast, peripherally mediated hypotensive responses were not affected by ethanol (Abdel-Rahman, 1989; Abdel-Rahman et al., 1992). These findings suggest that the ability of ethanol to adversely affect centrally mediated hypotensive responses involves, at least in part, the central nervous system. The possibility should be considered, however, that the peripheral hemodynamic effects of ethanol may influence its interaction with antihypertensive drugs. Acute ethanol administration may cause decreases (Abdel-Rahman et al., 1985; Chandler et al., 1989), increases (Abdel-Rahman, 1989; El-Mas and Abdel-Rahman, 1992), or no change (Abdel-Rahman et al., 1987a,b; Ireland et al., 1984) in blood pressure (BP). Moderate doses of ethanol dilate cutaneous blood vessels partly through a direct action on these vessels (Turlapaty et al., 1979).

Because clonidine lowers BP via activation of alpha-2 adrenoceptors and I\textsubscript{1}-imidazoline receptors (Bousquet et al., 1984, 1992; Chan et al., 1996; Timmermans and Van Zwiesten, 1982) and exhibits a relatively low I\textsubscript{1}/alpha-2 receptor affinity ratio (Ernsberger et al., 1993), whether one receptor site (I\textsubscript{1} or alpha-2) plays a greater role in ethanol/clonidine hemodynamic interaction could not be ascertained in previous studies (Abdel-Rahman, 1989; El-Mas et al., 1994b; El-Mas and Abdel-Rahman, 1997a). This issue was addressed in a more recent study from our laboratory (El-Mas and Abdel-Rahman, 1998) that investigated the effect of ethanol on hypotensive responses to rilmenidine and \( \alpha \)-methylnorepinephrine (\( \alpha \)-MNE), selective I\textsubscript{1} and alpha-2 adrenergic receptor agonists, respectively. Interestingly, the results of this study showed that ethanol counteracted decreases in BP

ABBREVIATIONS: SHRs, spontaneously hypertensive rats; BP, blood pressure; MAP, mean arterial pressure; HR, heart rate; CO, cardiac output; CI, cardiac index; SV, stroke volume; RVLM, rostral ventrolateral medulla; NTS, nucleus tractus solitarius; TPR, total peripheral resistance; i.c., intracisternal, NE, norepinephrine; \( \alpha \)-MNE, \( \alpha \)-methylnorepinephrine.
elicited by central administration of rilmenidine, whereas it had little or no effect on α-MNE-mediated responses (El-Mas and Abdel-Rahman, 1998). This finding suggested a selective interaction of ethanol with central pathways that are essential for the elicitation of I1 receptor-mediated hypotension (El-Mas and Abdel-Rahman, 1998). The reason why ethanol adversely affects I1- but not α-2 receptor-mediated hypotension and whether it involves the sympathetic nervous system are not clear. It is notable that decreases in BP potentiation and whether it involves the sympathetic nervous system were performed to evaluate the influence of subsequent for the elicitation of I1 receptor-mediated hypotension and α-2 receptors involving central sympathetic tone (Timmermans and Van Zwieten, 1982; Gomez et al., 1991). Furthermore, reported findings highlighted the importance of sympathetic activity in the antagonistic hemodynamic interaction between ethanol and centrally acting antihypertensive agents. This view is supported by the observation that centrally evoked reductions in sympathetic activity that mediate the hypotensive effect of clonidine and guanabenz in conscious rats are also counteracted by ethanol (Abdel-Rahman et al., 1992; El-Mas et al., 1994b). In our previous study (El-Mas and Abdel-Rahman, 1998), no measurements were made of plasma norepinephrine (NE) or the detailed hemodynamic responses to either agonist in absence and in presence of ethanol.

The primary goal of the present study was to test the hypothesis that a differential effect of ethanol on sympathoinhibitory responses to rilmenidine and α-MNE may contribute to its differential hemodynamic interaction with the two centrally acting antihypertensive agents. Furthermore, the roles of I1- or α-2 receptor-mediated changes in CO and TPR in the interaction were also investigated. Experiments were performed to evaluate the influence of subsequent ethanol administration on hemodynamic responses elicited by rilmenidine or α-MNE in conscious freely moving SHR. To facilitate interpretation of data, the present study used doses of rilmenidine (25 μg) and α-MNE (4 μg) that elicited in preliminary experiments similar hypotensive responses after intracarotid (i.c.) administration and had no effect on BP when given systemically. Furthermore, two doses of ethanol (0.5 and 1 g/kg) were administered to determine whether the interaction was dose related. Changes in mean arterial pressure (MAP), HR, CO, SV, and TPR evoked by i.c. administration of rilmenidine (25 μg) or α-MNE (4 μg) and subsequently administered ethanol (0.5 or 1 g/kg) or equal volume of saline were followed for 70 min. Plasma NE levels were measured as index of sympathetic activity. The studies were undertaken in conscious freely moving rats to avoid the confounding effects of anesthesia on the measured parameters (El-Mas et al., 1994b; El-Mas and Abdel-Rahman, 1997a). Furthermore, the present study used doses of ethanol (0.5 and 1 g/kg) that resulted in blood ethanol concentration comparable to those achieved after human consumption of moderate to intoxicating amounts of ethanol (Ireland et al., 1984; Abdel-Rahman et al., 1987a).

Materials and Methods

Thirty-seven male SHR (300–350 g; Charles River, Raleigh, NC) were used in the present study.

Intracisternal Cannulation. Four to 5 days before starting the experiment, a stainless steel guide cannula was implanted into the cisterna magna under methohexital anesthesia (50 mg/kg i.p.). The steel cannula (23G; Small Parts, Miami, FL) was passed between the occipital bone and the cerebellum so that its tip protruded into the cisterna magna. The cannula was secured in place with small metal screws and dental acrylic cement (Durelon; Thompson Dental Supply, Raleigh, NC) as described in our previous studies (Abdel-Rahman, 1992; El-Mas et al., 1994a). The guide cannula was considered patent when spontaneous outflow of cerebrospinal fluid was observed and by gross post-mortem histological verification after injection of 5 μl of fast green dye (EM Science, Cherry Hill, NJ). After i.c. cannulation, the rats were housed individually. Intravascular cannulation was performed 2 to 3 days later as described below.

Intravascular Cannulation. For measurement of BP, the method described in our previous studies was adopted (Abdel-Rahman et al., 1992; El-Mas et al., 1994b). Briefly, the rats were anesthetized by pentobarbital (50 mg/kg i.p.). Catheters (polyethylene 50) were placed in the abdominal aorta and vena cava via the femoral artery and vein for measurement of BP and i.v. administration of drugs, respectively. The catheters were inserted about 5 cm into the femoral vessels and secured in place with sutures. The arterial catheter was connected to a Gould-Statham pressure transducer (Oxnard, CA). And BP was displayed on a Grass polygraph (model 7D; Grass Instrument Co., Quincy, MA). Heart rate (HR) was computed from BP waveforms by a Grass tachograph and was displayed on another channel of the polygraph.

Measurement of Cardiac Output. The thermodilution technique described in previous studies, including our own (Yuan and Leenen, 1992; El-Mas et al., 1994a; El-Mas and Abdel-Rahman, 1997b), was used. A polyethylene 50 catheter was placed into the right atrium via the right jugular vein for saline injection. A thermostor (o.d. = 0.64 mm) consisting of Tetlon-coated constantan and copper wire with a 2- to 3-mm epoxy-coated tip was advanced into the aortic arch via the right carotid artery. The thermistor was connected to a Cardiomax II (Columbus Instrument, Columbus, OH) interfaced with an AT computer. This arrangement allowed acquisition of data and computation of cardiac output (CO; ml/min) and stroke volume (SV; μl/beat). Continuous monitoring and displaying of systolic BP, diastolic BP, MAP, and HR were obtained on the computer monitor as well as on a Grass polygraph. COs were measured by rapidly injecting a 0.1 ml of saline at room temperature into the right atrial catheter as a thermal tracer indicator. In addition to CO and SV measurements, the CI (CO/100 g b.wt., ml/min/100 g) and TPR (MAP/CI, mm Hg/ml/min/100 g b.wt.) were calculated.

Finally, the catheters and the thermistor were tunneled s.c. and exteriorized at the back of the neck between the scapulae. The catheters were flushed with heparin (200 U/ml) and plugged by stainless steel pins. Incisions were closed with surgical clips and swabbed with povidone-iodine solution. Each rat received an s.c. injection of the analgesic buprenorphine hydrochloride (Buprenex; 0.3 μg/rat) and an i.m. injection of 60,000 U of penicillin G benzathine and penicillin G procaine in an aqueous suspension (Durapen) and was housed in a separate cage. The experiment started 48 h later. Experiments were performed in strict accordance with institutional animal care and use guidelines.

Measurement of Plasma Norepinephrine Level. Norepinephrine (pg/ml) was measured by ultrafiltration of the collected plasma followed by high performance liquid chromatography with electrochemical detection. The ultrafiltration probe consisted of three loops of hollow dialysis fibers (10 mm each; molecular mass cutoff, approximately 30,000 Da) joined to a single, nonpermeable conducting tube (Bioanalytical Systems Inc., IN). The dialysis fibers were placed in the plasma, and the conducting tube was connected to a peristaltic pump (Harvard Apparatus) that withdrew fluid from plasma into the lumen of the probes at a rate of 2 μl/min. A PM-80 solvent delivery system with a model 7125 injector (20-μl loop; Bioanalytical Systems Inc.) was used for high performance liquid chromatography. The column was a SepStik Uniject micropore column (ODS 5 μm, 100 × 1 mm cartridge; Bioanalytical Systems Inc.). The mobile phase consisted of NaH2PO4 (0.1 M), EDTA (0.11 mM), and octane sulfonic acid.
acid (5 mM) modified with 2% acetonitrile and delivered at a rate of 0.9 ml/min. An amperometric detector model LC-4A was used (Bioanalytical Systems Inc.). The recovery of NE amounted to 70 to 80%, and the retention time was 4 min.

Measurement of Plasma Ethanol Concentration. The ethanol content of the collected plasma samples was measured using the enzymatic method described by Bernt and Gutmann (1974).

Protocols and Experimental Groups. Six groups of conscious freely moving SHRs (n = 6 or 7; Table 1) were used in this study to investigate the effect of ethanol (0.5 or 1 g/kg i.v.) or saline administration on hemodynamic responses to rilmenidine or α-MNE. On the day of the experiment, the thermistor was connected to a Cardiomax II for measurement of CO, and the arterial catheter was connected to a pressure transducer for measurement of BP and HR as mentioned above. A period of at least 30 min was allowed at the beginning of the experiment for stabilization of BP and HR. Each rat received an i.c. dose of rilmenidine (25 μg) or α-MNE (4 μg), and 10 min later, ethanol (0.5 or 1 g/kg) or equal volume of saline (1.3 ml/kg) was given i.v. over 1 min. These doses of rilmenidine and α-MNE have been shown in a previous study from our laboratory to elicit similar hypotensive responses after i.c. administration (El-Mas and Abdel-Rahman, 1998). Changes in BP, HR, CO, SV, and TPR were followed for an additional 60 min. Ethanol (1 g/kg) was administered as 95% in a volume of 1.3 ml/kg b.w.t. as described in our previous studies (Abdel-Rahman et al., 1992; El-Mas et al., 1994b).

In the same groups of rats, plasma NE, as an index of sympathetic activity (Abdel-Rahman et al., 1992; El-Mas et al., 1994b), was measured, and changes evoked by rilmenidine or α-MNE and subsequent ethanol or saline treatment were correlated with the changes in the hemodynamic responses. Three blood samples (0.35 ml each) were collected into tubes containing 10 μl of perchloric acid (0.1 M). The samples were centrifuged at 5000 rpm for 5 min, and the plasma was aspirated and stored at −80°C till analyzed. The blood drawn from the rats was replaced by an equal volume of saline.

Drugs. α-MNE hydrochloride, pentobarbital sodium (Sigma Chemical Co., St. Louis, MO), methohexital sodium (Brevital; Eli Lilly & Co., Indianapolis, IN), povidone-iodine solution (Norton Co., Rockford, IL), ethanol (Midwest Grain Products Co., Weston, MO), and Durapen (Vedco, Inc., Overland Park, KS) were purchased from commercial vendors. Rilmenidine dihydrogen phosphate was a gift from Servier Pharmaceutical Co. (France).

Statistical Analysis. Values are presented as mean ± S.E.M. MAP was calculated as diastolic pressure + one third pulse pressure (systolic and diastolic pressures). Analysis of variance followed by a Newman-Keuls post-hoc analysis was used to analyze the effects of subsequent ethanol or saline administration on hemodynamic responses (BP, HR, CO, SV, and TPR) evoked by rilmenidine or α-MNE. Simple contrasts were made with t test. Probability levels less than .05 were considered significant.

Results

Baseline values of MAP and HR were similar in all ethanol- and saline-treated groups used in this study (Table 1). The blood ethanol concentrations (mg/100 ml) measured 10 min after i.v. administration of ethanol were similar in SHRs pretreated with rilmenidine or α-MNE (Table 1).

Ethanol-Rilmenidine Hemodynamic Interaction in SHRs. The hemodynamic effects evoked by rilmenidine and subsequent ethanol or saline administration in conscious rats are shown in Figs. 1 through 3. Rilmenidine (25 μg i.c.) elicited immediate and prolonged decreases in BP and HR that lasted at least 70 min (Fig. 1A). Data pooled from all three groups of SHRs before and 10 min after rilmenidine (i.e., before 0.5 or 1 g/kg ethanol or saline administration) showed that the rilmenidine-evoked hypotension coincided with significant (P < .05) decreases in TPR (from 3.9 ± 0.17 to 3.2 ± 0.15 mm Hg/ml/min/100 g at 10 min; Fig. 2C), whereas CI (Fig. 2B) was not changed. The hypotensive effect of rilmenidine was associated with a decrease in sympathetic activity as indicated by the significant (P < .05) reduction in plasma NE (from 530 ± 80 to 330 ± 80 pg/ml) in the control (saline-treated) group (Fig. 4A).

Table 1

<table>
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<tr>
<th>Group</th>
<th>n</th>
<th>MAP (mm Hg)</th>
<th>HR (beats/min)</th>
<th>Blood Ethanol (mg%)</th>
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<td></td>
<td></td>
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</tr>
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<td>Saline</td>
<td>7</td>
<td>164 ± 5</td>
<td>357 ± 13</td>
<td>0</td>
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<tr>
<td>Ethanol (0.5 g/kg)</td>
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<td>162 ± 4</td>
<td>391 ± 15</td>
<td>65 ± 7</td>
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<tr>
<td>Ethanol (1 g/kg)</td>
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<td>154 ± 8</td>
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<tr>
<td>α-MNE</td>
<td></td>
<td></td>
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<tr>
<td>Saline</td>
<td>6</td>
<td>161 ± 6</td>
<td>387 ± 12</td>
<td>0</td>
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<tr>
<td>Ethanol (0.5 g/kg)</td>
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<td>158 ± 4</td>
<td>383 ± 8</td>
<td>70 ± 2</td>
</tr>
<tr>
<td>Ethanol (1 g/kg)</td>
<td>6</td>
<td>164 ± 5</td>
<td>373 ± 8</td>
<td>142 ± 6</td>
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</table>

Values are mean ± S.E.M.

Fig. 1. Effect of subsequent administration of ethanol (0.5 or 1 g/kg) or an equal volume of saline on hypotensive and bradycardic responses to rilmenidine (25 μg i.c.) in conscious unrestrained SHRs. Ethanol or saline (arrow) was administered i.v. 10 min after rilmenidine. Values are mean ± S.E.M., and number of rats in each group is shown in parentheses. *P < .05 versus respective postsaline values.
The effect of subsequent administration of ethanol on hemodynamic responses to rilmenidine depended on the dose (0.5 or 1 g/kg) of ethanol used. As shown in Figs. 1 and 3, the lower dose of ethanol (0.5 g/kg) had no effect on the hemodynamic responses to rilmenidine except for a significant \( P < .05 \) increase in TPR at 20 min (Fig. 3C). The higher dose (1 g/kg i.v.) of ethanol counteracted the hypotensive effect of rilmenidine and raised BP to levels similar to prerilmenidine values (Fig. 1A). The pressor effect of ethanol continued for the next 60 min and was associated with significant \( P < .05 \) increases in CI (Fig. 3A) and TPR (Fig. 3C). Ethanol-induced counteraction of the hypotensive response to rilmenidine was associated with increased plasma levels of NE, measured 10 min after i.v. ethanol (1 g/kg), to levels significantly \( P < .05 \) higher than the corresponding postsaline values (Fig. 4A).

**Ethanol/\( \alpha \)-MNE Hemodynamic Interaction in SHRs.** The hemodynamic effects of \( \alpha \)-MNE and subsequent ethanol or saline administration in conscious freely moving SHRs are depicted in Figs. 2, 5, and 6. \( \alpha \)-MNE (4 \( \mu \)g i.c.) produced significant \( P < .05 \) decreases in MAP (Figs. 2A and 5A) that were associated with significant \( P < .05 \) decreases in TPR (Fig. 5C). The hypotensive response elicited by \( \alpha \)-MNE before ethanol or saline administration, approximately 30 mm Hg, was similar to that produced by rilmenidine. The plasma NE level was significantly \( P < .05 \)
reduced by α-MNE from 465 ± 50 to 240 ± 15 pg/ml in control (saline-treated) group (Fig. 4B).

Treatment with ethanol (0.5 and 1 g/kg i.v.) during α-MNE-evoked hypotension elicited slight and dose-related increases in MAP that lasted less than 10 min, after which the MAP responses to α-MNE were similar in the ethanol and control groups (Fig. 5A). Ethanol (0.5 g/kg) caused slight increases in CI (Fig. 6A) and SV (Fig. 6B) and decreases in TPR (Fig. 6C) that reached statistical significance (\( P < .05 \)) only at 15 min compared with the postsaline values. The higher dose (1 g/kg) of ethanol produced significant (\( P < .05 \)) increases in TPR (Fig. 6C) and decreases in CI (Fig. 6A) and HR (Fig. 5b) at 40 and 50 min. Plasma NE levels were significantly (\( P < .05 \)) increased by ethanol (1 g/kg) but remained less than the baseline value (Fig. 4B). The increase in plasma NE levels caused by ethanol (1 g/kg) in rilmenidine-treated rats was significantly (\( P < .05 \)) greater than the corresponding increase obtained in α-MNE-treated rats (94 ± 22% versus 32 ± 22%).

**Discussion**

The most important findings of the present study include 1) i.c. administration of rilmenidine or α-MNE in conscious SHRs elicited hypotension that was mainly mediated via a reduction in TPR, 2) subsequent ethanol administration counteracted the hypotensive and TPR responses to rilmenidine but not α-MNE, and 3) ethanol counteracted the sympathoinhibitory responses (reductions in plasma NE) evoked by either hypotensive agents, but this effect was significantly greater (3-fold) in case of rilmenidine. It is concluded that the ability of ethanol to counteract hypotension evoked via activation of \( I_1 \)-imidazoline receptors (rilmenidine) but not alpha-2 adrenoceptors (α-MNE) may relate, at least in part, to its greater ability to interact with central pathways involved in \( I_1 \) receptor-mediated sympathoinhibition. Furthermore, sympathetically mediated changes in TPR and not CO seem to account for the antagonistic hemodynamic interaction between ethanol and rilmenidine.

In a recent study (El-Mas and Abdel-Rahman, 1998), we have shown that ethanol counteracted hypotensive responses to centrally administered rilmenidine but not α-MNE. This finding suggested a selective interaction between ethanol and central pathways involved in \( I_1 \) receptor-mediated hypotension (El-Mas and Abdel-Rahman, 1998). The mechanism of such a differential action of ethanol on centrally mediated hypotension is not known. Because decreases in BP evoked by activation of both \( I_1 \) and alpha-2 receptors involve inhibition of central sympathetic tone (Timmermans and Van Zwielen, 1982; Gomez et al., 1991), it is not clear whether the differential effect of ethanol on centrally mediated hypotension is related to differences in its effects on the associated sympathoinhibition. This notion is of particular importance
because the sympathetic activity has been implicated in the antagonistic hemodynamic interaction between ethanol and antihypertensive drugs (Abdel-Rahman et al., 1992; El-Mas et al., 1994b). Therefore, the primary objective of the present study was to determine whether the changes in the sympathetic activity and the associated changes in CO and TPR may explain the differential effect of ethanol on hypotensive responses to rilmenidine and α-MNE.

The relative contribution of reductions in CO and TPR to the hypotensive effects of rilmenidine and α-MNE has been controversial (Kisin and Yuzhakov, 1976; Messerli et al., 1981; Zannad et al., 1988; Levy et al., 1995). The present findings suggest that this differential effect of ethanol may relate, at least partly, to the differences in its effect on the sympathoinhibitory and TPR responses that mediated the hypotensive effects of both drugs. This view is supported by the finding that ethanol counteraction of the hypotensive effect of rilmenidine was associated with significant increases in plasma NE and TPR. In contrast, ethanol only slightly counteracted α-MNE-mediated decrease in TPR even though it significantly increased the sympathetic activity. The slight increases in TPR caused by ethanol in α-MNE-treated rats did not lead to the expected increase in BP because they were counterbalanced by a concomitant decrease in CI. It should be noted, however, that the increase in plasma NE levels by ethanol given after rilmenidine was 3-fold greater than that produced by the same dose of ethanol given after α-MNE. This greater sympathoexcitatory response to ethanol in rilmenidine-treated rats may explain its ability to elicit greater and longer-lasting increases in TPR and, subsequently, BP in these rats. The differential action of ethanol on hypotensive and TPR responses to rilmenidine (counteraction) and α-MNE (no effect) cannot be accounted for by differences in the magnitude or duration of the hypotensive response to the two drugs or by differences in ethanol concentration attained in the blood because blood ethanol concentrations were not significantly different in rats receiving different hypertensive agents. When administered alone, ethanol produces variable effects on BP (or no changes, Ireland et al., 1984; decreases, Chandler et al., 1989; increases, El-Mas and Abdel-Rahman, 1992). Even in studies that showed a pressor response to ethanol, the response was modest and short lived (<10 min; Abdel-Rahman et al., 1987a; El-Mas and Abdel-Rahman, 1992). In a study conducted in SHRs, we have shown that ethanol at the same dose (1 g/kg) used in the present study elicited slight increases in TPR but had no effect on BP due to a concomitant reduction in CI (Abdel-Rahman, 1994).

The reason for the greater sympathoexcitatory effect (increase in plasma NE) caused by ethanol in rilmenidine-compared with α-MNE-treated rats is not clear. This finding may suggest the presence of a lower sympathetic activity in rilmenidine-treated rats before ethanol administration. It is notable that our earlier reports have shown that the pressor and sympathoexcitatory responses to ethanol depend on the preexisting sympathetic activity (El-Mas et al., 1994b; El-Mas and Abdel-Rahman, 1997b). Therefore, a lower sympathetic activity in rilmenidine-treated rats would favor a greater sympathoexcitatory response to subsequently administered ethanol. The present finding, however, that rilmenidine and α-MNE produced similar decreases in plasma NE levels (40% versus 45%) argues against a role for the preethanol sympathetic activity in the differential effect of ethanol on sympathoinhibitory responses to the two hypotensive agents. The notion must be considered that plasma NE is a crude measure of sympathetic neural activity and may not accurately reflect changes in sympathetic outflows to different cardiovascular organs. For example, clonidine (mixed I1/alpha-2 receptor agonist) causes a greater inhibition in cardiac sympathetic nerve activity compared with its effect...
on splanchnic and renal sympathetic nerves (Ramage and Wilkinson, 1989). The present results may suggest that the sympathoinhibitory responses to I1 and alpha-2 receptor activation involve different neural pathways in the brainstem and that ethanol selectively interacts with the I1-receptor neural pathway. Alternatively, the possibility must be considered that ethanol produces its sympathoexcitatory action, which counteracts the I1-mediated sympathoinhibition, via activation of the pharmacologically unaltered alpha-2 receptor pathway. If the latter assumption is correct, then the weak sympathoexcitatory effect of ethanol in alpha-MNE-treated, compared with rilmenidine-treated, rats may suggest that the pharmacologically inhibited alpha-2 receptor neural pathway in alpha-MNE-pretreated rats may be blocked to the excitatory effect of ethanol. It is notable that binding (Ernsberger et al., 1994; El-Mas and Abdel-Rahman, 1995) and functional (Head et al., 1997) studies have confirmed the presence of imidazoline and alpha-2 adrenergic receptors in the RVLM. The latter brainstem area plays a major role in the sympathoinhibitory and hypotensive actions of rilmenidine (Gomez et al., 1991; Head et al., 1997) and alpha-MNE (Granata et al., 1986; Head et al., 1997). Recently, Head et al. (1997) suggested that I1 and alpha-2 receptors form one series along the same neuronal pathway in the RVLM and that activation of I1 receptors leads to activation of alpha-2 receptors and subsequent sympathoinhibition and hypotension. In agreement with this view is the finding in the alpha-2 adrenoceptor knockout mouse model that the hypotensive response to systemically administered imidazolines was abolished (MacMillan et al., 1996). Given the important role of the RVLM in the sympathoexcitatory effect of ethanol (Zhang et al., 1989) and in the I1-evoked hypotension (Ernsberger et al., 1990; Gomez et al., 1991), it is possible that the sympathoexcitatory effect of ethanol may be due to its interaction with the I1 receptor neural pathway. Nevertheless, as discussed above, the alpha-2 receptor neural pathway may also be involved in the sympathoexcitatory action of ethanol.

Another possible explanation for the differential hemodynamic interaction of ethanol with rilmenidine and alpha-MNE may relate to the notion that in addition to the RVLM, the nucleus tractus solitarius (NTS) has also been implicated in the hemodynamic effect of alpha-MNE (Bousquet et al., 1984; Granata et al., 1986; Ernsberger et al., 1990; Head et al., 1997). In effect, potent hypotensive and sympathoinhibitory responses can be elicited after microinjection of alpha-MNE into the NTS (Timmermans and Van Zwieten, 1982), a region where selective I1 receptor agonists have virtually no hypotensive effect (Zandberg and DeJong, 1977; Kubo and Misu, 1981; Head et al., 1997). Furthermore, ethanol microinjection into the NTS does not cause sympathoexcitation (Zhang et al., 1989). Therefore, it is conceivable to assume that ethanol counteracts the sympathoinhibitory responses mediated principally via activation of RVLM I1 receptors by drugs such as rilmenidine. This action involves, at least in part, ethanol sympathoexcitatory action that involves the same brainstem area (Zhang et al., 1989). However, functional and binding studies are needed to confirm the differential interaction of ethanol with I1 and alpha-2 receptor systems.

In conclusion, the present study provided evidence to support a role for the sympathetic control of TPR in the differential effect of ethanol on hypotensive responses caused by activation of I1 and alpha-2 receptors in conscious freely moving SHR rats. Subsequent ethanol administration selectively counteracted the hypotensive effect of rilmenidine through a sympathetically mediated elevation of TPR. In alpha-MNE-treated rats, ethanol elicited a lesser sympathoexcitatory response that was not sufficient to counteract alpha-MNE-mediated decreases in TPR and BP. These results, therefore, suggest a selective interaction of ethanol with central pathways involved in the hypotensive and sympathoinhibitory responses elicited by I1-receptor activation.

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