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Chronic ethanol attenuates centrally-mediated hypotension elicited via α_2-adrenergic, but not I_1-imidazoline, receptor activation in female rats

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Abstract

Aims—This study dealt with the effect of chronic ethanol administration on hemodynamic responses elicited by α_2-adrenergic (α-methyldopa) or I_1-imidazoline (rilmenidine) receptor activation in telemetered female rats.

Main methods—The effects of α-methyldopa or rilmenidine on blood pressure (BP), heart rate (HR) and their variability were investigated in rats that received liquid diet without or with ethanol (5% w/v) for 12 weeks. To evaluate the effect of each drug on cardiovascular autonomic control (BP and HR variability) in the absence or presence of ethanol, three time-domain indices of hemodynamic variability were measured: (i) standard deviation of mean arterial pressure (SDMAP), (ii) standard deviation of beat-to-beat intervals, and (iii) root mean square of successive differences in R-R intervals.

Key findings—In liquid diet-fed control rats, i.p. rilmenidine (600 μg/kg) or α-methyldopa (100 mg/kg) reduced BP along with decreases and increases, respectively, in HR. Both drugs had no effect on HR variability but reduced BP variability (SDMAP), suggesting a reduced vasomotor sympathetic tone. Ethanol feeding attenuated reductions in BP and SDMAP evoked by α-methyldopa but not by rilmenidine.

Significance—We conclude that chronic ethanol preferentially compromises α_2- but not I_1-receptor-mediated hypotension in female rats probably via modulation of vasomotor sympathetic activity. These findings highlight the adequacy of rilmenidine use to lower BP in hypertensive alcoholic females.

Keywords

Ethanol; Rilmenidine; α-Methyldopa; Hypotension; Female, Rats

The centrally acting antihypertensive agent clonidine, an imidazoline derivative, acts primarily within the rostral ventrolateral medulla (RVLM) of the brainstem to reduce central sympathetic outflow. Clonidine hypotension has been initially attributed to activation of central α_2 receptors (Timmermans and Van Zwieten, 1982). However, Bousquet et al. (1984,1992) proposed the

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existence of nonadrenergic "imidazoline" receptors in the RVLM, which are specifically sensitive to imidazolines and are involved in the hypotensive and sympathoinhibitory effects of clonidine and related drugs. Further research resulted in the introduction of the second-generation centrally acting imidazolines, rilmenidine and moxonidine. Both drugs have more selectivity for I_1 than for α_2 sites (Ernsberger et al., 1993; Chan et al., 1996) and elicit effective reductions in BP in controlled trials (Dupuy et al., 2000). The relatively lower affinity of rilmenidine and moxonidine, compared with clonidine, to α_2 sites has been suggested as the reason for their lesser side effects such as sedation and dry mouth (van Zwieten, 1997).

Our previous studies have shown that ethanol adversely affects the BP lowering effect of centrally acting drugs. Importantly, the nature and magnitude of the interaction of ethanol with antihypertensive drugs appears to be quite variable and depends primarily on factors such as whether these drugs act peripherally or centrally, the brainstem receptor involved (α_2 vs. I_1), and the regimen of ethanol administration (acute vs. chronic). In early studies, we reported that acutely administered ethanol compromises hypotension of central origin (e.g. clonidine) but not peripherally mediated hypotension (e.g. hydralazine) (Abdel-Rahman, 1989). Because clonidine exhibits almost similar affinities at α_2 and I_1 receptors, subsequent studies investigated the hemodynamic interaction of ethanol with clonidine-related drugs with selective agonistic activity at either receptor site. Ethanol was found to counteract the hypotensive and sympathoinhibitory effects of rilmenidine but not α-methylnorepinephrine, selective I_1 and α_2 agonists, respectively. These findings suggested a preferential interaction of ethanol with central pathways involved in I_1-receptor mediated hypotension (El-Mas and Abdel-Rahman, 1999a,b). On the other hand, long-term exposure to ethanol attenuates centrally-evoked hypotension regardless of the receptor (α_2 or I_1) involved (El-Mas and Abdel-Rahman, 2003, 2004). Because all previous studies that investigated the interaction of ethanol with centrally-evoked hypotension were undertaken in male rats, it remains unclear whether ethanol similarly interacts with I_1- and α_2-receptor-mediated hypotension in the female population.

The present study was undertaken to evaluate the effect of chronic (12 weeks) ethanol feeding on hypotensive responses caused by selective activation of the I_1 (rilmenidine) or α_2 (α-methyldopa) receptor in telemetered female rats. Changes in hemodynamic (BP and HR) variability, as measured by time-domain analysis (Stein et al., 1994; Sgoifo et al., 1997; El-Mas and Abdel-Rahman, 2003, 2004), were also determined to assess the role of cardiovascular autonomic control in the interaction. These experimental studies are clinically important because while it is known that ethanol intake results in inadequate BP control in treated hypertensive patients (Volicer et al., 1978; Puddey et al., 1987), very few studies evaluated the interaction between ethanol and antihypertensive medications in females.

Materials and Methods

Female Sprague-Dawley rats (9-10 weeks; 190-225 g; Harlan, Indianapolis, IN) were used in the present study. Upon arrival, rats were housed individually in standard plastic cages and allowed free access to water and Purina chow and were maintained on a 12-12-h light-dark cycle with light off at 7:00 p.m. The room temperature was maintained at 22±1°C. After one-week acclimatization, rats were fed a standard Lieber-DeCarli high protein liquid diet (Dyets Inc., Bethlehem, PA) for another week before ethanol feeding. Rats received the diet daily at 8:30 a.m. The experimental procedures were performed in accordance with the principles and guidelines of the Canadian Council on Animal Care and were approved by the Institutional Animal Care and Use Committee.

Ethanol feeding

Two groups of female rats (n=6-7) matched for body weight were used in the present study. Rats in the first group were provided ad libitum standard Lieber-DeCarli high protein liquid diet (Lieber and DeCarli, 1982) containing 5% w/v ethanol (36 % of total caloric intake) as described in our previous studies (El-Mas and Abdel-Rahman, 2004). The second group of rats was pair-fed and received isocaloric amount of dextrin/maltose (89.6 g/l) in place of ethanol, which allowed similar nutrient intake and fluid consumption to that of ethanol fed rats. Fresh diets were prepared every other day and stored in the refrigerator until dispensed. Rats were maintained on ethanol or control diet for 12 weeks.

Telemetry system

The telemetry system (Data Sciences Int., St. Paul, MN) used in this study has been described in our previous studies (El-Mas and Abdel-Rahman, 2003, 2004). The system consists of 5 major components: (i) implantable transmitter unit for measurement of BP, (ii) radio receiver to receive telemetered signals, (iii) ambient pressure monitor to measure absolute atmospheric pressure, (iv) consolidation matrix to multiplex multiple cage signals to the computer, and (v) a PC-based data acquisition system to process signals. The implanted sensor consisted of a fluid-filled catheter (0.7 mm diameter, 15 cm long, Model TA11PA-C40) connected to a highly stable low-conductance strain-gauge pressure transducer, which measured the absolute arterial pressure relative to a vacuum, and a radio-frequency transmitter. The tip of the catheter was filled with a viscous gel that prevented blood reflux and was coated with an antithrombogenic film to inhibit thrombus formation and maintain patency. The distal 1 cm of the catheter consisted of a thin walled thermoplastic membrane while the remainder of the catheter was composed of a thick-walled low-compliance urethane. The implants (2.5 cm length and 1.2 cm diameter) weighed 9 g and had a typical battery life of 6 months. A radio receiver platform (RLA1010, Data Sciences Int.) connected the radio signal to digitized input that was sent to a dedicated personal computer (Compaq, Pressario 9548). Arterial pressures were calibrated by using an input from an ambient-pressure monitor (C11PR, Data Sciences Int.).

Transmitter implantation

The method described in our previous studies (El-Mas and Abdel-Rahman, 2003, 2004) was adopted. The rats were anesthetized with i.p injection of a mixture of ketamine (90 mg/kg; Ketaject) and xylazine (10 mg/kg; Xyla-ject). The abdomen was opened with a midline incision (4 cm). Another incision (1.5 cm) was made along the inner thigh to expose the femoral artery. The abdominal wall was pierced with a large bore syringe needle (15 gauge) from the femoral side into the peritoneal cavity. The implant body was placed in the peritoneal cavity and the catheter (15 cm) was passed caudally through the syringe needle into the thigh area. A 5-cm portion of the catheter was inserted into the femoral artery and secured in place with sutures. The abdominal muscle was closed with non-absorbable suture incorporating the implant suture rib with alternating stitches. The skin (abdomen and thigh) was closed with surgical clips. Each rat received a subcutaneous injection of the analgesic ketorolac tromethamine (2 mg/kg; Toradol) and an intramuscular injection of 60,000 U of penicillin G benzathine and penicillin G procaine in an aqueous suspension (Durapen). Individual rat cages were placed on the top of the radio receivers and all data were collected using a computerized data acquisition system (Dataquest ART, Data Sciences Int.). The system is designed to cycle from animal to animal. Transmitter implantation was performed 9 weeks after ethanol or control diet feeding. Rats were left for 3 additional weeks before starting the experiment (i.e. saline, α-methyldopa or rilmenidine administration).

Hemodynamic effects of α-methyldopa or rilmenidine

In this experiment we investigated the influence of chronic ethanol feeding on acute hemodynamic effects of α-methyldopa or rilmenidine. Therefore, we measured BP, HR, and their variability in conscious telemetered female rats after 12 weeks of ethanol feeding before and for 7 hr after a single i.p. injection of saline (1 ml/kg), α-methyldopa (100 mg/kg), or rilmenidine (600 μg/kg) at 3 days intervals. These doses of α-methyldopa and rilmenidine have been shown to produce comparable falls in BP (El-Mas and Abdel-Rahman, 2004), which was important for data interpretation. Waveforms of BP for each rat was sampled at a rate of 500 Hz for 10 s every 10 min. Changes in mean arterial pressure (MAP) and HR from baseline values in pair-fed rats receiving liquid diet with or without ethanol (5%, w/v) were averaged in 20-min blocks (i.e. the average of two successive measurements) for analysis as in our previous studies (El-Mas and Abdel-Rahman, 2003, 2004).

Time-domain analyses

Three time-domain parameters were employed to measure hemodynamic variability as described in previous studies including ours (Stein et al., 1994; Sgoifo et al., 1997; El-Mas and Abdel-Rahman, 2003). The standard deviation of the mean arterial pressure (SDMAP) was taken as a measure of BP variability. HR variability was determined by computing the standard deviation of beat-to-beat intervals (SDRR) and the root mean square of successive beat-to-beat differences in R-R interval durations (rMSSD). The R-R intervals were computed from the HR values (i.e. the reciprocal of HR in msec) as in our previous studies (El-Mas and Abdel-Rahman, 2003). Our previous studies and others have shown that the time-domain indices of BP and HR variability correlate well with the frequency-domain measurements (Stein et al., 1994; Sgoifo et al., 1997; El-Mas and Abdel-Rahman, 2000). The SDRR is comparable to the total power of the spectrum of R-R variability, which measures the overall autonomic balance of the heart. The rMSSD correlates with the high frequency power of the spectrum and, therefore, more specifically quantifies the vagal influence on HR variability (Stein et al., 1994; Sgoifo et al., 1997). Changes from baseline values evoked by each treatment (saline, α-methyldopa or rilmenidine) in the short-term variability of MAP and HR were calculated by averaging each 1-hr values (i.e. 6 successive measurements at 10 min intervals) of SDMAP, SDRR and rMSSD for a total of 7 hr as described in our previous studies (El-Mas and Abdel-Rahman, 2003, 2004). Baseline values of different hemodynamic variables were taken as the average of the 3-hr period (9 am to 12 pm) that preceded drug treatments.

Measurement of plasma ethanol concentration

A blood sample was taken from each rat at the end of the 12-week period of the study and blood ethanol content was determined by the enzymatic method as in our previous studies (El-Mas and Abdel-Rahman, 2003, 2004).

Drugs

α-Methyldopa (Sigma Chemical Co., St. Louis, MO), Ketaject (ketamine), Xyla-ject (xylazine) (Phoenix Pharmaceuticals Inc., St Joseph, MI), Toradol (ketorolac tromethamine, Abbott Labs, Chicago, IL), Durapen (Penicillin G benzathine and penicillin G procaine, Vedco Inc., Overland Park, KS), and ethanol (Midwest Grain Products Co., Weston, MO) were purchased from commercial vendors. Rilmenidine dihydrogen phosphate was a gift from Servier Pharmaceutical Co., France.

Data and statistical analyses

All values are expressed as means±S.E.M. To obtain a measure of the cumulative BP effect of rilmenidine or α-methyldopa, the area under the curve (AUC, mm Hg.hr) was calculated for individual experiments using trapezoidal integration (Graph pad prism, version 3.0). The

repeated measures analysis of variance (ANOVA) followed by a Newman-Keuls post-hoc test was used to analyze the effects of ethanol feeding on hemodynamic responses to rilmenidine or α-methyldopa. These analyses were performed by SAS software Release 6.04 (SAS Institute Inc., Cary, NC) as in our previous studies (El-Mas and Abdel-Rahman, 2003). Probability levels less than 0.05 were considered significant.

Results

Baseline data

As shown in Table 1, prior to the administration of saline, α-methyldopa or rilmenidine, baseline BP, HR, and their variability indices (SDMAP, SDRR, and rMSSD) in ethanol (5% w/v, 12 weeks) and pair-fed control rats were not statistically different. Blood ethanol concentrations measured 12 weeks after ethanol feeding (5%) amounted to 151±14 mg/dl.

Effect of ethanol feeding on hemodynamic responses elicited by α-methyldopa

The time-course effects of α-methyldopa on BP, HR, and their time-domain variability indices in female telemetered rats treated chronically with ethanol (5% w/v) for 12 weeks or their control counterparts are shown in figures 1 and 2. Compared with the corresponding control (saline) values, α-methyldopa (100 mg/kg, i.p.) produced significant reductions in MAP in control rats that started at 60 min, and reached its peak (-15.2±2.5 mmHg) at 140 min. α-Methyldopa hypotension started to dissipate after 5 hr but remained significantly lower than corresponding values observed in control (liquid diet-fed) rats that received saline instead of α-methyldopa (Fig. 1A). The HR showed significant increases by α-methyldopa in control rats during the first 2 hr and subsided towards control (saline-treatment) levels thereafter (Fig. 1B). The BP variability (SDMAP) was significantly reduced by α-methyldopa at 4 and 5 hr (Fig. 2A) whereas indices of HR variability, SDRR or rMSSD, were not affected (Fig. 2B, C).

In ethanol-fed rats, the tachycardic effect of α-methyldopa was preserved (Fig. 1B) whereas the reduction in BP was attenuated for at least 3 hr compared with the effect of α-methyldopa when given to pair-fed (control) female rats (Fig. 1A). Further, ethanol feeding significantly attenuated the α-methyldopa-induced reduction in BP variability (Fig. 2A). Compared with saline treatment, α-methyldopa elicited significant reductions in rMSSD in ethanol-fed rats at 2 and 3 hr (Fig 2C).

Effect of ethanol feeding on hemodynamic effects of rilmenidine

Figures 3 and 4 show the effects of chronic ethanol feeding on hemodynamic responses elicited by rilmenidine in telemetered female rats. In pair-fed control rats, rilmenidine (600 μg/kg i.p.) produced significant reductions in BP that peaked at 60 min (-17.6±1.6 mmHg) and continued, with a lesser magnitude, for approximately 4 hr (Fig. 3A). Significant reductions in HR (for 2 hr, Fig. 3B) and SDMAP (at 4 hr, Fig. 4A) were also evident after rilmenidine administration in pair-fed rats, compared with corresponding control (saline) values. In ethanol-fed rats, the hypotensive action of rilmenidine was attenuated, compared with the hypotensive response observed in pair-fed rats during the first hour of the study followed by slight increases thereafter (Fig. 3A). The effects of rilmenidine on hemodynamic variability were not altered by ethanol feeding, except for a significant reduction in rMSSD at 2 hr (Fig. 4).

The AUC of the cumulative BP effect caused by α-methyldopa or rilmenidine over the entire 7 hr period in rats treated with or without ethanol is shown in figure 5. The AUC of the hypotensive effect of α-methyldopa was reduced by more than 40% ($P<0.05$) in ethanol-fed compared with corresponding values in pair-fed controls (Fig. 5A). In contrast, the AUC of the hypotensive response elicited by rilmenidine in the two groups of rats was not statistically different (Fig. 5B).

Discussion

Reported findings on acute and chronic effects of ethanol on hypotension elicited by clinically prescribed medications may not appropriately be extrapolated to the female population for two reasons. First, most of the reported studies have been undertaken in males (e.g. El-Mas and Abdel-Rahman, 1999a, 1999b, 2003, 2004). Second, experimental and clinical studies have demonstrated gender difference in the BP responses to ethanol (El-Mas and Abdel-Rahman, 1999c; Tobe et al., 2006). In the present study we investigated the influence of long-term ethanol treatment on hemodynamic responses elicited by rilmenidine or α-methyldopa in female rats. Rilmenidine, like moxonidine, has emerged as a second-generation centrally acting antihypertensive agent and is regarded a viable replacement for the first-generation drugs clonidine and α-methyldopa (van Zwieten, 1997; Dupuy et al., 2000). Two important findings are reported here. First, chronic ethanol administration attenuated the hypotensive effect of α-methyldopa and had no influence on the hypotension elicited by rilmenidine in female rats. Second, the vascular sympathetic tone appears to play a critical role in the ethanol-α_2-receptor interaction since α-methyldopa-evoked reduction of BP variability was virtually abolished by ethanol. These findings suggest that in randomly cycling female rats, ethanol feeding interrupts central α_{2A} but not I_1 receptor signaling. Although these studies were conducted in normotensive rats, the findings highlight the possibility that in female hypertensive individuals who are regular alcohol users, rilmenidine represents a better choice, than α-methyldopa, for the treatment of hypertension.

The present study revealed some principal differences in the hemodynamic profiles of rilmenidine and α-methyldopa in liquid diet-fed female rats. Although the magnitude of the hypotensive effect of the two drugs was comparable, the BP response to methyldopa was generally delayed in onset and of longer duration. This has been traditionally related to the view that α-methyldopa hypotension depends on its degradation in central neurons into α-methylnorepinephrine, which is the ultimate mediator of the hypotensive action (Sweet, 1984). Another important aspect of the hemodynamic differences between rilmenidine and α-methyldopa pertains to their effect on HR; decrease and increase, respectively. The bradycardic effect of rilmenidine is consistent with its ability to reduce central sympathetic outflow (van Zwieten, 1997). The paradoxical increase in HR by α-methyldopa, on the other hand, cannot be considered as a compensatory baroreflex response to the evoked hypotension because the increase in HR rapidly developed (within 20 min) after α-methyldopa administration and preceded the fall in BP as showed in this study and others (van der Maas et al., 1986). Alternatively, it has been suggested that the tachycardia is a peripherally mediated effect and involves direct activation of cardiac β-adrenoceptors following the conversion of α-methyldopa into to α-methyldopamine in cardiac sympathetic neurons (van der Maas et al., 1986). Pertinent to this view also is the finding that α-methyldopa elicits no tachycardia when administered centrally (van der Maas et al., 1986). Interestingly, in contrast to its tachycardic effect seen in rats, α-methyldopa produces bradycardia in humans (van Zwieten et al., 1984) and other animal species such as dogs (Lokhandwala et al., 1976) and rabbits (Badoer et al., 1983). The bradycardic action of α-methyldopa, unlike the tachycardia, is entirely of central origin and has a similar time course to that of the fall in BP (Lokhandwala et al., 1976; Badoer et al., 1983). Although discrepancies in biosynthetic enzymes in cardiac sympathetic neurons have been implicated in the species-related differences in the HR response to α-methyldopa (van der Maas et al., 1986), the exact mechanism that underlies the tachycardic response in rodents remains unclear and warrants further investigation.

The main objective of the current investigation was to evaluate whether chronically administered ethanol influences similarly or differently the α_2- and I_1-receptor-mediated hemodynamics in female rats. To accomplish this goal, we investigated the effect of ethanol (5% w/v in liquid diet for 12 weeks) on the hemodynamic responses elicited by selective

activation of I_1 (rilmenidine) or α_2 (α-methyldopa) receptors. The results showed that ethanol preferentially affected the hemodynamic actions of the two drugs. Most notable, ethanol significantly attenuated the α-methyldopa-evoked hypotension in contrast to no effect on rilmenidine-evoked hypotension. Such discrepancy in the effect of ethanol became more evident after analyzing the AUC of the hypotensive response by either hypotensive agent over the entire 7 hr period of the study. The reason for this receptor-dependent effect of ethanol on centrally evoked hypotension is not clear. Nonetheless, the preferential attenuation by ethanol of the hypotensive response elicited by α-methyldopa may relate to the ability of ethanol to diminish central α_2-adrenoceptor sensitivity (Szmigielski et al., 1989) and to reduce α_2 receptor density in the nucleus tractus solitarius (El-Mas and Abdel-Rahman, 2001a), a major neuroanatomical target for α-methyldopa (Kubo and Misu, 1981). Also, it is possible that chronic accumulation of acetaldehyde, the metabolic product of ethanol, may interfere with the degradation pathway of α-methyldopa (Collins et al., 1990), which mediates its hypotensive effect. The latter possibility seems unlikely in our model system because the tachycardic response elicited by α-methyldopa, which reflects the cardiac effect of the active metabolite α-methyldopamine (van der Maas et al., 1986), was not influenced by chronic ethanol administration (Fig. 1B). Whether chronic exposure to ethanol modifies the signaling and/or density of I_1 receptor in BP controlling nuclei of the brainstem has not been investigated. Nonetheless, the lack of ethanol effect on the cumulative hypotensive response elicited by rilmenidine over the 7 hr observation period seems to argue against this possibility. Together, our findings suggest that in female rats, ethanol feeding interacts in a receptor-dependent manner with neuronal pathways involved in the elicitation of centrally-evoked hypotension.

Time-domain analysis of hemodynamic variability was employed in the present study to reveal changes in cardiovascular autonomic control and their possible contribution to the hemodynamic interaction between ethanol and centrally acting hypotensive drugs. It has been established from time- or frequency-domain studies that sympathoinhibition contributes to the reduction in hemodynamic variability that parallels centrally-evoked hypotension (Elghozi et al., 1991; Janssen et al., 1991; Tulen et al., 1993). Also, the reduced BP variability produced by rilmenidine in hypertensive humans coincides with a predominant reduction in BP fluctuations in the mid-frequency range (0.1 Hz), which reflects sympathoinhibition (Girard et al., 1995). Along this line, the current demonstration that the hypotensive effect of α-methyldopa or rilmenidine was accompanied by a reduction in the variability of BP (SDMAP) but not HR (SDRR or rMSSD) points out to a selective inhibitory effect of the two drugs on vascular, but not cardiac, sympathetic activity. Given that ethanol significantly attenuated the depressant effect of α-methyldopa, but not rilmenidine, on BP variability, it is conceivable that ethanol might have acted selectively to induce functional changes in central pathways implicated in the sympathoinhibotry response to α_2 receptor activation.

The variability of adjacent inter-beat intervals (rMSSD) is an important determinant of the heart function as it largely reflects cardiac vagal activity (Stein et al., 1994; Sgoifo et al., 1997). Neither rilmenidine nor α-methyldopa affected rMSSD in control (liquid diet fed) female rats suggesting that the vagal cardiomotor activity was preserved in the presence of these drugs. It was only in ethanol-fed rats, however, that the two hypotensive drugs elicited significant reductions in rMSSD early during the course of their administration (see Figs. 2C, 5C). Considering that the reduction in rMSSD was not associated with any changes in SDRR, this may infer a shift in the cardiac sympathovagal balance towards sympathetic dominance. Although the underlying mechanism remains to be investigated, the reduction in rMSSD evoked by centrally acting drugs in the presence of ethanol might be attributed to the combined confounding effects of these intervening drugs on cardiovascular autonomic control.

Comparing the results of this study and our previous study (El-Mas and Abdel-Rahman, 2004) revealed important gender-related differences in the ethanol interaction with centrally

acting antihypertensive agents. Whereas the attenuation of the hypotensive effect of α-methyldopa caused by ethanol occurs in both genders, the rilmenidine-evoked hypotension was compromised by ethanol in male (El-Mas and Abdel-Rahman, 2004) and not in female rats (this study). Another difference relates to the ability of ethanol to attenuate the reduction in BP variability evoked by α-methyldopa but not rilmenidine in female rats (this study) in contrast to selectively attenuating the reduced BP variability caused by rilmenidine in the male rat (El-Mas and Abdel-Rahman, 2004). These discrepancies in the hemodynamic effects of ethanol cannot be accounted for by differences in the amounts or duration of ethanol consumption because rats in both studies received ethanol for a period of 12 weeks and exhibited similar blood ethanol levels. One considerable factor, however, may relate to the fact that normotensive female rats were used in the present study in contrast to spontaneously hypertensive male rats in our previous study (El-Mas and Abdel-Rahman, 2004). It is possible, therefore, that the cardiovascular structural, autonomic, and hormonal alterations that characterize hypertension (Biaggioni, 2003; Laurent et al., 2005) might be responsible for the contrasting hemodynamic effects of ethanol in the present and previous studies (El-Mas and Abdel-Rahman, 2004). We are not aware of any study that evaluated the interaction of ethanol with selective α_2/I_1 receptor agonists in the normotensive male rat. In addition to the effect of hypertension, sex (El-Mas and Abdel-Rahman, 1999c; Tobe et al., 2006) and the hormonal modulation of the α_2/I_1 receptor binding activity (Karkanias et al., 1997; Piletz and Halbreich, 2000) are other potential factors that might also contribute to the contrasting effects of ethanol on hypotension of central origin. More studies are clearly needed to investigate these possibilities.

It is important to comment on the role of HR in the hemodynamic interaction between ethanol and centrally acting drugs. Consistent with previous findings (El-Mas and Abdel-Rahman, 2001c, 2004), baseline HR was not affected by ethanol feeding. The comparison of HR values in ethanol-fed and pair-fed control rats prior to the administration of α-methyldopa or rilmenidine revealed no significant differences (see Table 1). Chronic ethanol also failed to alter the HR response to rilmenidine (bradycardia) or α-methyldopa (tachycardia). Similar observations were seen when both ethanol and rilmenidine were administered acutely (El-Mas and Abdel-Rahman, 1999a). It is unlikely, therefore, that HR responses might have contributed to the differential interaction of ethanol with the hypotensive effect of the two drugs is not likely. This view is bolstered by our previous finding that ethanol attenuation of the hypotensive effect of α-methyldopa in SHRs despite-ethanol evoked a reduction in the associated tachycardia (El-Mas and Abdel-Rahman, 2004). Together, these findings argue against a significant role for HR changes in the antagonistic BP interaction between ethanol and centrally acting antihypertensive agents.

The present findings highlight a compromising effect of chronic ethanol administration on α-methyldopa-evoked hypotension in female rats. This effect of ethanol seems to be preferentially directed against α_2–adrenergic receptor signaling because the I_1-mediated hypotension was not influenced by chronic ethanol administration. We further demonstrate that the increase in vascular sympathetic activity is critical to the interaction of ethanol with central α_2-receptor-containing neuronal pools. Although these findings were generated in normotensive rats, they may bear clinical relevance to the inadequacy of BP control in treated hypertensive patients who are regular alcohol users (Volicer et al., 1978; Puddey et al., 1987). Although our studies were conducted in normotensive rats, the findings infer that rilmenidine and possibly related selective I_1-receptor agonists (e.g. moxonidine) might constitute a better choice, than α-methyldopa, for BP control in hypertensive females who are regular users of alcohol. Moreover, because ethanol counteracted the reductions in BP variability caused by α-methyldopa, but not by rilmenidine, the latter might be more advantageous in the management of ventricular and vascular hypertrophy in female alcohol

users. Notably, reduction in BP variability by centrally acting drugs contributes to the regression of cardiovascular hypertrophy (Timio et al., 1987; Kohno et al., 1990).

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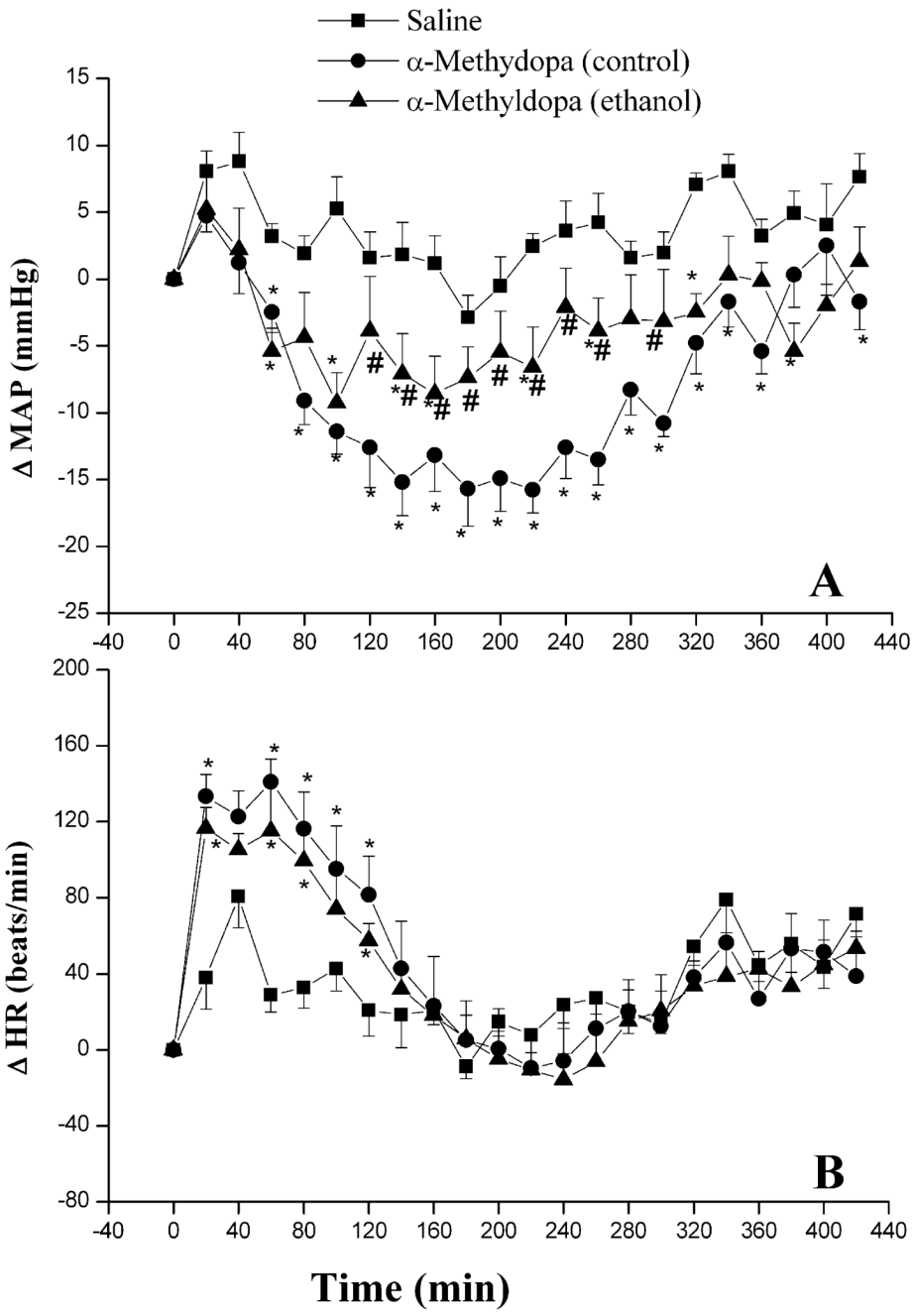

Figure 1.
Effect of chronic feeding of ethanol (5% w/v, 12 weeks) or control liquid diet on changes in mean arterial pressure (MAP) and heart rate (HR) evoked by α-methyldopa (100 mg/kg i.p.) in conscious telemetered female rats. Values are means±S.E.M. of 6-7 observations. * and $^{\#}P<0.05$ versus corresponding saline and α-methyldopa (control) values, respectively.

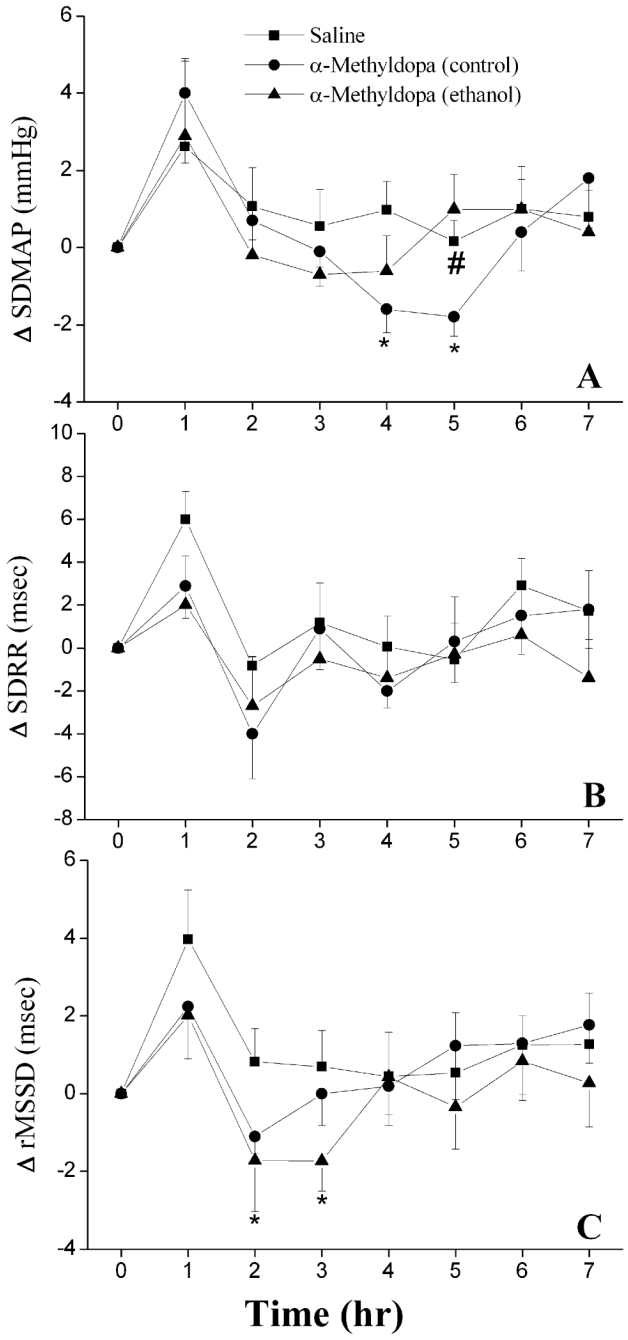

Figure 2.

Effect of chronic feeding of ethanol (5% w/v, 12 weeks) or control liquid diet on changes in the variability indices of mean arterial pressure (SDMAP) and heart rate (standard deviation of beat-to-beat intervals, SDRR, and the root mean square of successive beat-to-beat differences, rMSSD) evoked by α-methyldopa (100 mg/kg i.p.) in conscious telemetered female rats. Values are means±S.E.M. of 6-7 observations. * and $^{\#}P<0.05$ versus corresponding saline and α-methyldopa (control) values, respectively.

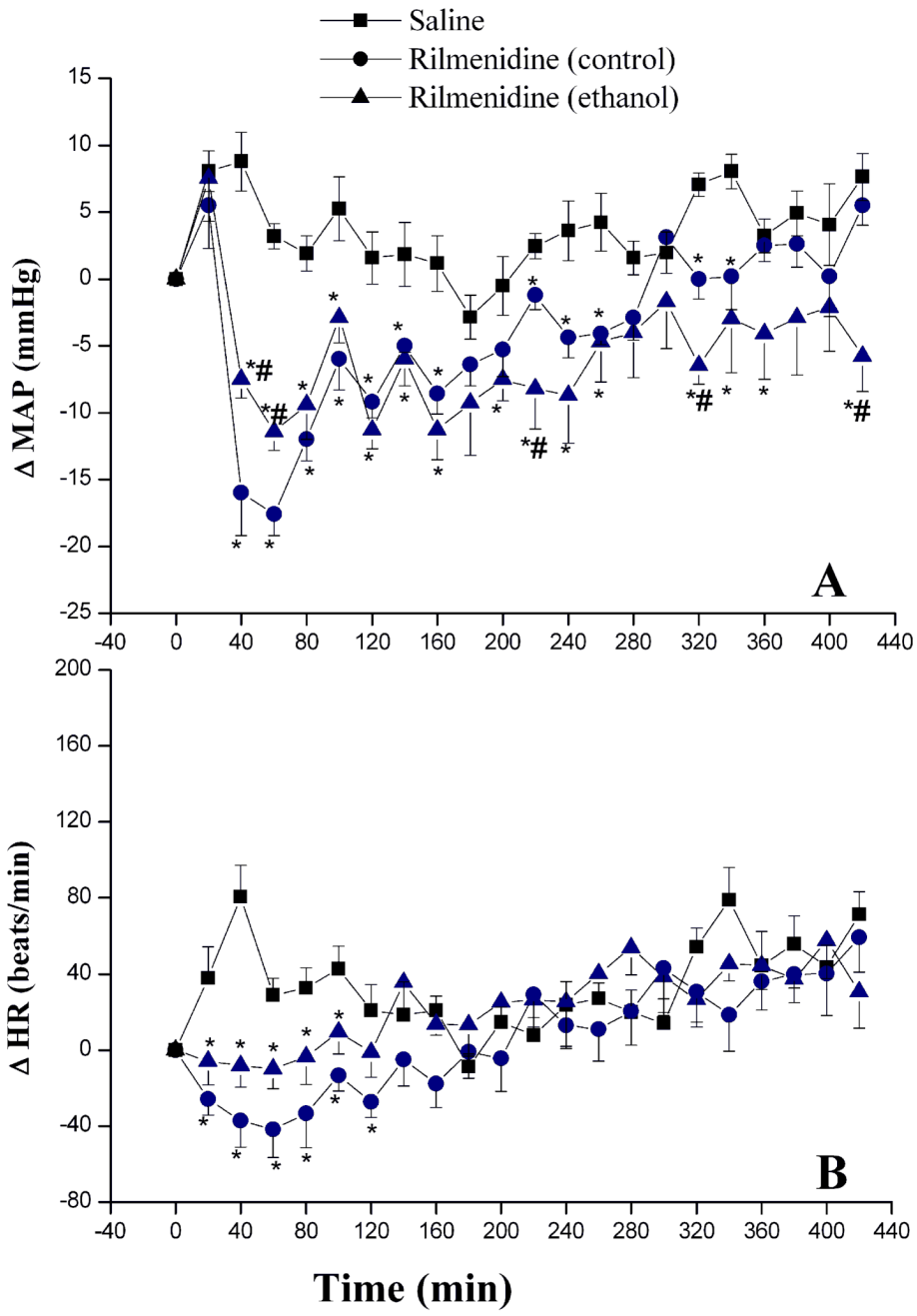

Figure 3.

Effect of chronic feeding of ethanol (5% w/v, 12 weeks) or control liquid diet on changes in mean arterial pressure (MAP) and heart rate (HR) evoked by rilmenidine (600 μg/kg i.p.) in conscious telemetered female rats. Values are means±S.E.M. of 6-7 observations. * and $^{\#}P<0.05$ versus corresponding saline and rilmenidine (control) values, respectively.

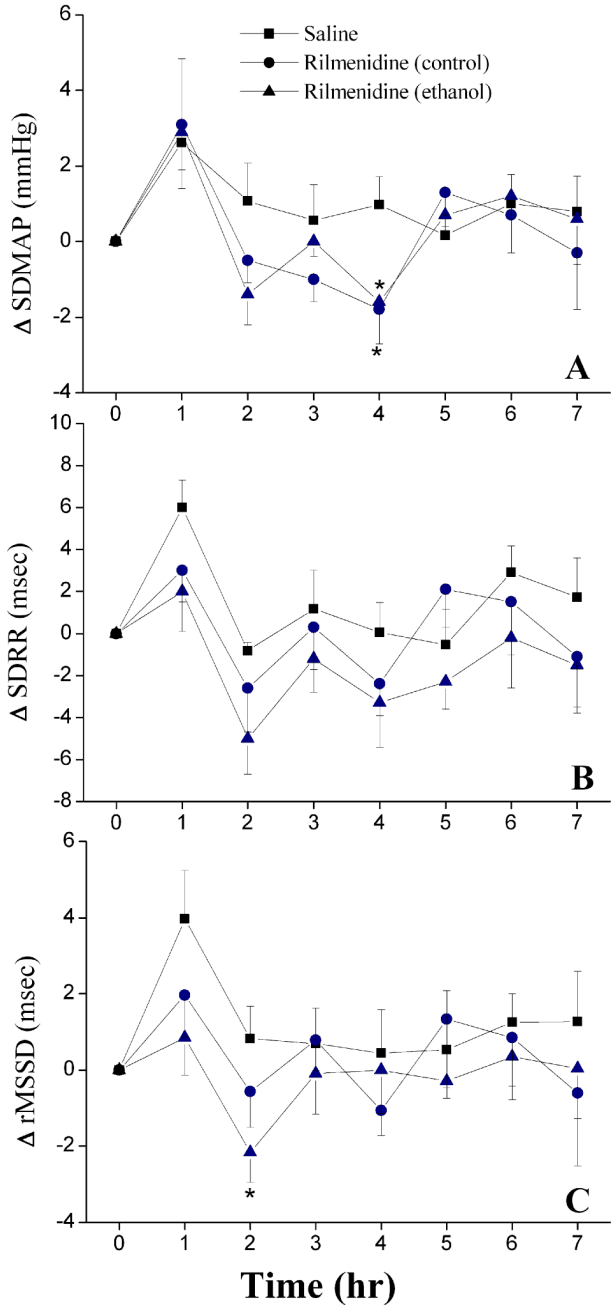

Figure 4.

Effect of chronic feeding of ethanol (5% w/v, 12 weeks) or control liquid diet on changes in the variability indices of mean arterial pressure (SDMAP) and heart rate (standard deviation of beat-to-beat intervals, SDRR, and the root mean square of successive beat-to-beat differences, rMSSD) evoked by rilmenidine (600 μg/kg i.p.) in conscious telemetered female rats. Values are means±S.E.M. of 6-7 observations. *P<0.05 versus corresponding saline values.

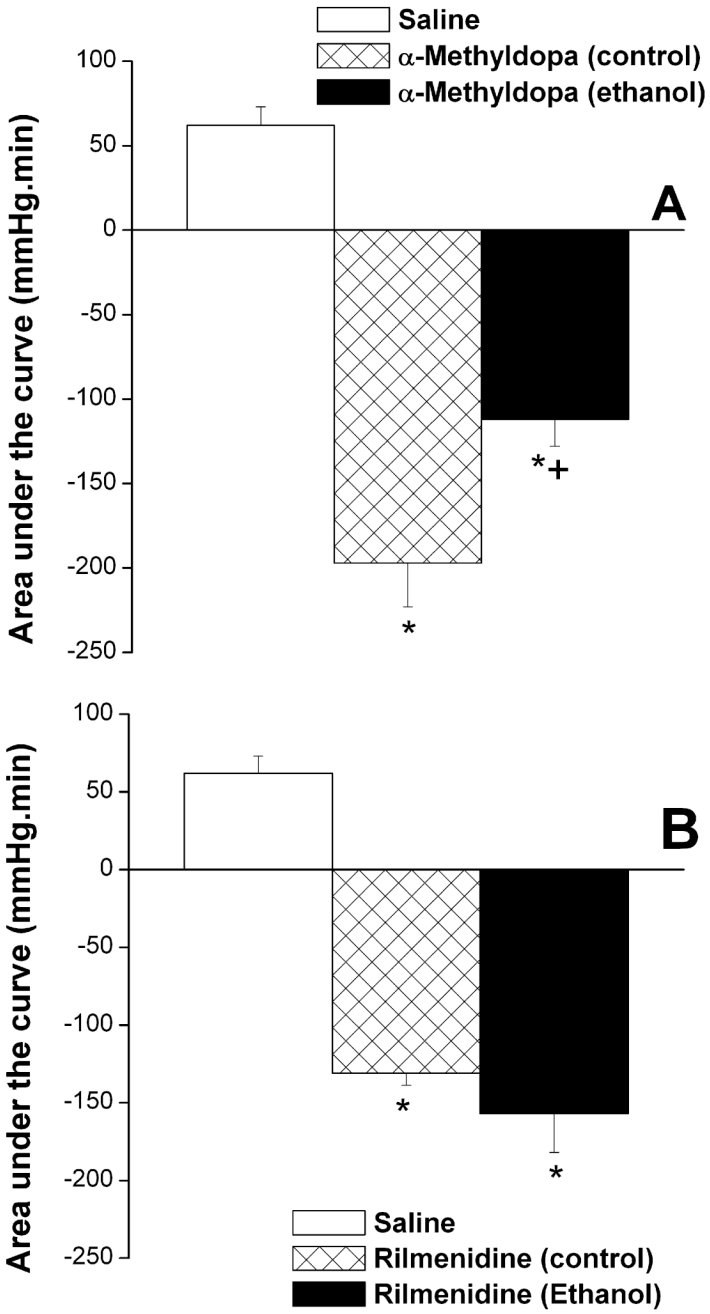

Figure 5.

Bar graphs showing the area under the curve of the hypotensive effect of i.p. α-methyldopa (100 mg/kg, panel A) or rilmenidine (600 μg/kg, panel B) in conscious telemetered female rats treated chronically with ethanol (5% w/v, 12 weeks) or control liquid diet. Values are means ±S.E.M. of 6-7 observations. * and $^{\#}P<0.05$ versus corresponding saline and control (α-methyldopa, panel A; rilmenidine, panel B) values, respectively.

Table 1

Baseline hemodynamic values of mean arterial pressure (MAP, mmHg), heart rate (HR, beats/min), MAP variability (SDMAP, mmHg), standard deviation of R-R intervals (SDRR, msec), and root mean square of successive beat-to-beat differences (rMSSD, msec).

Parameter	Control	Ethanol
MAP		
Pre-saline	98.1±4.2	97.0±3.1
Pre-α-methyldopa	101.8±3.7	96.9±3.3
Pre-rilmenidine	104.6±3.1	101.1±3.7
HR		
Pre-saline	367.7±23.4	346.3±10.1
Pre-α-methyldopa	356.7±11.5	345.3±9.1
Pre-rilmenidine	359.1±8.1	349.0±10.9
SDMAP		
Pre-saline	5.11±0.23	6.21±0.60
Pre-α-methyldopa	5.27±0.43	5.60±0.74
Pre-rilmenidine	5.36±0.41	5.99±0.66
SDRR		
Pre-saline	11.29±1.41	13.11±0.52
Pre-α-methyldopa	9.53±1.57	11.51±1.22
Pre-rilmenidine	11.94±1.31	13.28±1.64
rMSSD		
Pre-saline	5.44±0.64	4.92±0.32
Pre-α-methyldopa	5.24±0.93	4.96±0.51
Pre-rilmenidine	6.35±0.65	5.95±0.77

Values are means±SEM of 6-7 observations.