Radiotelemetric Evaluation of Hemodynamic Effects of Long-Term Ethanol in Spontaneously Hypertensive and Wistar-Kyoto Rats

MAHMOUD M. EL-MAS and ABDEL A. ABDEL-RAHMAN
Department of Pharmacology, School of Medicine, East Carolina University, Greenville, North Carolina
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ABSTRACT
This study determined the hemodynamic effects of chronic ethanol in telemetered freely moving age-matched spontaneously hypertensive (SHR) and Wistar-Kyoto (WKY) rats. Changes in blood pressure (BP), heart rate (HR), and plasma norepinephrine (as index of sympathetic activity) were evaluated in pair-fed rats receiving liquid diet with or without ethanol (5%, w/v) for 12 weeks. The SHRs exhibited higher baseline BP and lower HR compared with WKY rats. When normalized for body weight, daily ethanol intake was higher in SHRs compared with WKY rats. However, blood ethanol concentration was similar except for a higher level in SHRs at weeks 7 through 9. Ethanol had no effect on BP in WKY rats but caused decreases in BP in SHRs that reached a maximum (30 mm Hg) at week 5 and remained thereafter. Ethanol also caused reductions in the BP variability and the circadian fluctuations in BP in SHRs but not in WKY rats. Plasma norepinephrine levels were elevated by ethanol in WKY rats, but not in SHRs. The HR was not affected by ethanol in SHRs and showed increases in WKY rats. These findings suggest that chronic ethanol feeding differentially affects BP in SHRs (hypotension) and WKY rats (no effect). The lack of a hypotensive response to ethanol in WKY rats may relate, at least partly, to the associated sympathoexcitation. The present study used the telemetry technique for BP measurement, which eliminates the confounding and stressful effects of other conventional techniques.

Epidemiological studies have established that ethanol consumption leads to hypertension (Arkwright et al., 1982; Gruchow et al., 1985). The development of hypertension has been correlated to the duration and extent of ethanol intake (Arkwright et al., 1982; Gruchow et al., 1985). The cessation of ethanol intake restores blood pressure (BP) to predrinking levels (Potter and Beevers, 1984; Aguilera et al., 1999). Experimental findings, including our own, also support the notion that chronic ethanol consumption is associated with hypertension (Chan and Sutter, 1982; Chan et al., 1985; Abdel-Rahman and Wooles, 1987). Because the elevated BP was associated with increases in sympathetic activity (Chan et al., 1985), it has been suggested that sympahtoexcitation may have been enhanced by ethanol feeding and contributed to the development of hypertension (Chan et al., 1985). Furthermore, our own findings suggest a contributory role for impairment of baroreflex function in hypertension evoked by long-term ethanol feeding (Abdel-Rahman et al., 1985; Abdel-Rahman and Wooles, 1987). This notion is supported by the observation that baroreceptor reflex control of heart rate (HR) is known to be depressed in human (Bristow et al., 1969; Goldstein, 1983) and experimental (Gordon et al., 1981) hypertensive. Furthermore, impairment of baroreflex function precedes the development of hypertension in Dahl salt-sensitive rats (Gordon et al., 1981) and experimental (Gordon et al., 1981) hypertension. Furthermore, impairment of baroreflex function precedes the development of hypertension in Dahl salt-sensitive rats (Gordon et al., 1981) and experimental (Gordon et al., 1981) hypertension. Furthermore, impairment of baroreflex function precedes the development of hypertension in Dahl salt-sensitive rats (Gordon et al., 1981) and experimental (Gordon et al., 1981) hypertension. Furthermore, impairment of baroreflex function precedes the development of hypertension in Dahl salt-sensitive rats (Gordon et al., 1981) and experimental (Gordon et al., 1981) hypertension.

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ABBREVIATIONS: BP, blood pressure; HR, heart rate; SHR, spontaneously hypertensive rat; WKY, Wistar-Kyoto; NE, norepinephrine; BEC, blood ethanol concentration; MAP, mean arterial pressure.
namic effects of chronic ethanol feeding, suffered two limitations. First, ethanol was added to drinking water, which caused immediate and sustained reductions in fluid intake and gain in body weight (Howe et al., 1989; Beilin et al., 1992; Abdel-Rahman, 1994b). Plasma volume showed increases (Chan and Sutter, 1983), decreases (Pang et al., 1984), or no changes (Howe et al., 1989) after chronic ethanol feeding. Second, the tail-cuff plethysmography has been used in all previous studies to evaluate the hemodynamic effects of ethanol (Abdel-Rahman and Wooleys, 1987; Howe et al., 1989; Hatton et al., 1992; Abdel-Rahman, 1994b). This technique, even though noninvasive and of low cost, requires warming and restraining the animal, which cause stress and introduce a potential error in BP assessment (Ferrari et al., 1990; Brockway et al., 1991). Notably, Ferrari et al. (1990) have shown that the BP responsiveness to combined heat and restraint differs in hypertensive and normotensive rats (increases and decreases, respectively).

The main objective of the present study was to evaluate the hemodynamic responses to chronic ethanol feeding with, for the first time, the radiotelemetric technique that is a direct and minimally stressful procedure for BP measurement in freely moving animals (Hess et al., 1996; Webb et al., 1998). This procedure allows continuous and simultaneous measurements of BP and HR and acquisition of the data on a computer for analysis. Ethanol was provided as 5% (w/v) in Lieber-DiCarli high-protein liquid diet to age-matched SHRs and Wistar-Kyto (WKY) rats for 12 weeks. Control rats were simultaneously pair-fed isocaloric diet, which allowed similar nutrient intake and fluid consumption. Plasma norepinephrine (NE) levels, as index of sympathetic activity, were measured every 2 weeks. Ethanol intake and blood ethanol concentration (BEC) were measured to determine whether interstrain differences in BEC contributed to the strain-dependent hemodynamic effects of ethanol. Finally, the effect of ethanol was investigated on the circadian variations in BP. The daily 60-min means of mean arterial pressure (MAP) of ethanol-fed and control SHRs obtained over the 5th and 6th weeks were subjected to time-series analysis. Notably, the 5th week marked the beginning of a reduction in MAP variability in ethanol-fed SHRs.

**Materials and Methods**

Age-matched (10–11 weeks; Taconic, Germantown, NY) male SHRs (n = 26; 250–300 g) and WKY rats (n = 30; 320–370 g) were used in the present study. On arrival, the rats were housed individually in standard plastic cages and allowed free access to water and Purina chow and were maintained on a 12-h light/dark cycle with light off at 7:00 PM. The room temperature was maintained at 22°C. After 1 week of acclimatization, rats were fed a standard Lieber-DiCarli high-protein liquid diet (Dyets Inc., Bethlehem, PA) for 2 days before implantation of the telemetry device. Rats received the diet daily at 8:30 AM. All experiments were performed in strict accordance with institutional animal care and use guidelines.

**Telemetry System**

The telemetry system (Data Sciences Int., St. Paul, MN) used in this study has been previously described in detail (Hess et al., 1996; Webb et al., 1998). The system consists of five major components: 1) implantable transmitter unit for measurement of BP, 2) radio receiver to receive telemetered signals, 3) ambient pressure monitor to measure absolute atmospheric pressure, 4) a consolidation matrix to multiplex multiple-cage signals to the computer, and 5) a PC-based data acquisition system to process signals. The implanted sensor consisted of a fluid-filled catheter (0.7 mm in diameter, 15 cm in length; Model TA111PA-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, and the remainder of the catheter was composed of a thick-walled low-compliance urethane. The implants (2.5 cm in length and 1.2 cm in diameter) weighed 9 g and had a typical battery life of 6 months. Implants were gas-sterilized and provided precalibrated (relative to vacuum) by the manufacturer and calibrations were verified to be accurate within 3 mm Hg (Brockway et al., 1991). A radio receiver platform (RAL1010; Datasciences, Minneapolis, MN) connected the radio signal to digitized input that was sent to a dedicated personal computer (Pressario 9548; Compaq Computer, Houston, TX). Arterial pressures were calibrated by using input from an ambient-pressure monitor (C11PR; Datasciences).

**Transmitter Implantation**

The method described in previous studies (Hess et al., 1996; Webb et al., 1998) was adopted with the only modification that a femoral artery was catheterized instead of the abdominal aorta. Femoral catheterization was found to improve the survival rate and reduce trauma to the animals. The rats were anesthetized with i.p. injection of a mixture of ketamine (90 mg/ml, Ketaset; Phoenix Pharmaceuticals Inc., St. Joseph, MI) and xylazine (10 mg/ml, Xyla-ject; Phoenix Pharmaceuticals Inc.). 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 nonabsorbable suture incorporating the implant suture rib with alternating stitches. The skin (abdomen and thigh) was closed with surgical clips. Each rat received an s.c. injection of the analgesic ketorolac tromethamine (2 mg/kg, Toradol; Abbott Laboratories, Chicago, IL) and an i.m. injection of 60,000 U of penicillin G benzathine and penicillin G procaine in an aqueous suspension (Durapaq; Vedco Inc., Overland Park, KS). Rats were allowed to recover for 10 days before the start of experimentation.

**Data Acquisition and Analysis.** Individual rat cages were placed on the top of the radio receivers and all data were collected with a computerized data acquisition system (Datasync ART, Datasciences). The system is designed to cycle from animal to animal. Measurement of the hemodynamic variables (systolic BP, diastolic BP, MAP, and HR) started immediately after implantation of the telemetry units to ensure proper operation of the system. Waveforms of BP for each rat was sampled at a rate of 500 Hz for 10 s every 10 min. The data were averaged in 60-min blocks for analysis. All parameters were averaged over a 7-day period for weekly values.

**Measurement of Plasma NE**

NE (picograms per milliliter) was measured by ultrafiltration of the collected plasma followed by HPLC with electrochemical detection as described in El-Mas and Abdel-Rahman (1999). The ultrafiltration probe consisted of three loops of hollow dialysis fibers (10 mm length), with molecular mass cutoff 30,000 Da) joined to a single, nonpermeable conducting tube (Bioanalytical Systems, West Lafayette, IN). The dialysis fibers were placed in the plasma and the conducting tube was connected to a pump (Harvard Apparatus, Holliston, MA) 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) were used along with an amperometric detector model LC-4A (Bioanalytical Systems). The column used was a Sep-
Stik Unicject micro pore column ODS 5 µm, 100 X 1-mm cartridge (Bioanalytical Systems). The mobile phase consisted of NaH₂PO₄ (0.1 M), EDTA (0.11 mM), and octane sulfonic acid (5 mM) modified with 2% acetonitrile and delivered at a rate of 0.9 ml/min. 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 by the enzymatic method described by Bernt and Gutmann (1974) and used in our previous studies (El-Mas and Abdel-Rahman, 1998, 1999).

**Protocols and Experimental Groups**

Four groups of telemetered rats (two SHR and two WKY; n = 6 each) matched for body weight and baseline BP were used in the present study to investigate the hemodynamic responses to chronic ethanol feeding. Two to three days before and 10 days after implantation of the telemetry transmitters, all rats were provided the control liquid diet. Subsequently, the rats that would receive the ethanol-containing liquid diet were fed a liquid diet containing 2.5% (w/v) ethanol (Midwest Grain Products Co., Weston, MO) for 3 days, followed by liquid diet containing 5% (w/v; 36% of total caloric intake) ethanol for the remainder of the study. The other rats (controls) were pair-fed and received isocaloric amount of dextrin/maltose (89.6 g/l) in place of ethanol. Diets were prepared fresh every other day and stored in the refrigerator until dispensed. Diet intake (ml/100 g) was measured every day and the rats were weighed once a week. Rats were maintained on the ethanol or control diet for 12 weeks.

Four additional groups of rats (two SHR and two WKY; n = 7–9 each) were used in the present study and received the same treatments as detailed above but without telemetry transmitter implantation. These rats were used for withdrawing blood (from the tail vein) for the determination of BEC (0.4 ml, weekly) and plasma NE levels (0.35 ml, every 2 weeks) that were correlated to the changes in hemodynamics. Blood was not withdrawn from the telemetry rats to avoid any hemodynamic alterations due to animal handling and tail vein puncturing. The blood was collected at 10:00 to 11:00 AM (2 h after feeding) into heparinized tubes. Blood samples for NE determination were collected into heparinized tubes containing 10 f of perchloric acid (0.1 M). The collected blood samples were centrifuged at 5000 rpm for 5 min and the plasma was aspirated and stored at −80°C until analyzed. Liquid diet intake was measured every day, whereas body weight was measured weekly.

**Statistical Analysis.** Values are presented as mean ± S.E. The time course data and the between-group responses were analyzed by repeated-measures two-way ANOVA followed by a Fisher-protected least-significant difference post hoc analysis. This test distinguishes between-subject variability from within-subject variability and it was used to analyze the effects of chronic ethanol feeding on body weight, liquid diet and ethanol intakes, BEC, plasma NE levels, MAP, BP variability, and HR. The BP variability was determined by computing the standard deviation of MAP as in our previous study (El-Mas et al., 1994a). Probability levels less than .05 were considered significant. Time-series analysis to assess the circadian/diurnal fluctuations in MAP were performed on daily 60-min mean values by PROC SPECTRA, a component of the SAS statistical package (SAS Institute, Cary, NC).

**Results**

**Baseline Data.** Baseline hemodynamic values obtained from telemetered WKY rats and SHRs before ethanol feeding (week 0) showed interstrain differences. The SHRs exhibited higher MAP (144 ± 3 versus 101 ± 1 mm Hg) and BP variability (12.5 ± 0.5 versus 9.3 ± 0.3 mm Hg), and lower HR (330 ± 7 versus 396 ± 6 beats/min) compared with WKY rats. Plasma NE levels obtained from similarly treated groups of rats, to avoid the effect of the stress associated with blood sampling on the measured hemodynamics, were higher in SHR than in WKY rats (584 ± 17 versus 498 ± 19 pg/ml). The baseline values of the systolic BP, diastolic BP, and pulse pressure were similar in rats of the same strain (data not shown).

The SHRs exhibited lower baseline body weight compared with age-matched WKY rats (302 ± 9 versus 357 ± 12 g; Fig. 1). The body weight showed gradual and steady increases over the duration of the study in both ethanol and control pair-fed SHR and WKY rats (Fig. 1). Ethanol feeding had no effect on the gain in body weight in WKY rats and caused slight decreases in the gain in body weight in SHRs compared with control rats (Fig. 1). When normalized for body weight, the daily liquid diet intake (Fig. 2) and the ethanol intake (Fig. 3) were higher in SHRs compared with WKY rats starting from the second week until the end of the study. The liquid diet and ethanol intakes showed progressive increases over the course of the study, reached their peak at weeks 4 to 6, and started to decline thereafter (Figs. 2 and 3). BEC measured weekly was similar in the two strains of rats except for a higher level in SHRs at weeks 7 through 9 (Fig. 4). Ethanol was not detectable in the blood of control rats of either strain.

**Hemodynamic Effects of Chronic Ethanol Feeding.** Changes in MAP evoked by chronic ethanol feeding, as compared with control pair-fed rats, are shown in Fig. 5. In control pair-fed rats, the MAP showed slight increases over the duration of the study that amounted to 3.0 ± 1.3 and 8.1 ± 1.5 mm Hg in WKY rats and SHRs, respectively (Fig. 5). Starting with similar baseline MAP at week 0 (139 ± 3 versus 146 ± 5 mm Hg), ethanol feeding caused reductions in BP in SHRs (Fig. 5). Compared with the corresponding values of pair-fed control rats, the hypotensive response started as early as week 1 after ethanol feeding, was maximal at week 5 (~31.4 ± 3.2 mm Hg), and continued throughout the 12-week treatment period (Fig. 5). The hypotensive effect of ethanol in SHRs was associated with reductions in BP variably.
ability (the standard deviation of the MAP) that started at week 5 and continued until the end of the study (Fig. 6). The reductions in BP variability caused by ethanol were associated with a reduction in the circadian fluctuations in BP in the same rats (Fig. 7). The daily 60-min means of MAP exhibited fluctuations throughout the 2-week period (5th and 6th weeks) chosen for this analysis. The 5th week marked the beginning of a reduction in BP variability in SHRs. The application of power spectrum analysis, over its entire range, in ethanol-fed and control rats revealed two distinct peaks. The first clearly identifiable peak in the spectrum for the control animals occurred at a frequency of 0.042 cycle/h, which is 1 cycle every 24 h. The second peak, at a frequency of 0.084 cycle/h, corresponds to 1 cycle every 12 h. The data obtained at the above-mentioned frequencies demonstrated that although the spectrum for ethanol-fed SHRs showed a peak at these same frequencies, it is much less pronounced than for the control animals, which indicates that the circadian rhythm is suppressed in the presence of ethanol (Fig. 7, left, bottom). Unlike its effects in SHRs, ethanol caused slight decreases (~5 mm Hg) in MAP (Fig. 5), and had no effect on BP variability (Fig. 6) and the circadian fluctuations in MAP (Fig. 7) in WKY rats. Baseline BP values obtained at week 0 were similar in the control and ethanol WKY rats (103 ± 1 versus 100 ± 2 mm Hg). The lack of a hypotensive response to ethanol in WKY rats was associated with a sympathoexcitatory response as indicated by the increases in plasma NE levels (Fig. 8). Figure 8 summarizes the changes...
produced by ethanol or control diet in plasma NE levels, measured every other week, in SHRs and WKY rats. Baseline plasma NE levels obtained in the two WKY groups at week 0 were similar, 471 ± 21 versus 525 ± 30 pg/ml for the control and ethanol groups (n = 6 each), respectively. The ethanol evoked increases in plasma NE levels in WKY rats started at week 2 and continued until week 12 of the study (Fig. 8). In contrast, an increase in plasma NE levels by ethanol in SHRs, compared with control SHRs, was demonstrated only at week 2 (Fig. 8). Baseline plasma NE levels obtained in the two SHR groups at week 0 were similar, 582 ± 31 versus 586 ± 12 pg/ml in the control and ethanol-fed rats (n = 6 each), respectively.

Figure 9 depicts the HR responses to chronic feeding of ethanol or isocaloric control diet in WKY rats and SHRs. Baseline HR values obtained at week 0 were similar in the two groups of each strain, which served as control and ethanol-fed rats; WKY rats (399 ± 5 versus 392 ± 6 beats/min) and SHRs (324 ± 13 versus 336 ± 5 beats/min). In control groups (SHR and WKY), the HR was decreased during the first 2 weeks and then remained stable until the end of the study. A similar pattern was observed in ethanol-fed WKY rats. However, the smaller reductions in HR in ethanol-fed WKY rats resulted in higher HR values compared with control values during the first 8 weeks of the study (Fig. 9). In SHRs, ethanol caused no change in HR (Fig. 9).

**Discussion**

The present study used, for the first time, the radiotelemetry technique to investigate the chronic hemodynamic effects of ethanol in rats. The most important finding of the study was that ethanol feeding for 12 weeks elicited strain-dependent hemodynamic and sympathetic effects. Although ethanol had no effect on BP in WKY rats, it caused substantial decreases in BP in SHRs that started within 1 week and continued thereafter. The BP variability and the circadian fluctuations in BP also were reduced by ethanol in SHRs versus no effect in WKY rats. The inability of ethanol to lower BP in WKY rats may relate to the concomitant increases in sympathetic activity, as suggested by the higher plasma NE levels, and HR. The SHRs consumed greater amounts of ethanol but exhibited, except for weeks 7 through 9, similar BEC to those of WKY rats, suggesting that the variability in the hemodynamic responses to ethanol in the two rat strains may not relate to differences in BEC.

The present study showed that ethanol elicited variable hemodynamic profiles in normotensive and hypertensive rats. Ethanol produced decreases in BP and BP variability in SHRs versus no effect in WKY rats. The findings in SHRs support previous observations that demonstrated hypotensive effect for ethanol in SHRs (Howe et al., 1989; Beilin et al., 1992; Guillaume et al., 1996). In contrast, the BP responses to ethanol in normotensive rats have been conflicting (Abdel-Rahman and Wooles, 1987; Beilin et al., 1992; Hatton et al., 1992). Compared with respective controls, WKY ethanol-fed rats, but not SHRs, exhibited higher HR. The ethanol-evoked tachycardia in WKY rats appeared to be sympathetically mediated as suggested by the presence of higher plasma NE level in the nontelemetry ethanol-fed WKY rats. These sympathoexcitatory and tachycardic responses to ethanol may explain, at least in part, the lack of a hypotensive response to ethanol in WKY rats. It is notable, however, that the interpretation of HR responses and their significance were complicated by the finding that the HR in the control groups (SHR and WKY) showed gradual reductions over the first 2 weeks of the study (Fig. 9). Reported findings concerning the effect of ethanol feeding on HR are conflicting (Abdel-Rahman et al., 1985; Abdel-Rahman and Wooles, 1987; Howe et al., 1989). Although we allowed 10 days after instrumentation for recovery as reported by others (Hess et al., 1996; Webb et al., 1998), it seems that this period was not long enough for HR to stabilize even though it was adequate for BP. It seems advantageous in future studies that a longer time (3–4 weeks) is allowed for recovery.

The mechanism by which ethanol lowers BP in SHRs is not clear. It may be argued that the strain-dependent hypotensive effect of ethanol is related to the greater ethanol intake in SHRs compared with WKY rats. Nonetheless, the higher ethanol intake in SHRs was not associated with elevated BEC compared with WKY rats. With the exception of a higher level in SHRs at weeks 7 through 9, the BEC was similar in the two rat strains. In contrast, the hypotensive response to ethanol in SHRs started as early as week 1 and was maximal by week 5. Collectively, these findings do not support a role for differences in BEC in the strain-dependent
BP response to ethanol. The finding that SHRs consumed more ethanol is consistent with that of Khanna et al. (1990). The similar BEC in the two rat strains may relate, at least in part, to a higher metabolic rate in SHRs and subsequently a higher daily caloric requirement rather than an ethanol preference per se. Notably, the present results showed that the changes in the BEC were parallel to the corresponding time-related changes in the ethanol intake. The only exception, however, was the decline in BEC in WKY rats at week 4, whereas the ethanol intake remained at its peak until week 6 (Figs. 3 and 4). Although the reason for this discrepancy is not known, this finding infers that the metabolic function in WKY rats may be altered by ethanol feeding. Notably, the BEC achieved in the present study, particularly during the first few weeks (400 mg/dl), is not consistent with levels attained in humans after moderate alcohol consumption (Potter and Beevers, 1984; Abdel-Rahman et al., 1987). Furthermore, experimental findings, including our own (Abdel-Rahman and Wooles, 1987; Hatton et al., 1992), have shown that ethanol consumption by rats, at amounts similar to those of the present study, produced a BEC of 30 to 60 mg/dl. In these reported studies, however, ethanol was added to the drinking water (Abdel-Rahman and Wooles, 1987) or to regular liquid diet (Abdel-Rahman et al., 1985; Hatton et al., 1992) versus high protein diet in the present study. Whether the difference in BEC is due to differences in the diet regimen is not clear and needs further investigation. It is notable, however, that the diet nutritional composition has no impact on the systemic availability of ethanol in humans (Jones et al., 1997). The hypotensive effect of ethanol in SHRs also cannot be attributed to ethanol-mediated myocardial hyper-

Fig. 7. Daily 60-min means of arterial BPs of radiotelemetered ethanol-fed SHRs or WKY rats and pair-fed controls obtained during the 5th (upper left) and 6th (lower left) weeks of the experiment. The right-hand graphs show the power spectra for the 60-min means of arterial pressure obtained during the 2-week observation period for the four groups. The top center and right-hand graphs are the smoothed power spectra, over their entire range for the treatment and control groups. Note the two identifiable peaks at ~0.042 and 0.084 cycle/h; these peaks correspond to 1 cycle every 24 and 12 h, respectively. The bottom center and right-hand graphs depict the power spectra at the range of frequencies from 0.02 to 0.11 cycle/h to illustrate the difference in peak heights between the ethanol-fed and control groups. Note that these clearly identifiable peaks that correspond to fluctuations in mean BP every 12 and 24 h are virtually abolished by ethanol in SHRs but not in WKY rats.

Fig. 8. Changes in plasma NE levels evoked by ethanol feeding inagematched WKY rats and SHRs. Values are means ± S.E. of seven to nine observations. *P < .05 versus respective control values.
may be attributed, however, to the ability of ethanol to increase the metabolic rate and the resting energy expenditure (Klesges et al., 1994). The energy loss caused by ethanol is thought to be related to the induction of microsomal pathways or to the development of liver damage (Lieber, 1991).

The net BP response to ethanol represents the algebraic sum of its cardiovascular excitatory effects such as sympathoexcitation (Chan et al., 1985) and baroreflex attenuation (Abdel-Rahman and Wool es, 1987) on the one hand and the inhibitory effects such as direct myocardial depression (Kelback et al., 1985), vasodilation (Turlapaty et al., 1979), and α-adrenergic blockade (Abdel-Rahman et al., 1985) on the other. Given that SHRs exhibit elevated sympathetic activity (Abdel-Rahman, 1994a) and attenuated baroreflex function (Abdel-Rahman, 1994c) compared with normotensive rats, it is conceivable that the excitatory effects of ethanol would be less evident in SHRs. This assumption gains support from the present finding that ethanol increased the sympathetic activity in WKY rats but not SHRs. Furthermore, findings from our laboratory have shown that the sympathoexcitatory response to ethanol is inversely related to the preexisting sympathetic activity (El-Mas et al., 1994b) and ethanol attenuation in baroreflex function demonstrated in normotensive rats is absent in SHRs (Abdel-Rahman, 1994c). Collectively, the ability of ethanol to lower BP in SHRs but not in WKY rats may relate, at least partly, to the predominance of the inhibitory hemodynamic effects of ethanol in SHRs.

Analysis of the circadian fluctuations in BP revealed additional effects of ethanol on BP, which was evident in SHRs but not in WKY rats. Subjecting the daily 60-min means of MAP over the 5th and 6th weeks of treatment to power spectral analysis demonstrated circadian changes, which occurred at 12 and 24 h. The circadian fluctuations in BP, detectable clearly in liquid diet-fed rats, were maintained in ethanol-fed WKY rats but virtually absent in ethanol-fed SHRs. These findings suggest an impairment of this physiological phenomenon by ethanol in SHRs. Notably, ethanol-evoked reduction of the circadian rhythm coincided with a similar reduction in BP variability in the same SHRs. Although the mechanism by which ethanol produces these effects is not known, the present findings may suggest an inhibitory action of ethanol on the sympathetic control of BP in SHRs. Recent evidence suggests a dependence of the circadian fluctuations in BP on the sympathetic nervous system (Makino et al., 1997). Although the present study is the first to demonstrate an inhibitory action of ethanol on the circadian fluctuations of BP in SHRs, further studies are warranted to investigate the mechanism of this action.

In summary, the present study determined the long-term hemodynamic effects of ethanol in radiotelemetered rats. Ethanol evoked a strain-dependent effect on the BP, producing immediate (within 1 week) and sustained decreases in BP in SHRs versus no effect in WKY rats. A sympathoexcitatory response was demonstrated only in ethanol-fed WKY rats, which may have contributed, at least in part, to the lack of ethanol-mediated hypotension in these rats. The hypotensive effect of ethanol in SHRs may not be accounted for by the differences in fluid or nutrient intakes as the rats in the ethanol and control groups were pair-fed.
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Send reprint requests to: Abdel A. Abdel-Rahman, Ph.D., Department of Pharmacology, School of Medicine, East Carolina University, Greenville, NC 27838. E-mail: rahman@brody.med.ecu.edu