Decreased vascular responsiveness to noradrenaline following regular ethanol consumption

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- 1 Ten normal volunteers consumed 80 g of ethanol per day or abstained from ethanol for 4 consecutive days prior to measurements of blood pressure, heart rate, vascular responsiveness to noradrenaline (NA) and angiotensin II (AII) infusions and sympathetic responsiveness to isometric handgrip exercise in an open, random order, crossed study.
- 2 Supine systolic and diastolic pressures and heart rates, and erect systolic pressures rose significantly following ethanol.
- 3 Vascular responsiveness to NA infusions was reduced in all subjects following ethanol, while responses to AII infusions did not show a consistent pattern of change.
- 4 Plasma renin activity, plasma NA and adrenaline concentrations, and concentrations of the NA metabolite 3,4 dihydroxyphenylethylene glycol (DHPG) did not significantly differ following ethanol and control treatments.
- 5 The rise in plasma NA following 2 min isometric handgrip at 50% of maximal effort was greater following ethanol (0.24 ± 0.21 nM) than control (0.12 ± 0.10 nM) but the difference did not reach statistical significance.
- 6 The pressor effect of regular ethanol consumption and the reduced vascular reactivity to NA may both be the result of an increase in sympathetic activity that was not large enough to measurably alter resting plasma NA concentrations.

Keywords ethanol blood pressure noradrenaline angiotensin

Introduction

An association between ethanol consumption and hypertension has been noted in a number of population studies (Klatsky *et al.*, 1977; Kagan *et al.*, 1981; Arkwright *et al.*, 1982a; Cooke *et al.*, 1982; Wallace *et al.*, 1982; Cairns *et al.*, 1984). While acute ethanol intoxication (Kaysen & Noth, 1984) and hangover (Howes & Reid, 1985) have small and variable effects on blood pressure, moderate ethanol consumption for 3 days has been reported to elevate blood pressures in hypertensives (Potter & Beevers, 1984).

Chronic ethanol administration to rats increases central and peripheral noradrenaline

(NA) turnover (Pohorecky, 1974; Cohen *et al.*, 1980) and chronic alcoholics have clinical and biochemical evidence of sympathetic hyperactivity, particularly during ethanol withdrawal (Ogata *et al.*, 1971; Beevers *et al.*, 1982). It is, therefore, possible that increased sympathetic activity contributes to the rise in blood pressure that accompanies both ethanol withdrawal (Potter *et al.*, 1983) and regular, moderate ethanol consumption.

Plasma renin activity (PRA) is increased during ethanol withdrawal (Potter *et al.*, 1983), suggesting that the renin-angiotensin system

may also be involved in the pressor effect of ethanol. However, neither plasma NA levels nor PRA have been found to be elevated in moderate drinkers compared to teetotallers (Arkwright *et al.*, 1982b) or in hypertensives following a period of moderate drinking (Potter & Beevers, 1984). Plasma NA concentrations and PRA may be relatively insensitive indices of sympathetic and renin angiotensin system activity, and do not provide any information about changes in vascular effector mechanisms. In the present study, the possible roles of the sympathetic and renin angiotensin systems in the pressor response to moderate ethanol consumption has been further investigated by measuring vascular responsiveness to NA and angiotensin II (AII) infusions.

Methods

Five normotensive males and five normotensive females aged 25–41 years either abstained from ethanol for 4 days or consumed 80 g of ethanol daily (approximately 4 pints of beer or 200 ml of spirits) in the form of their choice between 17.00 and 24.00 h for 4 successive days in an open, crossed, random order study. The subjects were instructed to maintain their normal caffeine and food intake during each phase of the study, with the exception that no caffeine was consumed on the days when they attended for investigation. They were allowed to consume non-ethanolic drinks *ad libitum* during the entire study. None of the subjects was a smoker, and all usually consumed less than 40 g of ethanol on average per day. On the fifth day of each study period they attended at 09.00 h and were weighed prior to having an intravenous cannula inserted into an antecubital vein. After 30 min supine rest, blood was taken for plasma catecholamines, plasma renin activity, plasma cortisol levels, plasma ACTH levels, serum biochemistry and liver function tests. Supine blood pressures and heart rates were then measured every 2 min for 20 min using a semiautomatic indirect recorder (Sentron) and the values averaged excluding any initial recordings which differed by more than 5 mm Hg from values obtained after the blood pressures were stable. Blood pressures and heart rates were then measured after 1, 2 and 5 min standing. After a further 30 min supine rest, the change in plasma NA and systolic blood pressure after 2 min handgrip at 50% maximum effort was determined.

The subjects then rested supine for 20 min, after which blood pressure responses to vehicle (normal saline) and to progressively increasing infusion rates of NA (0.01, 0.02, 0.05, and

0.1 $\mu\text{g kg}^{-1} \text{ min}^{-1}$) were determined. 1 : 1000 NA tartrate solution containing 1 mg ml^{-1} sodium metabisulphate (Levophed, Winthrop) was diluted in normal saline to a final concentration of 0.1 $\mu\text{g kg}^{-1}$ subject's weight ml^{-1} , immediately prior to infusions. This solution was then infused at rates varying from 0.1 to 2 ml min^{-1} using a Braun Perfusor VI infusion pump. The total volume of this solution infused did not exceed 30 ml per subject on each study day. Blood pressure and heart rate measurements were made at 1 min intervals for 5 min at each infusion rate. Blood pressures were not allowed to rise more than 45 mm Hg systolic or 30 mm Hg diastolic above pre-infusion values. The subjects then rested for 1 h during which time they had a standard light lunch. Following 30 min supine rest after lunch, infusions of AII in progressively increasing doses of 0, 2.5, 5, 10, 25, 50, 100 and 250 $\text{ng kg}^{-1} \text{ min}^{-1}$ were given using the same procedure as described for NA. AII (Hypertensine, Ciba) was dissolved in normal saline to produce a final concentration of 25 ng kg^{-1} subject's weight ml^{-1} immediately prior to use. This solution was infused at rates varying from 0.1 to 5 ml min^{-1} . The total volume of this solution infused did not exceed 60 ml per subject on each study day. The blood pressure dose-response curves in individuals were fitted to a quadratic curve and the PD_{20} (dose of agonist required to raise mean arterial pressure by 20 mm Hg) calculated for each individual as previously described (Sumner *et al.*, 1982). NA infusions were always commenced between 10.30 and 11.00 h and AII infusions commenced between 13.00 and 13.30 h. Written, informed consent was obtained from all volunteers, and the protocol was approved by the Glasgow Northern Hospitals Research and Ethics Committee.

Plasma NA, adrenaline (A) and the NA metabolite 3,4-dihydroxyphenylethylene glycol (DHPG) were assayed by high performance liquid chromatography with electrochemical detection (Howes *et al.*, 1985). Plasma renin activity (PRA), plasma cortisol and plasma ACTH were measured by radioimmunoassay.

Twenty-four h urinary sodium and potassium excretion and urine volume were measured on the fourth day of each study period. All results were expressed as the mean $\pm$ s.d.

Results

Supine systolic and diastolic blood pressures and heart rates, and erect systolic blood pressures after 2 min standing were all significantly higher

Table 1 Supine and erect (following 2 min standing) blood pressures, heart rates, and body weights during ethanol and control study phases, measured between 09.30 and 10.00 h, and 24 h urinary K⁺ and Na⁺ excretion measured on the 4th day of each study phase.

	Control	Ethanol
<i>Supine</i>		
Systolic BP (mm Hg)	112 ± 8	120 ± 9**
Diastolic BP (mm Hg)	60 ± 6	66 ± 5***
Mean arterial pressure (mm Hg)	78 ± 6	84 ± 6***
Heart rate (beats min ⁻¹)	59 ± 9	64 ± 8**
<i>Erect</i>		
Systolic BP (mm Hg)	118 ± 10	126 ± 11*
Diastolic BP (mm Hg)	75 ± 7	73 ± 9
Heart rate (beats min ⁻¹)	78 ± 15	78 ± 11
Body weight (kg)	68.8 ± 11.1	69.0 ± 11.4
24 h Na ⁺ excretion (mmol)	184 ± 45	224 ± 73
24 h K ⁺ excretion	77 ± 7	71 ± 18

Values are the mean ± s.d. for 10 subjects. Significant differences between study phase: * $P < 0.05$, ** $P < 0.025$, *** $P < 0.001$ (Student's paired t -test).

at 09.30–10.00 h following ethanol than control (Table 1). Figure 1 illustrates the change in supine blood pressures and heart rates between ethanol and control phases in individual subjects. Ethanol elevated mean arterial pressures in all subjects, but the extent of the rise varied considerably (range 1–12 mm Hg). The rise in mean arterial pressure was significantly higher in males than in females ($P < 0.025$, Student's unpaired t -test). Mean arterial pressures prior to NA infusions (11.00 h) were also significantly higher following ethanol (84.5 ± 6.5) than control (78.6 ± 5.5) ($P < 0.001$, Student's paired t -test). Ethanol increased the PD₂₀ for NA in all subjects (Figure 2), indicating a decrease in vascular responsiveness to NA. PD₂₀ values for NA following ethanol (38.5 ± 1.2 ng kg⁻¹ min⁻¹) were significantly higher than for control (25.8 ± 9.0) ($P < 0.01$, Student's paired t -test).

Following lunch and immediately prior to AII infusions, mean arterial pressures were lower than before NA at 78.7 ± 7.3 and 75.2 ± 4.4 during the ethanol and control phases respectively. While mean arterial pressures were still higher at this time point for the ethanol phase than for the control phase, the difference was not statistically significant ($P = 0.133$).

Ethanol had no consistent effect on dose-response curves to AII and PD₂₀ values for AII following ethanol (18.6 ± 11.9 ng kg⁻¹ min⁻¹) did not differ significantly from control (24.16 ± 16.0) (Figure 3).

Changes in heart rates during NA and AII infusions following ethanol did not differ from control.

Plasma NA, A, and DHPG levels were similar following both ethanol and control phases (Table 2). The rise in plasma NA levels following isometric exercise appeared to be higher following ethanol, although the difference did not reach statistical significance (Table 2). Systolic blood pressure rises following isometric exercise were similar during ethanol (12.4 ± 7.2 mm Hg) and control (18.5 ± 13.3) phases ($P = 0.242$). PRA did not significantly differ between alcohol (13.33 ± 6.26 u ml⁻¹) and control (13.01 ± 7.35 u ml⁻¹) phases. PRA correlated significantly

Figure 1 Changes in blood pressures (mm Hg) and heart rates (beats min⁻¹) between ethanol and control phases of the study (ethanol–control); ■ males, □ females.

Figure 2 PD_{20} for noradrenaline (i.e. dose of agonist required to raise mean arterial pressure by 20 mm Hg) following 4 days of consuming 80 g of ethanol per day (Ethanol) and 4 days of abstaining from ethanol (Control). The lines join values from individual subjects; ■ males, □ females.

with PD_{20} values for AII infusions during the ethanol phase of the study ($r = 0.6824$, $P < 0.05$) but not during the control phase ($r = 0.4685$, $P = 0.172$).

Plasma cortisol levels were a little higher following ethanol (482 ± 154 nM) than control (414 ± 156 nM), but the difference was not significant ($P = 0.105$, Student's paired t -test). Plasma ACTH levels following ethanol (20.7 ± 11.1 ng l⁻¹) did not differ from control (19.1 ± 9.5 ng l⁻¹).

Twenty-four hour urine volume was higher during the ethanol phase (3441 ± 967 ml) than control (1401 ± 575) ($P < 0.025$). Twenty-four hour urinary sodium excretion was a little higher during the ethanol phase than control, but the difference was not statistically significant. Potassium excretion over the same period did not differ (Table 1). Serum biochemistry (NA⁺, K⁺, A⁻, HCO₃⁻, urea, creatinine, total Ca⁺⁺, phosphate, albumin, globulin, bilirubin, AST, ALT, LDH, γ -GT and urate) did not differ between the two study periods. The subjects' weights were the same on both study days (Table 1).

Discussion

These data confirm the findings of Potter & Beevers (1984) in hypertensive males that moderate ethanol consumption for several days elevates blood pressure. An interesting finding was the greater rise in mean arterial pressure in males than females. Klatsky *et al.* (1977) found

Figure 3 PD_{20} values for angiotensin II (i.e. dose of agonist required to raise mean arterial pressure by 20 mm Hg) following 4 days of consuming 80 g of ethanol per day (Ethanol) and 4 days of abstaining from ethanol (Control). The lines draw values from individual subjects; ■ males, □ females.

that the regular consumption of 10–20 g of ethanol per day was associated with fall in blood pressure in females, and that at higher levels of ethanol consumption the associated rise in blood pressure was greater in males. However, subsequent epidemiological studies have not confirmed this report (Cooke *et al.*, 1982; Cairns *et al.*, 1984).

The reduction in vascular reactivity to NA following ethanol in the present study suggests either a down regulation of postsynaptic α -adrenoceptors or adrenergic effector mechanisms, a specific effect of ethanol on α -adrenoceptors or a non-specific impairment of smooth muscle responsiveness. While a non-specific reduction in vascular responsiveness occurs following acute ethanol administration (Altura & Altura, 1983; Eisenhofer *et al.*, 1984), this is associated with a tendency for blood pressures to fall rather than rise (Eisenhofer *et al.*, 1984; Howes & Reid, 1985).

Diminished vascular responsiveness to NA due to down regulation of α -adrenoceptors may constitute indirect evidence that sympathetic hyperactivity participates in the pressor response to regular, moderate ethanol consumption. Chronic ethanol administration to rats increases NA turnover (Pohorecky, 1974; Cohen *et al.*, 1980) and decreases α_1 -adrenoceptor numbers in liver and brain (Ciofalo, 1980; Lee

Table 2 Plasma levels (nM) of noradrenaline, adrenaline and the catecholamine metabolite DHPG, and the change in plasma noradrenaline following 2 min isometric handgrip exercise during ethanol and control study phases (mean $\pm$ s.d.).

	Control	Ethanol
<i>Supine resting</i>		
Noradrenaline (nM)	0.79 $\pm$ 0.19	0.82 $\pm$ 0.29
Adrenaline (nM)	0.29 $\pm$ 0.19	0.30 $\pm$ 0.17
DHPG (nM)	3.99 $\pm$ 1.09	3.88 $\pm$ 1.01
Change in noradrenaline after isometric exercise	0.12 $\pm$ 0.10	0.24 $\pm$ 0.21

Values did not significantly differ between study phases (Student's paired *t*-test), although the difference in response to isometric exercise almost reached statistical significance ($P = 0.083$).

et al., 1983). Similarly, chronic alcoholics have evidence of increased noradrenergic activity (Ogata *et al.*, 1971) and attenuated α_2 -mediated changes in insulin and growth hormone release (Nygren & Sunblad, 1980). An increase in sympathetic activity following ethanol was also suggested in the present studies by the tendency for a greater rise in plasma NA following isometric exercise and the increase in resting heart rates. However, plasma NA and DHPG levels were similar during both the ethanol and control study phases. It is possible that reciprocal changes in α -adrenoceptor responsiveness provide a more sensitive index of changes in sympathetic activity under these circumstances than plasma NA levels.

While vascular responsiveness to NA was decreased following ethanol, vascular responsiveness to AII did not change in a consistent manner. It should be noted, however, that mean arterial pressures prior to AII infusions were not significantly higher following ethanol than control. This raises the possibility that the effects of ethanol on blood pressure and perhaps on vascular reactivity to AII differed during AII infusions compared to during NA infusions. It should also be noted that although two subjects had an apparent increase in vascular reactivity to ethanol in the other subjects the predominant affect of ethanol was to reduce vascular reactivity to AII. In addition, PRA activity following ethanol correlated significantly with the PD₂₀ values for AII infusions. Because of the above considerations, it is not possible to exclude the involvement of the renin angiotensin system in the elevation of blood pressure following regular, moderate ethanol consumption from the data in the present study.

It was of interest to note the greater urine output during the ethanol phase than during the control phase. This most likely resulted from a combination of a greater intake of fluid in the form of alcoholic drinks and a diuresis secondary to acute suppression of arginine vasopressin (AVP) secretion by ethanol (Eisenhofer & Johnson, 1982). However, any net diuretic effect of ethanol was presumably compensated by an increase in non-alcoholic fluid intake as the subjects' body weights and erect heart rates were the same on both study days. It is therefore unlikely that the changes in vascular reactivity observed were the result of alterations in fluid balance. It should also be noted that 24 h sodium excretion tended to be higher during the ethanol phase than the control phase. Sodium loading has been reported to diminish vascular α_2 -adrenoceptor mediated responses in rats (Kohlmann *et al.*, 1985). It is, therefore, possible that differences in sodium intake between the ethanol and control phases contributed to the differences in vascular reactivity to NA. However, such a contribution is unlikely to have been substantial as in some subjects sodium excretion was actually lower during the ethanol phase and the difference in sodium excretion between study phases was not statistically significant.

While the present study may provide evidence that sympathetic hyperactivity contributes to the rise in blood pressure that follows regular ethanol consumption, it is quite possible that other mechanisms are involved. For instance, plasma cortisol levels have been shown to rise following regular ethanol consumption (Potter & Beevers, 1984) and to correlate with blood pressure in regular moderate drinkers (Arkwright *et al.*, 1984) and alcoholics during withdrawal (Potter *et al.*, 1983). However, while plasma cortisol levels were elevated by 16% following ethanol in the present study, the difference was not statistically significant.

It is clear that further studies are needed to characterise the relationship between alterations in adrenoceptors, sympathetic activity and blood pressure following regular, moderate ethanol consumption and to evaluate further changes in the renin angiotensin system. However, the present study has demonstrated that changes in sympathetic function which may be related to an elevation of blood pressure do occur following regular, moderate ethanol consumption in man.

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