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Influence of intravenous infusion of ethanol on regional blood flow in conscious rats

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Abstract—The effects of intravenous infusions of ethanol and saline (0·9% NaCl) on mean arterial pressure (MAP), heart rate (HR), total peripheral resistance (TPR), cardiac contractility (dP/dt_{max}) and systemic haemodynamics were studied in conscious, unrestrained rats by the radioactive microsphere technique. Saline (0·03 and 0·06 mL min^{-1} kg^{-1} for 12 min each dose) in the time-control group did not affect MAP, HR, TPR, dP/dt_{max} or vascular conductances in any organs or beds. While the low dose ethanol (2·4 mg min^{-1} kg^{-1}) did not alter MAP, HR, TPR, systemic haemodynamics or dP/dt_{max}, the high dose (4·8 mg min^{-1} kg^{-1}) slightly reduced MAP and TPR but did not affect HR, cardiac output or dP/dt_{max}. Both doses of ethanol vasodilated the intestine and spleen, but vasoconstricted the skin. The high dose caused additional vasodilatation in the heart and testes and the low dose also constricted the skeletal muscle bed. Our results show that ethanol, at non-hypotensive or slightly hypotensive doses, has marked vasodilator effects in the heart, intestine, spleen and testes.

The acute cardiovascular effects of ethanol are complex and may include central (Zhang et al 1989; Varga & Kunos 1990) or peripheral (Carpentier & Gallardo-Carpentier 1987) modulations of autonomic discharge and peripheral vasodilatation (Abel 1980; Kettunen et al 1983; Kupari 1983; Pescio et al 1983; Kawasaki et al 1990) or vasoconstriction (Kettunen et al 1983; Drummond & Shrager 1985; Koskinen et al 1986). Ethanol reduced total peripheral resistance (Kupari 1983; Kettunen et al 1983), increased portal venous (Kawasaki et al 1990) and coronary (Abel 1980; Pescio et al 1983) flows but caused pulmonary vasoconstriction (Kettunen et al 1983; Drummond & Shrager 1985; Koskinen et al 1986). Depending on the dose, ethanol either increased or decreased portal venous flow (Jenkins et al 1986). A non-hypotensive dose of ethanol in anaesthetized rats and conscious, nonstressed rats was found to decrease blood pressure of conscious, stressed animals (Sparrow et al 1987). The vasodilator effects of ethanol is suggested to be due to the interference of both calcium influx and release at the membrane level (Turlapaty et al 1979). The constrictor effect, on the other hand, is attributed to the potentiation of the effects of endogenous vasoactive agents, such as catecholamines and vasopressin (Edgarian & Altura 1976; Altura et al 1976) but not angiotensin II (Edgarian & Altura 1976), and the direct effect of ethanol on blood vessels (Fewings et al 1966; Altura et al 1990). Ethanol reduced ventricular contractility in conscious (Horwitz & Atkins 1974) and pentobarbitone-anaesthetized dogs (Friedman et al 1979).

There is no available information on the dose-response effects of ethanol on the distribution of regional blood flows. The aim of this study was to examine the acute effects of two doses of ethanol on blood pressure, cardiac output and contractility as well as regional haemodynamics. The high dose was selected to be one which interfered with the gait of the rats. Conscious, unrestrained rats were studied in order to avoid the use of anaesthetic drugs which are known to suppress vascular smooth muscle tone, myocardial function and cardiovascular reflexes. Anaesthetics also modulate the effects of ethanol thereby confounding the interpretation of results.

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Materials and methods

Surgical preparation. Two groups (n = 6 each) of male Sprague-Dawley rats, 370–390 g, were used. The rats were briefly anaesthetized with halothane (1·5% in air) for the insertion of cannulae (PE50) into both iliac arteries, iliac vein and the left ventricle (via the right carotid artery). All cannulae were filled with heparinized (25 int. units mL^{-1}) saline (0·9% NaCl) and tunnelled subcutaneously to the back of the neck, exteriorized and secured. The animals were given 24 h recovery from the effects of anaesthesia and surgery before use.

Before the commencement of experiments, baseline values of blood pressure, heart rate and left ventricular pressure were monitored for 1 h. Pressures were recorded with pressure transducers (PD 23B Gould Statham, CA, USA) connected to a Grass polygraph. Heart rate (HR) was electronically derived from the upstroke of the arterial pulse pressure by a Grass Tachograph (Grass, Model 7P4G). Contractility (dP/dt_{max}) was derived from the upstroke of left ventricular pressure by a differentiator (Grass, Model 7P20C). The effects of 12 min infusions of each dose of saline (0·03 and 0·06 mL kg^{-1} min^{-1}) and ethanol (2·4 and 4·8 mg kg^{-1} min^{-1}, same volumes given as for saline) on mean arterial pressure (MAP), HR, dP/dt_{max}, cardiac output, total peripheral resistance (TPR) and regional blood flows were examined. Both doses of ethanol (or saline) were infused into the same group of rats with the low dose given first and no recovery between doses.

Microsphere technique. Suspensions of microspheres (15 μm diam., New England Nuclear, MA, USA), labelled with either ^{57}Co, ^{113}Sn or ^{103}Ru (25 000–35 000 microspheres in 200 μL for each rat) were injected into the left ventricle immediately before and 12 min after the start of each infusion of saline or ethanol. The time taken for the injection of the microspheres and blood withdrawal was less than 1·5 min. The method has been described in detail (Pang 1983). The order of injection of the labelled microspheres was rotated in each experiment in order to eliminate variabilities due to different counting efficiencies of the isotopes. Reference blood samples were withdrawn (Harvard infusion/withdrawal pump, MA, USA) from the iliac arterial cannula at 1 mL kg^{-1} min^{-1} for the determination of cardiac output and regional blood flows. After the injection of the final set of microspheres, the animals were killed by an overdose of pentobarbitone. Blood samples, tissue samples, syringes used for injections and collection of blood and test tubes used for holding the microsphere samples were counted for radioactivity using a Searle 1185 automatic gamma counter (Nuclear-Chicago, IL, USA). The ^{113}Sn counts were corrected by subtracting ^{103}Ru spillover (7%) while ^{57}Co counts were corrected for ^{103}Ru (25%) and ^{113}Sn (16%) spillovers. Only 40 g each of the muscle and skin were taken for counting. The samples of skin were obtained from the dorsal and ventral areas and the muscle samples were taken from the chest, abdomen, limbs, diaphragm and back.

Data and statistical analysis. Blood flows to various organs were expressed as total flow in the organ or tissue and conductance (i.e. total flow divided by MAP). Conductance was calculated in order to assess active changes in vascular tone. Statistical

Table 1. Effects of ethanol and saline on mean arterial pressure (MAP), cardiac output (CO), total peripheral resistance (TPR), heart rate (HR), first derivative of left ventrical pressure (dP/dt_{max}) in two groups of conscious rats (n = 6 per group). Values (mean ± s.e.m.) were determined in controls and 12 min after the start of the infusion of each dose of ethanol or saline.

	Ethanol			Saline		
	Control	2·4 (mg min^{-1} kg^{-1})	4·8	Control	0·03 (mL min^{-1})	0·06
MAP (mmHg)	103 ± 3	109 ± 5	98 ± 5*	113 ± 2	114 ± 5	120 ± 7
CO (mL min^{-1})	110 ± 10	115 ± 7	111 ± 5	112 ± 11	109 ± 7	105 ± 10
TPR (mmHg min^{-1} mL^{-1})	0·98 ± 0·09	0·96 ± 0·05	0·90 ± 0·07*	1·0 ± 0·09	1·1 ± 0·08	1·1 ± 0·08
HR (beats min^{-1})	350 ± 11	378 ± 9	362 ± 8	369 ± 11	367 ± 7	407 ± 22
dP/dt_{max} (mmHg s^{-1})	9582 ± 436	10583 ± 396	9500 ± 447	10750 ± 382	10917 ± 396	11333 ± 401

* Significantly different from saline-treated controls ($P < 0·05$).

analyses were carried out by the analysis of variance followed by Duncan's multiple range test with $P < 0·05$ taken as the criterion for statistical significance.

Drugs. Ethanol was obtained from the Department of Chemistry at the University of British Columbia and diluted with distilled water. Halothane and sodium pentobarbitone solutions were obtained from Ayerst Laboratories (Montreal, Canada) and Canada Packers Inc. (Cambridge, Canada), respectively.

Results

Neither saline nor ethanol (both doses) significantly altered MAP, cardiac output, TPR, HR and dP/dt_{max} from the corresponding baseline values within the same group (Table 1). However, when the effects of ethanol were compared with those of saline in the time-control group, it was found that the high dose significantly reduced MAP and TPR. None of the other parameters in the ethanol groups were different from those in the control group.

Both doses of ethanol increased blood flows in the heart, intestine, spleen and testes and decreased flow in the skin (Table 2). Saline caused a time-dependent increase in blood flow in the heart, but did not alter flows in other organs or tissues.

Conductance for individual vascular beds was found to reflect active changes in smooth muscle tone independent of changes in MAP (Table 3). Saline did not alter vascular conductances in any beds. Overall, ethanol caused generalized vasodilatation with the exception of the skin and muscle which were vasoconstricted. Both doses of ethanol significantly increased conductance in the intestine, caecum and spleen and reduced conductance in the skin. In addition, the high dose increased conductance in the heart and testes and the low dose reduced muscle conductance. The effects on muscle and skin conductance were not dose-dependent; while the low dose reduced muscle and skin conductances by 42 and 52%, the high dose reduced conductances by 26 and 32%, respectively, compared with the corresponding baseline values.

Discussion

The results of this study show that acute infusions of ethanol, at doses which have slight or no effects on MAP, HR and cardiac contractility, caused marked vasodilatation in the heart, gastrointestine, spleen and testes but vasoconstriction in the muscle and skin. Others have also reported that ethanol increases splanchnic (Kawasaki et al 1990) and coronary (Abel 1980; Pescio et al 1983) flows. Ethanol nonspecifically attenuated the dilator responses of vasoactive drugs in the splanchnic terminal vascular bed in-situ (Altura et al 1979). Our results also show that, while vasodilatations elicited by ethanol in most beds show dose-dependency, vasoconstriction changes in the muscle and skin were greater for the small than for the large dose.

The mechanism by which ethanol causes vasoconstriction in the muscle and skin is unclear. Since the low, non-hypotensive dose caused more vasoconstriction than the high, hypotensive dose, the response is not simply a consequence of hypotension-induced increase in vasomotor tone. Ethanol has been shown to

Table 2. Blood flows to the various organs and tissue samples. Values (mL min^{-1}, mean ± s.e.m.) were determined in the control before the infusion of either ethanol or saline and 12 min after the start of the infusion of each dose of ethanol or saline in two groups of conscious rats (n = 6 each).

	Ethanol			Saline		
	Control	2·4 (mg min^{-1} kg^{-1})	4·8	Control	0·03 (mL min^{-1})	0·07
Lung	1·4 ± 0·4	1·0 ± 0·1	1·3 ± 0·4	1·0 ± 0·1	1·6 ± 0·4	1·0 ± 0·2
Heart	4·6 ± 0·3	6·4 ± 0·4[a]	7·0 ± 0·7[a]	5·0 ± 0·4	5·4 ± 0·4	6·5 ± 0·9[a]
Liver	1·5 ± 0·3	1·3 ± 0·3	1·8 ± 0·6	1·3 ± 0·4	1·4 ± 0·2	1·8 ± 0·5
Stomach	1·4 ± 0·1	1·3 ± 0·2	1·6 ± 0·6	1·8 ± 0·3	1·8 ± 0·4	1·6 ± 0·3
Intestine	14·6 ± 1·0	20·6 ± 0·0[a]	20·5 ± 2·0[a]	14·6 ± 2·0	14·5 ± 2·0	15·2 ± 3·0
Caecum	3·1 ± 0·3	4·5 ± 0·6	4·2 ± 0·6	3·3 ± 0·5	3·4 ± 0·6	3·6 ± 0·8
Colon	2·3 ± 0·5	2·7 ± 0·4	3·3 ± 0·6	2·2 ± 0·2	2·0 ± 0·4	2·1 ± 0·4
Kidneys	23·5 ± 1·7	25·4 ± 1·6	30·0 ± 3·0	21·2 ± 0·0	19·3 ± 2·2	18·2 ± 1·0
Spleen	1·6 ± 0·1	3·3 ± 0·8[a]	3·8 ± 0·7[a]	2·7 ± 0·7	2·8 ± 0·4	3·4 ± 0·4
Muscle (40 g)	4·6 ± 0·8	3·1 ± 0·8	3·3 ± 0·5	5·1 ± 0·9	4·3 ± 0·3	3·8 ± 0·5
Skin (40 g)	6·7 ± 0·3	3·8 ± 0·3[a]	4·0 ± 0·3[a]	5·9 ± 0·8	5·4 ± 0·8	4·5 ± 0·5
Testes	1·2 ± 0·1	1·4 ± 0·1[a]	1·8 ± 0·1[a]	1·5 ± 0·1	1·4 ± 0·2	1·6 ± 0·2
Brain	1·8 ± 0·1	1·9 ± 0·3	2·1 ± 0·2	2·1 ± 0·2	2·1 ± 0·2	2·4 ± 0·3

[a] Significantly different from their respective control values ($P < 0·05$).

Table 3. Conductances in the various organs and tissue samples. Values (mL min^{-1} $mmHg^{-1}$ × 100, mean ± s.e.m.) were determined in the control and 12 min after the start of the infusion of each dose of ethanol or saline in two groups of conscious rats (n = 6 each).

	Ethanol			Saline		
Organ	Control	2·4 (mg min^{-1} kg^{-1})	4·8	Control	0·03 (mL min^{-1})	0·06
Lung	1·3 ± 0·4	1·0 ± 0·1	1·4 ± 0·7	1·0 ± 0·1	1·2 ± 0·3	0·7 ± 0·1
Heart	4·0 ± 0·2	6·0 ± 0·3	7·0 ± 0·8[a]	4·5 ± 0·2	4·6 ± 0·3	5·1 ± 0·6
Liver	1·4 ± 0·4	1·1 ± 0·4	1·7 ± 0·7	1·1 ± 0·2	1·0 ± 0·2	1·5 ± 0·4
Stomach	1·1 ± 0·2	1·3 ± 0·2	1·3 ± 0·2	1·3 ± 0·2	1·4 ± 0·3	1·3 ± 0·2
Intestine	13·2 ± 1·0	19·0 ± 1·0[a]	20·0 ± 1·0[a]	12·7 ± 2·0	11·3 ± 2·0	10·0 ± 3·0
Caecum	2·8 ± 0·2	4·0 ± 0·4[a]	4·0 ± 0·5[a]	2·7 ± 0·5	3·1 ± 0·6	2·7 ± 0·5
Colon	2·0 ± 0·5	2·3 ± 3	3·2 ± 0·4	2·8 ± 0·1	1·6 ± 0·3	1·6 ± 0·3
Kidneys	22·8 ± 1·7	23·5 ± 2·2	32·0 ± 4·0	16·0 ± 2·7	17·3 ± 2·4	15·0 ± 1·0
Spleen	1·3 ± 0·2	2·7 ± 0·6[a]	3·2 ± 0·7[a]	2·0 ± 0·2	2·5 ± 0·5	2·8 ± 0·5
Muscle (40 g)	4·3 ± 0·8	2·5 ± 0·6[a]	3·2 ± 0·4[b]	4·5 ± 0·6	4·0 ± 0·4	3·0 ± 0·4
Skin (40 g)	6·2 ± 0·2	3·0 ± 0·4[a]	4·2 ± 0·4[ab]	5·0 ± 0·7	4·5 ± 0·8	4·0 ± 0·4
Testes	1·0 ± 0·1	1·1 ± 0·1	1·8 ± 0·1[ab]	1·1 ± 0·1	1·0 ± 0·2	1·1 ± 0·1
Brain	1·8 ± 0·1	1·6 ± 0·2	2·1 ± 0·3	1·8 ± 0·1	1·8 ± 0·1	2·0 ± 0·3

[a] Significantly different from their respective control values ($P < 0·05$). [b] Significantly different from the first ethanol infusion ($P < 0·05$).

have a direct and dose-dependent vasoconstricting effect on rat cremaster muscle microvasculature in-situ (Altura et al 1990) and to potentiate the contractile effects of pressor agents in arterial and venous smooth muscles (Altura et al 1976; Edgarian & Altura 1976). In-vitro studies show that ethanol releases calcium from intracellular stores in rat hepatocytes; the mechanism may involve the production of inositol 1,4,5 trisphosphate (Reinlib et al 1990). It is not known if the vasoconstrictor effect of ethanol in the muscle and skin is due to direct action or to potentiation of the effects of endogenous vasopressor agents.

In summary, ethanol, at non-hypotensive or slightly hypotensive doses, has great influence on regional blood flow. It causes marked vasodilatation in the heart, intestine, spleen and testes, but vasoconstriction in the muscle and skin.

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