No effect of ethanol ingestion on β -adrenoceptor-mediated circulatory responses to isoprenaline in man

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The acute effects of ethanol on circulatory responses to isoprenaline and atropine were investigated in 21 and 15 normal male subjects respectively. Each subject acted as his own control by participating twice, once after consumption of ethanol (1.0 ml kg⁻¹, 20% v/v in orange juice) and once after orange juice. Ethanol increased baseline heart rate and forearm blood flow, but had no effect on heart rate and forearm blood flow responses to isoprenaline, or on heart rate responses to atropine. Baseline blood pressure and blood pressure responses to isoprenaline were also unaffected by ethanol. It is concluded that acute ethanol ingestion has no physiologically significant effect on β -adrenoceptor responsiveness as assessed by the cardiovascular responses to bolus doses of isoprenaline.

Keywords isoprenaline ethanol β -adrenoceptor heart rate blood pressure

Introduction

Acute ethanol ingestion causes a well recognized increase in heart rate (Kupari, 1983). The mechanism of this has not been established. One possibility could involve an effect on cardiac β -adrenoceptors. In the long term it has been shown that ethanol impairs β -adrenoceptor-mediated circulatory responses as indicated by reduced heart rate reactivity to β -adrenoceptor agonists in alcoholics (Hugues *et al.*, 1974) and chronic alcoholic rats (Segel & Mason, 1982). The short term effects are not known, although acute ethanol consumption has been shown to impair α -adrenoceptor-mediated pressor responses (Eisenhofer *et al.*, 1984). In the present study we have examined the acute effects of ethanol on β -adrenoceptor-mediated circulatory responses in man using bolus injections of isoprenaline, a sympathomimetic drug which causes activation of both β_1 - and β_2 -adrenoceptors (Innes & Nickerson, 1975). The effects of ethanol on heart rate responses to atropine were also studied to examine for a possible effect of ethanol on parasympathetic control of heart rate.

Methods

Twenty-one male subjects aged 21–33 years and weighing 57–82 kg participated in investigations which began between 12.00 and 14.00 h. Subjects refrained from drinking caffeinated beverages and smoking cigarettes on the day of investigation and from ethanol for 24 h. Each subject acted as his own control by participating in two separate investigations, once after drinking 1.0 ml kg⁻¹ ethanol (20% v/v ethanol with orange juice) over 10–15 min and once after an equivalent volume of orange juice. A light lunch was provided during drinking periods. To control for possible time-order effects the order of investigations was randomised with a period of 2–10 weeks between investigations. Informed consent was obtained from subjects before investigations, which were approved by the Wellington Hospital Ethics Committee.

Isoprenaline sensitivity tests were carried out 120 $\pm$ 20 min after ingestion of ethanol or orange juice using a method adapted from those described by Cleaveland *et al.* (1972) and George *et al.* (1972). Isoprenaline sulphate (Isuprel, Winthrop Lab.) was injected into a forearm

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vein, by way of a three way tap, in doses of 0.19, 0.27, 0.44, 0.94 and up to maximums of 1.78 or 3.34 μg (weight as the active base), until a heart rate increase of 30–35 beats min^{-1} was obtained. Each dose was made up to 1 ml with 5% dextrose and was flushed into the circulation with 5 ml of 0.9% saline. Placebo injections were also administered randomly and each dose was separated from the other by 5–10 min to allow heart rate to return to baseline.

The increase in heart rate was determined from the six shortest R–R intervals following each dose, measured using a Mingograf 62 electrocardiogram (Seimens-Elema) at a chart speed of 25 mm s^{-1} . For each isoprenaline sensitivity test the dose required to raise heart rate by 25 beats min^{-1} (CD_{25}) was calculated from the log-linear relationship between increase in heart rate and dose of isoprenaline. Three blood pressure determinations were made between 0.5 and 2.5 min following each dose of isoprenaline using an automatic sphygmomanometer (Nissei model DS 102). Changes in blood pressure were calculated from the mean of the three blood pressure determinations. The average variability of four consecutive measurements made in each of six subjects using the automatic sphygmomanometer was 1.5% and 3.2% for systolic and diastolic blood pressures respectively. In five subjects forearm blood flow was measured by venous occlusion plethysmography using an electrically-calibrated, mercury-filled strain gauge (Hokanson *et al.*, 1975), connected to the arm not being used for injection of isoprenaline. Blood flows were measured over an 8 s period at intervals of 15 s using an automatic cuff inflator at a pressure in the collecting cuff of 50 mm Hg. Changes in blood flow were calculated from the peak blood flow response, one curve being used at each dose for each measurement. Baseline heart rates, blood pressures and blood flows were calculated from the mean of six determinations made before injections of isoprenaline.

In a second study 1.8 mg atropine sulphate was administered over 5 min through a forearm intravenous cannula in 15 male subjects aged 21–29 years. Administration of atropine was carried out on two separate occasions in each subject, once at 120 ± 30 min after consumption of 1 ml kg^{-1} ethanol (20% v/v ethanol with orange juice) and once after orange juice. Heart rate and blood pressure were recorded before atropine and 10–20 min after atropine with subjects in the same position.

Statistical significance of differences between control investigations and investigations after ethanol was assessed using the Wilcoxon signed-rank test for related samples.

Results

Ethanol consumption was associated with significantly ($P < 0.01$) higher baseline heart rates ($\pm$ s.d. mean) of 71 ± 9 compared with 65 ± 11 beats min^{-1} during control investigations (Table 1). Peak heart rates remained higher during bolus injections of isoprenaline after ethanol but were not significantly different from those of control studies at any administered dose. The dose-response curve for increases in heart

Figure 1 Dose-response curves for the increase ($\pm$ s.e. mean) in heart rate (upper, $n = 21$), decrease in diastolic blood pressure (middle, $n = 21$) and increase in forearm blood flow (lower, $n = 5$) responses to isoprenaline in control studies ($\circ$ --- $\circ$) and studies with ethanol ingestion ($\bullet$ — $\bullet$). There were no significant differences between dose-response curves with and without ethanol. Heart rate and blood pressure were determined in 21 subjects and blood flow in five subjects.

Table 1 Circulatory responses ($\pm$ s.d. mean) to bolus injections of isoprenaline with (E) and without (C) ethanol

Dose isoprenaline (μ g)		Heart rate (beats min^{-1})	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Forearm blood flow ($\text{ml } 100 \text{ ml}^{-1} \text{ min}^{-1}$)
0	C	65 $\pm$ 11*	118 $\pm$ 9	60 $\pm$ 9	2.2 $\pm$ 0.4
	E	71 $\pm$ 9	117 $\pm$ 11	60 $\pm$ 9	5.2 $\pm$ 3.7
0.19	C	74 $\pm$ 13	119 $\pm$ 10	56 $\pm$ 10	4.5 $\pm$ 1.9
	E	78 $\pm$ 8	116 $\pm$ 13	55 $\pm$ 10	7.0 $\pm$ 4.8
0.27	C	79 $\pm$ 13	120 $\pm$ 10	54 $\pm$ 11	5.2 $\pm$ 1.6
	E	81 $\pm$ 9	117 $\pm$ 12	54 $\pm$ 10	8.0 $\pm$ 4.6
0.44	C	82 $\pm$ 12	121 $\pm$ 10	51 $\pm$ 10	7.3 $\pm$ 2.3
	E	86 $\pm$ 8	120 $\pm$ 12	49 $\pm$ 11	8.7 $\pm$ 4.9
0.94	C	89 $\pm$ 11	124 $\pm$ 11	47 $\pm$ 9	10.2 $\pm$ 2.8
	E	92 $\pm$ 8	124 $\pm$ 13	45 $\pm$ 10	10.9 $\pm$ 3.9
1.78	C	95 $\pm$ 11	127 $\pm$ 12	42 $\pm$ 10	12.2 $\pm$ 2.8
	E	98 $\pm$ 11	127 $\pm$ 13	40 $\pm$ 11	12.2 $\pm$ 4.2

* $P < 0.01$ when compared between control and ethanol studies.

rate showed a slight shift to the right following ethanol consumption but at no dose was the heart rate response significantly less after ethanol than in control studies (Figure 1). From the individual dose-response curves the doses of isoprenaline required to increase heart rate by 25 beats min^{-1} (CD_{25}) were not found to differ significantly with and without ethanol. During control studies the CD_{25} ($\pm$ s.d. mean) was $23.3 \pm 19.5 \text{ ng kg}^{-1}$ while after ethanol the CD_{25} was $27.5 \pm 17.7 \text{ ng kg}^{-1}$ bodyweight.

Blood pressure was 117/60 and 118/60 mm Hg with and without ethanol and changed to respective values of 127/40 and 127/42 mm Hg after 1.78 μ g isoprenaline (Table 1). Blood pressures before and during isoprenaline administration and blood pressure responses to isoprenaline showed no differences between studies with and without ethanol (Figure 1). All five subjects in whom blood flow measurements were made were found to have increased forearm blood flow after ethanol, flows ($\pm$ s.d. mean) being 2.2 ± 0.4 and $5.2 \pm 3.7 \text{ ml } 100 \text{ ml}^{-1} \text{ min}^{-1}$ for control studies and studies with ethanol respectively (Table 1). Forearm blood flow increased with increasing doses of isoprenaline, reaching values of 12.2 ± 2.8 and 12.2 ± 4.2 after 1.78 μ g isoprenaline for control studies and studies after ethanol respectively.

In studies involving injection of atropine, ethanol consumption was associated with significantly ($P < 0.01$) higher baseline heart rates ($\pm$ s.d. mean) of 72 ± 9 compared to 67 ± 9 beats min^{-1} during control studies. Ethanol consumption did not affect the heart rate response to atropine. Heart rates rose by 35 ± 11 beats min^{-1} after atropine in control studies and by

34 ± 9 beats min^{-1} after atropine in studies with ethanol ingestion.

Discussion

The results indicate that acute ethanol consumption has no physiologically significant effect on β -adrenoceptor-mediated circulatory responses to isoprenaline as assessed from the heart-rate dose-response curves. Thus the cardiovascular effects of acute ethanol ingestion are unlikely to be due to any direct effect of ethanol on cardiac responsiveness to β -adrenoceptor stimulation.

The heart rate response to isoprenaline is secondary not only to β -adrenoceptor stimulation but also to baroreceptor-mediated responses to isoprenaline's vasodilatory action (Arnold & McDevitt, 1983). The blood pressure responses to isoprenaline with and without ethanol did not differ. However, because circulatory responses to bolus injections of isoprenaline are short lasting, blood pressure should ideally be measured intra-arterially. In the present study peak changes in blood pressure probably were not measured and it is possible that differences in peak blood pressure responses in studies with and without ethanol may have been present. Peak forearm blood flow responses were however measured in five subjects and, apart from an effect of ethanol on baseline values, there was little effect of ethanol on isoprenaline-induced changes in blood flow.

Increased baseline forearm blood flow after ethanol in the present study is in line with previous work showing decreased peripheral resistance (Kupari, 1983) and vasodilation (Fewings

et al., 1966) after ethanol. The ethanol-induced increase in heart rate may represent a reflex response to ethanol-induced vasodilation and depressed α -adrenoceptor-mediated vasoconstriction (Eisenhofer *et al.*, 1984), acting to maintain a normal baseline blood pressure. The finding that ethanol did not affect the heart rate response to atropine suggests, however, that the ethanol-induced tachycardia is not a vagally mediated response.

It is concluded that there are no physiologi-

cally significant effects of acute ethanol ingestion on heart rate and forearm blood flow responsiveness to β -adrenoceptor stimulation. The tachycardia after ethanol is unlikely to be due to vagal withdrawal or to an effect of ethanol on cardiac β -adrenoceptor responsiveness.

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References

- Arnold, J. M. O. & McDevitt, D. G. (1983). Contribution of the vagus to the haemodynamic responses following intravenous boluses of isoprenaline. *Br. J. clin. Pharmacol.*, **15**, 423–429.
- Cleaveland, C. R., Rangno, R. E. & Shand, D. G. (1972). A standardised isoproterenol sensitivity test. *Arch. intern. Med.*, **130**, 47–52.
- Eisenhofer, G., Lambie, D. G. & Johnson, R. H. (1984). Effects of ethanol ingestion on α -adrenoceptor-mediated circulatory responses in man. *Br. J. clin. Pharmacol.*, **18**, 581–586.
- Fewings, J. D., Hanna, M. J. D., Walsh, J. A. & Whelan, R. F. (1966). The effects of ethyl alcohol on the blood vessels of the hand and forearm in man. *Br. J. Pharmacol. Chemother.*, **27**, 93–106.
- George, C. F., Conolly, M. E., Fenyvesi, T., Briant, R. & Dollery, C. T. (1972). Intravenously administered isoproterenol sulphate dose-response curves in man. *Arch. intern. Med.*, **130**, 361–364.
- Hokanson, D. E., Sumner, D. S. & Strandness, D. E. (1975). An electrically calibrated plethysmograph for direct measurement of limb blood flow. *IEEE Trans. Biomed. Eng.*, **22**, 25–29.
- Hugues, F. C., Munera, Y., Julien, D. & Marche, J. (1974). Exploration de la fonction bêta adrénergique chez l'homme l'épreuve à l'isoprénaline. *Coeur. Med. Interne*, **13**, 527–533.
- Innes, I. R. & Nickerson, M. (1975). Norepinephrine, epinephrine, and the sympathomimetic amines. In *The pharmacological basis of therapeutics*, fifth edition, eds Goodman, L. S. & Gilman, A., pp 477–513. New York: Macmillan.
- Kupari, M. (1983). Acute cardiovascular effects of ethanol. A controlled non-invasive study. *Br. Heart J.*, **49**, 174–182.
- Segel, L. D. & Mason, D. T. (1982). Beta-adrenergic receptors in chronic alcoholic rat hearts. *Cardiovasc. Res.*, **16**, 34–39.

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