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Ethanol produces coronary vasospasm: evidence for a direct action of ethanol on vascular muscle

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The effects of ethanol and acetaldehyde on basal tension of canine small and large coronary arteries were examined *in vitro*. Ethanol in a concentration as little as 8.5 mM can induce threshold contractions of coronary arteries. High concentrations of ethanol produce concentration-dependent coronary vasospasms equivalent to those induced by supra-maximal concentrations of KCl. Acetaldehyde (10^{-5} to 10^{-2}M) resulted in concentration-dependent relaxation of basal tone. Use of a variety of pharmacological antagonists (i.e., phentolamine, methysergide, diphenhydramine, metiamide, propranolol and indomethacin) did not attenuate or prevent the spasmogenic actions of ethanol. These findings could help to explain why alcohol can induce cardiac depression, arrhythmias, cardiomyopathy and the higher than normal incidence of sudden death observed in 'binge' drinkers.

Introduction Ever since the early work of Heberden in 1772, it has been thought that alcohol (ethanol) can exert effects on coronary blood flow. Although it has been apparent from numerous studies over the past 100 years that long-term ingestion of ethanol and its congeners can induce myocardial muscle damage in both animals and man (see reviews by Rubin, 1979; Ashley & Rankin, 1980; Alderman & Coltart, 1982; Altura & Altura, 1982; Friedman, Geller & Lieber, 1982), it is not clear how this is brought about. Moreover, even though ethanol is known to be capable of producing myocardial depression and decreased cardiac contractility (see references in Rubin, 1979; Ashley & Rankin, 1980; Alderman & Coltart, 1982; Friedman *et al.*, 1982), it is not clear how this is accomplished. Recently, a higher than normal incidence of arrhythmias has been observed in human subjects during 'binge' drinking in the complete absence of any manifestations of cardiomyopathy (Ettinger, Wu, De Lacruz, Weisse, Ahmed & Regan, 1978). Interestingly, such patients as well as those presenting with alcoholic cardiomyopathy, and dogs fed alcohol, have a high incidence of unexplained sudden death (Alderman & Coltart, 1982; Friedman *et al.*, 1982). Since myocardial ischaemia, both acutely and over a long period of time, could at least in theory result in the latter as well as alcoholic-induced myocardial damage, we wondered whether ethanol is capable of inducing sustained vasoconstriction of coronary arteries.

We have found that alcohol, in a concentration as low as 8.5 mM (equivalent to 38 mg/dl) can induce contractions of small (0.3–1.0 mm o.d.) and large isolated coronary arteries, irrespective of the region of the canine myocardium. In addition, we have shown that these vasospasms cannot be attributed to actions on adrenoceptors, or on histamine or 5-hydroxytryptamine receptors; nor can they be attributed to a release of prostaglandins or to actions of the major metabolite of ethanol, acetaldehyde.

Methods Mongrel dogs of either sex weighing 10–20 kg were anaesthetized with pentobarbitone sodium (Nembutal, 30 mg/kg). After thoracotomy, the hearts were removed immediately and coronary arteries were isolated. Because of possible segmental differences in coronary reactivity (Altura, 1966) the preparations included vessels taken from coronary arteries of different sizes (1–2 mm o.d. and 0.3–1.0 mm o.d.) from both left and right coronary arteries. Helical strips, cut from segments of these coronary arteries were 20 to 25 mm long by 0.5 to 1.0 mm wide. These were suspended isometrically under 1 g of tension (circumflex, right and left coronary arteries) or 0.5 g of tension (left and right coronary branch arteries) and incubated in normal Krebs-Ringer bicarbonate solution (Turlapaty & Altura, 1980) at 37°C through which a mixture of O_2 (95%) and CO_2 (5%) was bubbled. Force of contraction was measured with Grass FT-03 force-displacement tranducers and recorded on a Grass model 7 polygraph. Two hours after being incubated under tension, the preparations were exposed to KCl (80 mM), ethanol and acetaldehyde (cumulative or single doses). A supramaximal dose of KCl was used as a stimulant so that we could assess the vasoactive effects of ethanol and acetaldehyde. In other experiments, we determined whether incubation of coronary arteries with specific antagonists (i.e. phentolamine methanesulphonate 0.5 μg/ml; methysergide maleate 0.5 μg/ml; diphenhydramine hydrochloride 0.5 μg/ml; metiamide 0.5 μg/ml; propranolol hydrochloride 0.5 μg/ml; and indomethacin 0.5–1.0 μg/ml), in concentrations that antagonize their respective agonists, would interfere with the coronary actions of ethanol. At least 4 animals were

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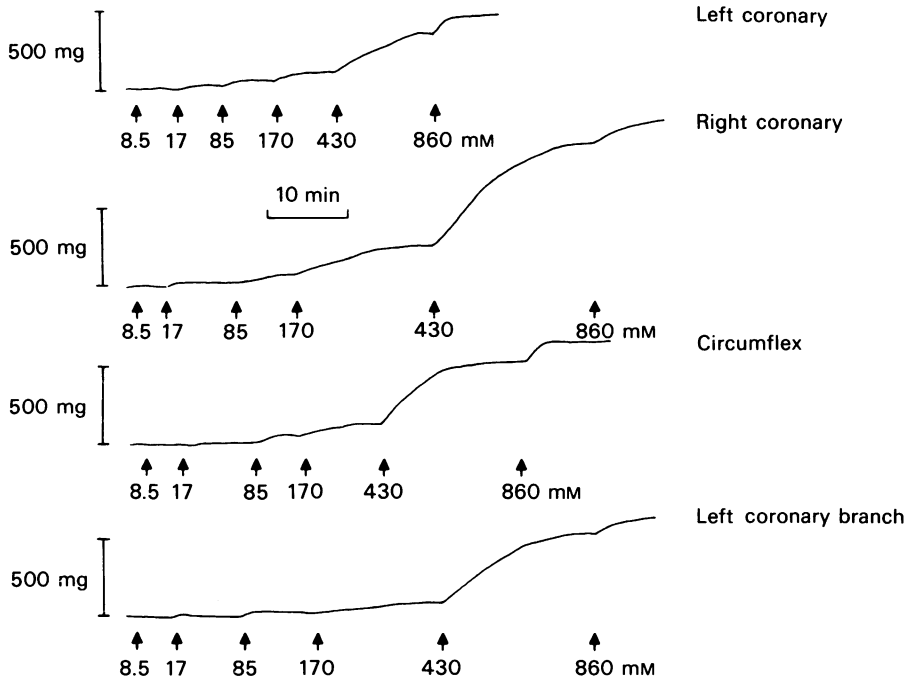

Figure 1 Typical responses of large and small isolated coronary arteries of the dog to cumulative addition of ethanol (at arrows).

used for each agonist and antagonist; each antagonist was added to the muscle chambers 10–15 min before challenge with ethanol.

Results The representative tracings shown in Figure 1 clearly indicate that cumulative addition of alcohol to the muscle chambers result in a concentration-dependent increase in tension, in large and small coronary arteries, with approximately 8.5 mM (i.e., 38 mg/dl) being the concentration of ethanol required for threshold contractile effects. All types of coronary arteries examined revealed similar concentration-related contractions when alcohol was introduced into the muscle chambers ($n = 30$). These contractions were sustained for prolonged periods of time (e.g. >60 min). Interestingly, a concentration of ethanol of approximately 430 mM resulted (Figure 1) in coronary spasms which were equal to maximal contractions induced by 80 mM KCl. Although not shown, addition of acetaldehyde, either in single or cumulative doses (10^{-5} to 10^{-2} M), resulted in a concentration-dependent reduction (relaxation) in basal tension ($n = 4$), the opposite of what was observed for ethanol. Incubation of coronary arteries with phentolamine, methysergide, diphenhydramine, metiamide, propranolol or indomethacin failed to attenuate or prevent the spasmogenic actions of ethanol.

Discussion Although numerous, previous studies in experimental animals have demonstrated that blood alcohol levels as low as 50 mg/dl can result in cardiac depression (e.g., reduced stroke volume, elevated left ventricular end-diastolic pressure, reduced left ventricular peak dp/dt), the reasons for this have not been elucidated (Friedman *et al.*, 1982). Moreover, ever since the early studies of Steel (1893), the reasons for development of an alcoholic cardiomyopathic syndrome with its sequelae of cardiac muscle damage events in humans has been perplexing (Rubin, 1979; Alderman & Coltart, 1982; Friedman *et al.*, 1982). Although it has been suggested that nutritional deficiencies may play an important role in the latter, it is difficult to account for the acute myocardial depressant actions of alcohol or the arrhythmias in 'binge' drinkers in terms of such a concept. The fact that ethanol's major and toxic metabolite, acetaldehyde, has been shown to result in an elevation of cardiac output and coronary vasodilatation (Friedman *et al.*, 1982), which is supported by our present findings of a direct vasorelaxant action on coronary arteries, would seem to preclude its in-

volvement in ethanol-induced cardiac depression and cardiomyopathy.

The results described here which demonstrate that ethanol can exert potent and concentration-dependent contraction of all types of canine coronary arteries could aid in explaining why this alcohol can induce cardiac depression, arrhythmias, cardiomyopathy and the higher than normal incidence of sudden death observed in 'binge' drinkers. The facts that various receptor blocking agents and a cyclo-oxygenase inhibitor do not interfere with ethanol-induced spasms, and that acetaldehyde does not mimic the spasmogenic action of ethanol on coronary arteries, suggests that alcohol-induced contractions of coronary vascular smooth muscle are independent of either the release or synthesis of common vasoactive mediators. Ethanol in the mammalian heart *in situ* could produce concentration-dependent vasoconstriction, vasospasm and ischaemia which, depending upon the intensity and focus, could result in cardiac depression, arrhythmias and sudden death. Over a period of months and years, a gradual, but progressive, increase in coronary ischaemia, brought about by progressive coronary constriction, could result in the well-known syndrome of cardiomyopathy.

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References

ALDERMAN, E.L. & COLTART, D.J. (1982). Alcohol and the heart. *Br. med. Bull.*, **38,** 77–80.

ALTURA, B.M. (1966). Differential actions of polypeptides and other drugs on coronary inflow vessels. *Am. Heart. J.*, **72,** 709–711.

ALTURA, B.M. & ALTURA, B.T. (1982). Microvascular and vascular smooth muscle actions of ethanol, acetaldehyde and acetate. *Fedn. Proc.*, **41,** 2447–2451.

ASHLEY, M.J. & RANKIN, J.G. (1980). Hazardous alcohol consumption and diseases of the circulatory system. *J. Studies Alcohol*, **41,** 1040–1070.

ETTINGER, P.O., WU, C.F., DE LACRUZ, C., WEISSE, A.B., AHMED, S.S. & REGAN, T.J. (1978). Arrhythmias and the 'Holiday Heart': alcohol-associated cardiac rhythm disorders. *Am. Heart J.*, **95,** 555–562.

FRIEDMAN, H.S., GELLER, S.A. & LIEBER, C.S. (1982). The effect of alcohol on the heart, skeletal and smooth muscles. In *Medical Disorders of Alcoholism. Pathogenesis and Treatment.* ed. Lieber, C.S., pp. 436–479. Philadelphia: W.B. Saunders Co.

HEBERDEN, W. (1772). Some account of a disorder of the breast. *M. Trans. Coll. Physicians (London)*, **2,** 59–67.

RUBIN, E. (1979). Alcoholic myopathy in heart and skeletal muscle. *New Engl. J. Med.*, **301,** 28–33.

STEEL, G. (1893). Heart failure as a result of chronic alcoholism. *Med. Chron.*, **18,** 1–22.

TURLAPATY, P.D.M.V. & ALTURA, B.M. (1980). Magnesium deficiency produces spasms of coronary arteries: relationship to etiology of sudden death ischemic heart disease. *Science*, **208,** 198–200.

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