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Review

Potential mechanisms for cardiovascular protective effect of ethanol

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ABSTRACT

Epidemiological studies demonstrate a significant protective effect of moderate alcohol consumption on the incidence of cardiovascular diseases which accounts for the majority of deaths in the Western world. In this review, possible mechanisms to explain the cardioprotective effect of ethanol are discussed. While the prevailing theory supported by a number of clinical and animal studies indicates that the ability of ethanol to elevate serum high-density lipoprotein (HDL) cholesterol levels is an important mechanism in ameliorating cardiovascular disease, other mechanisms whereby ethanol could exert its beneficial effect have been proposed. Namely, its ability to affect platelet function and endothelial cell and vascular smooth muscle cell function (*In this review, the terms alcohol and ethanol are used interchangeably*).

EPIDEMIOLOGY

Chronic alcohol abuse is associated with increased cardiac morbidity and mortality owing to hypertension, cardiomyopathy, hepatic cirrhosis and certain cancers as well as accidents and suicides[1,2]. In contrast, many epidemiological studies have demonstrated a significant protective effect of moderate alcohol consumption on the incidence of cardiovascular disorders such as stroke, hypertension, myocardial infarction and coronary artery disease (CAD)[1－4]. The greatest benefit occurs at 1－2 drinks/day, with continued protection up to 4 drinks/day. Blood alcohol content (BAC) is usually described as grams of alcohol per 100 mL of blood, expressed as "g %". One 4-ounce (120 mL) glass of wine or 12 ounce (360 mL) beer contains enough alcohol to increase a person's BAC by about 0.02 %, which is approximately equivalent to 5 mmol/L ethanol. Because vascular disease is such an important cause of death in middle and old age, moderate alcohol consumption is also associated with a reduction in total mortality.

EFFECT OF ETHANOL ON LIPID LEVELS

One of the first mechanisms proposed for the cardioprotective effect of ethanol was its ability to elevate serum high density lipoprotein (HDL) levels[5,6]. HDL is thought to protect arteries against atherosclerosis by removing cholesterol deposits from the blood vessel wall and transporting it back to the liver for excretion in the bile (reverse cholesterol transport). In addition, HDL has several other protective effects on the arterial system, affecting many cells in the vasculature (for review[7]). The association between atherosclerosis and high levels of low-density lipoproteins (LDLs) has been established as one of the major risk factors for atherosclerosis[8]. More recently, evidence which suggests that ethanol can reduce LDL levels and inhibit the injurious actions of high levels of LDL cholesterol has emerged[9,10]. Recent analyses using computer models predictive of cardiovascular disease suggest that 50 % － 60 % of the benefit of alcohol could be attributed to its favourable effects on HDL and LDL levels[6].

INTERACTION OF ETHANOL WITH PLATELETS

There is a considerable experimental and clinical evidence to indicate that ethanol directly inhibits platelet function. Platelets are involved in the generation of atherosclerotic lesions by formation of mural thrombi at sites of endothelial cell injury and by stimulation of smooth muscle cell proliferation by the release of platelet-

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derived growth factor[11]. Platelets also accumulate over ruptured atherosclerotic plaques leading to the generation of platelet-fibrin thrombi and thromboembolic phenomena. The link between the inhibition of platelet function by ethanol and the cardioprotective effects of moderate drinking relates to this role of platelets in the complication of atherosclerosis.

Several epidemiological studies demonstrate an inverse correlation between alcohol consumption and ADP- and collagen-stimulated platelet aggregation[12]. Bleeding time, which is strongly affected by platelet number and aggregability, was transiently increased following acute ingestion of alcohol by nonalcoholic volunteers, in the absence of any effect on other parameters of coagulation[13]. However, bleeding times were unaffected by acute alcohol ingestion in other studies[14]. Direct inhibition of platelet function has also been demonstrated in *in vivo* rabbit and dog models of thrombosis[15,16]. While ethanol has little effect on platelet shape change or primary aggregation, it inhibits the secondary phase of platelet aggregation and secretion *in vitro* in response to several stimuli including ADP, thrombin, collagen and platelet-activating factor[17,18]. A number of studies indicate that a likely signal transduction target in platelets for ethanol is phospholipase A_2 and ethanol has been shown to inhibit the formation of arachidonic acid and TXA_2[19]. cAMP-dependent phosphorylation represents an important inhibitory pathway in platelets. Diverse effects of ethanol on platelet cAMP production have been reported. Hwang *et al* demonstrated that preincubation of ethanol with platelet rich plasma resulted in a dose-dependent increase in cAMP levels[20], whereas DePetrillo and Swift reported an ethanol induced transient decrease in human platelet cAMP levels[21]. There have also been reports of no effect of ethanol on platelet cAMP levels[22]. These divergent results are likely due to differences in experimental conditions (eg, acute *vs* chronic exposure) and doses used.

EFFECT OF ETHANOL ON eNOS AND PROSTACYCLIN

Recently, evidence has emerged that ethanol targets and alters endothelial cell function. The endothelium is recognized as an important regulator of vascular tone[23] and a key player in atherogenesis[24]. It is now accepted that fairly modest changes in the normal phenotype of the endothelial cell can result in the sequence of events resulting in the development of atheroma[24]. Endothelium-derived paracrine agents are an important mechanism behind the multi-functional role of the endothelium. Among the most important of these is endothelium-derived relaxing factor (EDRF), identified as nitric oxide (NO). Nitric oxide is synthesized by the heme-containing enzyme nitric oxide synthase (NOS) from *L*-arginine in a reaction that produces stoichiometric amounts of *L*-citrulline[25]. Three isoforms of NOS have been identified by gene cloning. Two are constitutively expressed and one, the inducible NOS (iNOS) is produced *de novo* in response to inflammatory cytokines. Activation of NOS and release of NO results in stimulation of a soluble guanylyl cyclase leading to a profound increase in intracellular cGMP levels within most target cells[25]. NO plays a pivotal role in regulating blood flow by inhibiting smooth muscle contraction as well as platelet aggregation and adhesion[25]. In addition, NO has been shown to inhibit vascular smooth muscle cell proliferation[26].

Previous studies, the majority in the central nervous system regarding iNOS, have provided data to support a specific interaction between ethanol and the NOS/NO axis. Chen and LaBella demonstrated that alcohol noncompetitively inhibited rat brain NOS activity[27]. Ethanol treatment blocked LPS-mediated induction of iNOS gene expression in the lung[28] while in cultured vascular smooth muscle cells ethanol potentiated interleukin-1β-stimulated iNOS expression[29]. More recently, investigators have examined the direct effect of ethanol on constitutive endothelial cell NOS (eNOS) in cultured cells. An ethanol enhancement of the NOS response to agonists such as bradykinin has been reported in bovine pulmonary artery endothelial cells[30]. Shear stress due to blood flow is an extremely important physiological pathway for eNOS activation[31]. Hendrickson *et al* demonstrated a stimulatory effect of ethanol on basal and flow-stimulated eNOS activity, mediated in part by a mechanism involving a pertussis toxin sensitive G protein[32]. In another study, the ethanol augmentation of NO production was associated with increased eNOS protein and mRNA expression[33]. These studies invite speculation that the beneficial effects of ethanol consumption are mediated, at least in part, by ethanol-induced stimulation of eNOS activity. However, further *in vivo* experiments using NOS inhibitors will be required to provide definitive proof.

The effects of ethanol on prostacyclin (PGI_2), another endothelium-derived vasodilator and potent inhibitor of platelet aggregation, have also been investigated.

Ethanol increased PGI_2 production in cultured human umbilical vein endothelial cells and elevated plasma levels of PGI_2 in volunteers administered ethanol[34]. Guivernau *et al*, found that while ethanol did not affect vascular PGI_2 release in control rats, in aortae from alcohol-fed animals ethanol stimulated PGI_2 production[35]. These data imply that this response to ethanol may be altered by chronic alcohol consumption. In any case, ethanols' modulatory effect on vascular PGI_2 production could also contribute to its cardioprotective effects *in vivo*.

EFFECT OF ETHANOL ON SMC PROLIFERATION AND MIGRATION

Arterial smooth muscle cell (SMC) migration and proliferation are two distinct processes that play an important role in the pathogenesis of atherosclerosis as well as in the normal development of blood vessels and the arterial response to injury (for review[36,37]). In addition, accelerated smooth muscle cell proliferation and migration is a characteristic feature in arteries of hypertensive patients and animals[38,39]. Consequently, there has been extensive interest in defining both positive and negative regulators of SMC migration and growth and many factors have been identified that may play a role in this process. An ethanol-induced reduction in neointimal formation following balloon injury has been reported in both rabbit and pig models[40,41]. This inhibition of intimal hyperplasia was observed following either local delivery of ethanol or alcohol feeding[40,41]. The preservation of arterial lumen diameter was achieved by decreasing neointimal proliferation in part by decreasing LDL oxidation in these animals[40]. However the main pathogenesis of neointimal formation is smooth muscle cell migration, proliferation and extracellular matrix production. In a recent study using rabbit iliac arteries following balloon angioplasty, significant inhibition of SMC phenotype conversion from contractile to synthetic was observed following ethanol treatment that was indicative of an inhibition of smooth muscle cell proliferation[42].

Several studies have provided compelling evidence for a role of mitogen activated protein kinases (MAPKs) in regulating smooth muscle cell growth[43]. MAPKs, (also called extracellular signal-regulated kinases or ERKs) are a family of protein kinases activated as part of a cascade by phosphorylation on both threonine and tyrosine residues. MAPKs are rapidly activated in response to ligand binding by both growth factor receptors with intrinsic tyrosine kinase activity, such as the platelet-derived growth factor and epidermal growth factor receptor, and receptors that are coupled to heterotrimeric guanine nucleotide binding proteins (G proteins) such as the thrombin receptor[44-46]. Members of the MAPK family include the ERKs (ERK-1 and ERK-2) which are activated by MEK (also referred to as MAPK kinase). In proliferating cells it has been postulated that activated ERK-MAPKs phosphorylate specific cytoplasmic and nuclear proteins needed for passage through certain checkpoints in the cell cycle (eg G1/S and G2/M)[47,48]. Recently, Hendrickson *et al* demonstrated that ethanol, at physiologically relevant concentrations, inhibited serum-stimulated growth and MAPK activity in cultured smooth muscle cells in the absence of any effect on cell viability[49].

Vascular smooth muscle cell migration plays a crucial role in progressive intimal thickening leading to atherosclerosis and restenosis following injury. Pulse pressure due to pulsatile flow induces SMC migration by a mechanism mediated in part by urokinase type plasminogen activator (uPA)[50]. The direct effect of ethanol on vascular smooth muscle cell chemokinesis was assessed using human smooth muscle cells in static culture and those exposed to pulsatile flow. Ethanol pretreatment dose-dependently inhibited basal and flow-induced migration, in the absence of any effect on uPA mRNA expression[51]. Since SMC migration and proliferation are an integral part of the process of vascular restructuring and remodelling following injury or hemodynamic load, it is tempting to speculate that the inhibitory actions of ethanol on these cell processes demonstrated *in vitro*, may be relevant to its cardioprotective effects *in vivo*.

EFFECT OF ETHANOL ON FIBRINOLYSIS

Moderate alcohol consumption may mediate additional cardioprotection by promoting fibrinolysis through changes in the activity, level, or interaction of one or more components of the fibrinolytic system. The inactive proenzyme plasminogen is activated to the proteolytic enzyme plasmin which digests fibrin-dependent blood clots, by two plasminogen activators, tissue-type plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA)[52]. The system is regulated by a series of plasminogen activator inhibitors, the most prevalent of which is plasminogen activator inhibitor type 1 (PAI-1). Endothelial cells are a major site of synthesis of fibrinolytic proteins (t-PA, u-PA and PAI-1) and thus play a

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key role in the regulation of this process. The hypothesis is that any factor, eg, ethanol, that affects one or more of these components, resulting in increased endothelial cell-mediated fibrinolytic activity, will reduce the risk of thrombosis, CAD and myocardial infarction. This association was first suggested by a study of about 80 000 nurses who drank moderately and who were found to have a lower risk of both acute coronary events and ischemic stroke, but an increased risk of hemorrhagic stroke, suggesting that perturbation of fibrinolytic components may be involved[53]. Ridker *et al* demonstrated a strong positive association between alcohol and plasma t-PA antigen levels in healthy men participating in the Physicians Health Study, grouped according to amounts of alcohol consumed[54]. Plasma t-PA levels were significantly higher and the rate of heart events lower, in drinkers versus nondrinkers. Following these epidemiological data, there have been a number of *in vitro* studies on the molecular regulatory effects of ethanol on endothelial cell-mediated fibrinolysis. Laug demonstrated an ethanol-induced increase in t-PA secretion in cultured bovine aortic endothelial cells[55]. An increase in t-PA and u-PA mRNA and a simultaneous decrease in PAI-1 mRNA in cultured human endothelial cells, concomitant with increased surface localized EC fibrinolytic activity has been shown[56,57]. Miyamoto *et al* reported that ethanol enhances agonist-stimulated cAMP-dependent t-PA gene transcription in human and bovine EC through differential modulation of a G protein[58]. These *in vitro* studies may explain the increased fibrinolytic activity found in the plasma of persons consuming moderate amounts of alcohol.

CONCLUDING REMARKS

The evidence presented in this review suggests that ethanol may mediate its protective effect with respect to cardiovascular disease at many different levels. While the favourable effect of ethanol on plasma lipoprotein levels is believed to be a predominant mechanism, potentially important beneficial effects of ethanol on platelets and vascular endothelial cells and smooth muscle cells have more recently been recognized. Ethanol inhibits platelet aggregability, enhances NOS activity and fibrinolytic activity in endothelial cells, and inhibits the proliferation and migration of smooth muscle cells. Thus ethanol appears capable of inhibiting several key steps in the atherogenic process, at least *in vitro*. Further *in vivo* studies will be necessary to firmly establish whether these ethanol effects contribute to the beneficial effect of moderate alcohol consumption on CAD.

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乙醇心血管保护作用的潜在机制

关键词：醇类；血管平滑肌；内皮；动脉粥样硬化

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