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The prevention of myocardial ultrastructural changes by perindopril, atenolol and amlodipine in chronic alcohol administered rats

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Abstract

The effects of perindopril, an angiotensin converting enzyme inhibitor, atenolol, a beta adrenergic receptor blocker and amlodipine, a calcium channel blocker were investigated in chronic alcohol administered rats. Adult male Wistar rats (240–320 g) were used in the present study. Alcohol was given to rats by a modified liquid diet for 21 days. Perindopril (2.5 and 5 mg kg^{-1}), atenolol (5 and 10 mg kg^{-1}) and amlodipine (5 and 10 mg kg^{-1}) were injected to rats in different groups intraperitoneally for 21 days. Control rats were pair fed by an isocaloric liquid diet containing sucrose as a caloric substitute for alcohol. Saline was injected to control rats for 21 days. Rats were anesthetized with ether. Their hearts were removed and 1 mm^3 samples from left ventricles were fixed. Five fields per heart were examined and photographed with transmission electron microscope. Blood alcohol levels were also measured spectrophotometrically. Daily alcohol consumption of the rats was in a range of 12.09–15.5 g kg^{-1}. Blood alcohol concentrations were found as 145.63 mg dl^{-1} at 21st day of alcohol consumption. Chronic alcohol consumption caused some marked myocardial injuries. Perindopril and atenolol but not amlodipine produced some significant beneficial effects on alcohol-induced myocardial damages. Our results imply that perindopril and atenolol but not amlodipine have protective effects on heavy chronic alcohol consumption-induced myocardial injury in rats.

Keywords: Amlodipine; Perindopril; Atenolol; Alcohol consumption; Myocardial ultrastructure

1. Introduction

Alcohol abuse and dependence remain among the greatest substance abuse problem worldwide [1]. There was evidence for a dose–response relationship between level of alcohol consumption and risk of harm for liver cirrhosis, cancers of the oropharynx, larynx, oesophagus, rectum, liver and breast, and stroke. Cardiovascular disease is one of the most important risk factors and the leading cause of death in most regions of the world [2]. Although there was evidence for a protective effect of low alcohol consumption against risk of coronary heart disease, an increased risk of cardiac arrhythmias, cardiomyopathy and sudden coronary death were associated with heavy drinking [3]. In addition, chronic alcohol consumption is closely linked to hypertension [4] and hypertension together with hyperlipidemia is one of the most significant risk factor for cardiovascular diseases [5,6].

It has been shown that chronic ethanol ingestion caused left ventricular dysfunction in rats [7]. Both chronic moderate and heavy alcohol consumption exacerbate myocardial ischemia-reperfusion injury [8]. Coronary death also contributed significantly to the excess mortality in alcohol-dependent men and an increased vulnerability for sudden coronary death to persist for a considerable time after discharge from detoxification [9]. In that point, drug selection and use in alcoholic patients with cardiovascular disease have been gained a significant importance.

Antihypertensive drugs such as angiotensin converting enzyme (ACE) inhibitors, calcium channel blockers and beta adrenoceptor blockers have already been used for reducing cardiovascular risk factors in patients with cardiovascular diseases [10]. The various kind of antihypertensive drugs show marked

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differences in their ability to prevent or reverse cardiac problems such as myocardial hypertrophy, differences primarily related to their mechanism of action [11,12]. The effectiveness and safety of these drugs in alcoholic patients or chronic heavy alcohol users that have also cardiovascular risk factors or diseases have not been clearly known. Oral chronic alcohol treated rat model [13] could be useful for investigating the harmful effects of alcohol on cardiovascular system and evaluating the effects of drugs. Thus, this study was organized to investigate the effects of perindopril, an ACE inhibitor, amlodipine, a calcium channel blocker, and atenolol, a beta adrenoceptor receptor blocker, on chronic alcohol-induced myocardial injury in rats.

2. Materials and methods

2.1. Animals and laboratory

All procedures in the present study are in accordance with the Guide for the Care and Use of Laboratory Animals as adopted by the National Institutes of Health (USA). Forty-two adult male Wistar rats (240–320 g) were the subjects in the present study. They were housed in a quiet and temperature- and humidity-controlled room ($22 \pm 2\,^{\circ}C$ and $60 \pm 5\%$, respectively) in which a 12-h light/12-h dark cycle was maintained (07:00–19:00 h light).

2.2. Chronic ethanol administration to rats

The rats were housed individually in metal cages. Ethanol was given to rats by a liquid diet for 21 days as previously described [13]. The rats received a modified liquid diet with or without ethanol ad libitum. No extra chow or water was supplied. The composition of the modified liquid diet with ethanol is cow's milk 925 ml (Mis Süt, Turkey), 25–75 ml ethanol (96.5% ethyl alcohol; Tekel, Turkish State Monopoly), Vitamin A 5000 IU (Akpa İlaç Sanayi, Turkey) and sucrose 17 g [14]. This mixture supplies 1000.7 kcal L^{-1}.

At the beginning of the study, rats were given modified liquid diet without ethanol for a week. Then, liquid diet with 2.4% (v/v) ethanol was administered for three days. The ethanol concentration was increased to 4.8% (v/v) for the following 3 days and finally to 7.2% (v/v) for 14 days. An isocaloric liquid diet containing sucrose as a caloric substitute to ethanol was also given to control rats. Liquid diet was prepared daily and presented at the same time of the day (10:00 h). The weight of the rats was recorded every day and the daily ethanol intake was measured and expressed as grams per kilogram per day.

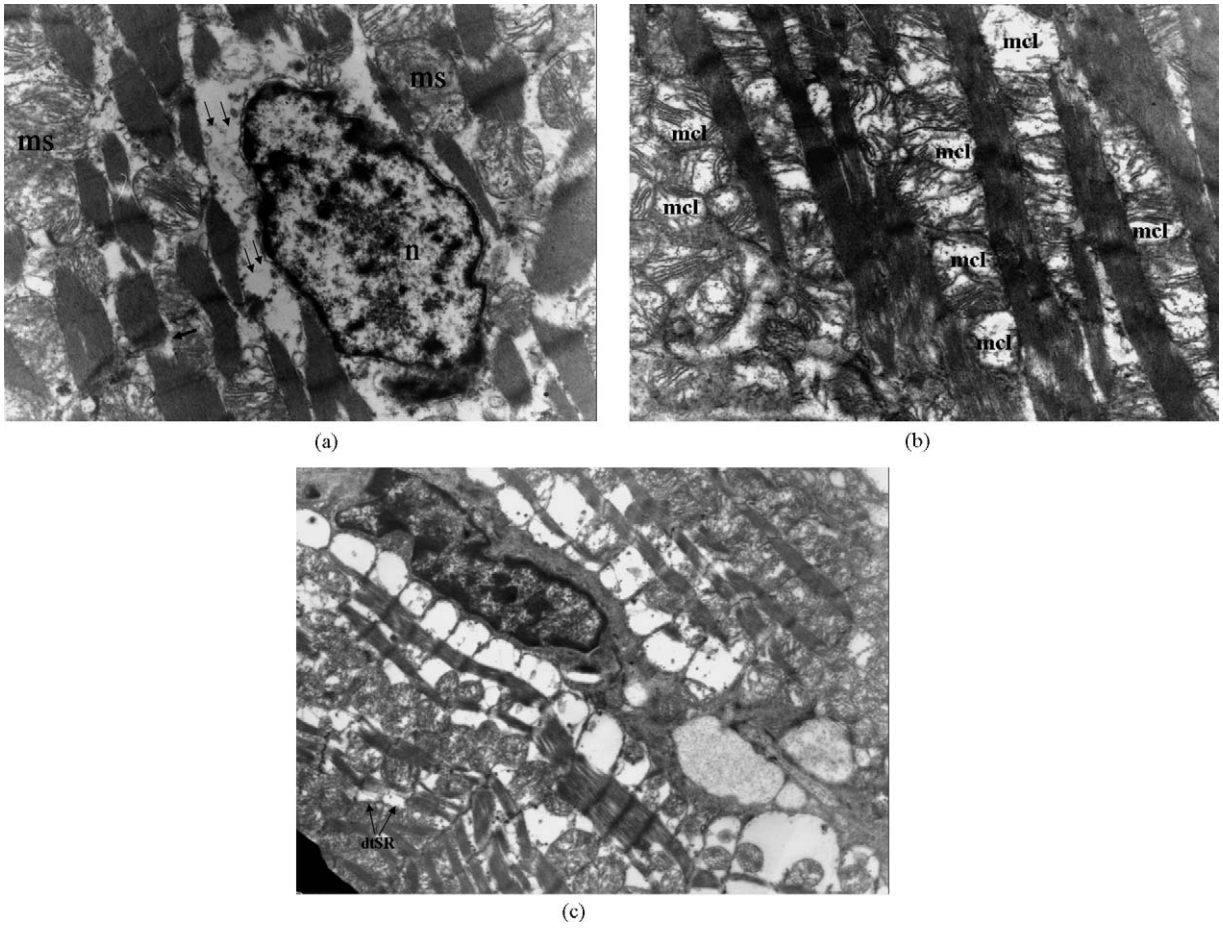

Fig. 1. Thin section from the ventricle of rat in control group. (a) Loss of myofibrils involving perinuclear area (double arrow), mitochondrial swelling (ms), breaks in myofibrils (thick arrow), nucleus (n). (b) Prevalent mitochondrial cristalysis (mcl). (c) dilated tubules of sarcoplasmic reticulum (dtSR) which are confined to perinuclear areas and areas of myofibrillar loss + SR proliferation.