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Ellagic acid inhibits cardiac arrhythmias, hypertrophy and hyperlipidaemia during myocardial infarction in rats

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ABSTRACT

Objective. The objective was to evaluate the protective effect of ellagic acid against experimentally induced cardiac arrhythmias, hypertrophy and its association with altered lipid metabolism during myocardial infarction in rats.

Methods. Rats were treated with ellagic acid (7.5 and 15 mg/kg) orally for a period of 10 days. After 10 days of pretreatment, isoproterenol (100 mg/kg) was injected subcutaneously at an interval of 24 h for 2 days to induce myocardial infarction. On the 12th day, the cardiac rhythm was observed. The rats were sacrificed and the heart was isolated from each rat. Ventricular hypertrophy and myocardial necrotic scores were analysed in the myocardium. Lipid peroxidation products in the plasma were analysed. Changes in the lipid profile were measured using the plasma and heart tissue homogenates of normal and experimental rats.

Results. Isoproterenol-induced rats showed arrhythmias, hypertrophy and increased levels of myoglobin, creatine kinase-MB, lipid peroxidation products compared to the normal control rats. Ventricular hypertrophy and increased myocardial necrotic scores were observed in isoproterenol-induced rats. Oral pretreatment with ellagic acid restored pathological arrhythmias, ventricular hypertrophy, lipid peroxidation, altered lipid profile and myocardial necrosis in the isoproterenol-induced myocardial infarcted rats.

Conclusions. Oral pretreatment with ellagic acid was safe and effective in cardio protection against ISO-induced arrhythmias, hypertrophy and myocardial necrosis. Anti lipid peroxidation property and anti hyperlipidaemic activity through 3-hydroxy-3 methyl glutaryl CoA reductase inhibition by ellagic acid may be the reasons for the beneficial action of ellagic acid against experimentally induced myocardial infarction.

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1. Introduction

Cardiac arrhythmias result in disturbed impulse formation and conduction that affect cardiac contractility, causing ischaemia, infarction and sudden death. It can be associated with other cardiovascular complications, such as stroke and congestive heart failure [1]. Left ventricular hypertrophy is a powerful risk factor leading to contractile dysfunction and heart failure [2]. Hypertrophied myocardium can generate arrhythmias and it is one of the main ways in which cardiomyocytes respond to mechanical and neurohormonal stimuli. A study by Liu et al [3] found that dyslipidaemia is an

Abbreviations: MI, myocardial infarction; ISO, isoproterenol; PVC, premature ventricular contraction; VF, ventricular fibrillation; CK-MB, creatine kinase-MB; HDL, high density lipoprotein; LDL, low density lipoprotein; VLDL, very low density lipoprotein; FFA, free fatty acid; HMG-CoA reductase, 3-hydroxy-3 methyl glutaryl CoA reductase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells.

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independent predictor of cardiac arrhythmias in the acute phase of myocardial infarction (MI). Therefore, it is of great interest to identify a drug moiety which can act against arrhythmias, hypertrophy and hyperlipidaemia in order to prevent fatalities.

Many synthetic drugs are used for the treatment of heart diseases and trying to prevent MI. However, they cannot meet the demands due to multiple etiological factors of MI, and their certain adverse effects [4]. Thus, a number of recent studies focused on identifying new therapeutic strategies to prevent or reverse cardiac failure. Alternative therapies using phyto-nutrients are becoming increasingly popular as these nutrients have no or minimal side effects and are cost effective. Polyphenols are excellent cardioprotectants. Ellagic acid (4,4′,5,5′,6,6′-hexahydroxydiphenic acid 2,6,2′,6′-dilactone) is one of the polyphenolic compounds found naturally in strawberries, raspberries, grapes and pomegranates [5]. It has shown anti-inflammatory, hepatoprotective and chemopreventive activities [6–8]. A recent study in our laboratory showed ellagic acid exhibits cardioprotective activity against experimentally induced MI [9].

It has been reported that isoproterenol (ISO), a β-adrenergic receptor agonist, has deleterious effects on the heart, when administered in higher doses, by inducing oxidative stress, myocardial damage and necrosis [10]. ISO-induced arrhythmias, hypertrophy and alterations in lipid metabolism in rats have been extensively discussed [11,12]. The model is characterized by extraordinary technical simplicity, reproducibility and acceptably low mortality [13].

The present study was designed to investigate the potential preventive effect of ellagic acid against ISO-induced cardiac arrhythmias, ventricular hypertrophy and myocardial necrosis in connection with its anti-lipid peroxidation and anti-hyperlipidaemic activities.

2. Materials and methods

2.1. Experimental animals

All the experiments were carried out with male albino Wistar rats (*Rattus norvegicus*) weighing 180–200 g, purchased from Mahaveer Enterprises, Hyderabad, India. They were housed in polypropylene cages (47×34×20 cm) lined with husk, renewed every 24 h under a 12 h light/dark cycle at around 22 °C with 50% humidity. The rats had free access to water and food. The rats were fed on a standard pellet diet (Pranav Agro Industries, Pune, Maharashtra, India). The experiment was carried out according to the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals, New Delhi, India and approved by the Institutional Animal Ethical Committee of Jayamukhi College of Pharmacy (Approval No. 022; 28.2.2010).

2.2. Drugs and chemicals

Ellagic acid and isoproterenol were purchased from Sigma Chemical, St. Louis, MO, USA. Sodium sulphite, dimethyl sulfoxide, potassium tetraborate, deoxyribose, nitroblue tetrazolium reagent and hydroxylamine hydrochloride were purchased from Himedia, Mumbai, India. All other chemicals used in the study were of the highest analytical grade.

2.3. Induction of experimental myocardial infarction

ISO (100 mg/kg body weight) was dissolved in saline and injected subcutaneously to rats at an interval of 24 h for 2 days to induce MI [14].

2.4. Experimental design

The rats were divided into six groups of six rats each. Group I: normal control rats were given 2 mL of saline orally by gastric intubation daily for a period of 10 days; Group II: normal rats were treated with ellagic acid (7.5 mg/kg) dissolved in 2 mL of saline orally by gastric intubation daily for a period of 10 days; Group III: normal rats were treated with ellagic acid (15 mg/kg) dissolved in 2 mL of saline orally by gastric intubation daily for a period of 10 days; Group IV: normal control rats were given 2 mL of saline orally by gastric intubation daily for a period of 10 days and then subcutaneously injected with ISO (100 mg/kg) in 2 mL of saline at an interval of 24 h for 2 days (on 11th and 12th day); Group V: rats were pretreated with ellagic acid (7.5 mg/kg) in 2 mL of saline orally by gastric intubation daily for a period of 10 days and then subcutaneously injected with ISO (100 mg/kg) at an interval of 24 h for 2 days (on 11th and 12th day); Group VI: rats were pretreated with ellagic acid (15 mg/kg) in 2 mL of saline orally by gastric intubation daily for a period of 10 days and then subcutaneously injected with ISO (100 mg/kg) once a day for 2 days (on 11th and 12th day).

2.5. Determination of arrhythmias score

Twenty four hours after the second dose of ISO, the electrocardiogram is recorded for the rats of all the groups. The electrocardiogram is analyzed using a digital acquisition and analysis system (AD Instrument Power Lab). The rats are anesthetized with ketamine hydrochloride (100 mg/kg) intraperitoneally. Rectal temperature is continuously monitored and maintained within 37–38 °C using a heat pad and heat lamp. Electrocardiographic transducers were inserted subcutaneously into the right forelimb and into each hind limb as mentioned in the AD instruments' protocol. The signal is acquired for about 3 min using Lab Chart 7.0 for Windows software on Lenovo ThinkPad. The recorded signal was free of noise and electrical interference. Each test takes ~10–12 min including anesthetic induction and recovery time. The changes in the heart rhythm were observed and recorded. Arrhythmias were calculated by a modified scoring system explained by Fryer et al [15]. Arrhythmias scores were assigned as follows: 0≤10 premature ventricular contraction (PVCs)/3-min period; 1≤10 to 50 PVCs/3-min period; 2≥50 PVCs/3-min period; 3=1 episode of VF/3-min period; 4=2 to 4 episodes of VF/3-min period; and 5≥4 episodes of VF/3-min period [16,17].

2.6. Sample preparation

After measuring the arrhythmic score, the rats were sacrificed by cervical decapitation and blood was collected in two tubes, i.e., one with anticoagulant (ethylene diamine tetra acetic acid) for plasma separation, and another without anticoagulant for serum separation. Both the plasma and serum were separated from each sample and used for the biochemical

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