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Original article

Piperine modulates isoproterenol induced myocardial ischemia through antioxidant and anti-dyslipidemic effect in male Wistar rats

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ABSTRACT

Myocardial infarction due to ischemia accounts for majority of deaths among cardiovascular disorders. Isoproterenol (ISO) induced myocardial infarction and the protection offered by piperine was investigated in the present report. Lipid profile analysis by determining the levels of cholesterol, phospholipids, triglycerides and lipoproteins in serum and heart tissues showed anti-dyslipidemic action of piperine against ISO induced myocardial injury by modulating the ISO induced altered lipid profiles, maintaining to near control values. ISO treatment increased TBARS levels, PCC, serum markers of heart, depleted antioxidant status (GSH, SOD, CAT, GPx and GST) in tissues and, total, protein- and non-protein-sulfhydryl levels in serum and heart tissues. Piperine pre-treatment decreased the levels of serum markers, lipid peroxidation and PCC with increased antioxidant status in the heart tissues of ISO administered rats. Increased levels of the glycoprotein components in serum and decreased levels in heart tissues upon ISO administration were restored to near normal levels by piperine pre-treatment. Our present reports also showed the modulatory effect of piperine on membrane bound ATPase's showing protection against ISO induced changes in membrane fluidity. The present study proved piperine as a potent therapeutic agent with its antioxidant and anti-dyslipidemic action against ISO induced myocardial infarction.

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1. Introduction

Globally, cardiovascular diseases (CVD) constitute a leading cause of death and ischemic heart disease (IHD) accounts for majority of deaths from cardiovascular disorders in both developing and developed countries [1–3]. Ischemic tissue generates oxidative free radicals, often leading to chain reactions which contribute to cell death [4]. Myocardial infarction (MI), the predominant outcome of ischemia is developed when there is an imbalance between myocardial oxygen supply and demand, results in myocardial hypoxia [2]. Acute MI is characterized by varying degree of chest pain, sweating, weakness, vomiting, arrhythmia, loss of consciousness, and even sudden death [5].

Although the pathophysiology of cellular damage due to ischemia is complex, reactive oxygen species are known to play a major role [3] and are a target for therapeutic interventions. Isoproterenol (ISO), a synthetic catecholamine and a β-adrenergic agonist causes severe oxidative stress in the myocardium, resulting

Abbreviations: ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; CAT, catalase; CK, creatine kinase; CVD, cardiovascular diseases; MI, myocardial infarction; DMSO, dimethyl sulfoxide; GPx, glutathione peroxidase; GSH, glutathione; GST, glutathione S- transferase; HDL, high density lipoprotein; ISO, isoproterenol; LCAT, lecithin-cholesterol acyltransferase; LDH, lactate dehydrogenase; LDL, low density lipoprotein; LPO, lipid peroxidation; PCC, protein carbonyl content; PLs, phospholipids; SOD, superoxide dismutase; TBARS, thiobarbituric acid reactive substances; TGs, triglycerides; VLDL, very low density lipoprotein.

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in infarct like necrosis of the heart muscles [6]. Generation of highly cytotoxic free radicals through autoxidation of catecholamines has been implicated as the important causative factor in ISO induced cardiac injury among other proposed mechanisms [1]. Higher levels of catecholamines deplete the energy reserve of cardiac muscle cells, leading to complex biochemical and structural changes that cause irreversible cellular damage and ultimately necrosis [2,7]. Experimental and clinical studies on heart failure proves that there is increased generation of reactive oxygen species such as superoxide anion (O^{2-}) and hydroxyl radicals (OH^{-}) which are involved in the formation of lipid peroxides, cell membrane damage, and destruction of antioxidative defense system [8]. MI induced by ISO shows many metabolic and morphologic changes in the heart tissues of the experimental animals similar to those observed in human MI which serves as a well standardized model to evaluate several cardiac dysfunctions and to study the efficacy of various natural and synthetic cardioprotective agents [3]. Recent interest of researchers has been focused on phytochemicals and polyphenols such as the flavonoids, alkaloids, and xanthones derived from different plant species to serve as potential therapeutic agents in the prevention and management of cardiovascular diseases due to their antioxidant nature.

Piperine is a major plant alkaloid of black pepper (*Piper nigrum*) consumed by a large number of people worldwide. The compound is known to possess several pharmacological actions, such as antioxidant, anti-platelet, analgesic, anti-inflammatory, immunomodulatory [9], anti-anxiety, anti-depressant, anti-thyroid, hepatoprotective [10], anti-arthritic [11], anti-fertility, anti-obesity, adulticidal, anti-hyperlipidemic, bioavailability enhancer, melanin inhibitory, anti-cancer, cardio- and radioprotective [9] properties. Based on these evidences, the present study aims to elucidate whether piperine could offer protection against ISO induced myocardial ischemia in male Wistar rats by analyzing the serum markers, antioxidant status, lipid profile, sulfhydryl content, glycoprotein levels, membrane bound ATPases and histoarchitecture of the heart of male Wistar rats.

2. Materials and methods

2.1. Chemicals

Isoproterenol and piperine were obtained from Sigma Aldrich Pvt. Ltd., Bangalore, India. All other chemicals used were of analytical grade and were purchased from HiMedia laboratories, Mumbai, India.

2.2. Animals and experimental design

The study used male albino wistar rats (weighing 200 ± 10 g) purchased from small animal breeding station, college of veterinary and animal sciences Mannuthy, Thrissur, Kerala. Animals were maintained at a temperature of 26 ± 2 °C with a normal 12 h light/dark cycle. The animals were allowed to have commercially available pelleted rat chow (Sai Durga Private Limited, Bangalore) and water ad libitum. The experiment was carried out in strict accordance with the recommendations in the guide for the Care and use of Laboratory Animals of the National Institutes of Health (NIH), USA and Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), India. Approval was obtained from Institutional Animal Ethics Committee, PSG Institute of Medical Sciences and Research (Ethical approval number: 209/2013/IAEC). After a week of acclimatization, rats were divided into five groups containing six rats each. Piperine at 20 mg/kg body weight, suspended in DMSO was given by oral intubation method for 10 days followed by ISO treatment for 2 days subcutaneously at 80 mg/kg body weight suspended in normal saline at an interval of 24 h. The group I rats received normal saline. Group II animals received DMSO and served as vehicle control. Group III animals received piperine. Group IV animals received ISO and rats in group V were pre-treated with piperine for 10 days followed by ISO treatment for 2 days. The experimental animals were anaesthetized with diethyl ether after completion of the treatment period and killed by cervical decapitation. The serum separated from the collected blood was used for biochemical assays. The heart tissues were dissected out, washed in ice cold saline, patted dry and weighed. 100 mg of this tissue were homogenized and used for biochemical investigation. A small portion of the tissue was stored in 10% formalin for histological analysis. The remaining tissues were stored in −80 °C for further investigations.

2.3. Analysis of serum cardiac markers

Damage to heart tissues was studied by analyzing the leakage of creatine kinase (CK) and lactate dehydrogenase (LDH) in serum. Serum CK activity was assayed by the method of Okinaka et al. [12]. Assay of LDH activity in serum was measured by the method of King [13].

2.4. Histopathological examination

The heart tissues were qualitatively analyzed for histological alterations after fixing in 10% formalin. The tissues were then processed for dehydration and clearing of fixative and embedded in paraffin wax. Sections of heart (3–5 μm thickness) were cut and stained with hematoxylin and eosin (H and E) dyes for morphological observation under the microscope.

2.5. Estimation of ROS levels in heart tissues

ROS levels in the homogenates of heart tissue samples were determined as per the method described by Parthasarathy et al. [14].

2.6. Assay of lipid peroxidation and protein carbonyl content in heart tissues

Lipid peroxidation in the heart tissue homogenates was analysed by the method of Ohkawa et al. [15] and the carbonyl contents of the protein in the tissue homogenates were estimated by method of Levine et al. [16].

2.7. Determination of reduced GSH and enzymic antioxidant status in the heart tissues

Heart tissues homogenized in chilled Tris HCl buffer (0.1 M) pH 7.4 was used for the estimation of reduced GSH and antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and glutathione s-transferase (GST). Reduced GSH content in the heart tissues were estimated by the method of Moron et al. [17]. Activity of SOD was estimated by Marklund and Marklund method [18] and CAT by the method of Takahara et al. [19]. Estimation of GPx and GST were done using the methods of Rotruck et al. [20] and Habig et al. [21] respectively.

2.8. Analysis of serum and tissue glycoproteins

Glycoproteins such as hexose, hexosamine, fucose, and sialic acid were estimated in both serum and heart tissues. Serum and tissue glycoproteins were extracted as described in our previous study [6]. The levels of hexose, hexosamine, fucose, and sialic acid

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