Original Paper

Cellular Physiology and Biochemistry

Cell Physiol Biochem 2011;27:273-280

Accepted: January 11, 2011

Sesamol Attenuates Isoproterenol-induced Acute Myocardial Infarction via Inhibition of Matrix Metalloproteinase-2 and -9 Expression in Rats

Srinivasan Periasamy[a], Fan-E Mo[b], Shin-Yi Chen[a], Chih-Ching Chang[a] and Ming-Yie Liu[a,c]

Departments of [a]Environmental and Occupational Health and [b]Cell Biology and Anatomy, National Cheng Kung University College of Medicine, Tainan, [c]Sustainable Environment Research Center, National Cheng Kung University, Tainan

Key Words

Sesamol • Blood pressure • Heart rate • Electrocardiography • Isoproterenol • Myocardial infarction • Matrix metalloproteinase-2 • Matrix metalloproteinase-9

Abstract

Background/Aims: The protective role of sesamol and its possible action against isoproterenol-induced myocardial injury and infarction is unknown. We tested the hypothesis that sesamol's protection against myocardial infarction is associated with the inhibition of matrix metalloproteinase (MMP)-2 and MMP-9. Methods: Four groups of experimental rats were subcutaneously injected with sesamol (0, 1, 3, or 10 mg/kg) and then, 2 h later, intraperitoneally injected with isoproterenol (100 mg/kg 24 h apart on 2 consecutive days) to induce myocardial infarction. Control rats were treated with saline only. Blood pressure (BP), heart rate (HR), and electrocardiography (ECG) wave durations, serum creatine phosphokinase isoenzymes (CKMB), lactate dehydrogenase (LDH), myocardial histology, MMP-2, and MMP-9 were assessed 24 h after the last dose of isoproterenol was given. Results: BP was lower, and HR, ECG wave durations, CKMB, LDH, myocardial injury, MMP-2, and MMP-9 levels were higher in experimental rats than in control rats. BP was significantly higher, and all the other parameters were significantly lower in the rats treated with sesamol than in those treated with isoproterenol only. Conclusions: Sesamol effectively prevented myocardial infarction, at least in part, by controlling proteolytic activities and the expression of MMP-2 and -9 in isoproterenol-treated rats.

Introduction

Acute myocardial infarction (MI) is an important ischemic heart disease and a leading cause of morbidity and mortality worldwide. Approximately one third of all MIs are silent, without chest pain or other symptoms [1]. MI occurs more often in elderly patients and patients with diabetes mellitus [2]. Isoproterenol, a beta adrenergic

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Ming-Yie Liu, PhD
Department of Environmental and Occupational Health, National Cheng Kung University College of Medicine, 138 Sheng-Li Road, Tainan 70428 (Taiwan)
Tel. +886-6-235-3535 ext. 5805, Fax +886-6-275-2484
E-Mail myliu@mail.ncku.edu.tw

agonist, induces MI in rats [3] and it depletes the energy reserve of cardiac muscle cells, which leads to complex biochemical and structural changes that cause irreversible cellular damage and ultimately infarct-like necrosis [4, 5]. The acute phase of myocardial necrosis and repair mimics what occurs in patients: changes in serum enzymes [3], blood pressure (BP), heart rate (HR) [6], electro cardiogram (ECG), histology [3], and matrix metalloproteinase (MMP) in heart tissue [7]. The rat model of isoproterenol-induced MI offers a standardized non-invasive technique for studying the effects of various potential cardioprotective therapies [3].

Sesame oil, derived from the plant species *Sesamum indicum* L., is used to increase resistance to lipid peroxidation and to protect against multiple organ injury [8]. Sesamol, an effective nonfat antioxidant, is the active component of sesame and sesame oil [9]. Sesamol attenuates oxidative stress and protects against liver and kidney injury [10-13]. In the present study, we investigated the effect of sesamol against isoproterenol-induced MI. We examined the correlated functional (BP, ECG), biochemical, and histopathologic changes in cardiac performance-related MMP-2 and MMP-9 expression in rats with isoproterenol-induced MI.

Materials and Methods

Animals

Male Sprague Dawley rats weighing 200-250 g were obtained from and housed in our institution's Laboratory Animal Center. The rats were housed individually in a room with a 12-h light/dark cycle and with central air conditioning (25°C, 70% humidity). They were allowed free access to tap water and pelleted rodent diet (Richmond Standard; PMI Feeds, St. Louis, MO). The animal care and experimental protocols were in accord with nationally approved guidelines.

Chemicals

Isoproterenol hydrochloride, sesamol, and sodium thiopental were purchased from Sigma-Aldrich Chemical Co. (St. Louis, MO, USA). All other chemicals used were analytical grade. Isoproterenol solution was made as a 10% solution using sterile physiological saline.

Experimental design

The rats were divided into five groups of six. Group-I rats (controls) were intraperitoneally (i.p.) injected with saline (1 mL) 24 h apart on 2 consecutive days. Group-II to Group-V rats were injected with isoproterenol (100 mg/kg/d; i.p.) 24 h apart on 2 consecutive days. Group-III to group-V rats were subcutaneously injected with sesamol (1, 3, or 10 mg/kg/d) and, 2 h later, isoproterenol (100 mg/kg/d; i.p.) 24 h apart on 2 consecutive days.

Hemodynamic and functional measurements

The rats were anesthetized with sodium thiopental (40 mg/kg; i.p.). BP parameters (diastolic pressure (DP), systolic pressure (SP), and HR) and ECG parameters (P, PR interval, QRS interval, and T wave durations) were measured using SINGA Xction View II (Singapore). All data were analyzed using Xction View 2.0 software.

Collecting blood

Blood was collected in serum separation tubes from a femoral vein via venipuncture while the rats were under mild ether anesthesia. The tubes were left at room temperature for 30 min to clot and then centrifuged at 1000 x g at 4°C for 10 min.

Assessing myocardial infarction

We assessed MI by measuring the levels of serum creatine phosphokinase isoenzymes (CKMB) and lactate dehydrogenase (LDH) in serum using a biochemistry analyzer (Fujifilm Dri-Chem 3500s; Fujifilm, Kanagawa, Japan). MI was confirmed using histological studies. A small piece of heart tissue was cut from each rat and placed in 4% phosphate-buffered formalin. The tissue pieces were dehydrated using a graded percentage of alcohol and then fixed in paraffin wax for 1 h to form blocks. The blocks were trimmed and cut into 4-μM-thick sections, stained with hematoxylin and eosin, and then mounted using Depex-Polystyrene dissolved in xylene mountant. The permanently mounted sections of liver tissue were examined under a microscope (Eclipse E 600; Nikon Instech, Kawasaki, Japan) (magnification: 100x) to assess myocardial injury.

Protein assay

Protein concentrations in heart tissue were determined using a protein assay (Bio-Rad Laboratories, Hercules, CA, USA). Bovine serum albumin was used as a standard.

Quantitative zymography

MMP-2 and MMP-9 were investigated using quantitative zymography techniques as previously described [14]. In brief, 100 mg of frozen pieces of heart were washed in PBS to remove blood components. Three wet weight volumes of 50 mM/L of Tris-HCl (pH 7.6) were added and incubated in ice for 15 min, and the suspension was sonicated twice for 30 s at 100 W. After 3 wet weight volumes of 125 mM/L of Tris-HCl (pH 6.8), 4% sodium dodecyl sulfate (SDS), and 20% glycerol had been added, the suspensions were homogenized again, centrifuged, and the supernatant containing the total SDS-soluble material was collected. Discontinuous SDS-polyacrylamide gels (PAGE) (7.5% or 10%) containing gelatin were prepared, and samples containing 40 μg of protein were separated on the gel. After electrophoresis, the gels were washed in Triton X-100 and incubated in 5 mM/L $CaCl_2$ for 18 h at 37°C. Coomassie Brilliant Blue-stained gels were scanned on a laser densitometer (Scanner; Alpha Innotech, Tokyo, Japan). Proteolytic activity was analyzed and quantified using an

Parameters	Group I[a]	Group II	Group III	Group IV	Group V
DP (mmHg)	86.30 ± 23.27*	52.98 ± 05.48#	56.04 ± 12.41#	54.58 ± 10.32#	70.27 ± 9.39*
SP (mmHg)	109.90 ± 17.93*	84.24 ± 10.89#	79.13 ± 11.99#	84.04 ± 08.75#	99.32 ± 07.96*
HR (cpm)	385.54 ± 29.15*	445.64 ± 10.32#	421.60 ± 24.90#	414.74 ± 32.97#	378.04 ± 28.02*
P wave duration (ms)	6.70 ± 3.539*	15.10 ± 2.24#	12.64 ± 3.51#	13.54 ± 3.66#	9.74 ± 2.53*
PR interval (ms)	18.87 ± 12.85*	35.57 ± 6.07#	18.37 ± 6.07*	20.50 ± 10.44*	22.57 ± 15.63*
QRS duration (ms)	17.03 ± 5.20*	27.30 ± 10.70#	26.77 ± 16.05*#	24.13 ± 15.001*#	19.50 ± 10.99*
T wave duration (ms)	33.84 ± 6.83*	50.77 ± 9.86#	44.84 ± 4.66*	45.97 ± 7.92*	38.97 ± 6.26*

Table 1. Effects of sesamol on functional parameters of the heart in isoproterenol-treated rats. [a]Group-I rats were intraperitoneally (i.p.) injected with saline (1 mL/kg). Group-II rats were injected with isoproterenol (100 mg/kg; i.p.) 24 h apart on 2 consecutive days. Group-III, -IV, and-V rats were subcutaneously injected with sesamol (1, 3, and 10 mg/kg, respectively) and, 2 h later, with isoproterenol 24 h apart on 2 consecutive days. Blood pressure parameters (diastolic pressure (DP), systolic pressure (SP), heart rate (HR), P, PR, QRS, and T wave durations) were measured 24 h after the last dose of isoproterenol. Data are means ± SD. #P < 0.05 vs. Group I; *P < 0.05 vs. Group II.

Alpha Imager (Alpha Innotech).

Quantification of MMP-2 and MMP-9 expression

Heart tissue was homogenized in 200 µL of ice-cold protein lysis buffer and then kept in ice for 30 min. The homogenized protein lysate was centrifuged (12000 rpm, 30 min), and a protein assay dye (Bio-Rad) with bovine serum albumin as the standard was used to determine protein concentration in the supernatant. Electrophoresis was used to separate 30 µg of protein in 8-12% SDS-PAGE, and then the product was transferred to nitrocellulose sheets (NEN Life Science Products, Boston, MA, USA) with a Western blot apparatus (Bio-Rad) run at 1.2 A for 3 h. After they had been blocked in 5% non-fat skim milk in TBST (Tris-buffered saline with Tween-20), the immunoblots were incubated with primary MMP-2 (Sigma-Aldrich) primary MMP-9 rabbit monoclonal antibody (dilution 1:3000) (Epitomics, Burlingame, CA, USA) in 5% non-fat skim milk. After they had been washed three times, the blots were incubated with secondary antibody conjugated with horseradish peroxidase (dilution 1:3000) (R&D Systems, Minneapolis, MN, USA). Immunoblots were incubated in a reagent (Western Lightning Plus-ECL Substrate; PerkinElmer Life Sciences, Boston, MA, USA). After 1 min, immunoblots were exposed to X-ray film (Biomax Light Film; Eastman Kodak Company, Rochester, NY, USA).

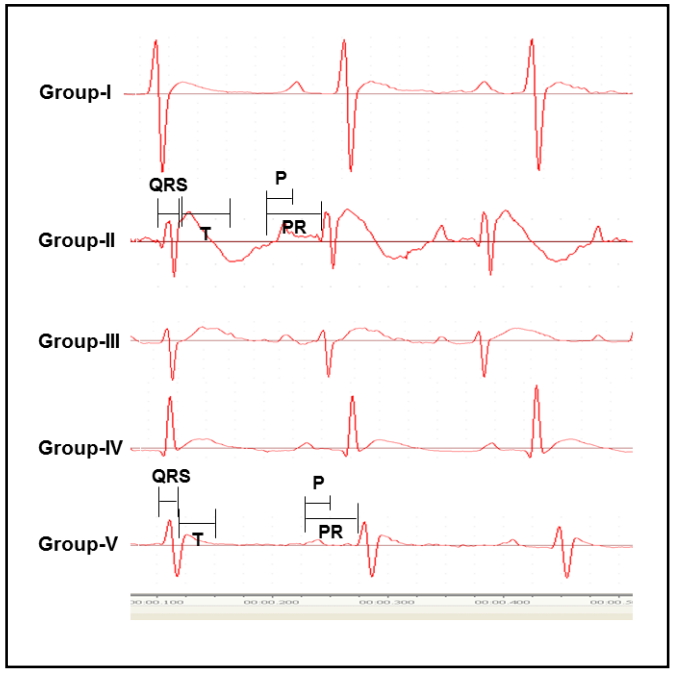

Fig. 1. Representative ECG graphs of the experimental rats.

Immunohistochemical staining of MMP-2 and MMP-9

Tissue sections were deparaffinized, rehydrated, and then incubated with MMP-2 (dilution 1:400) (Sigma-Aldrich) primary MMP-9 rabbit monoclonal antibody (dilution 1:150) (Epitomics) overnight at 4°C and developed (Ultra Vision Detection System Anti-Rabbit, HRP/DAB (Ready-To-Use) Kit; Thermo Fisher Scientific, Fremont, CA, USA). The cellular nuclei of the sections were counterstained with hematoxylin, cleared, and mounted using 3H-diethylphenylxanthine (DPX, a potent adenosine receptor antagonist). The stained slides were scored using photomicrographs (Image-Pro Plus 4.0; Media Cybernetics, Bethesda, MD, USA) taken randomly at ten different locations under a light microscope.

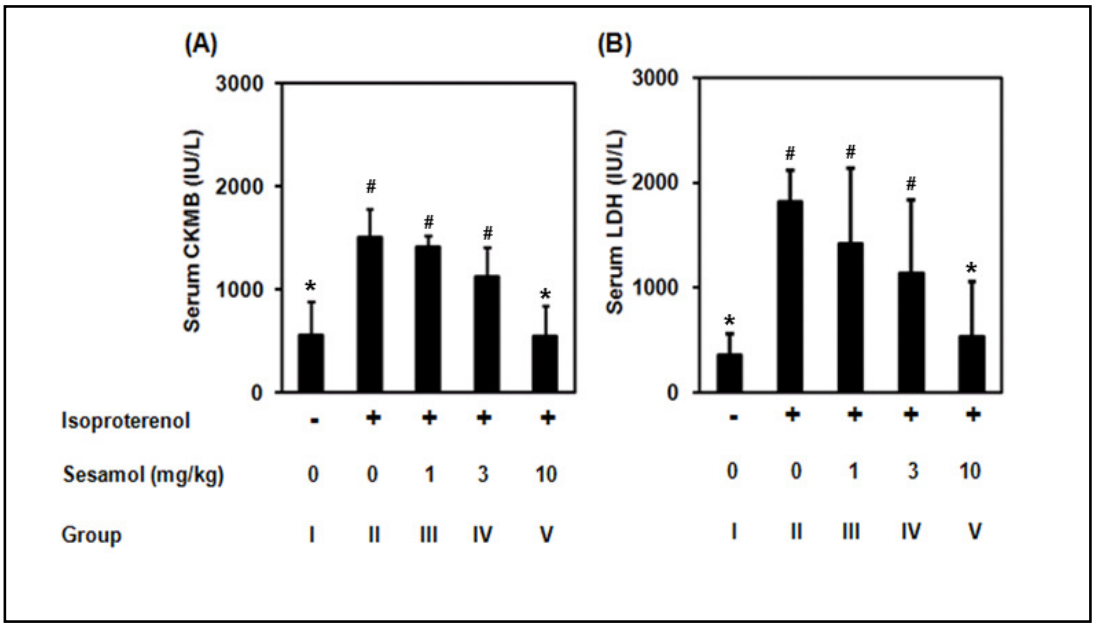

Fig. 2. Effects of prophylactic sesamol on myocardial infarction markers in isoproterenol-challenged rats. Serum samples for (A) creatine phosphokinase isoenzymes (CKMB) and (B) lactate dehydrogenase (LDH) were collected and measured 24 h after last dose of isoproterenol. Data are means ± SD. #P < 0.05 vs. Group I; *P < 0.05 vs. Group II.

Statistical analysis

The statistical analysis was done using SPSS 11.0.1 (SPSS, Chicago, IL, USA). Data are expressed as means ± SD. Differences in the measured variables between each group were assessed using Fisher's least significant difference test. Significance was set at P < 0.05.

Results

Prophylactic effects of sesamol on functional parameters in isoproterenol-treated rats

To evaluate the effect of sesamol on the functional parameters of the heart in isoproterenol-induced MI, we measured SP, DP, HR, P, PR, QRS, and T wave durations. DP and SP were significantly (P < 0.05) lower and HR, P, PR, QRS, and T wave durations significantly higher in Group-II rats than in Group-I rats (Table 1; Fig. 1). DP and SP were significantly (P < 0.05) higher; HR, P, PR, QRS, and T wave durations were significantly (P < 0.05) lower; and normal heart function was maintained in Group-V rats (treated with 10 mg/kg/d of sesamol).

Prophylactic effects of sesamol on myocardial infarction markers and injury in isoproterenol-treated rats

To assess the protective effect of sesamol on isoproterenol-induced MI, we measured serum CKMB and LDH levels. Both were significantly (P < 0.05) higher in Group-II rats than in Group-I rats. CKMB (Fig. 2A) and LDH levels (Fig. 2B) were significantly (P < 0.05) lower in Group-V rats. Histopathologic examination of myocardial tissue (Fig. 3A and B; Table 2) from Group-II rats revealed that the infarcted zone had large areas of myocardial tissue damage in the subendocardium of the left ventricle. Extensive myofibrillar degeneration, which is related to a dense inflammatory infiltration of cells with severe interstitial edema, was also found. These changes in myocardial tissue ranged from the myofibrillar infiltration of cells with a loss of the normal striation pattern to distinct granular degeneration with coagulative necrosis of the myofibrils. Sesamol significantly (P < 0.05) decreased fragmentation of fibers and inflammation in Group-V rats.

Groups	Severity of myocardial injury[a]
Group I	No changes
Group II	+ + +
Group III	+ + +
Group IV	+ +
Group V	+

Table 2. Effect of sesamol on the degree of myocardial injury in rats with isoproterenol-induced MI. [a]+, mild changes; + +, moderate changes; + + +, severe changes.

Prophylactic effects of sesamol on MMP-2 and MMP-9 expression in isoproterenol-treated rats

To examine the effect of sesamol on the proteolytic degradation of myocardial tissue, we evaluated MMP-2

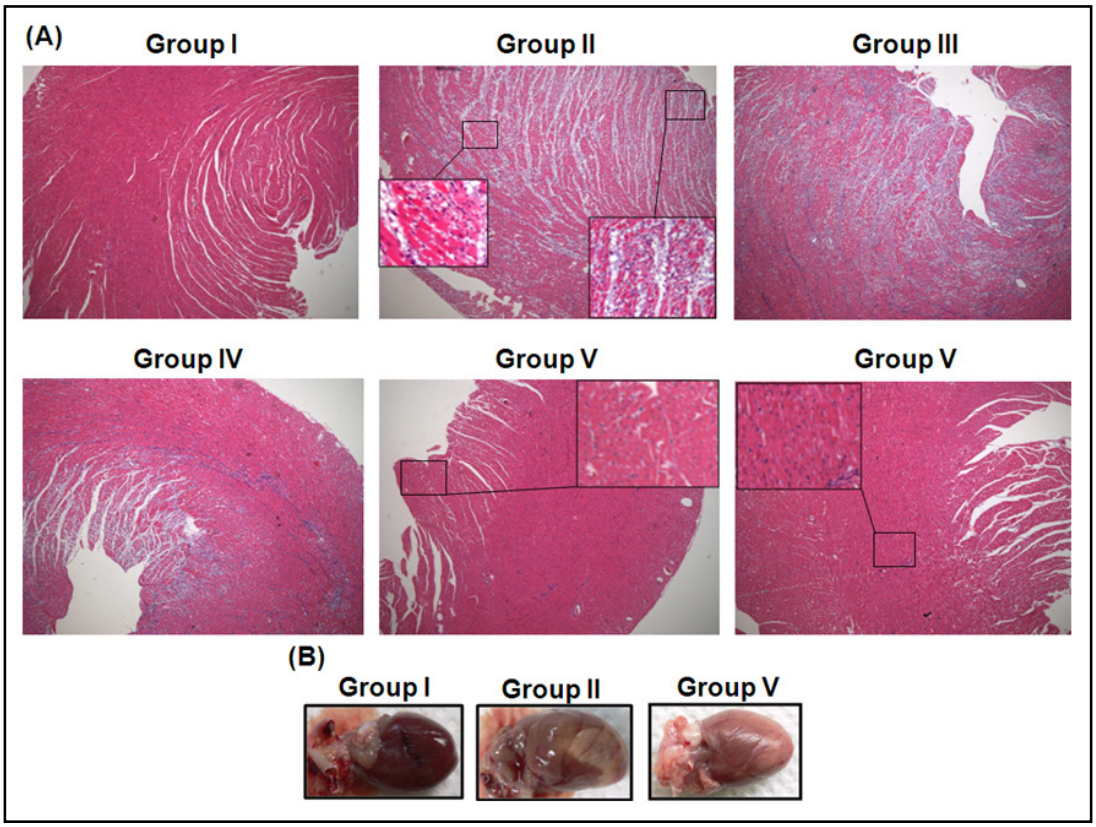

Fig. 3. Effects of prophylactic sesamol on histopathologic features of myocardial tissue in isoproterenol-treated rats. Myocardial tissue samples were collected 24 h after the last dose of isoproterenol. Photomicrographs were taken at [10x].

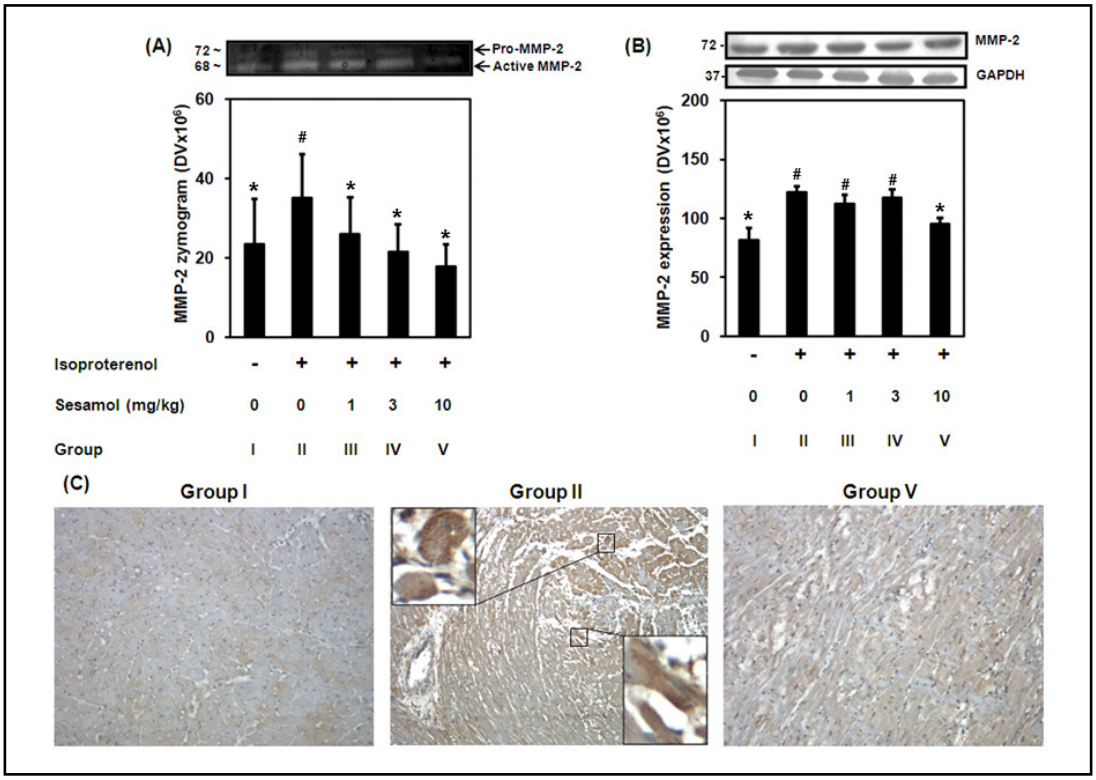

Fig. 4. Effects of prophylactic sesamol on MMP-2 proteolytic activity and expression in isoproterenol-challenged rats. The effects of sesamol on MMP-2 proteolytic activity were assessed using zymography in isoproterenol-treated rats. (A) MMP-2 zymogram; (B) MMP-2 protein expression; (C) MMP-2 immunohistochemistry. Data are means ± SD. #P < 0.05 vs. Group I; *P < 0.05 vs. Group II.

and MMP-9 in isoproterenol-treated rats. The proteolytic activity and expression MMP-2 (Fig. 4A, B, and C) and MMP-9 (Fig. 5A, B, and C) was significantly ($P < 0.05$) higher in Group-II than in Group-I rats. Sesamol significantly ($P < 0.05$) inhibited the proteolytic activity of MMP-2 in Group-III, -IV, and -V rats, and significantly

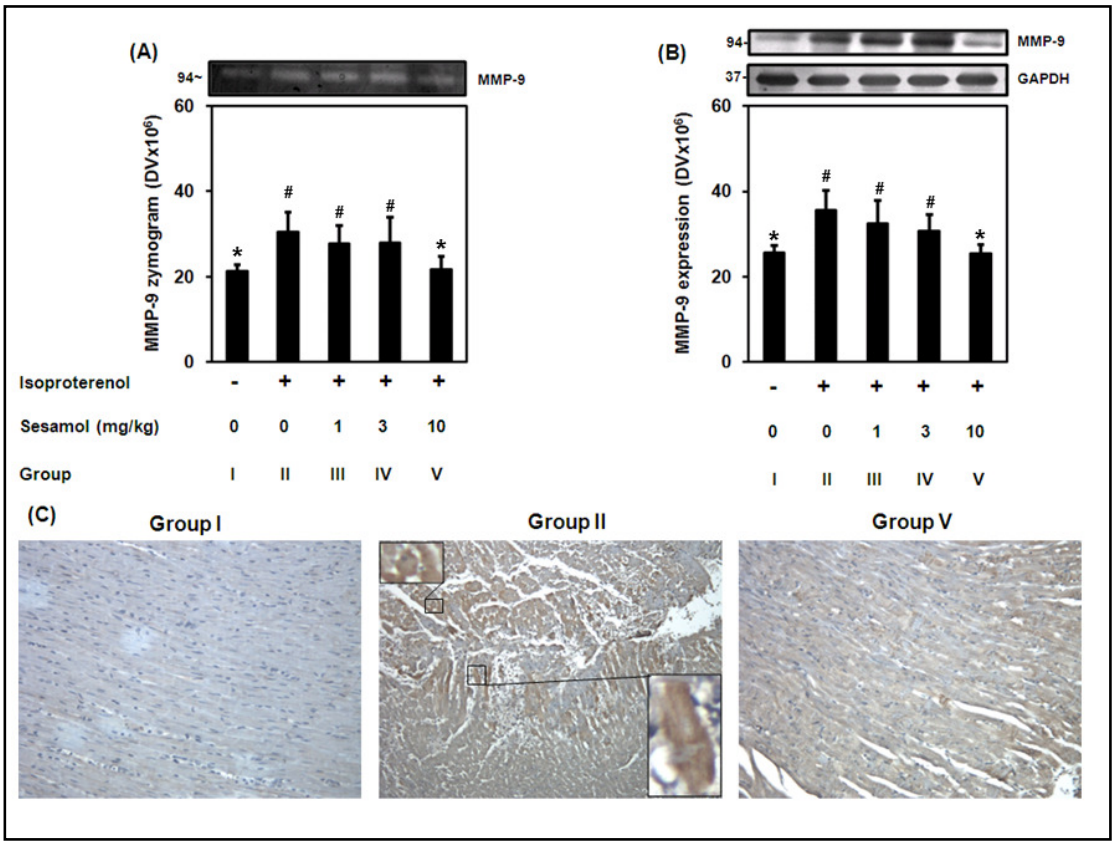

Fig. 5. Effects of prophylactic sesamol on MMP-9 proteolytic activity and expression in isoproterenol challenged rats. The effects of sesamol on MMP-9 proteolytic activity were assessed using zymography in isoproterenol-treated rats. (A) MMP-9 zymogram; (B) MMP-9 protein expression; (C) MMP-9 immunohistochemistry. Data are means ± SD. $^{\#}P < 0.05$ vs. Group I; $^{*}P < 0.05$ vs. Group II.

($P < 0.05$) inhibited the expression of MMP-2 and MMP-9 in Group-V rats.

Discussion

We found that sesamol protected against MI by attenuating the isoproterenol-induced changes in the functional parameters of the heart. Furthermore, sesamol inhibited myocardial markers, injury, and the proteolytic activity and expression of MMP-2 and MMP-9 in isoproterenol-induced MI in rats.

Inhibiting the proteolytic activity and expression of MMP-2 and MMP-9 in the myocardial tissue may be sesamol's most significant protective effect in isoproterenol-induced MI. MMP-2 [15-18] and MMP-9 [15] are upregulated in myocardial tissue in isoproterenol-induced MI. This leads to changes in the functional parameters of the heart: decreased SP and DP, increased HR [3, 6, 19], increased P, T, QRS, and PR wave durations in ECG [20, 21], and the leakage of the myocardial injury markers CKMB and LDH in serum [3, 22-24]. Histopathologic analysis of the isoproterenol-treated myocardial tissue revealed an infarcted zone with inflammation, myofibrillar degeneration, and necrosis, which agrees with the findings in other studies [3, 22, 25]. MMPs, a large family of endopeptidases, degrade extracellular matrix proteins, and are fundamental for tissue remodeling, including heart tissue [26-28]. MMP-2 (gelatinase A) and MMP-9 (gelatinase B) are higher than normal in a variety of experimental heart-failure models as well as in the failing human heart [17, 27]. Within the heart, cardiac fibroblasts are considered to be the main source of the synthesis and secretion of MMPs. However, other heart cell types, including cardiac myocytes, are also suggested to secrete a variety of MMPs. MMP-2 and MMP-9 play a major role in extracellular membrane remodeling because of their ability to initiate and continue the degradation of fibrillar collagen [26]. Increased MMP-2 expression and proteolytic activity during heart failure may induce cardiac myocyte loss due to apoptosis [17], and ultimately lead to MI and heart failure. Sesamol's mechanism of action against MI might be inhibiting the expression and proteolytic activity of MMP-2 and MMP-9, which attenuates myocardial injury and damage, and thereby it maintains the normal functioning of the heart.

The clinical implications of the present study are that sesamol has the potential to protect against MI in patients who have a greater risk of cardiovascular

complications. One report [29] showed that seven doses of 50 mg of sesamol were effective against isoproterenol-induced MI through a lipid peroxidation and antioxidant mechanism in rats. The present study showed that two doses of 10 mg of sesamol protected against MI in rats. Sesamol's early inhibition of the proteolytic activity and expression of MMP-2 and MMP-9 might be an effective life-saving strategy in preventing MI in human patients.

In conclusion, sesamol inhibited the proteolytic activity and expression of MMPs in rats with isoproterenol-induced MI. We hypothesize that sesamol is a pharmacological MMP inhibitor and offers a novel strategy for preventing MI in humans. However, further studies are required to confirm this hypothesis.

Acknowledgements

This research was supported by grant NSC 99-2221-E-006-064-MY3 from the Taiwan National Science Council.

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