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Original Article

Curcumin reduces myocardial damage and improves antioxidant capacity of myocardial tissue in diabetic rats

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Abstract: Objective: To investigate the effects of curcumin on myocardial damage and its antioxidant capacity in myocardial tissue of diabetic rats. Methods: A rat model of diabetic heart disease was established. 3 Thirty adult male SD rats were randomly and equally divided into the blank group, the diabetic group, and the curcumin group. Starting with successful modeling, 200 mg/kg of curcumin suspension was given to the rats per day by intragastric administration. The rats in the blank group and the diabetic group were given normal saline daily and all treatments lasted 4 weeks. The systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and cardiac function of the rats were determined with physiological recorders. Blood glucose, blood lipids and myocardial enzymes in serum, SOD, MDA PKCα protein and PKC activation strength in the myocardial tissue were measured as well. Results: The SBP, DBP, MAP, LVEDP and LVSP in the diabetic group were significantly lower than those in the blank group and the curcumin treatment group ($P<0.05$). The FBG, TC and TG as well as AST, LDH, and CK-MB levels in the diabetic group were significantly higher than those in the blank group and the curcumin treatment group ($P<0.05$); the expression of MDA in the diabetic group was significantly higher than that in the blank group, and the SOD expression was lower than that in the blank group ($P<0.05$); the expression of MDA in the curcumin treatment group was significantly lower than that in the control group, and the SOD expression was significantly higher than that in the control group ($P<0.05$); the expression of PKCα protein in the diabetic group was significantly higher than that in the blank group ($P<0.05$). However, the PKCα and PKC activation strength in the curcumin treatment group was significantly lower than that in the diabetic group ($P<0.05$). Conclusion: Curcumin reduces myocardial damage, and increases the antioxidant capacity in myocardial tissue.

Keywords: Curcumin, diabetes, myocardial damage, antioxidant capacity

Introduction

Diabetic cardiomyopathy (DCM), as a cardiovascular complications, is a cardiac structure and function disorder independent from coronary atherosclerotic heart disease and other known diseases caused by diabetes [1]. DCM will cause changes of heart function during diastole and systole stages and eventually induces heart failure, which is also one of the main causes of death in diabetic patients [2]. At present, the studies on pathogenesis of DCM are limited, but some studies [3] believe that metabolism disorder, oxidative stress and mitochondrial damage of myocardial cells may be mechanisms of DCM, and other studies found that DCM can be effectively treated by decreasing blood glucose and improving lipid metabolism disorders [4, 5].

Curcumin is the principle ingredient of the herbal plant curcuma longa L, which can lower blood pressure, improve ventricular hypertrophy and lipid metabolism disorders [6]. In recent years, the therapeutic effects of curcumin on metabolic diseases such as diabetic nephropathy [7] and insulin resistance [8] have attracted broad interest and are reported constantly. Furthermore, the therapeutic efficacy of curcumin on cardiovascular diseases has also been studied, and it is believed that curcumin can improve the dysfunction of vascular endothelium cells by regulating NO and ROS [9].

In diabetic patients, harmful substances are produced in myocardial tissue, such as free radicals, which will eventually cause oxidative damage to cardiomyocytes [10]. When free radicals increase, oxidation reactions are activated, resulting in more peroxide product-malondialdehyde (MDA) [11]. Superoxide dismutase (SOD) is a factor that protects cells from damage by scavenging oxygen superoxide anion radicals [12]. Myocardial enzyme is an enzyme produced by the myocardium, and clinically the content of serum myocardial enzymes is often detected to determine the degree of myocardial injury [13]. Protein Kinase C (PKC) is a family of serine-threonine kinases found in most cell types, whose activity has a strong influence on a wide variety of signal transduction events. When oxidative stress is enhanced, PKC is activated and inhibits myofibrillar ATPase activity, which ultimately affects myocardial contractility and diastolic capacity [14].

Therefore, we evaluated myocardial damage and antioxidant capacity of rats by detecting hemodynamics, cardiac function, MDA, SOD, myocardial enzymes, PKCα protein and PCK activation strength to assess the effects of curcumin in diabetic rats.

Materials and method

Animals and experimental materials

Thirty clean SD rats, with weights (200.45± 20.21 g) were selected. All rats were purchased from Shanghai Slack Laboratory Animal Center (the production license was SCXK (Shanghai) 2012-0002). The rats were kept at a constant temperature 22°C, with a light-dark (12 h-12 h) cycle. The model establishment process in rats complied with the requirement of the Experimental Animal Ethics Committee of the hospital. Curcumin was purchased from Sigma, USA, lot numbered C1386. The physiological recorder (SurgiVet V9204) for was purchased from Beijing Youchengjiaye Biological Technology Co., Ltd., and PKCα and β-tubulin antibodies were purchased from Beijing Zhongshan Jinqiao Biological Company. PKC activation strength kit was purchased from Promega, USA.

Animal model establishment

After one week of feeding, 10 of rats were included in the blank control group, and the other 20 rats were injected with STZ (60 mg/kg). The model establishment was regarded as successful when the glucose concentration of the rats was ≥16.7 mmol/L after one week [15]. The 20 rats with successful modeling were randomly divided into the diabetic group (N=10) and the curcumin treatment group (N=10). After successful modeling, the rats in the curcumin treatment group were given 200 mg/kg of curcumin suspension every day by intragastric administration and the rats in the blank group and the diabetic group were given the normal saline by intragastric administration every day, and all treatments lasted 4 weeks.

Detection indexes in rats

After treatment, the SBP, DBP, MAP and cardiac function of rats in each group were detected by a physiological recorder. The cardiac function indexes includes left ventricular end-diastolic pressure (LVEDP) and left ventricular systolic pressure (LVSP). Afterwards, blood glucose (FGB) and blood lipids (including total cholesterol TC and triglyceride TG) and myocardial enzymes were detected in the serum of rats. The myocardial enzyme indicators include AST, LDH and CK-MB. Finally, the rats were sacrificed by cervical dislocation, the heart tissue of the rats was frozen for storage, and SOD and MDA were detected. Every procedure was approved by the Animal Care and Use Committee of the Second Xiangya Hospital of Central South University.

Detection of MDA and SOD

The SOD was measured strictly following the hydroxylamine method per use instructions of the kit. Frozen heart tissues were thawed, prepared in tissue suspensions and then centrifuged. After centrifugation, samples and reagents were added according to the kit instructions, incubated for 20 min at 37°C and the absorbance at 450 nm was detected. The expression of cardiac MDA was detected by the thiobarbituric acid method. The tissue supernatant was prepared as described above. Samples and reagents were added according to the kit instructions. The solution was placed in a water bathed for 45 min at 95°C and centrifuged for 100 min at 4000 r/min, and then the supernatant was used in the measurement of absorbance at 532 nm.

PKCα protein determination in myocardial tissue

The tissue suspension was first prepared, then tissue lysate was added for tissue lysis and

Table 1. Hemodynamic indexes in the three groups of rats

Index	Blank group n=10	Diabetic group n=10	Curcumin treatment group n=10	F	P
SBP (kPa)	17.4±2.0*	10.8±1.7	14.3±1.6*	34.61	<0.001
DBP (kPa)	14.9±1.3*	8.1±0.9	11.6±1.6*	68.56	<0.001
MAP (kPa)	11.2±1.6*	9.4±1.2	11.5±1.3*	6.801	<0.050

Note: *Compared with diabetic group, P<0.05.

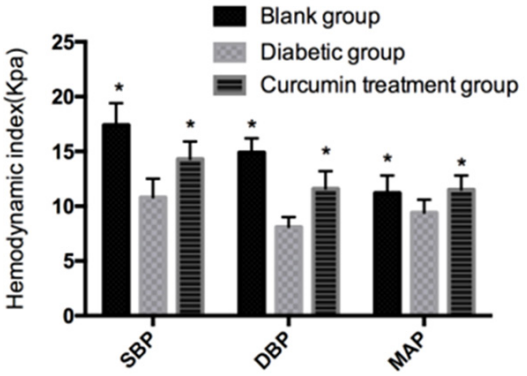

Figure 1. Hemodynamic indexes of aorta in the three groups of rats. The aortic hemodynamics indicators of the three groups of rats, the SBP, DBP and MAP in the diabetic group were significantly lower than those in the blank group (P<0.05), however, the SBP, DBP and MAP in the curcumin treatment group were significantly higher than those in the diabetic group (P<0.05). Note: *Compared with diabetic group, P<0.05.

the solutions were mixed on ice. The mixture solution was centrifuged at 13000 r/min for 10 min. After centrifugation, the primary mouse monoclonal antibodies against PKCα (1:1000) and β-tubulin (1:1000) were added, they were incubated overnight at 4°C. Then HRP-labeled goat anti-rabbit IgG antibody was added, and incubated for 1 h at room temperature, then PBS solution was used to rinse and ECL developer was used to reveal the immunoreactive bands.

Analysis of PCK activation strength

The tissue was lysed according to the above methods. After lysing, analysis of PCK activation strength was carried out according to the PKC activity detection kit. The samples were separated by 0.8% agarose gel, the phosphorylated protein strip was scraped off, the strip was dissolved by heating to a temperature of 95°C, and then the absorbance value was measured at 570 nm.

Statistical methods

SPSS 17.0 (Asia Analytics Formerly SPSS China) was used for statistical analysis. The independent t test was used for comparison of measurement data between groups. One-way analysis of variance was used for comparison between groups, followed by post hoc Bonferroni test. The chi-square test was adopted for the comparison of counting data and P< 0.05 implied a statistically significant difference.

Results

Aortic hemodynamic determination in the three groups of rats

After treatment, the values of SBP, DBP and MAP in the test group were (17.4±2.0) kPa, (14.9±1.3) kPa and (11.2±1.6) kPa, respectively; the values of SBP, DBP and MAP in the diabetic group were (10.8±1.7) kPa, (8.1±0.9) kPa and (9.4±1.2) kPa, respectively; the values of SBP, DBP and MAP in the curcumin group were (14.3±1.6) kPa, (11.6±1.6) kPa and (11.5±1.3) kPa, respectively. The values of SBP, DBP and MAP in the diabetic group were significantly lower than those in the blank group and curcumin treatment groups. (P<0.05, **Table 1** and **Figure 1**).

Detection of cardiac function indexes in the three groups of rats

The LVEDP and LVSP in the blank group were (-1.55±0.89) kPa and (19.23±2.41) kPa respectively; the LVEDP and LVSP in the diabetic group were (-0.59±0.27) kPa and (12.57±1.38) kPa respectively; the LVEDP and LVSP in the curcumin treatment group were (-1.28±0.61) kPa and (17.66±1.89) kPa, respectively. The LVEDP and LVSP in the diabetic group were significantly lower than those in the control group (P<0.05); the LVEDP and LVSP in the curcumin

Table 2. Cardiac function indexes in the three groups of rats

Index	Blank group n=10	Diabetic group n=10	Curcumin treatment group n=10	F	P
LVEDP (kPa)	1.55±0.89*	0.59±0.27	1.28±0.61*	5.944	<0.050
LVSP (kPa)	19.23±2.41*	12.57±1.38	17.66±1.89*	32.22	<0.050

Note: *Compared with diabetic group, P<0.05.

Table 3. Blood glucose and blood lipids in the three groups of rats

Index	Blank group n=10	Diabetic group n=10	Curcumin treatment group n=10	F	P
FBG (mmol/L^{-1})	5.41±0.73*	17.92±3.88	5.56±2.78*	66.27	<0.001
TC (mmol/L^{-1})	1.86±0.31*	5.24±1.97	2.68±1.14*	17.67	<0.001
TG (mmol/L^{-1})	0.78±0.24*	1.67±0.45	0.87±0.32*	19.86	<0.001

Note: *Compared with diabetic group, P<0.05.

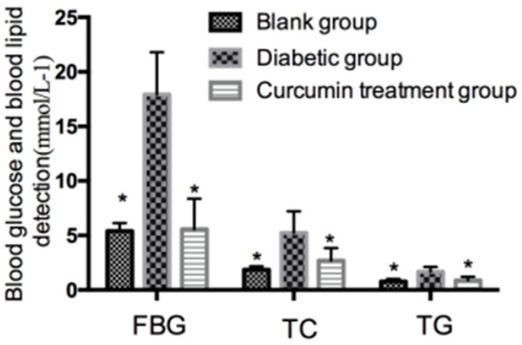

Figure 2. Blood glucose and blood lipid levels in the three groups of rats. Blood glucose and blood lipid levels in the three groups of rats. The FBG, TC and TG levels in the diabetic group were significantly higher than those in the blank group (P<0.05). The FBG, TC and TG in the curcumin treatment group were significantly lower than those in diabetic group (P<0.05). Note: *Compared with the diabetic group, P<0.05.

treatment group were significantly higher than those in the diabetic group (P<0.05, **Table 2**).

Blood glucose and blood lipid levels in the three groups of rats

After treatment, the FBG, TC and TG in the three groups of rats were detected. The levels of FBG, TC and TG in the blank group were (5.41±0.73) mmol/L^{-1}, (1.86±0.31) mmol/L^{-1} and (0.78±0.24) mmol/L^{-1}, respectively; the levels of FBG, TC and TG in the diabetic group were (17.92±3.88) mmol/L^{-1}, (5.24±1.97) mmol/L^{-1} and (1.67±0.45) mmol/L^{-1}, respectively; the levels of FBG, TC and TG in the curcumin treatment group were (5.56±2.78) mmol/L^{-1}, (2.68±1.14) mmol/L^{-1} and (0.87±0.32) mmol/L^{-1}, respectively. The FBG, TC and TG levels in the diabetic group were significantly higher than those in the blank group (P<0.05). The FBG, TC and TG in the curcumin treatment group were significantly lower than those in diabetic group (P<0.05, **Table 3** and **Figure 2**).

Detection of myocardial enzymes in the three groups of rats

The expression levels of AST, LDH and CK-MB in the blank group were (85.81±2.54) IU/gprot, (67.81±11.43) IU/gprot and (254.92±27.33) IU/gprot, respectively; the expression of AST, LDH and CK-MB in the diabetic group were (126.73±5.11) IU/gprot, (149.51±13.56) IU/gprot and (701.84±39.65) IU/gprot, respectively; the expression of AST, LDH and CK-MB in the curcumin treatment group were (98.95±6.14) IU/gprot, (105.53±10.28) IU/gprot and (428.21±31.42) IU/gprot, respectively. The expression of AST, LDH and CK-MB in the diabetic group were significantly higher than those in the blank group, and the difference was statistically significant (P<0.05); the AST, LDH and CK-MB in the curcumin treatment group were significantly lower than those in the diabetic group (P<0.05, **Table 4**).

Detection of MDA and SOD in the three groups of rats

The expression levels of MDA and SOD in the blank group were (6.95±0.31) nmol/mgprot and (131.54±21.43) U/mgprot, respectively; the expressions of MDA and SOD in the diabetic group were (8.25±0.28) nmol/mgprot and (47.51±18.64) U/mgprot, respectively; the expr-

Table 4. Detection of myocardial enzymes in the three groups of rats

Index	Blank group n=10	Diabetic group n=10	Curcumin treatment group n=10	F	P
AST (IU/gprot)	85.81±2.54*	126.73±5.11	98.95±6.14*	186.4	<0.001
LDH (IU/gprot)	67.81±11.43*	149.51±13.56	105.53±10.28*	119.4	<0.001
CK-MB (IU/gprot)	254.92±27.33*	701.84±39.65	428.21±31.42*	460.7	<0.001

Note: *Compared with diabetic group, P<0.05.

Table 5. Expression of MDA and SOD in the three groups of rats

Index	Blank group n=10	Diabetic group n=10	Curcumin treatment group n=10	F	P
MDA (nmol/mgprot)	6.95±0.31*	8.25±0.28	7.13±0.27*	60.16	<0.001
SOD (U/mgprot)	131.54±21.43*	47.51±18.64	112.51±14.65*	57.03	<0.001

Note: *Compared with diabetic group, P<0.05.

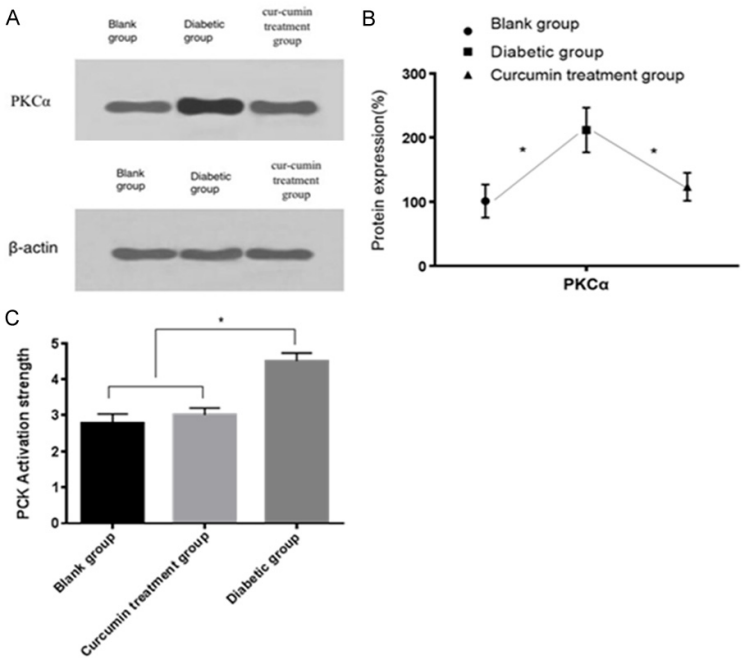

Figure 3. Expression of PKCα protein in the three groups of rats. A. PKCα protein expression in the three groups of rats was detected by Western Blot. B. The expression of PKCα protein in the diabetic group was significantly higher than that in the blank group (P<0.05). C. PKC activation strength in the curcumin treatment group was slightly higher than that in the blank group. The PCK activation strength of the diabetic group was significantly higher than that of the blank group and the curcumin treatment groups (P<0.05). Note: *indicates P<0.05.

essions of MDA and SOD in the curcumin treatment group were (7.13±0.27) nmol/mgprot and (112.51±14.65) U/mgprot, respectively. The expression of MDA in the diabetic group was significantly higher than that of the blank group and the expression of SOD was significantly lower than that in the blank group (P< 0.05). The expression of MDA in the curcumin treatment group was significantly lower than that in the control group, and the SOD expression was significantly higher than that in the control group (P<0.05, **Table 5**).

Expression of PKCα protein in the three groups of rats

The expression level of PKCα protein in the blank group, the diabetic group and the curcumin treatment group were (101.23± 25.76)%, (211.87±34.66)% and (123.41±21.83)%, respectively. The expression of PKCα protein in the diabetic group was significantly higher than that in the blank group (P<0.05). However, the PKCα protein in the curcumin treatment group was significantly lower than that in the diabetic group (P<0.05, **Figure 3**).

Analysis of PCK activation strength in the three groups of rats

The absorbance value of PCK activation strength in the blank group, diabetic group and curcumin treatment group was (2.78±0.26), (4.51±0.22) and (3.01± 0.19). The PCK activation strength in the curcumin treatment group was slightly higher than that in the blank group. The PCK activation strength in diabetic group was significantly higher than that in the blank group and curcumin treatment groups (P<0.05) (**Figure 3C**).

Discussion

Cardiovascular complications have been one of the leading causes of death in diabetic patients [16, 17]. Glucose utilization in diabetic patients is reduced and the glucose metabolism disorder occurs, leading to the compensatory increase of mitochondria in cardiomyocytes [18]. Once this compensatory effect occurs, oxidative damage increases and adversely affects cardiac function [19]. Studies have found that curcumin plays an antioxidant role in free-radical scavenging capacity, and up-regulates various antioxidant enzymes [7, 20]. Other scholars [21] found that curcumin may inhibit myocardial fibrosis and further reduces myocardial damage by inhibiting cardiac cell proliferation in diabetic rats. Studies have also shown that curcumin alleviates heart damage by improving sugar in take capacity of diabetic rats [22].

In this study, we established adiabetic rat model by STZ, and detected the myocardial-related indicators in each group of rats after 4 weeks of treatment. The results showed that the content of myocardial enzymes AST, LDH and CK-MB in rats who were not treated with curcumin were significantly higher than those in the blank group. However, the content of myocardial enzymes AST, LDH and CK-MB in the curcumin treatment group were significantly decreased compared those in the diabetic group ($P<0.05$), indicating that curcumin improves myocardial injury in rats. Afterwards, we compared the fasting blood glucose, blood lipids and cardiac function in the three groups of rats after treatment, and the results revealed that fasting blood glucose and blood lipids in diabetic rats were significantly higher than those in the blank group, and LVEDP and LVSP in the diabetic group were significantly lower than those in the control group ($P<0.05$). However, blood glucose and blood lipids in the curcumin treatment group were significantly lower than those in the diabetic group, and the LVEDP and LVSP in the curcumin treatment group were significantly higher than those in the diabetic group ($P<0.05$). This indicated that diabetic rats may suffer from blood sugar and blood lipidemia disorders, as well as diastolic and systolic dysfunction of the heart, but curcumin treatment will effectively improve blood sugar, dyslipidemia, as well as diastolic and systolic dysfunction of the heart. Studies have shown that [23] curcumin may decrease blood sugar by up-regulating the expression of insulin growth factor-1, which may explain the hypoglycemia of rats after curcumin treatment. Studies have shown that the diastolic and systolic dysfunction of diabetic patients are caused by increased oxidative stress [24, 25]. The results of this study found that the MDA was significantly higher in the heart tissue of diabetic rats than that in the blank group. The SOD was significantly lower in the heart tissue of diabetic rats than that in the blank group ($P<0.05$). However, after four weeks of treatment, MDA in the heart tissue of the curcumin group was significantly lower than that in the diabetic group, and SOD was significantly increased, which indicated that curcumin can effectively reduce oxidative stress in the hearts of diabetic rats and increases the activity of SOD.

At present, the regulation mechanism of curcumin on oxidative stress in diabetic rats has not been reported in many studies, but some studies also found that the PI3K/AKT signaling pathway regulates the oxidative stress response in diabetic rats and that curcumin can regulate the activity of the PI3K/AKT signaling pathway [26, 27].

Finally, we detected PKCα protein and PKC activity in the three groups of rats and the results showed that the expression of PKCα protein and PKC activity in the diabetic group was significantly higher than that in the blank group ($P<0.05$), however, the PKCα protein and PKC activity in the curcumin treatment group was significantly lower than that in the diabetic rats ($P<0.05$). In this study, the expression of PKCα protein was reduced after curcumin treatment. We speculate that curcumin can inhibit the activation of PCKα protein, but there is no relevant research to confirm this conclusion. Above all, the application of curcumin in diabetic rats will effectively alleviate myocardial damage, improve the antioxidant capacity of rats, and is worthy of clinical promotion. However, the specific mechanism of curcumin treatment in the improvement of myocardial injury in diabetic rats was not investigated in the study, and the therapeutic effects of different doses of curcumin were not studied. Due to the unclear mechanisms of action of curcumin, we also have limitations, this makes our conclusions worthy of further verification.

Disclosure of conflict of interest

None.

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