JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY
ARTICLE

J. Agric. Food Chem. 2009, 57, 8635–8642 8635
DOI:10.1021/jf9020625

# Beneficial Effects of Taurine on Cardiac Abnormality in NZB/W F1 Mice Fed with a High-Cholesterol Diet

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A significantly higher prevalence of cardiovascular disease (CVD) is reported in patients with systemic lupus erythematosus (SLE) as compared with the general population and accounts for approximately 30% of deaths in SLE patients. However, the mechanism of and treatments for CVD in patients with SLE are still unclear. To explore the effects of taurine on cardiac abnormality in SLE, NZB/W F1 mice were used as the experimental model by receiving control, cholesterol, or cholesterol/taurine diets, respectively. Improved cardiac histopathological changes were observed in left ventricle tissues from the cholesterol/taurine group as compared to the control or cholesterol group. Significant reductions of TUNEL-positive cells, Fas death receptor-related components, mitochondrial-dependent apoptosis, cardiac fibrosis, and fibrotic signaling components were detected in the left ventricle tissues from the cholesterol/taurine group as compared to the control or cholesterol group. Additionally, cardiac IGR1R survival signaling components were significantly increased in the left ventricle tissues from the cholesterol/taurine group as compared to the control or cholesterol group. These findings revealed the protective effects of taurine against the cardiac abnormalities in NZB/W F1 mice and may suggest the potential for clinical application of taurine in treatment of CVD in SLE.

**KEYWORDS: Systemic lupus erythematosus (SLE); taurine; cardiovascular disease (CVD); NZB/W F1**

## INTRODUCTION

Systemic lupus erythematosus (SLE) is known as a systemic autoimmune disorder that affects various organs including the heart. Indeed, cardiac involvement has been indicated in patients with SLE (*1*, *2*). Previous studies have reported that patients with SLE have significantly increased risk of death as compared with the general population, while cardiovascular disease (CVD) accounts for nearly 30% of deaths in SLE patients (*3*−*7*).

Evidence has demonstrated that a high cholesterol diet contributes to hypercholesterolmeia and CVD risk, which has been recognized as an elementary public health policy (*8*, *9*). Recently, the relationships among dietary cholesterol, CVD, and SLE have become a popular issue under intense research. In a prospective study of outcomes in 229 patients with SLE from the Johns Hopkins Lupus Cohort, hypercholesterolemia is recognized as one of the important CVD risk factors that should be routinely employed in the management of SLE patients (*4*). Additionally, similar results were also reported in other studies (*10*−*12*). However, the etiology of or treatments for CVD in patients with SLE is still unclear.

Taurine is the major intracellular free $\beta$-amino acid in most mammalian tissues, which can be synthesized from methionine and cysteine and obtained largely from the diet, predominantly through eggs, meat, and seafood (*13*, *14*) such as oysters and squid (*15*, *16*). Additionally, taurine is also known as a conditional nutrient that plays crucial roles in protecting biological systems from various injuries (*17*, *18*). Taurine is known to attenuate oxidant stress (*19*), pro-inflammatory cytokines (*20*), and apoptosis (*21*−*25*), as well to reduce the serum lipids, lipid oxidation (*26*), and blood pressure in a spontaneously hypertensive rat model (*27*). Additionally, taurine has been demonstrated to attenuate cardiac apoptosis by preventing the formation of the Apaf-1/caspase-9 apoptosome (*22*−*24*).

Although these studies (*22*−*24*) indeed demonstrated the protective effects of taurine against cardiac abnormality, little is known about the effects of taurine in the hearts of SLE. In the current study, we demonstrated the beneficial effects of taurine on the hearts of NZB/W F1 mice fed with a cholesterol-rich diet by reducing the cardiac abnormalities and enhancing the IGF1R survival signaling components.

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Published on Web 08/14/2009

## MATERIALS AND METHODS

**Mice and Diets.** Female NZB/W F1 mice, a well-known and popularly utilized lupus-prone mice strain, were purchased from the animal center, National Taiwan University, Taiwan, and housed in an animal room at 22 ± 2 °C with a 12/12 h light−dark cycle under supervision of the Institutional Animal Care and Use Committee at Chung Shan Medical University. The disease condition of mice was determined by monitoring the proteinuria biweekly with Albustix test strips from the age of 12 weeks as described elsewhere (*25*, *28*). Chow diet, soybean oil, and cholesterol were purchased (TestDiet Division, PMI Nutrition International/Purina Mills LLC, Richmond, IN). Taurine was purchased from Sigma (Sigma, St. Louis, MO), and the ingredients of the experimental diets were prepared as follows. The control diet was composed of 93% rodent 5001 chow diet and 7% soybean oil. The cholesterol diet was composed of 92% rodent 5001 chow diet, 7% soybean oil, and 1% cholesterol. The cholesterol/taurine diet was composed of 91% rodent 5001 chow diet, 7% soybean oil, 1% cholesterol, and 1% taurine as described in our recent study (*25*). Thirty female NZB/W F1 mice, 112 days old, were divided into three groups (10 mice/group) and were given control, cholesterol, and cholesterol/taurine diets for 12 weeks, respectively. Mice were sacrificed at the age of 196 days old by $CO_2$ asphyxiation and rinsed in 70% ethanol solution. Heart tissues of the mice were obtained after $CO_2$ sacrifice and stored at −80 °C until use.

**TUNEL Assay.** The left ventricular tissues of hearts from NZB/W F1 mice were embedded into OCT compound (Tissue-Tek, Miles Inc., Elkhart, IN) and snap frozen in liquid nitrogen. The frozen tissue blocks were sectioned at 5 μm and fixed in 4% paraformaldehyde (Sigma) in 0.1 M phosphate-buffered saline (PBS), pH 7.4, for 20 min at room temperature. After they were washed for 30 min with 0.1 M PBS, the tissue sections were incubated with 3% $H_2O_2$ in methanol for 10 min at room temperature. The TUNEL reaction mixture was freshly prepared according to the manufacturer's instruction (Roche Applied Science, Inc., United States), and a total volume of 100 μL of terminal deoxytransferase reaction mixture was incubated with the tissue sections for 1 h at room temperature in the dark. The tissue sections were then rinsed with 0.1 M PBS containing DAPI and observed with a fluorescence microscope. The number and percentage of TUNEL-positive cells were counted and determined by counting $1 \times 10^3$ cardiac cells from five randomly selected fields. All measurements were performed by at least three independent animals in a blind manner.

**Western Blotting.** The left ventricular tissues of hearts from NZB/W F1 mice were analyzed for immunoblotting, and similar results were observed in the same group. The loading sample for each lane of Western blot was a pool of three randomly selected mice of the same group. Sodium dodecyl sulfate−polyacrylamide gel electrophoresis (SDS-PAGE), using 12.5% acrylamide gel, was performed as previously described (*29*). Protein samples were denatured for 5 min in boiling water with sample buffer (0.0625 M Tris−HCl buffer, pH 6.8, containing 2.3% SDS, 5% 2-mercaptoethanol, and 10% glycerol). Samples applied to the gel were run at 100−150 V for 1.5 h and electrophoretically transferred to a nitrocellulose membrane (Amersham Biosciences, Piscataway, NJ). The membrane was then soaked in PBS with 5% nonfat dry milk for 30 min at room temperature to saturate irrelevant protein binding sites. Antibodies against TNF-α, Fas ligand, Fas, FADD, activated-caspase-8, t-Bid, Bcl-2, Bax, activated-caspase-9, activated-caspase-3, FGF, p-ERK, ERK, uPA, MMP-2, MMP-9, IGF1R, PI3K, p-AKT, AKT, and α-tubulin (Upstates, Charlottesville, VA; Santa Cruz Biotechnology, Santa Cruz, CA) were diluted in PBS with 2.5% BSA and incubated for 1.5 h with gentle agitation at room temperature. The membranes were washed twice with PBS-Tween for 1 h, and secondary antibody conjugated with horseradish peroxidase (HRP) was added. Pierce's Supersignal West Dura HRP Detection Kit (Pierce Biotechnology Inc., Rockford, IL) was used to detect antigen−antibody complexes. The blots were also scanned and quantified by densitometry (Appraise, Beckman-Coulter, Brea, CA).

**Hematoxylin-Eosin and Sudan III Staining.** The left ventricular tissues of hearts from NZB/W F1 mice were embedded into OCT compound (Tissue-Tek, Miles Inc.) and snap frozen in liquid nitrogen. For Sudan III staining, the frozen sections were sectioned at 5 μm and socked in 50% ethanol before immersion in the dark in the Sudan III solution in 70% ethanol for 20 min. The sections were then washed with 50% ethanol and immersed in hematoxyl solution for 3 min as the negative stain. Photomicrographs were obtained using Zeiss Axiophot microscopes.

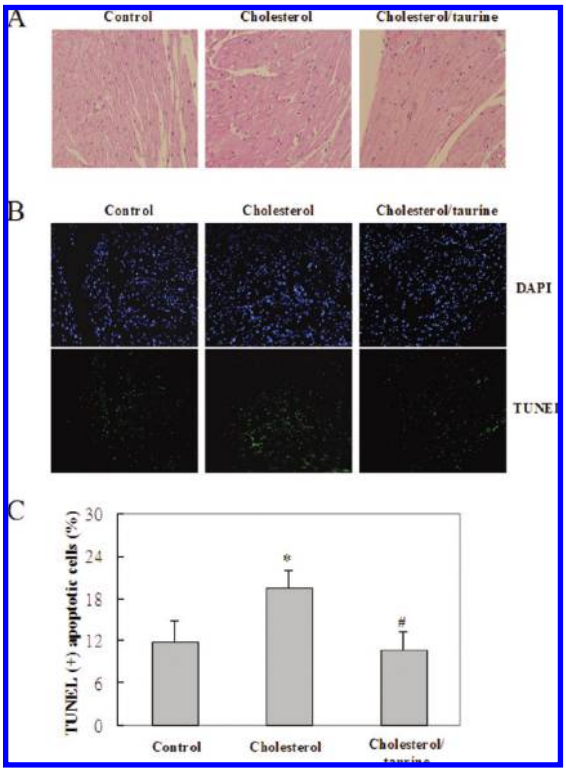


**Figure 1.** (**A**) Histopathological analysis of cardiac tissue sections with hematoxylin and eosin staining and (**B**) representative stained apoptotic cells of cardiac sections with TUNEL assay in NZB/W F1 mice fed with different supplementations. (**C**) The percentages of apoptotic cells were calculated. The images of myocardial architecture were magnified 100 times. Bars present the percentage of TUNEL-positive cells relative to total cells (10 mice × 10 scope field count in each group) and indicate mean values ± SD. * and # indicate significant differences as compared to the control or cholesterol group, respectively.

**Statistical Analysis.** All of the statistical analyses were performed using SPSS 10.0 software (SPSS Inc., Chicago, IL). Three independent experiments were repeated. Statistical analyses were performed using the analysis of variance plus posterior multiple comparison test to test the difference. $P < 0.05$ was considered statistically significant. The significant differences were stressed with symbols as shown in figures.

## RESULTS

**Cardiac Histopathological Changes in NZB/W F1 Mice Fed with Different Dietary Supplements.** To investigate whether the myocardial architecture and cardiac apoptosis were increased in the hearts of NZB/W F1 mice fed with different dietary supplements, we performed a histopathological analysis of the left ventricular tissue with hematoxylin and eosin staining and TUNEL assay. We found that the ventricular myocardium in the cholesterol group showed a more abnormal architecture as compared to the control group, which revealed cardiomyocyte disarray and an increased interstitial space. In contrast, a less abnormal architecture in the cholesterol/taurine group was observed as compared to the cholesterol group (**Figure 1A**). Additionally, we found that hearts stained with the TUNEL assay showed increased TUNEL-positive cardiac cells in the cholesterol group, whereas decreased TUNEL-positive cells were observed in the cholesterol/taurine group (**Figure 1B**). The average percentages of TUNEL-positive cardiac cells in control, cholesterol, and

cholesterol/taurine groups were 11.91 ± 2.82, 19.57 ± 2.56, and 10.73 ± 2.55, respectively (**Figure 1C**).

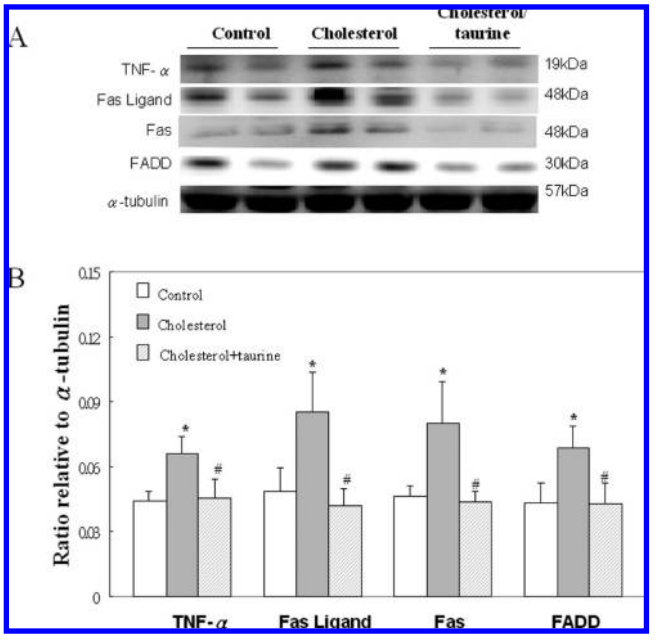


**Figure 2.** (**A**) Protein products of TNF-α (19 kDa), Fas ligands (37 kDa), Fas (48 kDa), and Fas-associated death domain (FADD, 30 kDa) in the left ventricles of hearts from NZB/W F1 mice fed with different supplementations were measured by Western blotting analysis. α-Rubulin (57 kDa) served as an internal control. (**B**) Bars represent the relative protein quantification of TNF-α, Fas ligands, Fas, and FADD on the basis of α-tubulin. * and # indicate significant differences as compared to the control or cholesterol group, respectively.

**Changes of Fas Death Receptor-Related Components in the Hearts of NZB/W F1 Mice Fed with Different Dietary Supplements.** To study the variation of Fas death receptor-associated apoptosis in the hearts of NZB/W F1 mice, Western blotting was performed (**Figure 2**). The protein products of TNF-α, Fas ligands, Fas receptors, and FADDs extracted from the left ventricles of excised hearts in the cholesterol group were significantly increased as compared to the control group (**Figure 2A**). In contrast, significantly decreased protein products of TNF-α, Fas ligands, Fas receptors, and FADDs were detected in the cholesterol/taurine group (**Figure 2A**). The ratios of the protein products of TNF-α, Fas ligands, Fas receptors, and FADDs relative to α-tubulin were calculated and are shown in **Figure 2C**.

**Changes of Mitochondrial-Dependent Apoptotic Components in the Hearts of NZB/W F1 Mice Fed with Different Dietary Supplements.** To investigate the variation of mitochondrial-dependent apoptotic components in the cardiac tissues of NZB/W F1 mice, the protein products of activated caspase-8 and t-Bid were examined with Western blotting (**Figure 3**). Significantly increased protein products of activated caspase 8 and t-Bid were detected in the left ventricles of excised hearts in the cholesterol group as compared to the control group, whereas the significantly decreased protein products of activated caspase 8 and t-Bid were observed in the cholesterol/taurine group as compared to the cholesterol group (**Figure 3A**). **Figure 3B** revealed the relative protein quantification of activated caspase 8 and t-Bid on the basis of α-tubulin, respectively (**Figure 3B**). In addition, significantly increased Bcl-2 protein was detected in the left ventricles of excised hearts in the cholesterol/taurine group as compared to the control or cholesterol group, respectively (**Figure 4A**). However, a significantly increased Bax protein level was observed in the cholesterol group as compared to the control group, whereas a significantly decreased Bax protein level was detected in the

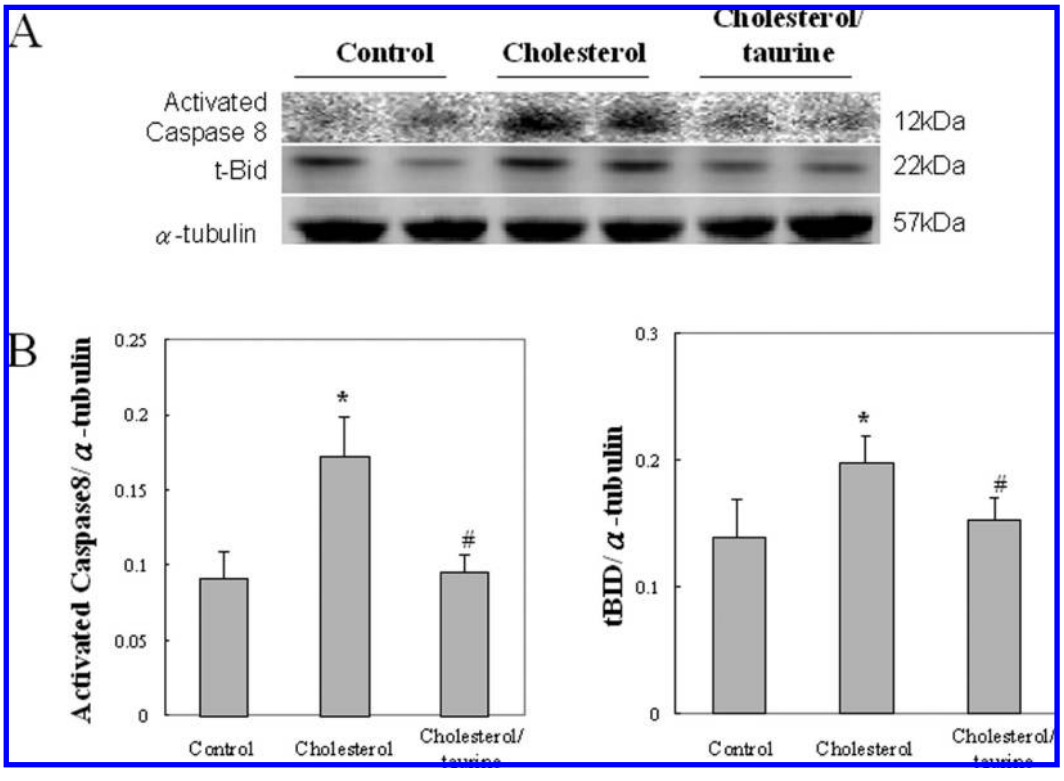


**Figure 3.** (**A**) Protein products of activated caspase-8 (12 kDa) and tBid (22 kDa) in the left ventricles of hearts from NZB/W F1 mice fed with different supplementations were measured by Western blotting analysis. α-Tubulin (57 kDa) served as an internal control. (**B**) Bars represent the relative protein quantification of activated caspase-8 and tBid on the basis of α-tubulin. * and # indicate significant differences as compared to the control or cholesterol group, respectively.

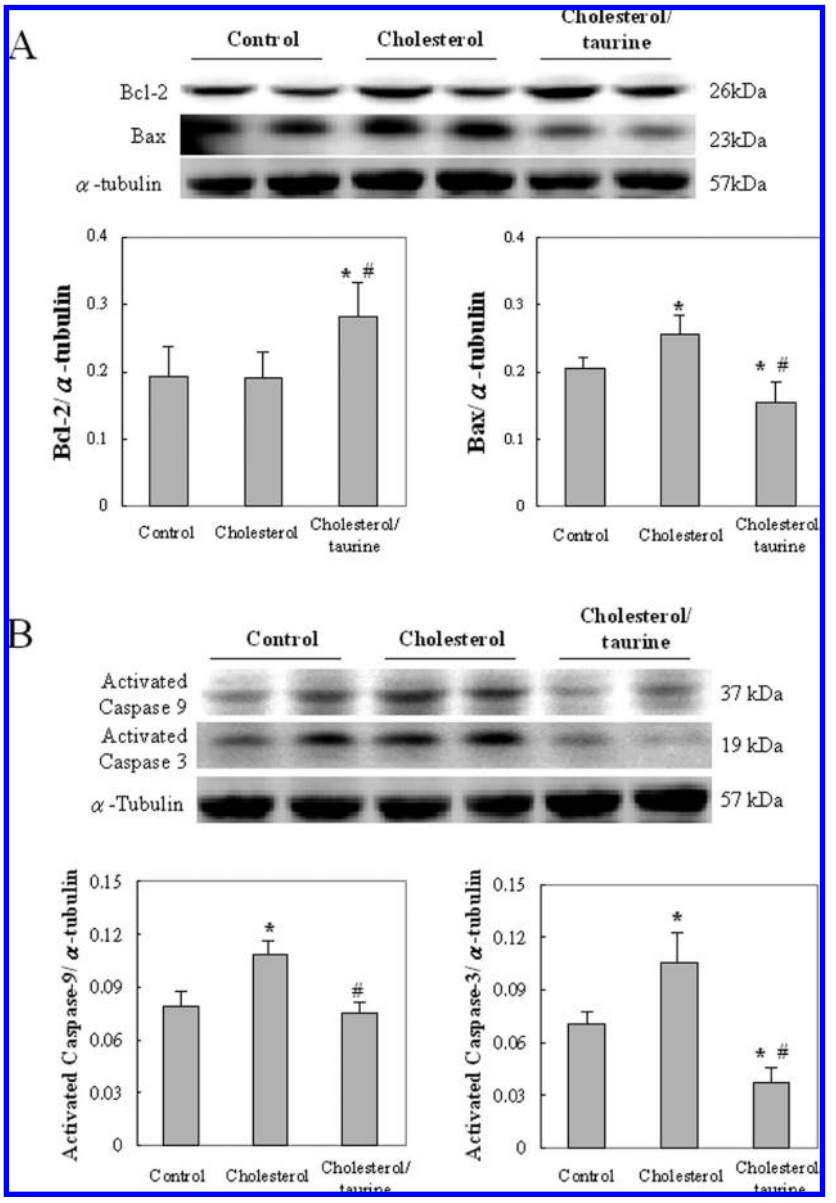


**Figure 4.** (**A**) Protein products of Bcl-2 (26 kDa), Bax (23 kDa), (**B**) activated caspase-9 (37 kDa), and activated caspase-3 (19 kDa) in the left ventricles of hearts from NZB/W F1 mice fed with different supplementations were measured by Western blotting analysis. α-Tubulin (57 kDa) served as an internal control. Bars represent the relative protein quantification of Bcl-2, Bax, activated caspase-9, and activated caspase-3 on the basis of α-tubulin. * and # indicate significant differences as compared to the control or cholesterol group, respectively.

cholesterol/taurine group as compared to the cholesterol group (**Figure 4A**). To further investigate the downstream signal components of the mitochondrial-dependent signaling pathway, activated caspase-9 and caspase-3 were measured by Western blotting. Activated caspase-9 and caspase-3 levels were significantly increased in the cholesterol group as compared to the control group. In contrast, activated caspase-9 and caspase-3 levels were significantly decreased in the cholesterol/taurine group as compared to the cholesterol group (**Figure 4B**).

**Change of Cardiac Fibrosis in the Hearts of NZB/W F1 Mice Fed with Different Dietary Supplements.** We found that hearts stained with Masson trichrome showed more fibrosis, increased collagen deposition, and myofibril disarray in the cholesterol group as compared to the control or cholesterol/taurine group in 200 magnification images (**Figure 5A**). To further confirm the increased cardiac fibrosis in the hearts of NZB/W F1 mice fed with cholesterol, FGF, p-ERK, ERK, uPA, MMP-2, and MMP-9 were examined with Western blotting (**Figure 5B**). The protein levels of FGF, P-ERK, uPA, and MMP-2 were significantly increased in the cholesterol group as compared to the control group, whereas the protein levels of FGF, P-ERK, uPA, MMP-2, and MMP-9 were significantly decreased in the cholesterol/taurine group as compared to the cholesterol group (**Figure 5B**). The relative protein quantification of p-ERK on the basis of ERK in the left ventricles of mice from control, cholesterol, and cholesterol/taurine groups were $0.125 \pm 0.011$, $0.282 \pm 0.053$, and $0.045 \pm 0.011$, respectively (**Figure 5C**). Additionally, the relative protein quantification of FGF, uPA, MMP-2, and MMP-9 on the basis of α-tubulin was shown in **Figure 5D**.

**Change of Cardiac Survival Signaling Components in the Hearts of NZB/W F1 Mice Fed with Different Dietary Supplements.** To further investigate the variation of cardiac survival signaling components in the hearts of NZB/W F1 mice, the protein levels of IFG1R, PI3K, P-AKT, and AKT were examined (**Figure 6**). The protein products of IGF1R and PI3K were significantly

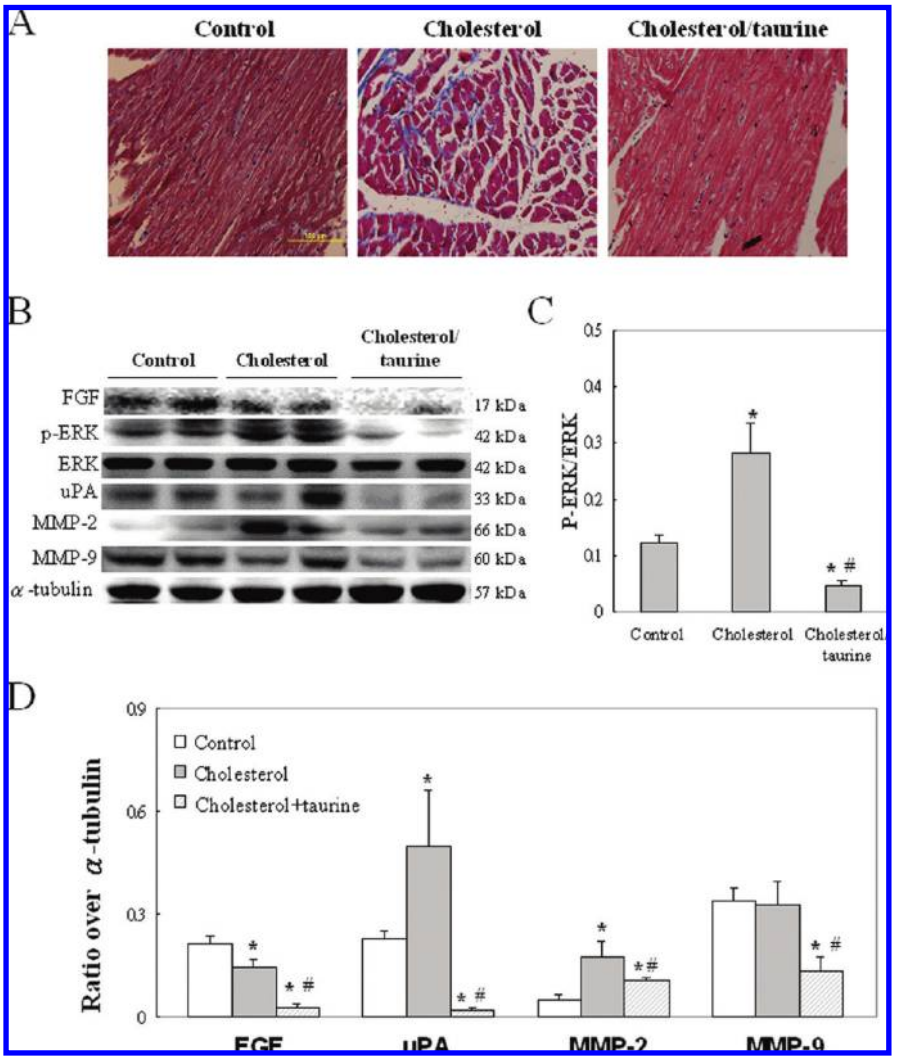


**Figure 5.** (**A**) Protein products of IGF1R (100 kDa), PI3K (80 kDa), P-Akt (60 kDa), and Akt (60 kDa) in the left ventricles of hearts from NZB/W F1 mice fed with different supplementations were measured by Western blotting analysis. α-Tubulin (57 kDa) served as an internal control. (**B**) Bars represent the relative protein quantification of IGFIR and PI3K on the basis of α-tubulin and the ratio between P-Akt and Akt, respectively. * and # indicate significant differences as compared to the control or cholesterol group, respectively.

decreased in the hearts from the cholesterol group as compared to the control group. In contrast, the protein levels of IGF1R and PI3Kwere significantly increased in the cholesterol/taurine group as compared with the control or cholesterol group, respectively (**Figure 6A**). The relative protein quantification of IGF1R and PI3K on the basis of α-tubulin is shown in the upper panel of **Figure 6B**. Additionally, the ratio of p-AKT relative to AKT was significantly decreased in the cholesterol group as compared to the control group, whereas the significantly increased ratio of p-AKT relative to AKT was detected in the cholesterol/taurine group as compared to the control or cholesterol group, respectively (**Figure 6B**, lower panel). The relative protein quantification of p-AKT on the basis of AKT in the left ventricles of mice from control, cholesterol, and cholesterol/taurine groups was 0.837 ± 0.170, 0.586 ± 0.129, and 1.148 ± 0.173, respectively (**Figure 6B**).

## DISCUSSION

Cardiovascular disorder has been widely recognized as an indelible global issue of humans and the most lethal concern to patients with SLE, which accounts for nearly 30% of deaths in SLE. However, little is known about the pathogenesis of and treatment for cardiac abnormality in patients with SLE. In this study, we indicated aggravated cardiac abnormalities, including degenerated histopathological changes, increased apoptosis, and fibrosis, in left ventricle tissues from NZB/W F1 mice fed a cholesterol-rich diet. In contrast, taurine supplementation reduced these cardiac abnormalities significantly and activated the cardiac IGR1R survival signaling components in the meantime.

Hypercholesterolemia is a crucial factor for developing CVD (*21*, *28*, *30*) and has been associated with SLE (*1*−*7*). A previous study has indicated that hypercholesterolemia was more frequently documented in the medical records than reported by the patients (*3*). Another study has reported that 75.4% of 134 patients with SLE had elevated total cholesterol and suggested that the best predictors of CAD were sustained hypercholesterolemia, lung involvement, and age at onset of SLE over 35 years (*6*). Besides, increased cardiovascular involvements have been known in patients with SLE. Previous studies have indicated that abnormal intracardiac anatomy was frequently revealed in SLE patients and strongly associated with raised anticardiolipin antibodies (*31*). A similar result was described in other studies that asymptomatic diastolic dysfunction, premature myocardial infarction, and atherosclerosis (carotid plaque) were more prevalent among patients with SLE than the controls (*2*, *32*, *33*). However, little is known about the cardiac pathological mechanism in SLE. Using a popular lupus mice model, we first indicated

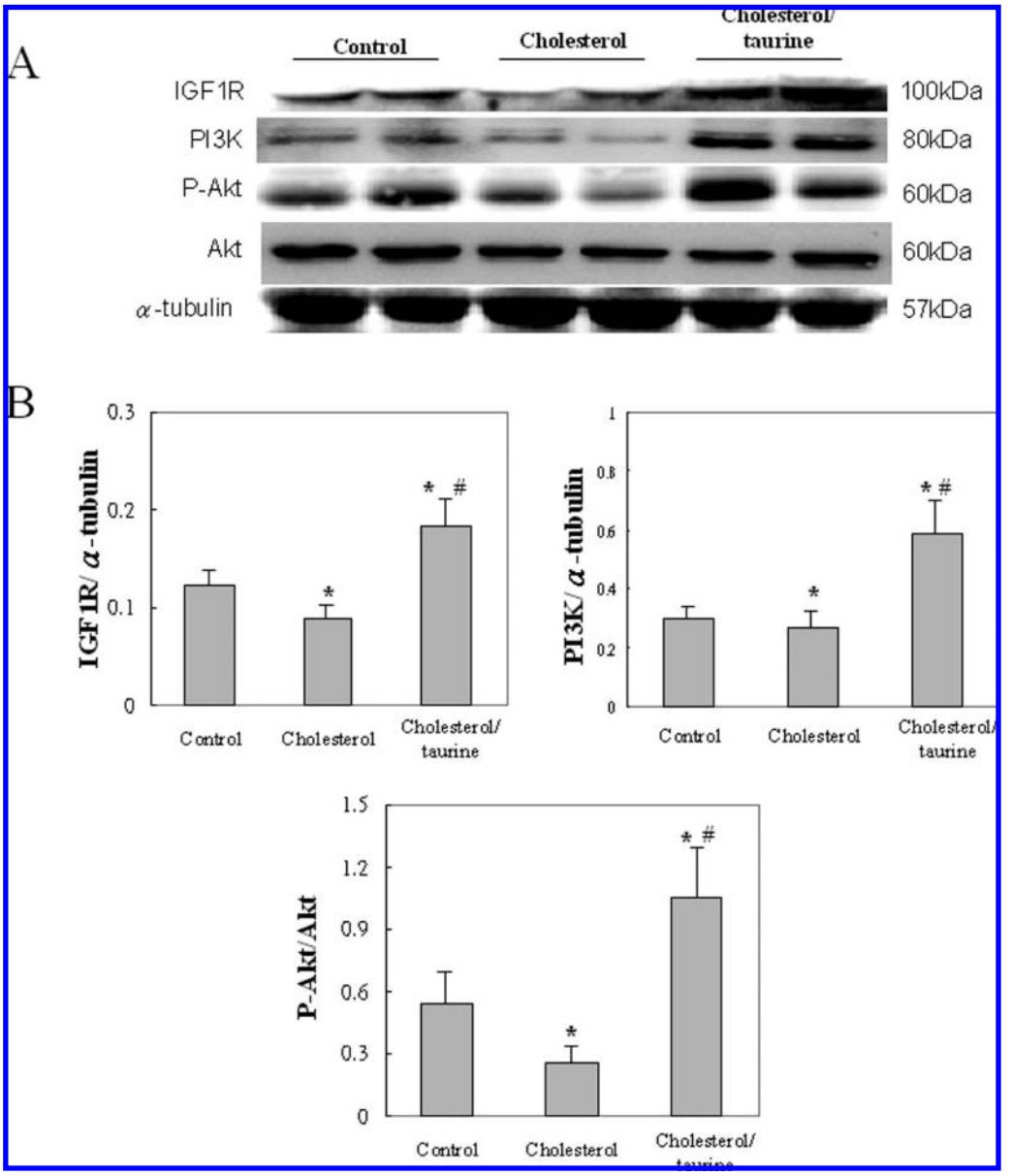


**Figure 6.** (**A**) Histopathological analysis of cardiac tissue sections with Masson trichrome staining and (**B**) the protein products of FGF (37 kDa), p-ERK (26 kDa), ERK (26 kDa), uPA (26 kDa), MMP-2 (26 kDa), and MMP-9 (26 kDa) in the left ventricles of hearts from NZB/W F1 mice fed with different supplementations were measured by Western blotting. α-Tubulin (57 kDa) served as an internal control. (**C**) Bars represent the ratio of P-Akt/Akt and (**D**) the relative protein quantification of FGF, p-ERK, ERK, uPA, MMP-2, and MMP-9 on the basis of α-tubulin. * and # indicate significant differences as compared to the control or cholesterol group, respectively.

the cardiac abnormalities including aggravated histopathological changes, both Fas- and mitochondrial-dependent apoptosis, and increased fibrotic signaling molecules in the left ventricles of hearts from NZB/W F1 mice fed a high-cholesterol diet; meanwhile, taurine attenuates these pathological phenomena and is demonstrated to have beneficial effects on cardiac disorders in SLE.

Taurine is a conditionally essential nutrient and the major intracellular free β-amino acid in most mammalian tissues that regulates immune response and protects biological system against various injuries (*34*). Previous studies have indicated that taurine reduces reactive oxygen intermediate-dependent hepatocyte injury (*18*, *19*) and attenuates the production of proinflammatory cytokines (*20*). The protective effects of taurine in reducing serum lipid and lipid oxidation (*26*) and preventing the formation of the Apaf-1/caspase-9 apoptosome (*23*) were well-documented. Additionally, taurine also exerts a protective effect on the heart. In cultured neonatal rat cardiac myocytes, taurine attenuates angiotensin II-induced hypertrophy (*33*). Another study indicated that taurine attenuates cardiac dysfunction and apoptosis induced by $Ca^{2+}$ paradox via reducing MAPK and apoptotic signaling components (*35*). Similar effects of taurine were observed in the current study. Significantly reduced apoptotic positive cells were detected in left ventricle tissues of the cholesterol/taurine group as compared to the cholesterol group. Both Fas- and mitochondrial-dependent apoptotic signaling components such as TNF-α, Fas ligand, Fas, FADD, activated caspase-8, t-Bid, Bax, activated caspase-9, and activated-caspase-3 were significantly reduced in left ventricle tissues of the cholesterol/taurine group as compared to the cholesterol group. Additionally, less fibrosis was observed in left ventricle tissues of the cholesterol/taurine group as compared to the cholesterol group as well as the reduced fibrotic signaling components such as FGF, p-ERK, ERK, uPA, MMP-2, and MMP-9. These findings indeed

demonstrated the cardiac protective effects of taurine in SLE by reducing the signaling components of cardiac apoptosis and fibrosis.

The insulin-like growth factor (IGF)-I is a peptide hormone in most tissues and plays crucial roles in many biological processes mediated by the IGF-I receptor, including the regulation of protein turnover, potent mitogenic, and cell differentiation (*36*). A previous study has indicated that IGF-1 is essential in the proliferative capacity of rat ventricular myocytes during postnatal development (*37*). IGF-I regulates zebrafish embryogenesis by promoting cell survival and cell cycle progression (*38*). A recent study further implied that IGF-1 acts as a vascular protective factor and is beneficial in the treatment of chronic heart failure (*39*). Although much is known about the global effects of IGF1R-mediated signaling on cell growth and vascular protection, the effect of taurine on IGF1R-mediated signaling in SLE is not verified. In the current study, we revealed significantly increased levels of IGFIR and related downstream signaling components, including PI3K and P-Akt, in left ventricles of mice from the cholesterol/taurine group and suggested the function of taurine on cardiac survival in SLE.

Taurine has been commonly used in the treatment of several diseases such as myocardial failure in cats and liver injury in chronic hepatitis patients (*40*, *41*) with the dosages of 10 g/kg diet for animals (*42*, *43*) and 1 g/kg body weight for humans (*41*). Although many studies have utilized plasma taurine concentration to define the taurine status in animals (*41*−*43*), little is known in humans. However, taurine indeed reveals the effects on cardiac protection by reducing the abnormal histopathological changes, Fas-dependent apoptosis, mitochondrial-dependent apoptosis, fibrosis, and fibrotic signaling molecules in the left ventricle tissues of NZB/W F1 mice as well as the increased IGFIR cardiac survival signaling components in NZB/W F1 mice. These findings may provide clues in understanding the cardiac protective mechanism of taurine and probably suggested the therapeutic potential of taurine on treating SLE patients with CVD.

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**Received June 16, 2009. Revised manuscript received July 27, 2009. Accepted July 28, 2009. This study was supported by Grant NSC96-2320-B-040-025-MY3 from the National Science Council and Department of Health, Taiwan, Republic of China.**