Original Article

CARDIOPROTECTIVE EFFICACY OF TAURINE ON LIPID-METABOLISM OF ISOPROTERENOL-INDUCED MYOCARDIAL INFARCTION

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ABSTRACT

Objective: The present study aimed to evaluate the effect of pre-treatment with taurine on rats in which MI had been induced using isoproterenol (ISO).

Methods: Rats were randomly allocated into three groups; the 1st group is the normal control (C) one, the 2nd is the isoproterenol cardiotoxic (ISO) one and the 3rd group is the taurine pretreated (T-ISO) one.

Results: The activities of the cardiac biomarker enzymes, AST, LDH, CK and CK-MB were elevated in the ISO-treated group. The membrane-bound Na^+-K^+ and Ca^{2+} ATPase enzyme activities were decreased in the ISO-treated group. The lipid profile either in sera or cardiac tissues was increased in ISO-treated rats except for HDL-cholesterol and phospholipids. The cholesterol ester synthetase (CES) activity was elevated, while lecithin: Cholesterol acyltransferase (LCAT) and lipoprotein lipase (LPL) activities were decreased in the myocardial infarcted rats. In addition, the high level of the troponins I and T was an indication of cardiac necrosis. Pre-treatment with Taurine, however, ameliorated all of these changes, in addition to its effect in improving the oxidation process, as measured by lipid peroxidation and the antioxidant enzymes, superoxide dismutase and peroxidase enzymes.

Conclusion: Taurine showed amelioration effects on the changes in lipid profile, oxidative stress and myocardial infarction biomarkers and therefore, can be protected against cardiotoxicity.

Keywords: Taurine, isoproterenol (ISO), Cardiac biomarker enzymes, Lipid profile, Antioxidant defense system, Myocardial infarction.

INTRODUCTION

Cardiovascular disease (CVD) remains the main cause of death in both developed and developing countries. Studies have shown that high levels of total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL) cholesterol and apolipoproteins A-I, and low levels of high-density lipoprotein (HDL) cholesterol are the risk factors of CVD [1]. Of the many well-known model's isoproterenol (ISO)-induced myocardial necrosis, this rat model has often been used to evaluate several cardiac dysfunctions. ISO causes stress in the myocardium and a severe increase in the levels of serum and myocardial lipids, and also increases the level of LDL cholesterol in the blood, which in turn leads to coronary heart disease [2]. A number of patho-physiogenic mechanisms have been outlined to explain the lesions produced by ISO in experiments. Peroxidation of endogenous lipids has been shown to be a major factor in the cardiotoxic action of isoproterenol. Reactive oxygen species may contribute to atherogenesis and lead to the progression of atherogenic lesions by promoting oxidation of LDL [3].

Impairment of contractility during myocardial injury is primarily associated with deregulation of intracellular Ca2+homeostasis which plays an important role in mediating myocardial injury [4]. A marked increase in cytosolic free calcium ([Ca2+]i) has been reported in myocardial ischemic injury, and the occurrence of intracellular Ca2+overload has been suggested to lead to arrhythmias, contractile failure and ultimately cell death [5]. Cardiac troponins (cTn) have become well-known gold-standard blood biomarkers with high sensitivity and specificity for myocardial degeneration [6]. These contractile proteins are released from the myocardium in proportion to the degree of tissue injury and disruption of myocytes. The Tn regulatory complex binds to the thin, actin myofilament via tropomyosin (TnT) and mediates both calcium activation (TnC) and inhibition (TnI) of the ability of thick and thin myofilaments to slide to produce contraction. There are cardiac and skeletal muscle-specific forms of TnI and TnT, although not for TnC [7]. There is growing evidence to suggest that increases in the serum concentration of cTn may be more sensitive than histologic analysis and other objective measures of cardiac myocyte injury [8].

Taurine (2-aminoethanesulfonic acid) is a conditionally-essential amino acid which is not utilized in protein synthesis, but rather is found free or in simple peptides. First discovered as a component of ox bile in 1827, Raiha [9] revealed that it was significant in human nutrition [10]. Several studies have shown that taurine is more essential in certain aspects of mammalian development, and have demonstrated that low levels of taurine are associated with various pathological lesions, including cardiomyopathy [11], retinal degeneration and growth retardation, especially if deficiency occurs during development [12]. It is also stabilised cell membranes [13] and acts as an antioxidant [14]. Derived from methionine and cysteine metabolism, taurine is known to play an important role in numerous physiological functions. While conjugation of bile acids is perhaps its best-known function, this accounts for only a small proportion of the total body pool of taurine in humans. Other metabolic actions of taurine include detoxification, membrane stabilization, osmoregulation, and modulation of cellular calcium levels. Clinically, taurine has been used in the treatment of a wide variety of conditions, including cardiovascular diseases, epilepsy and other seizure disorders, macular degeneration, Alzheimer's disease, hypertension, hepatic disorders, cystic fibrosis and diabetes [15-19]. The current study was an attempt to demonstrate that the hypolipidaemic and membrane stabilizing effects of taurine, in addition to its advantage as a natural antioxidant amino acid, allow it to play a role as a prophylactic agent in respect to myocardial infarction.

MATERIALS AND METHODS

Animal modeling and experimental design

White male albino rats (Rattus norvegicus), weighing 120–150g were used. They were obtained from the animal house of Helwan town, Cairo, Egypt. Animals were housed individually in polypropylene cages under standard conditions (22 °C) receiving rat

pellet diet and water *ad libitum*. They were acclimatized under standard laboratory conditions of temperature and humidity with a normal photoperiod (12 h light: dark cycle) for seven days. All animal experiments were performed in accordance with guidelines for the Care and Use of Laboratory Animals that approved by the animal Ethics Committee at Beni-Sueif University.

Rats were randomly allocated into three groups (n =8). The first and second ones are intubated for two weeks with normal phosphate buffer saline (PH 7.4). The third one treated daily with taurine dissolved in normal saline (100 mg/kg bwt.) for two weeks by gastric intubation. After dose and previous preliminary studies; 70 mg/kg body weight isoproterenol for two consecutive days is the most effective inducible dose [20]. So, at the last two days of the experiment, the 2nd and 3rd groups were injected subcutaneously with 70 mg/kg body weight isoproterenol for two consecutive days. The 1st group is the normal control (C) one; the 2nd is the isoproterenol cardiotoxic (ISO) one and the 3rd group is the taurine pretreated (T-ISO) one. All groups are decapitated after the two days of isoproterenol injection [20].

Tissue homogenate preparation

At the end of the experimental period, heart from control and experimental groups were excised and washed with ice-cold saline (NaCl 0.9%) to remove blood. The heart was weighed for calculating relative heart weight. For the biochemical estimations, the ventricular heart tissues were homogenized in ice-cold saline using Teflon homogenizer, and centrifuged; the supernatants were separated and used for the biochemical and oxidative stress estimations.

Estimation of serum markers

Sera from each group were frozen and stored at-20 ° until biochemical determination. Cardiac enzymes biomarkers; aspartate transaminase (AST) activity was determined according to the kinetic method of Schumann and Klauke [21], Lactate dehydrogenase (LDH) activity was determined according to method of Young [22], Creatine phosphokinase (CK) activities were determined by the method of Okinaka [23], Creatine phosphokinase of M-type (CK-MB) activity was determined according to method of Young [24].

Triglycerides concentration was determined according to the method of Buccolo and David [25]; Total cholesterol was estimated according to the method of Allian *et al.* [26]; phospholipids were determined according to the method of Connerty [27] and the method described by Boden *et al.* [28], was followed for the estimation of free fatty acids. Lipoproteins were also determined; HDL-cholesterol concentration was measured according to the method of Allain *et al.* [26], LDL-and VLDL-cholesterol concentration were determined according to Friendewald *et al.* [29] formula. Lipoprotein (a) was determined according to the method of Kamstrup *et al.* [30]. Cardiovascular risk (CVR) indices were calculated according to Hegele [31] formula and anti-atherogenic index (AAI) was determined according to Guido and Joseph, [32] formula. Troponin I (TPI) and troponin T (TPT) were determined using an enzyme-linked immunosorbent assay (ELISA) by the method of Bhaskar and Rao [33].

Estimation of tissue markers

Tissue homogenate measurements included triglycerides, total cholesterol, phospholipids and free fatty acids by the methods mentioned above. The activities of the lipid metabolizing enzymes such as cholesterol ester synthetase (CES), lecithin: Cholesterol acyltransferase (LCAT) and lipoprotein lipase (LPL) were determined in the heart sample as suggested by Kothari *et al.* [34], Hitz *et al.* [35] and Slater *et al.* [36] respectively. Activities of $Na^+ K^+$ ATPase and Ca^{2+} ATPase in heart homogenate were estimated by the Swann and Steketee [37], and Ohnishi [38], respectively.

Assessment of myocardial oxidative stress

Myocardial lipid peroxides were measured according to the method of Preuss *et al.* [39] and the proteins content was determined by biuret method. Also, the myocardial antioxidant enzyme activities, superoxide dismutase (SOD) and peroxidase (POX) were determined according to the chemical method of Marklund and Marklund [40] and Kar and Mishra [41], respectively.

Statistical analysis

Analysis of Variance on SPSS software package (version 20) was used to test the present data. Data were expressed as mean±SE. One-way analysis of variance (ANOVA) was used to study the significant differences. The level of significance was taken as p<0.05. In the case of significant difference, the Multiple Range Comparisons (Duncan's test) was selected from the post Hoc window on the same statistical package to detect the distinct variance between means.

RESULTS

Effect of ISO on relative heart weight

The changes in the relative heart weight in the experimental groups are illustrated in fig. 1, with the highest relative heart weight being in the isoproterenol (ISO) induced group (0.569), which was significantly elevated, compared to the control group (0.347). This elevation, however, decreased significantly (0.447) in the prophylactic taurine group.
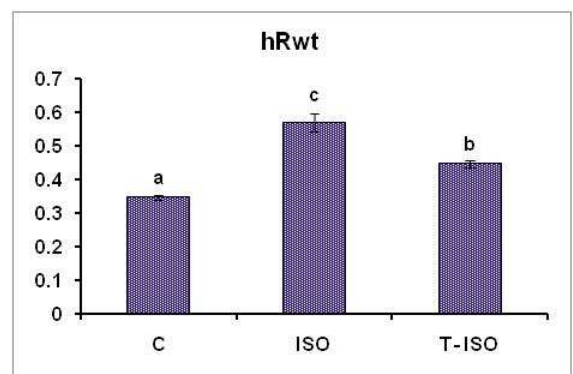

Fig. 1: Prophylactic effect of taurine on heart relative weight of isoproterenol cardiotoxic rats,-(c) Control, (iso) Isoproterenol, (T-iso) Taurine+Isoproterenol,-Data expressed as mean±SE for six rats/group,-Values with the same superscript letter are similar (non-significant, P>0.05) whereas others aren't (significant, P<0.05)

Serum cardiotoxicity

The serum cardiotoxicity was represented by the enzymatic biomarkers of cardiotoxicity (table 1). The ISO group increased significantly (P<0.001) for all the measured enzymes. Changes in the serum lipid profile, which are illustrated in table 2, indicate a very highly significantly (P<0.001) increased level of triglycerides, cholesterol, and free fatty acids as compared to the control group. Phospholipids, meanwhile, were significantly (P<0.001) decreased in the ISO group compared to the control group. Changes in lipoproteins (LDL, vLDL, and lipoprotein A) followed the same pattern as that of the lipid profile, while HDL was significantly (P<0.001) decreased (table 3). The cardiovascular risk factors were increased in the ISO group compared to the control one and ameliorated in T-ISO group (table 4). In respect to the anti-atherogenic factor, the ISO group showed the lowest level, followed by T-ISO group than the control one. Regarding lipid metabolizing enzymes (fig. 2), cholesterol ester synthetase (CES) was significantly ameliorated in the T-ISO group in comparison to the ISO-group and control group of 3.910 nmol esterified cholesterol/100g tissue. In respect to lecithin, meanwhile, cholesterol acyltransferase (LCAT) and lipoprotein lipase (LPL) were decreased significantly in the ISO-induced cardiotoxic group compared to measurements of 18.80 nmol esterified cholesterol/100g tissue and 12.667 nmol FFA liberated/100g tissue in the taurine-treated group. The control group, in contrast, exhibited 24.60 nmol esterified cholesterol/100g tissue and 18.433 nmol FFA liberated/100g tissue. The muscle troponin types I and T illustrated in fig. 3, showed a significant (P<0.001) increase in the ISO group compared to the control group but increased to a lesser extent in the taurine protected group.

Table 1: Prophylactic effect of taurine on serum cardiotoxic biomarkers enzymes in cardiotoxic rats

Groups	AST (IU/l)	LDH (IU/l)	CK (IU/l)	CK-MB (IU/l)
Control	64.167±4.757[a]	157.833±14.845[a]	154.338±19.116[a]	44.167±3.572[a]
Isoproterenol	138.667±2.871[c]	725.000±39.569[c]	469.667±17.761[c]	96.667±4.079[c]
Taurine+Isoproterenol	97. 417±2.922[b]	426.500±27.956[b]	259.500±22.803[b]	63.000±3.225[b]

-Data expressed as mean±SE for six rats/group, -Values with the same superscript letter are non-significantly different (P>0.05).

Table 2: Prophylactic effect of taurine on serum lipid profile in cardiotoxic rats

Groups	Tg (mg/dl)	TCh (mg/dl)	PL (mg/dl)	FFA (mg/dl)
Control	84.100±3.511[a]	86.000±3.502[a]	118.400±6.089[c]	20.532±1.069[a]
Isoproterenol	176.167±5.282[c]	149.500±4.311[c]	62.467±4.980[a]	35.468±2.394[c]
Taurine+Isoproterenol	125.667±5.451[b]	114.300±3.222[b]	94.687±5.515[b]	25.392±0.402[b]

-Data expressed as mean±SE for six rats/group, -Values with the same superscript letter are non-significantly different (P>0.05).

Table 3: Prophylactic effect of taurine on serum lipoproteins level in cardiotoxic rats

Groups	HDL-Ch (mg/dl)	LDL-Ch (mg/dl)	vLDL-Ch (mg/dl)	Lipoprotein-A (mg/dl)
Control	64.833±3.628[c]	37.667±0.919[a]	17.217±0.594[a]	22.200±1.303[a]
Isoproterenol	37.833±2.088[a]	79.000±2.852[c]	31.517±1.130[c]	42.290±1.327[c]
Taurine+Isoproterenol	53.333±1.542[b]	57.667±3.148[b]	23.267±0.617[b]	28.367±0.911[b]

-Data expressed as mean±SE for six rats/group, -Values with the same superscript letter are non-significantly different (P>0.05).

Table 4: Prophylactic effect of taurine on cardiovascular risk and anti-atherogenic factors in cardiotoxic rats

Groups	R1 (TCh/HDL)	R2 (LDL/HDL)	R3 (Tg/HDL)	Anti-atherogenic, (HDLx100 TCh-HDL)
Control	1.345±0.078[a]	0.587±0.034[a]	1.313±0.079[a]	355.763±41.183[b]
Isoproterenol	3.783±0.362[c]	2.135±0.174[c]	4.385±0.183[c]	43.498±2.996[a]
Taurine+Isoproterenol	2.150±0.059[b]	1.083±0.054[b]	2.358±0.082[b]	91.167±4.175[a]

-Data expressed as mean±SE for six rats/group, -Values with the same superscript letter are non-significantly different (P>0.05).
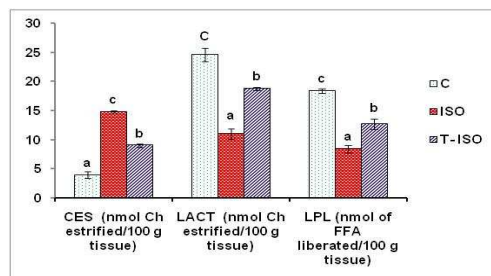

Fig. 2: Prophylactic effect of taurine on lipid metabolizing enzymes of isoproterenol cardiotoxic rats, Data expressed as mean±SE for six rats/group, -Values with the same superscript letter are similar (non-significant, P>0.05) whereas others aren't (significant, P<0.05)
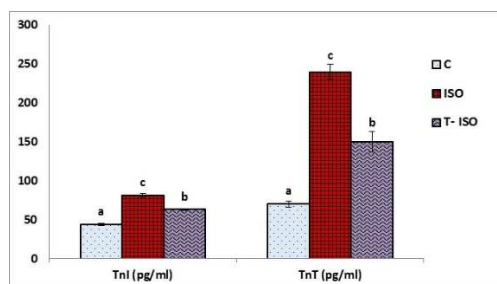

Fig. 3: Prophylactic effect of taurine on troponin I and troponin T in the serum of isoproterenol cardiotoxic rats. Data expressed as mean ± SE for six rats/ group. Values with the same superscript letter are similar (non-significant, P > 0.05) whereas others aren't (significant, P < 0.05).

Tissue cardiotoxicity

Fig. 4 showed that ISO induction led to a significant (P<0.001) decrease in the protein content in comparison to the control group in the heart tissue while pre-treatment with taurine served to maintain the protein content from the high decrement in the heart tissue. The membrane ATPase bound enzyme activities (Na+-K+and Ca2+ATPase) are illustrated in fig. 5, which demonstrates that they showed the same behavioral activities. Na+-K+ ATPase recorded the highest activity in the control group followed by the taurine pre-treatment group then the ISO-treated group. Also, Ca2+ATPase recorded the highest activity in the control group followed by the taurine pre-treatment group then the ISO-treated one. Table 6 indicate the ameliorative effect of taurine on the lipid content in the heart tissue, as all the increased cholesterol, triglycerides, free fatty acids contents after isoproterenol injection decreased with taurine treatment while it reincreased the decreased phospholipids. The oxidation process was evaluated by the lipid peroxidation process and two antioxidant enzymes (fig. 6). In comparison to the control group, lipid peroxidation was significantly elevated (P<0.001) in the ISO cardio toxified group while the superoxide dismutase (P<0.01) and peroxidase (P<0.001) enzymes were significantly decreased. The taurine pre-treated group showed amelioration in the oxidation process with decreased lipid peroxidation and increased antioxidant enzymes.
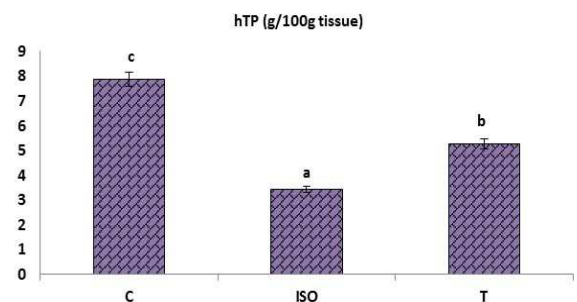

Fig. 4: Prophylactic effect of taurine on protein content in the heart tissue of isoproterenol cardiotoxic rats. Data expressed as mean ± SE for six rats/ group. Values with the same superscript letter are similar (non-significant, P > 0.05) whereas others aren't (significant, P < 0.05).

Fig. 5: Prophylactic effect of taurine on membrane-bound Na+-K+ATPase and Ca2+ATPase in the heart tissue of isoproterenol cardiotoxic rats, Data expressed as mean±SE for six rats/group, Values with the same superscript letter are similar (non-significant, P>0.05) whereas others aren't (significant, P<0.05)
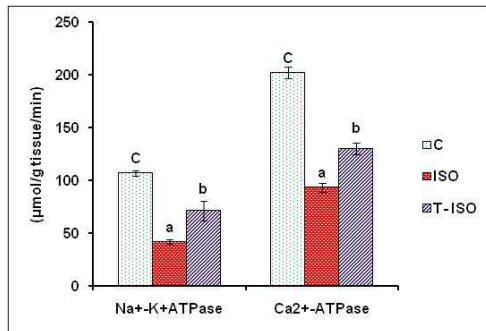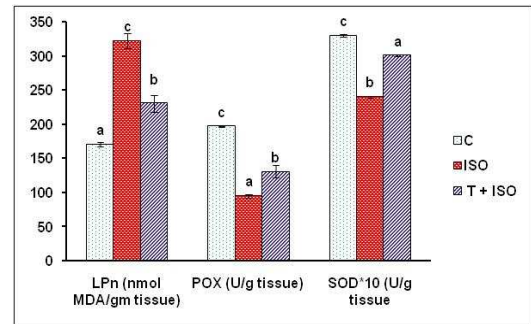

Fig. 6: Prophylactic effect of taurine on lipid peroxidation, superoxide dismutase, and peroxidase activities in the heart tissue of isoproterenol cardiotoxic rats, Data expressed as mean±SE for six rats/group, Values with the same superscript letter are similar (non-significant, P>0.05) whereas others aren't (significant, P<0.05)

Table 5: Prophylactic effect of taurine on lipid profile level in the heart tissue of cardiotoxic rats

Groups	Tg (mg/dl)	TCh (mg/dl)	PL (mg/dl)	FFA (mg/dl)	C/P ratio
Control	8.333±0.039[a]	10.453±0.094[a]	34.667±0.558[c]	1. 263±0.144[a]	0.294±0.004[a]
Isoproterenol	9.367±0.086[c]	12.320±0.105[c]	16.500±0.847[a]	3.648±0.272[c]	0.738±0.028[c]
Taurine+Isoproterenol	8. 740±0.037[b]	11.333±0.037[b]	24.867±0.804[b]	2.491±0.159[b]	0.469±0.029[b]

-Data expressed as mean±SE for six rats/group, -Values with the same superscript letter are non-significantly different (P>0.05).

DISCUSSION

This study tested the use of taurine as a natural antioxidant agent affecting the myocardial cells and serving to protect the heart from infarction. To evaluate its cardioprotective efficacy, several parameters were checked. Firstly isoproterenol was used to induce the experimental model of myocardial infarction since this is considered a standard model to study the beneficial effects of many drugs and cardiac functions [42]. Isoproterenol was observed in increasing the relative heart weight, which is in accordance with many previous studies showing cardiac hypertrophy [43-45]. It was also shown that isoproterenol leads to myocardial necrosis characterized by increased end-diastolic volume, end-diastolic pressure and left ventricular wall thickness. The cardiac hypertrophy after acute administration of isoproterenol is possibly also due to the accumulation of intramuscular water and the formation of interstitial fibrosis, especially at the subendocardial and apical cardiac levels, as well as invasion by inflammatory cells [46]. The formation of fibers and accumulation of intramuscular water explains the decrease in the protein content of cardiac tissue that was recorded in ISO-treated rats.

Taurine is a non-protein sulphur containing an amino acid that has been shown to play several essential roles in the human body [47]. It has been proved that taurine makes up more than 50% of the total free amino acid pool in the mammalian heart [48]. Earlier studies have demonstrated that pathology develops in the myocardium if the animal is depleted of taurine stores either through a taurine deficient diet or use of taurine transport antagonists [49]. This means that it is a principal constituent in and for the myocytes. Its effect on increased myocardial weight has been previously studied [50, 51], and it has been found to prevent the hypertrophy of the myocytes, possibly due to its osmoregulatory effect, avoiding myocyte swelling [52] and protecting their normal constituents from fibrosis.

The cardiotoxic parameters indicated an increase in AST, LDH, CK, CK-MB activities and a decrease in the membrane-bound Na+-K+and Ca2+ATPase enzyme activities. The cardiac troponins (I and T) biomarkers increased in the serum of the myocardial infarcted rats. ISO induction also led to a disturbance in the oxidation process as lipid peroxidation increased and the antioxidant enzymes SOD and POX decreased. These results parallel those of many studies [42], [53-55]. Several mechanisms for the cardiotoxic effects of high levels of ISO have been suggested. These mechanisms include: 1)

functional hypoxia and ischemia, 2) coronary insufficiency, 3) alterations in metabolism, 4) decreased the level of high-energy phosphate stores, 5) intracellular Ca2+overload, 6) changes in electrolyte contents and 7) oxidative stress. These changes are interpreted as complex entities [54]. These previous studies have also reported that oxidative stress is, probably, one of the main mechanisms through by which ISO exert its toxic effects. The oxidized products have the ability to interact with sulphydryl groups of various proteins and also lead to the production of superoxide anions and subsequently hydrogen peroxide. This results in changes in microsomal permeability, mitochondrial Ca2+uptake and a decrease in ATP production. This explains the decrease in ATPase activities which are also negatively affected by peroxidation of the membrane lipids and the formation of highly reactive hydroxyl radicals which cause protein, lipid and DNA damage [56]. These effects explained the increased MDA content and decreased antioxidant enzyme activities in the cardiac tissue of the ISO-intoxicated group because superoxide radicals generated at the site of damage decrease their activities and the accumulation of superoxide anions itself damages the myocardium. This accounts for the elevation of serum activity of AST, LDH, CK and CK-MB and serum level of cTn-I and cTnT in the current experiment several hours after ISO-administration. Myocytes death or altered membrane permeability causes the cytosolic contents to eventually enter the systemic circulation, where they may be detected as markers of the ischemic heart disease.

The osmoregulatory activity of taurine appears to be an important determinant of cell survival [57]. Taurine is an amino acid that differs from the more familiar amino acids both in being a sulphonic rather than a carboxylic amino acid and in being a β amino acid rather than an α amino acid. Its dipolar character may weaken charge dependent, protein-protein interactions and inhibit the force-generating myosin-actin interaction [58], decreasing myocytes activity, preserving energy and preventing cardiac hypoxia. This may explain the low level of the cardiac dysfunction biomarker enzymes, as it maintains the cells from death [57], and also elucidates the importance of taurine to the myocardial structure and contractile function, which agrees with the amelioration of the membrane-bound enzyme activities shown here. Taurine influences the activity of the sarcoplasmic reticular Ca2+ATPase through at least two factors. First, it enhances the phosphorylation of the sarcoplasmic reticular phosphoprotein, phospholamban [59].

Because the phosphorylation of phospholamban enhances the rate of Ca2+uptake by the sarcoplasmic reticulum, it, therefore, increases the rate of myocardial relaxation [60]. Second, due to its antioxidant activity: according to Park *et al.* [61] the activity of the sarcoplasmic reticular Ca^{2+}ATPase is inhibited by oxidative stress as lipid peroxidation is increased. It is known that sarcoplasmic reticular Ca2+uptake and release play key roles in regulating [Ca^{2+}] binding to troponin. It is not surprising; therefore, that taurine is required for normal systolic and diastolic function. The activation of the Na$^+$-K$^+$ATPase by taurine may be explained by its role in spanning membrane bound protein known as phospholamban protein from a sensitive volume channel which was found that its decrement leads to the decrease in Na$^+$-K$^+$ATPase activity [62].

Taurine can interact with the natural phospholipids of the biological membranes and protect the membrane organization against free radical attack, restoring the activity of membrane-bound enzyme ATPase. It can also preserve the sulph-hydral 'SH' group and inhibit membrane lipid peroxidation and the consequent alterations in the activity of various ATPases [63]. By these means, and by preserving the energy in the cell, it maintains the ATPase activity, as indicated in the treated group. Preserving the energy, maintaining the phospholipid content in the membrane and regulating the ionic balance in the cell, it protects the myocytes from death and prevents cytosolic leakage, as indicated by the low enzyme activities and low Tns level in our treated group. Lipid metabolism plays an important role in myocardial necrosis produced by ischemia [64]. An excess of lipids in the circulation is considered to accelerate the development of arteriosclerosis. This experiment indicated a disruption in lipid parameters after ISO-induction, which is compatible with many previous studies [65-67].

In respect to the lipid metabolizing enzymes in the present study there was a significant decrease in cardiac LCAT and LPL activity but a significant increase in the activity of CES in ISO-intoxicated rats. HDL is the main substrate for LCAT for cholesterol esterification and incorporation [68, 69]. An inverse correlation between TG and LPL activity has been reported. The hypertriglyceridemia observed in ISO-intoxicated rats is due to the decreased activity of LPL in the heart and decreased uptake of triglycerides from the circulation, which also leads to an elevated flux of fatty acids and impaired removal of very low-density lipoprotein (VLDL) from the serum [70]. The increase in the levels of FFA in ISO-intoxicated rats is due to the increased lipolysis of triglycerides from adipose tissue stores. This enters into the myocardium since the heart can utilize FFA for its energy requirements; the excess FFA may be used for the synthesis of TG, resulting in hypertriglyceridemia. Also, the, increased peroxidation of membrane phospholipids releases free fatty acids by the action of phospholipase A2, which is activated by Ca^{2+}ion accumulated in the cell [71]. The increased activity of CES in ISO-intoxicated rats results in the accumulation of ester cholesterol which in turn results in myocardial membrane damage [72, 73].

The significant increase observed in the lipid accumulation in cardiac tissue homogenate from the ISO group is in accordance with the results of other investigations [74, 75]. These authors referred to the high lipid content enhanced lipid biosynthesis by cardiac cAMP, which is increased and reported as the primary causes of ISO-induced cardiotoxicity [75]. The changes in membrane cholesterol content affect its fluidity, permeability to ions, the activities of membrane-bound enzymes and increased degradation of phospholipids [74]. Accelerated phospholipid degradation with the increased ratio of cholesterol/phospholipids (C/P ratio) could produce membrane dysfunction, resulting in cell injury and ultimate cell death. Another option, with very promising results in the context of cardiovascular risk stratification and assessment of the effectiveness of lipid-lowering interventions, is the use of lipid ratios, which have the added advantage of being easy to use in clinical practice and the changes in these ratios are better indicators of cardiovascular disease risk than the absolute levels of individual lipids [76].

There are many studies showing the hypolipidemic effect of taurine in ISO-treated rats [77-79]. The oldest and best-documented function of taurine is its conjugation with bile acids in bile salt synthesis [80]. The hypolipidemic effect of taurine is partly due to the inhibition of cholesterol absorption in the intestine [81]. It also works by increasing the conversion of cholesterol to bile acid by enhancing 7-α hydroxylase, the rate-limiting enzyme of hepatic cholesterol catabolism, and conjoining with bile acids, this is indicated by enhanced mRNA expression and enzymatic activity of 7a-hydroxylase [82]. Murakami *et al.* [83] also showed that taurine induced lower cholesterol level in diabetic rats by increasing LDL-receptors, thereby mediating LDL turnover. It has also been suggested that taurine may be responsible for the increase of HDL, modifying cholesterol synthesis in the liver and/or balance of each of the serum lipoprotein fractions containing cholesterol [84]. Taurine is a hypocholesterolemic agent [85], possibly by enhancing LDL receptor binding in the liver [86]. The reduced levels of triglyceride following taurine treatment are explained by its LPL-lowering effect [87].

CONCLUSION

The finding of the current study clearly demonstrated that taurine significantly protected against the toxic effects of ISO *via* alleviating the altered cardiac biomarker enzymes which may be mediated by attenuate the oxidation mechanism system. In addition, hyperlipidemia and its cardiovascular complications were markedly ameliorated through increasing HDL level and enhancement of LDL turnover.

ACKNOWLEDGMENT

CONFLICT OF INTERESTS

Declared none

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