Full Length Research Paper

Beneficial effect of taurine in spontaneous hypertensive rats: Implication of its antioxidant activity

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Taurine, a sulfur-containing amino acid, has been reported to play an antihypertensive role but the mechanism underlying this activity is yet to be defined. In this study, we investigate the effect of taurine on blood pressure by oral administration in conscious spontaneously hypertensive rats (SHR). Total heart weight, left ventricular weight, lipid peroxidation as well as glutathione (GSH) and superoxide dismutase activities (SOD) were determined together with histopathological examination of heart tissue. Results indicate that four weeks of oral taurine administered significantly decreased the systolic blood pressure from 174.6 ± 6.4 to 140.08 ± 8.2 mm Hg (p < 0.05). This was associated with significant reduction of the left ventricular mass in cardiac tissues. Lipid peroxidation of the heart tissue was depressed, while SOD and GSH activities significantly increased in SHR under taurine treatment. Moreover, histological inspection of cardiac sections revealed a smaller cardiomyocytes diameter in taurine- treated animals when compared to controls. We conclude that taurine reduces blood pressure in SHR and decreases cardiac hypertrophy by impacting the antioxidant activity.

Key words: Taurine, antioxidant, hypertension, spontaneous hypertensive rats.

INTRODUCTION

Hypertension is one of the leading causes of disability or death, due to stroke, heart attack, and kidney failure. It has been suggested that increased oxidative stress may be a cause and/or a consequence of hypertension. A diet low in saturated fat, enriched with carbohydrate complexes as well as specific nutrient supplementation is highly recommended. In this context, taurine is the end product of the degradation of methionine and cysteine.

Although, it can be endogenously synthesized, the essential source of taurine is through food intake (Sturman and Kayes, 1980). Studies have been shown that this molecule plays a role in maintaining constant cell volume and osmolarity as well as in regulating membrane excitability (Bidri and Choay, 2003). Clinically, taurine has protective effects in pathological condition that is congestive heart failure, myocardial infarction and cardio-

myopathy (Chapman et al., 1993). At relatively high doses, taurine prevents premature ventricular contraction induced by epinephrine and digoxin (Read and Welty, 1963). In addition, taurine is a potent antioxidant and a neuromodulator with developmental function in the brain and the retina (Gupta et al., 2005). Nevertheless taurine keeps on intriguing the investigators due to lack of information as well as the diversity of the physiological roles it can accomplish.

We are interested in defining the role of taurine as a potential natural substance in protecting the cardiovascular system from injuries. We have previously shown that 1) taurine increased prostacycline/thromboxane balance in the myocardium by blockade of noradrenalin liberation after stimulation of sympathetic nerves in isolated rabbit heart and 2) protected the myocardium against the detrimental effects of oxygen free radicals (Pham et al., 1987; Chahine et al., 1994; Chahine and Feng, 1998; Hanna et al., 2004). Here we show that taurine decreased the systolic pressure and antagonized hypertrophy-induced in hypertensive rats. We propose a role for taurine as a potential natural protective substance.

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MATERIALS AND METHODS

Spontaneously hypertensive rats (SHR)

Male SHR weighing 250 - 275 g were purchased from Charles River Laboratories International, Inc. and housed for at least 1 week before initiation of drug treatment at 11 weeks of age. In this model of SHR, we measured systolic blood pressure by plethysmography at the tail artery (Deblois et al., 1997). We compared two groups of SHR, the first one was given taurine orally in drinking water at concentration of 1g/l for 4 weeks, the second group was kept without any taurine intake (n = 10 in each group). A group of 6 WKY was used as a control. Rats were then sacrificed, and heart mass, left ventricular mass, Histopathological investigation, lipid peroxidation of heart tissue as well as glutathione (GSH) and superoxide dismutase activities (SOD) were determined for all groups.

Histopathological studies

Transmural specimen from the free wall of the left ventricular myocardium were fixed in 10 % formalin embedded in paraffin, counterstained with hematoxylin-eosin and observed using light microscopy.

Morphometric analysis of each heart section was performed with a computer-based morphometric system. At least five cross-sections of each heart were examined, and the measurements were averaged for statistical analysis. To evaluate the mean diameter of LV cardiomyocytes, the shortest diameter of each cardiomyocyte was measured only in nucleated transverse sections stained with hematoxylin and eosin. One hundred fifty cardiomyocytes in each LV were measured using an ocular micrometer disc with a linear scale at a magnification of 400 ×, and the average cardiomyocyte diameter of each specimen was calculated (Mori et al., 2004).

Biochemical studies

We used the thiobarbituric acid colorimetric method as previously described (Mateescu et al., 1995) for assessing myocardial malondialdehyde (MDA) production to obtain the level of induced lipid peroxidation, as there is a direct correlation between the two. Superoxide dismutase (SOD) and glutathione (GSH) activities in the hearts were determined by a colorimetric method using the Superoxide dismutase assay kit 706002 and the Glutathione Assay Kit 703002 respectively, according to the manufacturer's instructions (Cayman Chemical Company Ann Arbor, Michigan 48108 USA).

Ethics

All animal experiments were conducted in accordance with the NIH Guide for the Care and Use of Laboratory Animals (Institute of Laboratory Animal Resources, National Academy Press, Washington, DC, USA).

Drugs

All chemicals were purchased from Sigma Aldrich Co, except where otherwise mentioned.

Statistical analysis

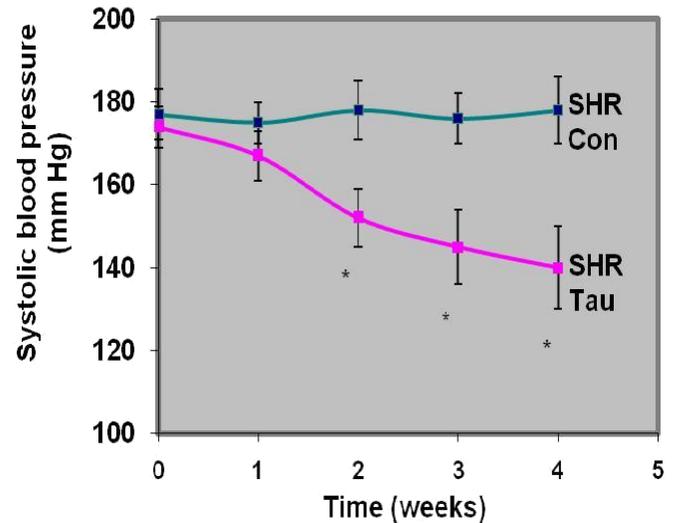Data were analyzed by analysis of variance and unpaired Student's

Figure 1. Systolic blood pressure of spontaneous hypertensive rats (SHR) receiving or not a supplementation of taurine 1 g/l in drinking water. Recorded by plethysmography via the caudal artery. n=10, p< 0.05 versus time 0.

t-test with Bonferroni correction for multiple comparisons when appropriate. The paired t test was used to compare the changes in blood pressure before and after treatment. Results are presented as the mean ± SEM. A value of p < 0.05 was considered to be statistically significant.

RESULTS

Cardiodynamics

Taurine administered orally in drinking water at concentration of 1 g/l for 4 weeks in SHR showed lower systolic blood pressure from 174.6 ± 5.4 to 167.2 ± 6.1 (first week), 152.5 ± 7.0 (second week), 145.1 ± 9 (third week) and 140.08 ± 9.8 mm Hg at four weeks after taurine administration, (p < 0.05) (Figure 1). In contrast, systolic blood pressure was not affected in untreated SHR. We also found (Table 1) that taurine significantly reduced the heart weight to 0.96 ± 0.04 g (p < 0.05) compared to 1.17 ± 0.03 g in untreated SHR and normotensive rats (1.03 ± 0.02 g). The left ventricular weight data corroborated this finding: 0.70 ± 0.03 g (p < 0.05) compared to 0.82 ± 0.01 g in untreated SHR and 0.75 ± 0.02 for the normotensive rats.

Biochemistry

Compared to heart tissue of the control group, lipid peroxidation of heart tissue from SHR was significantly increased; while GSH and SOD activities significantly decreased. In SHR receiving taurine as compared to untreated animals, lipid peroxidation decreased while

Table 1. Normotensive rats (WKY) and hypertensive rats (SHR), treated or non treated with taurine (1g/L) in drinking water during 4 weeks. * p < 0.05 versus SHR non treated. Hw : Heart weight, Bw : Body weight, LV : left ventricle weight, MDA: Malondialdehyde of myocardial tissue. GSH: glutathione activity. SOD: superoxide dismutase activity.

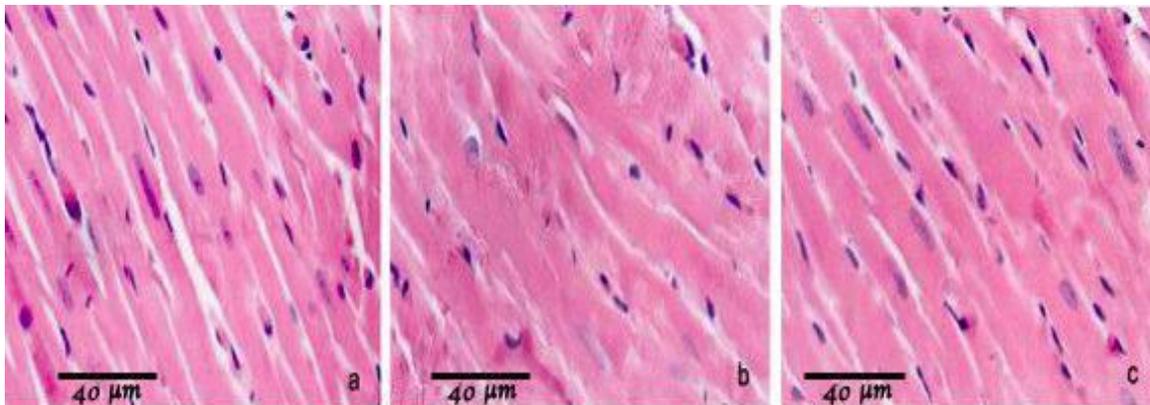|	WKY	SHR	SHR+T
Hw (g)	1.03 ± 0.02	1.17± 0.03	0.96 ± 0.04 *
Hw/ Bw (g/kg)	4.12 ± 0.07	5.13± 0.08	4.42 ± 0.09 *
LVw (g)	0.75 ± 0.02	0.82± 0.01	0.70 ± 0.03 *
LVw/Bw (g/kg)	3.0 ± 0.04	3.6 ± 0.05	3.16 ± 0.04 *
Cardiomyocyte diameter (µm)	12.5 ± 2.8	21.4 ± 2.2	16.8 ± 2.5 *
MDA (nmol/mg protein)	1.6 ± 0.07	2.4± 0.1	1.8 ± 0.08 *
GSH (µmole /mg protein)	0.25 ± 0.02	0.19± 0.02	0.23 ± 0.03*
SOD (unit/mg protein)	23.5 ± 2.2	15.1 ± 1.3	21.9 ± 2.4*

Figure 2. Light micrographs from left ventricular myocardium. a: WKY group; b: SHR group; c: SHR group treated with taurine (original magnification ×400). Compared to WKY, the increased size of cardiomyocytes was countered by 4 weeks treatment with taurine in SHR.

GSH and SOD activities increased significantly (p < 0.05) but without reaching the values of the control (Table 1).

Histopathology

Histopathological observation of sectioned myocardium from SHR showed that cadiomyocytes diameter was significantly larger than that in normotensive rats (Table 1). This phenomenon was countered by 4 weeks treatment of taurine in SHR. Myofiber disarray was also observed in left ventricular tissues of SHR group. However, following treatment with taurine, ventricular cardiomyocytes were regularly arranged when compared to untreated group (Figure 2).

DISCUSSION

A taurine deficiency was first reported in hypertensive patients (Ogawa et al., 1985). Thereafter, Inoue et al. (1986) showed that taurine, injected in the ventricular cerebral cavity, may decrease blood pressure in hypertensive rats via the inhibition of sympathetic tone. After administration of taurine to young hypertensive patients, both their arterial pressure and the circulated adrenaline diminished (Fujita et al., 1987). Oral administration of taurine was also associated with decrease in blood pressure of hypertensive rats (Harada et al., 2004). kinins may be implicated in this effect (Thirunavukkarasu et al., 2004).

After injection of taurine in ventricular cerebral cavity, Yoshioka et al. (2007) showed that the diminished blood pressure in hypertensive rats was through a decrease in cerebral monoamines. A modulation of the renin angiotensin system (Schaffer et al., 2000) and or vasodilator liberation (Kamata et al., 1996) by taurine are not excluded from this effect. In this context, Ristori and Verdetti (1991) have found a direct effect of taurine on vascular muscle, partially dependant of the endothelium

and do not block the vasoconstrictor effect of noradrenalin. Abebe and Mozaffari (2000) have demonstrated an antagonist effect of taurine against noradrenalin, in a non competitive way also partially dependant on the presence of endothelium. A taurine transporter in vascular muscle of rat aorta has been reported recently by Liao et al. (2007) which can help in finding the exact mechanism of action.

It is evident that the hypotensive mechanism of action of taurine is complex. This is not surprising because this substance possesses many potential targets in the organism. We are pioneered in using taurine 1 g/l in drinking water of SHR. Moreover, our results concerning the weight difference of left ventricle and the total antioxidant activity of plasma in rats and humans are innovatory. These results indicated that taurine treatment reduced blood pressure of SHR via a complex mechanism including an antioxidant activity. Concerning the mechanism through which taurine may act it is surely multifactorial by acting as a regulator of osmotic pressure, and by preventing calcium overload.

The capacity of taurine to increase total antioxidant activity of plasma does not play a direct role on arterial pressure, rather, this may be done via free radical scavenging effect of taurine against hydroxyl or superoxide radicals which possess a vasoconstricting effect (Halliwell, 1994; Tsai and Jiang, 2010). This corroborates our precedent findings *in vitro* and in isolated heart (Hanna et al., 1994). Finally, the potential ability of taurine to reverse left ventricular hypertrophy (Xu et al., 2008; Chapman et al., 1993) has a significant clinical benefit; decreasing cardiac morbidity and mortality due to hypertension.

ACKNOWLEDGEMENT

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