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EFFECTS OF TAURINE ON VASCULAR TENSION AND STATE OF BLOOD MAGNESIUM

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Abstract

Many biological, physiological and pharmacological functions of taurine have been identified in various tissues and species including building blocks of protein, membrane stabilization, detoxification, antioxidation, osmoregulation, modulation of ion flux, control of calcium (Ca^{2+}) homeostasis and as a neurotransmitter or neuromodulator. The present study investigated the effect of taurine on vascular tension and blood ionized Magnesium (iMg^{2+}) status. In this study Sprague-Dawley rats were used and surgical isolation of outer jugular vein and right carotid artery was done and then artery and vein were cannulated. Taurine was infused (100 and 250 mg/kg bw) through jugular vein and blood pressure was recorded continuously with Biopac computerized system connecting with a pressure transducer MP150 through the carotid artery catheter. *In vivo* biphasic effect of taurine where initial transient increase of mean arterial pressure (MAP) following sustain decreasing than normal in both doses and *in vitro* vaso-relaxant effect of taurine was observed. The relaxation mechanism is endothelium dependent where taurine induced for activation of (Nitric Oxide) NO/cGMP signaling cascade and this mechanism is responsible for ultimate decrease in MAP. Blood ionized and total magnesium (tMg^{2+}) in taurine infused rats were measured in a time and dose dependent manner and found a significant increase in blood iMg^{2+}. Our study suggests that taurine can reduce elevated blood pressure, increases blood iMg^{2+} and thus counteracted the deleterious effects.

Keywords: Taurine, sprague-dawley, aortic tension, magnesium, NO/cGMP.

Introduction

Taurine (2-aminoethanesulphonic acid) is a non-essential amino acid which can be derived from diet or synthesized from the amino acid cysteine, if there is enough cysteine and pyridoxal-5-phosphate (co-enzyme B-6). Taurine is highly concentrated in animal and fish protein and it is the most abundant freely existing and sulfur-containing amino acid found in high concentration in the skeletal muscle, heart and blood (Huxtable, 1992), nerve, brain, liver, and other organs (Jacobsen and Swimth, 1968). It acts as endogenous antioxidant and membrane stabilizing agent in many biological, physiological, and pharmacological functions in various tissues and species including membrane stabilization (Pasantes *et al.,* 1985), detoxification (Huxtable, 1992), antioxidation (Gordon *et al.,* 1992; Nittynen *et al.,* 1999; Rahman *et al.,* 2011; Timbrell *et al.,* 1995), osmoregulation (Nieminen *et al.,* 1988; Thurston *et al.,* 1980), modulation of ion flux (De Luca *et al.,* 1996; Franconi

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et al., 1982), control of Ca^{2+} homeostasis (Huxtable and Bressler, 1973), and as a neurotransmitter or neuromodulator (Davison and Kaczmarec, 1971; Fujita *et al*., 1987; Huxtable, 1981). In our recent research we found that taurine has blood pressure reducing effect in vivo which has been elucidated by in vitro experiment on isolated aortic ring tension. Taurine has been implicated in a number of cardiovascular functions, including the regulation of blood pressure (Trachtman *et al.,* 1998). With regards to the cardiovascular system, reduction of taurine in tissues, plasma and urine has been detected in certain disease states such as hypertension (Pion *et al.,* 1987). In this regard, it has been reported that oral supplementation of taurine has been shown to lower blood pressure in several animal models of hypertension, also in humans (Mitante and Lombardini, 2002). However, there have been several studies to determine the mechanism for vasorelaxation effect of taurine, in vitro. It has been reported that taurine causes reduction of nor epinephrine (Nephedipine-NE) precontracted aortic ring from stroke-prone spontaneously hypertensive rats (SHRSP) but not Wister Kyoto (WKY) rats (Li *et al.,* 1996). Besides, another report shows that taurine could also inhibit the KCl-precontracted aortic ring of the rabbit ear artery but not NE-precontracted (Franconi *et al.,* 1982). Recently, there has been increased concern about ascertaining the importance of nutrients in the regulation of blood pressure and pathogenesis of hypertension (McCarron *et al.,* 1982). It is well known that dietary nutrients such as sodium (Na^{+}), potassium (K^{+}), Ca^{2+} and Mg^{2+} play important role to influence blood pressure (Fujita *et al.,* 1984; Resnick, 1999). There is considerable suggestive evidence, primarily from epidemiological as well as animal studies, that Mg^{2+} nutrition has an important impact on vascular health, and that poor Mg^{2+} status may be associated with increased risk for hypertension, atherogenesis, coronary spasm, sudden-death (non-occlusive), cardiac arrhythmias, insulin resistance and diabetic complications (Altura and Altura, 1981; Elamin and Tuvemo, 1990; Ryan and Brady, 1984). Moreover, several investigators have suggested that dietary protein and amino acids could also influence blood pressure and thus affect the development of hypertension (Sved *et al.,* 1979; Yamori *et al.,* 1984). Recently, emphasis has been focused on the relationship between taurine and cardiovascular disease (Huxtable *et al.,* 1980). Furthermore, taurine could exert its antihypertensive action in man in a similar fashion, similar vasorelaxation effects like L-arginine of endothelium which is related with endothelium as well as NO/cGMP mediated decrease of mean blood pressure by relaxing vasculature, inhibiting Ca^{2+} channel but also normalizing the increased sympathoadrenomedullary tone in young patients with borderline hypertension (Fujita *et al*., 1987). The current study is designed for observing the in vivo and in vitro effect of taurine on the vascular tension as well as blood ions in this regards.

Materials and Methods

Reagents

Taurine, phenylephrine (PE), heparin, urethane (ethyle carbamate), acetylcholine (Ach), saponin, nifedipine, L-NG-nitro-arginine methyl ester (L-NAME), L-NG-nitro-arginine (L-NNA) were purchased from Sigma Chemical Co. (St. Louis, MO, USA)

and the chemicals were dissolved in saline or K-H (Krebs–Henseleit) buffer as required for respective experiment.

Animal rearing

Male Sprague-Dawley rats (220-250gm, 8 wk) were purchased from Bio-Safety Research Institute of Chonbuk National University, Jeonju Korea. Throughout the study, all the animals were reared in polystyrene case and housed in a room with constant temperature (23±5°C) and humidity (60±5%) and light from 6 a.m. to 6 p.m. Animals were fed a standard diet and allowed free access to tape water. All procedures were approved by the Institutional Animal Care and Use Committee at the Chonbuk National University, Republic of Korea.

Blood pressure measurement

Rat is anesthetized by urethane and is placed in a supine position and warmed using an isothermal heating pad. A longitudinal incision was made near the thoracic entrance then trachea was opened and a tracheal tube was inserted making a small incision to relief the breathing labor. Surgical isolation of right carotid artery and left jugular vein was done. Arterial and venous catheterization was done according to the method described by Lorenz and Robbins (1997). A small incision was made on both artery and vein with a fine scissors and then catheters were inserted and ligated using catheter of outer dimension (OD) 0.96 mm and inner dimension (ID) 0.58 mm into common carotid artery for collection of blood and monitor blood pressure and a catheter of 0.35 mm ID and 1.05 mm OD (Fisher Scientific) for jugular vein then for intravenous administration of normal saline and drugs. Arterial blood pressure (ABP) was measured with Biopac computerized data acquisition system (BioPac System, MP 150 CE `DA 100B or C', Biopac System Inc.), using Acqknowledge 2.0 software using pressure transducer attached with the catheter head which was connected to the blood pressure module and the pressure signal was amplified by an amplifier and finally the real time pressure was collected by computer. So the above method we collected blood and monitor pressure through carotid catheter as required and the same time taurine was administered through the jugular catheter at the mentioned time.

Aortic rings preparation

Rats were sacrificed and the descending thoracic aorta was excised as soon as possible and placed in 30mg modified Krebs-Henseleit (K-H) solution with the following composition (mM): NaCl, 133; KCl, 5; $CaCl_2$, 2.5; $MgSO_4$, 1.2; KH_2PO_4, 1.0; glucose, 11.0; $NaHCO_3$, 24. After removal of adhering fat and connective tissue, the aorta was cut into rings of about 2-3 mm in width. And the ring were mounted between two silver hook in tissue bath chamber perfused with K-H solution which was maintained at 37°C and gassed continuously with a 95% O2 and 5% CO_2 mixture. Arterial ring mounted over two rigid parallel stainless steel tubes, one fixed in place and the other attached to an isometric transducer (Cambridge Technology Inc., Water town, MA, USA.) connected to a multi recording system (Gould Instrument System Inc., USA, Model 3400). The mounted ring was immersed in a water-jacketed organ bath containing 5 ml of a 37°C modified K-H buffer and base tension was settled.

Determination of vascular reactivity

When the ring were settled in the perfusion bath it was perused for 10 min without recording for the stabilization of the aortic ring. The tension was recorded isometrically via a force-displacement transducer (400A, Cambridge) connected to recording system (3400, Gould). After equilibration at resting tension of 250-300 μg, the aortic ring were given two successive stimulations with high KCl (40 mM) solution, which was prepared by replacing NaCl with equimolar KCl in K-H solution. In order to measure vasodilator responses, ring were contracted with PE (2.0 μM) and the endothelial integrity was confirmed by eliciting a relaxation with Ach (1 μM). After the action of PE contraction was stabilized, 1 mM taurine with 2 μM PE solutions was perfused for 5.0 minutes and the effects was directly recorded on carbon tracing paper. Saponin (0.3 mg/ml) which was dissolved in K-H solution was perfused for 12-15 minutes to denude the endothelium and the process was repeated again in the saponin denuded aortic ring. All inhibitors were pretreated for 1 hour before contraction of PE.

Measurement of blood ions

Blood sample were collected before using of taurine once then itravenous taurine was injected at the dose of 100 mg/kg in a group and 250 mg/kg in other group and the blood samples were drawn at 10, 30, and 60 minute time points from both groups. Blood ionized Mg^{2+} (iMg^{2+}), normalized Mg^{2+} (nMg^{2+}), ionized Ca^{2+} (iCa^{2+}), normalized Ca^{2+} (nCa^{2+}), Na^{+}, Cl^{-}, K^{+}, pH, and Hematocrit (Hct) were measured by NOVA analyzer using ion selective electrode (NOVA, stat profile M). After preparation of animal and vascular catheterization fresh blood samples were collected through carotid artery cannula on indicated time point in the haparinized syringe and NOVA analysis was done immediately with whole blood.

Statistical analysis

The results are presented as means±standard error of the mean (SEM). The data were analyzed using the Student's t-test and the repeated-measures analyses of variance ANOVA. A probability less than 0.05 was considered as statistically significant difference.

Results

Effect of taurine on blood pressure

The effect of taurine on mean arterial blood pressure (MAP) was assessed in normotensive rats. Rat were infused with 100 mg/kg and 250 mg/kg taurine through intravenous infusion and blood pressure was recorded continuously. In contrast, MAP after infusion of taurine in 100 mg/kg was less effective than that of 250 mg/kg taurine infusion, whereas only saline treatment did not change MAP in rats. Tracings of the changes in blood pressure depicting the development of change of blood pressure following infusion of taurine are marked by arrow in Figure 1. The onset of blood pressure reduction was found 6-7 min after taurine infusion with initial transient increase within 1-2 min immediately after infusion of taurine. Figure 1 tracing B and C shows the result of in vivo experiment with taurine and the results show biphasic effect of taurine on blood pressure. Continuous invasive monitoring of the changes of ABP variability

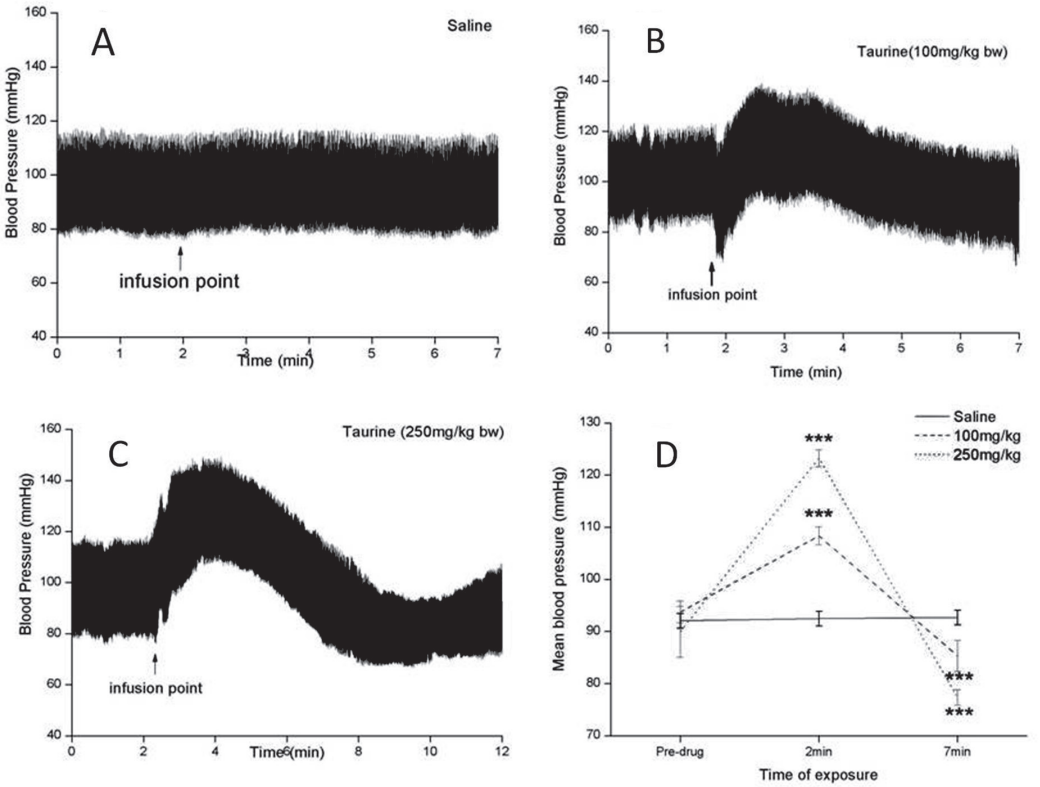

Fig. 1. Effects of taurine on initiation of change of MAP. (A). Tracing of uniform MAP when equal volume of saline are used, (B). Tracing shows the MAP change where taurine 100 mg/kg was used, (C). Tracing of MAP where taurine 250 mg/kg was infused and the onset of reduction of MAP. Arrow indicates the infusion point of taurine. (D). Shows the time and dose dependent change of MAP after infusion of taurine. Solid line indicate MAP where only saline was infused, the large dot line indicate the change due to taurine 100 mg/kg and the small dot line indicate the change due to taurine 250 mg/kg. Results expressed as mean±SD, ***p< 0.001* significant difference vs control, n=6.

in the anesthetic state allowed for a complex investigation of spontaneous cardiovascular variations. MAP were measured in a group of 6 male rats of 220-250 g weight. Finally, the MAP of taurine treated groups was compared with the MAP of a control group, which is treated with only saline (Fig. 1A). Figure1 tracing A, represents the arterial blood pressure of saline infused rat and displaying the result. Figure 1D reveals the calculated value of the change of MAP which indicates a biphasic effect of taurine i.e, taurine induce a immediate increase of MAP 16% and 36% according to the dose 100 and 250 mg/kg and after 6-7 min; respctively. The MAP was found to decrease 9% and 14% accordingly for both dose mentioned above. But when only saline was infused there was no change of MAP. Moreover, the power in the low frequency band in systolic, diastolic and MAP was diminished (Data not shown).

Aortic ring tension:

Fig. 2 tracing A and B are representative original tracing of 6 experiment shows the effect of taurine on rat aortic rings. In Fig. 2A, taurine causes remarkable relaxation with slight transient contractile tendency of the ring, also time factor in relaxation after infusion of taurine is an important factor here. After 5-6 min of use of taurine relaxation occurs, which is very similar with the in vivo experiment. In Fig. 2B, the endothelium of aortic ring was denuded by saponin 0.3 mg/ml. After 20 min flow of saponin the endothelium was completely denuded then contraction induced by PE (2 µmol). After reaching of maximum contraction taurine has been used but there was no relaxation. This phenomenon indicates that the relaxation induced by taurine is endothelium dependent. We hypothesized that taurine has similar vasorelaxation effects like L-arginine of endothelium which is related with endothelium as well as NO/cGMP pathway. These results suggest that taurine induced hypotension might be related to increase of

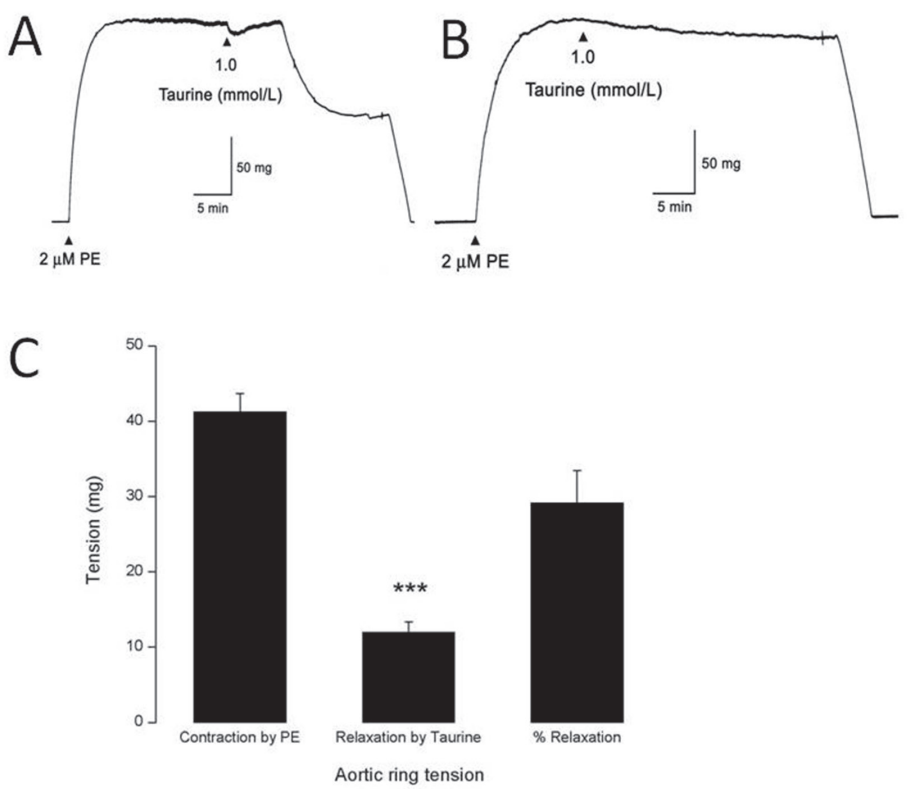

Fig. 2. ***In vitro*** **effect of taurine on vascular tension development on rat aortic rings. (A) Typical tracing of relaxant effect of taurine on Phenylephrine (PE) precontacted endothelium-intact (+E) rat aortic rings, but delayed action with slight transients increased contractile effect. (B). Taurine have no effect on saponine denuded endothelium (-E) of aortic ring. (C). The % of tension developed to the maximum tension evoked by 2µmol PE. Arrows represented the point of addition of taurine. Tracings are representative of six separate experiments. Result are expressed as mean±SD. ****P<0.001* means significant difference with PE precontracted maximum tension , n=6.**

NO and consequent vasodilatation. Figure 2C describes the contraction and relaxation by PE and taurine. The mean contraction developed by PE is 41.25 mg and the relaxation occurs by the taurine is 12.04 mg. i.e, taurine causes about 29% relaxations of PE precontracted (+E) aortic rings. Therefore, the figures defined clearly that blood pressure affected by time dependent fashion of exposure to taurine in vitro.

Blood ionized magnesium

Fig. 3 shows that blood iMg^{2+} concentration was increased by a dose dependent and time dependent manner of taurine infusion. The maximum increase was found on maximum dose and after one hour in comparison with the pre-infusion concentration. We found iMg^{2+} increased significantly in 100 mg/kg after 30 min but increase of dose to 250 mg/kg gives the significant difference of iMg^{2+} within 10 min of exposure.

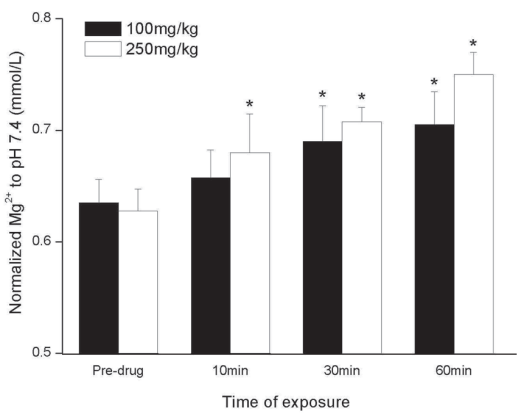

Fig. 3. Effect of taurine on blood ionized magnesium (iMg^{2+}). Gradual increase of iMa^{2+} as time passes with both the dose of 100 and 250 mg/kg of taurine. The concentration was lowest in normal (pre-exposure) blood and highest concentration was recorded after one hour of injection of taurine. Results are expressed as mean±SEM, *$p<0.05$ was considered as significant difference vs pre-drug, n=10.

Ionized calcium and magnesium ratio

We hypothesized that pre-treatment iMg^{2+} levels and/or the ratio of iCa^{2+} to iMg^{2+} (iCa^{2+}/iMg^{2+}) may have been confounding variables in this study. Both elements share left/right-sided cell. Good Mg^{2+} status thus restrains the influx of Ca^{2+} while supporting the activity of transporters that remove Ca^{2+} from the cytoplasm. Figure 4 shows gradual decrease of iCa^{2+}/iMg^{2+} ratio. The maximum and significant decrease of the ratio occurs after 1 hour in comparison with the pre-drug condition. We measured pH, hematocrit, Na^+, K^+ and Cl^- but we did not find significant difference in case of pH, hematocrit, Na^+ and Cl^- ions. Only K^+ increased significantly after 60 min of exposure in comparison with pre exposure condition. Table 1 shows the overall findings of these ions.

Discussion

Taurine is the most important and abundant amino acids in the heart, surpassing the combined quantity of all the others. The vascular endothelium of the coronary arteries has been identified as the important organ that locally regulates coronary perfusion and cardiac function by paracrine secretion of NO and vasoactive peptides (Podesser and Hallström, 2007). Taurine and probable cause of excess NO formation and scavenge ROS, relative shortage of substrate and cofactors leads to uncoupling of inducible nitric oxide synthase (iNOS), resulting in superoxide production, activating transcription factors that subsequently again increase iNOS expression. Increased superoxide production and decreased NO bioavailability is present in human and experimental animal models of hypertension. There is ample evidence

Table 1. Blood ionic condition after treatment with Taurine *in-vivo*

Time of Sample collection(min)	Taurine (mg/kg bw)	pH	Hct	Na+	K+	Cl-
Pre-drug	100	7.37 ± 0.01	41.75 ± 1.1	143 ± 2	4.8 ± 0.2	103 ± 0.81
	250	7.44 ± 0.02	42.5 ± 1.7	142 ± 1.2	5.25 ± 0.21	102 ± 0.61
10	100	7.36 ± 0.02	42.5 ± 0.9	143 ± 2	5.25 ± 0.3	102 ± 1.37
	250	7.41 ± 0.02	41.25 ± 1.75	141 ± 1.22	5.42 ± 0.21	102 ± 1.37
30	100	7.38 ± 0.01	40.75 ± 0.2	141 ± 1	5.67 ± 0.5	103 ± 1.6
	250	7.42 ± 0.05	40.25 ± 1.31	140 ± 1.32	5.85 ± 0.15	103± 1.6
60	100	7.40 ± 0.05	37.75 ± 1.7	140 ± 3	5.42 ± 0.3*	104 ± 1.1
	250	7.48 ± 0.05	37.5 ± 2.06	140± 0.05	6.05 ± 0.36*	104 ± 1.18

Nova measurement of pH, Hematocrit, Na^+, K^+ and Cl^- ions. Data are presented as mean±SEM and *$p<0.05$ considered as significant difference vs control, n=10

that in spontaneous hypertensive rat NO bioavailability is decreased and ROS is increased (Kunes *et al.,* 2004). Routine cardiac surgery or cardiologic interventions lead to a serious temporary or persistent disturbance in NO homeostasis (Podesser and Hallström, 2007). Therefore maintenance of normal NO homeostasis seems to be an important factor for protection from hypertension as well as hypotension, reducing myocardial oxygen consumption and metabolism (Eun *et al.,* 2010). When insufficient substrate or cofactors present, NOS can become uncoupled and become a source of superoxide (Cosentino *et al.,* 1998; Katusic, 2001). Aminoguanidine, a specific inhibitor of inducible NO syntase (iNOS), reduced BP in adult spontaneous hypertensive rat (SHR) (Hong *et al.,* 2000), while a specific NOS inhibition with N-nitro-L-arginine (L-NNA) increases BP in SHR (Verhagen *et al.,* 2001). Indeed, we found that treatment with the specific iNOS inhibitor L-N6- (1-Iminoethyl) lysine (L-NIL) reduced aortic ring tension during taurine induced relaxation in isolated rat aortic ring. Taurine, as amino acid precursor, corrects this and reduces MAP and aorta superoxide production (Trachtman *et al.,* 1998). In case of *in vivo* experiment we found that the initial immediate increase after infusion of taurine (Fig. 1 tracing B and C) and then slow decease. A similar slow action of taurine in in vitro experiment we found but this phenomenon is not completely understood. Reviews according to Nazer and Van Breemen (1998) suggest that, in the normal venous smooth muscle the fast component of the iCa^{2+} decline could be modulated by pharmacological interventions that stopped the plasma membrane Ca^{2+} adenosine-triphosphatase, the plasma membrane Na^+-Ca^{2+} exchanger or the sarcoplasmic reticulum, but the slow component was insensitive to such maneuvers. In the present study, we attempted to determine the values of whole blood iMg^{2+} (Fig. 3) and the ratio of iCa^{2+}/iMg^{2+} in blood (Fig. 4) induced by taurine in rats. Good Mg^{2+} status restrains the influx of Ca^{2+} while supporting the activity of transporters that remove Ca^{2+} from the cytoplasm (Ho *et al.,* 1988). The increased iCa^{2+} consequent to poor Mg^{2+} status can be expected to increase the

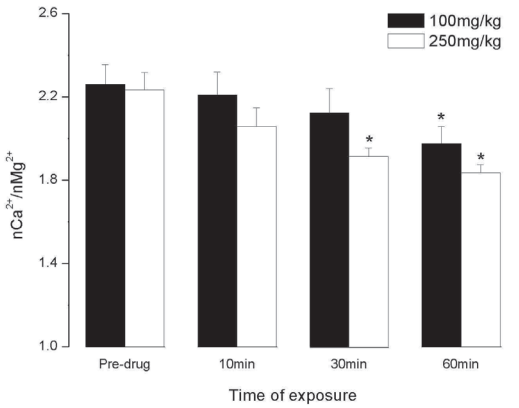

Fig. 4. Effect of taurine on the ratio of blood iCa^{2+}/iMg^{2+} in taurine treated rat. A gradual decrease of iCa^{2+}/iMg^{2+} in a time and dose dependent manner is evident. Results are expressed as mean±SEM and *$p<0.05$ is considered as significant difference vs pre-drug, n=10.

susceptibility of protein kinase C (PKC) to activation by agonists or metabolic conditions (such as hyperglycemia or high-fat diets) that promote diacylglycerol synthesis (Phillips *et al.,* 1989). Increased iCa^{2+} also activates calmodulin-dependent signalling pathways which, in conjunction with PKC activation, promote vasoconstriction, smooth muscle hyperplasia or hypertrophy (as in atherogenesis or hypertensive medial hypertrophy), platelet aggregation, insulin resistance and possibly diabetic microangiopathy (Considine and Caro, 1993; Rasmussen *et al.,* 1987; Sauro and Zorn, 1991; Williams and Schrier, 1992). Extracellular Mg^{2+} functions much like a Ca^{2+} channel blocker, reducing Ca^{2+} influx (Altura and Altura, 1987), the nature of the Ca^{2+} channels which Mg^{2+} blocks is still not well defined. Review suggests that when resistance arteries are perfused *in vitro* with a physiological Ca^{2+} solution, a high Mg^{2+} concentration in the perfusate blocks Ca^{2+} uptake and induces vasodilatation; conversely, a lower Mg^{2+} concentration promotes vasoconstriction (Altura and Altura, 1984). Healthy cardiac myocytes show a higher free intracellular Mg^{2+} concentration than do other cells, maintaining a concentration gradient by active transport (Hess and Weingart, 1981). Taurine can be expected to complement many of the vascular-protective benefits of good Mg^{2+} status, and moreover may have considerable value in its own right. These considerations encourage the development of Mg^{2+} taurate (Iseri, 1984) as a supplemental nutrient. These parallels are likely to reflect a common underlying mechanism of action, controlling iCa^{2+} by limiting Ca^{2+} influx while activating transporter proteins which extrude Ca^{2+} (McCarty, 1996; Arfuzir *et al*., 2018). Good Mg^{2+} status thus restrains the influx of Ca^{2+} while supporting the activity of transporters that remove Ca^{2+} from the cytoplasm. Ionized Ca^{2+} and Mg^{2+} ratio (Fig. 4) overall our data point is important to use for iMg^{2+} and the ratio of iCa^{2+}/iMg^{2+} in the diagnosis and treatment of disease. K^{+} ion is also important for normal blood pressure management. In the cell, taurine keeps K and iCa^{2+} inside the cell while keeping excessive Na out. In this sense it works like a diuretic.

Conclusion

Taurine was found to have mean blood pressure reducing tendency which has been elucidated by both *in vivo* and *in vitro* experiments where the blood vessel was dilated in a mechanism of cGMP/eNOS pathway. We also found interference with ionic balance due to taurine infusion which affects blood pressure by dilation of blood vessel. Further research is required to unveil the exact mechanism blood vessels relaxation effect of taurine and as therapy for hypertension.

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