4. Taurine regulation of blood pressure and vascular resistance

Abdeslem El Idrissi¹,²,³ Evelyn Okeke¹, Xin Yan²,³, Francoise Sidime²,³ and Lorenz Neuwirth²,³

¹Department of Biology, ²Center for Developmental Neuroscience, ³City University of New York, Graduate School, Staten Island, NY 10314, USA

Abstract. Taurine plays an important role in the modulation of cardiovascular function by acting not only within the brain but also within peripheral tissues. We found that IV injection of taurine to male rats caused hypotension and tachycardia. A single injection of taurine significantly lowered the systolic, diastolic and mean arterial pressure blood pressure in freely moving long Evans control rats. We further confirm the vasoactive properties of taurine using isolated aortic rings preparations. Mechanical responses of circular aortic rings to pharmacological agents were measured by an isometric force transducer and amplifier. We found that bath application of taurine to the aortic rings caused vasodilation which was blocked by picrotoxin. Interestingly, picrotoxin alone induced a constriction of the aortic ring in the absence of exogenously added taurine, suggesting a tonic activation of GABA_A receptors either by circulating taurine or GABA. Additionally, we found that the endothelial cells express high levels of taurine transporters and GABA_A receptors. We have
previously shown that taurine activates GABA$_A$ receptors and thus we suggest that the functional implication of GABA$_A$ receptors activation is the relaxation of the arterial muscularis, vasodilation and a decrease in blood pressure. Interestingly however, the effects of acute taurine injection were very different that chronic supplementation of taurine. When rats were supplemented taurine (0.05%, 4 weeks) in their drinking water, taurine has significant hypertensive properties. The increase in blood pressure was observed however only in females, males supplemented with taurine did not show an increase in systolic, diastolic or mean arterial pressure. In both genders however, taurine supplementation caused a significant tachycardia. Thus, we suggest that acute administration of taurine may be beneficial to lowering blood pressure. However, our data indicate that supplementation of taurine to females caused a significant increase in blood pressure. It remains to be seen the effect of taurine supplementation on hypertensive rats.

**Abbreviations**

*Epi*, epinephrine; *GAD*, glutamic acid decarboxylase *GABA*, *γ*-Aminobutyric acid.

**1.1. Introduction**

*γ*-Aminobutyric acid (GABA), one of the major inhibitory neurotransmitters in the central nervous system and is also found in many peripheral tissues. GABA has been shown to play an important role in the modulation of cardiovascular function by acting not only within the central nervous system but also within peripheral tissues. GABA has been reported to reduce blood pressure in experimental animals (Takahashi et al., 1955) and humans (Elliott and Hobbiger, 1959) following its systemic or central administration, and it has been suggested that the depressor effect induced by systemic administration of GABA is due to the blockade of sympathetic ganglia. The blood–brain barrier is impermeable to GABA, and its concentration in the brain is not changed following i.v. injection (Roberts; Tsukada and Gelder). Thus, the antihypertensive effects seen following i.p. or i.v. administration of GABA are due to its actions within the peripheral tissues presumably, blood vessels or autonomic nervous system. It has been reported that GABA can modulate the vascular tone by suppressing the noradrenaline release in the isolated rabbit ear artery and rat kidney (Manzini; Monasterolo and Fujimura). The effects produced by GABA in many kinds of peripheral tissues as well as within the central nervous system are mediated by at least two distinct receptor types, GABA$_A$ and GABA$_B$. It has been reported that GABA inhibits sympathetic neurotransmission in the rabbit ear artery through the stimulation of a presynaptic of GABA$_B$ receptor.
Taurine and hemodynamics

subtype (Manzini et al., 1985), and that GABA acts on presynaptic GABA$_B$ receptors to suppress neurotransmitter release (and thereby attenuate renal vasoconstriction) during the activation of the sympathetic nervous supply to the rat kidney (Monasterolo and Fujimura). Baclofen, a selective GABA$_B$ receptor agonist, attenuated the perivascular nerve stimulation-induced increase in perfusion pressure and noradrenaline release to the same extent as did GABA itself (Bowery, 1993). Consistent with this, it has been reported that baclofen has hypertensive properties after systemic or intracerebro-ventricular administration in rats (Persson and Crambes). Furthermore, these inhibitory effects of GABA were completely antagonized by the selective GABA$_B$ receptor antagonist, saclofen (Bowery, 1993), but not by the selective GABA$_A$ receptor antagonist, bicuculline (Curtis and Kwan). These results strongly suggest that GABA acts on presynaptic GABA$_B$ receptors to inhibit noradrenaline release, and thus the increase in perfusion pressure, induced by perivascular nerve stimulation. Because taurine has been shown to act as an agonist for GABA$_A$ receptors (El Idrissi et al, 2003), we tested the effects of taurine on cardiovascular function, specifically on blood pressure and heart rate. But unlike GABA, taurine crosses the blood-brain barrier. Thus the effects of taurine on cardiovascular function could be mediated either centrally or peripherally. Based on the results of the present study, we show that taurine injection significantly lowered systemic blood pressure in fully awake rats. Using aortic rings preparation, we further confirmed that taurine acts as a vasodilator. In the aortic preparations taurine-induced vasorelaxation may be due primarily to the activation of GABA$_A$ receptors expressed on smooth muscle. Interestingly however, the chronic supplementation of taurine to rats resulted in gender-specific increase in blood pressure. This increase in blood pressure was observed only in females, males supplemented with taurine did not show any increase in systolic, diastolic or mean arterial pressure. In both genders however, taurine supplementation caused a significant tachycardia.

Taurine is usually described as a free amino acid and does not participate in protein synthesis. Most animals (but not cats) can synthesize taurine from cysteine in a reaction pathway that involves decarboxylation and multiple oxidations of the sulfhydryl group (Huxtable, 1992). However, capacity for endogenous synthesis is limited in humans and the majority of body taurine stores are usually derived from food sources. The neonatal brain contains high levels of taurine (Huxtable, 1989, 1992; Sturman, 1993; Kuriyama and Hashimoto, 1998). As the brain matures its taurine content declines and reaches stable adult concentrations that are second to those of glutamate, the principal excitatory neurotransmitter in the brain. Taurine levels in the brain significantly increase under stressful conditions (Wu, et. al., 1998), suggesting that taurine may play a vital role in neuroprotection. A possible
mechanism of taurine’s neuroprotection lies in its calcium modulatory effects. We have shown that taurine modulates both cytoplasmic and mitochondrial calcium homeostasis (El Idrissi and Trenkner, 1999, 2003, 2004). Furthermore, taurine acts as an agonist of GABA<sub>A</sub> receptors (Quinn and Harris, 1995; Wang et al., 1998; del Olmo et al., 2000; Mellor et al., 2000; El Idrissi et al., 2003; El Idrissi and Trenkner, 2004). The effect of taurine on excitable tissues has been well studied with the exception of smooth muscle cells where not much attention has been devoted. Ristori and Verdetti have shown that that perfusion of aortic rings from rats with taurine perfusion (1-10 mM) reduced basal tone and had a relaxant effect on rings preconstricted with KCl or norepinephrine (Ristori and Verdetti, 1991). This effect was not mediated by endothelium or by muscarinic or adrenoreceptors, and thus probably represented a direct effect of taurine on vascular smooth muscle cells. Although the mechanism of vasorelaxation mediated by taurine were not elucidated, taurine may be minimizing [Ca<sup>2+</sup>]<sub>i</sub> by enhancing the activity of calcium transporting enzymes. Consistent with this, taurine has been shown to stimulate Ca-ATPase and Na/Ca-antiport in cardiac sarcolemma. In cardiac myocytes, taurine inhibits the rise in [Ca<sup>2+</sup>]<sub>i</sub> induced by beta adrenergic receptor stimulation (Failli et al., 1992). Clearly, more work is required to define the impact of taurine on calcium transport mechanisms in vascular smooth muscle; however, the net effect of these actions appears to be a reduction of [Ca<sup>2+</sup>]<sub>i</sub>. The calcium modulatory role of taurine has been well established (El Idrissi and Trenkner, 1999, 2003, 2004; El Idrissi 2005). In this study, we found that the effect of taurine on blood pressure was dependent on the duration of treatment. Acute taurine injection induced hypotension whereas chronic supplementation proved hypertensive but interestingly, only in females. Several clinical studies indicate that chronic oral administration of taurine reduces elevated blood pressures (Meldrum et al., 1994). Therefore, it seems that the effects of taurine on blood pressure are not only gender-specific but also depend on the level of blood pressure prior to taurine supplementation. Thus, the findings of this study cast some light on the ability of dietary taurine to regulate blood pressure. The benefit of dietary supplementation may depend on the model examined (Failli et al., 1992; Nara et al., 1978; Nakagawa, et al., 1994; Meldrum et al., 1994).

1.2. Methods

1.2.1. Animals

All rats used in this study were 2- to 3-month-old Long Evans. All rats were housed in groups of three in a pathogen-free room maintained on a
12 hr light/dark cycle and given food and water ad libitum. All procedures were approved by the Institutional Animal Care and Use Committee of the College of Staten Island/CUNY, and were in conformity with National Institutes of Health Guidelines. The number of rats sufficient to provide statistically reliable results was used in these studies.

1.2.2. Immunohistochemistry

Cryosections of thoracic aorta were placed onto gelatin-subbed slides. Non-specific binding sites were blocked using 4% bovine serum albumin (BSA), 2% normal goat serum (NGS), and 0.05% Triton X-100 in 0.01M phosphate-buffered saline (pH 7.2). Following the blocking step, the slides were rinsed in an antibody dilution cocktail (ABD) consisting of 2% BSA and 1% NGS in 0.01M PBS. Primary antibodies (Chemicon International) employed were directed against β subunit of the GABA_A receptors (mouse host) and taurine transporter (rabbit host) and diluted 1:500 in ABD. For these studies, the mouse anti-GABA_A receptors were paired with rabbit taurine transporter. The primary antibodies were incubated overnight at 4°C and then unbound antibodies rinsed with ABD. Secondary antibodies were all raised in goat and directed against appropriate primary antibody type. The anti-mouse IgG was conjugated to Alexa Fluor 488 (Invitrogen/Molecular probes) and the anti-rabbit IgG was conjugated to Cy5 (Jackson Immunological). Images were obtained by confocal microscopy (Leica SP2 AOBS). To determine relative changes in protein expression, the gain and offset was identical for all comparisons. Images were reconstructed from Z stack using Leica software (Fig. 9A) or Imaris x64 software (Fig. 9B).

1.2.3. Blood pressure measurements

For indirect blood pressure and heart rate readings, the rats were placed in a chamber at 37 °C for 10 min, and then transferred to a standard setup with heating pad and acrylic restrainer, tail cuff and pulse sensor (CODA monitor, Kent Scientific, Torrington, CT). The tail cuff was connected to a blood pressure monitor that through an arrangement of inlet and outlet valves permitted inflation and deflation of the cuff at a constant rate. The tail cuff pressure was continuously recorded with a solid state pressure sensor (Kent Scientific). The signals from the pulse and pressure sensors were conveniently amplified and then digitized with an analog–digital board directly on the blood pressure monitor. For each indirect BP determination the inflation and deflation readings were always recorded, as well as the compression interval. The indirect measurements were all performed by the
same person, who was kept blind about the purpose of the study. The animals quickly became familiar with the procedure and remained calm within the restrainer. In the rare cases when signs of discomfort were present the procedure was interrupted and the animal was disqualified from the study.

1.2.4. *Ex-vivo* measurements of vascular response

Long Evans rats (250–350 g) were anaesthetized with intraperitoneal injection of 50 mg/kg pentobarbitol. After opening the chest, descending aorta was removed and immediately placed in a Petri dish containing ice-cold physiological Krebs solution (in mM: 119.9 NaCl, 6 KCl, 15.6 NaHCO3, 1.2 MgCl26H2O, 11.7 Glucose, 2.5 CaCl2, 2H2O, pH 7.4). Rats were killed by an overdose of anesthetic. The peri-aortic fibroadipose tissue was carefully removed with fine microdissecting forceps and iridectomy scissors paying special attention not to damage the aortic wall. The thoracic aorta was then cut into rings (3 mm in length) with the help of a paper ruler placed under the Petri dish. After dissection, the rings were calibrated at room temperature for 45 min in aerated (95% O2/5% CO2) Krebs solution. Each of the rings was suspended horizontally in the same organ chamber (volume 4 ml) between two stainless steel hooks. One of the hooks was fixed to the chamber wall whereas the other was attached to an isometric force transducer (Refined Myograph Systems, Kent Scientific, Torrington, CT). The rings were continuously superfused with prewarmed (37°C), aerated (95% O2/5% CO2) Krebs solution. The rings were initially stretched until resting tension reached 2 g and allowed to equilibrate for 15 min. During this period the resting tension was continuously monitored and, if needed, readjusted to 2 g by further stretching. All subsequent measurements represent force generated above this baseline. Mechanical responses to pharmacological stimulation of circular preparations were measured by means of an isometric force transducer (Refined Myograph Systems, Kent Scientific, Torrington, CT) and amplifier (PowerLab, ADInstruments, Colorado Springs, CO) and were visualized using a graphic recorder (ADInstruments LabChart 7, Colorado Springs, CO). Data was sampled at 100 kHz and band-pass filtered between 0.3 Hz and 3 kHz.

1.2.5. Statistical analysis

Statistical significance was determined by Student’s t-test. Each value was expressed as the mean ± SEM. Differences were considered statistically significant when the calculated P value was less than 0.05.
1.3. Results

1.3.1. Taurine supplementation increases systemic blood pressure

To investigate the effects of taurine on the regulation of hemodynamics and peripheral resistance, we supplemented taurine (0.05%) to rats in their drinking water for 4 weeks and monitored their blood pressure. We found that the effects of taurine on blood pressure were gender-specific. While the blood pressure of adult male rats was not affected by taurine supplementation (Fig. 1), females on the other hand showed a significant increase in systolic, diastolic and mean arterial pressure (Fig. 2).

![Figure 1](image1.png)

**Figure 1.** Blood pressure measurements from male rats supplemented with taurine (0.05%) for four weeks. Taurine induced a slight but not significant decrease in systolic (SBP), diastolic (DBP) and mean arterial pressure (MAP). Rats were two months old and 15 rats were used for this experiment.

1.3.2. Taurine effects on cardiac function

While the effects of taurine on peripheral resistance were gender-specific with only females being affected, the effect of taurine supplementation on cardiac function was observed in both males and females. In response to 4 weeks of taurine supplementation, rats of both gender showed a drastic increase in heart rate (Fig. 3). The increase in heart rate in response to the increase in
Figure 2. Blood pressure measurements from female rats supplemented with taurine (0.05%) for four weeks. Taurine induced a significant (p<0.01) increase in systolic (SBP), diastolic (DBP) and mean arterial pressure (MAP). Rats were two months old and 15 rats were used for this experiment.

vascular resistance in female could be a mechanism to increase tissue perfusion. However, the tachycardia observed in males in the absence of an effect on vascular resistance may suggest a direct effect of taurine on heart physiology. This could be mediated at the myocardiocytes level (e.g. regulation of calcium homeostasis and contractile properties) or through interaction of taurine with the autonomic nervous system innervating the heart.

1.3.3. Taurine injection lowered peripheral resistance

To further characterize the vasoactive properties of taurine, we measured blood pressure in response to acute injection of taurine (43 mg/kg). Taurine was injected in the tail vein and blood pressure was monitored 15 min post injection. In response to taurine injection rats showed a drastic decrease in systolic, diastolic and mean arterial pressure (Fig. 4). The observed effects of acute taurine injection on vascular resistance could be mediated by direct interaction of taurine with endothelial or smooth muscle cells, or alternatively
Figure 3. Heart rate measurements from male female rats supplemented with taurine (0.05%) for four weeks. Taurine induced a significant (p<0.01) increase heart rates in both genders. Rats were two months old and 15 male and 15 female rats were used for this experiment. These measurements were taken from the same rats used in Fig 1 and 2. Recording of heart rate was simultaneous with blood pressure.

Through modulation of the nervous control of the cardiovascular function. The effect of taurine on peripheral resistance after acute injection was not gender-specific. Both males and females responded by a drop in blood pressure.
Figure 4. Blood pressure measurements from rats injected with taurine (43 mg/kg). Rats received an intravenous injection of taurine into the tail vein and blood pressure was measured 15 min post injection. Taurine induced a significant (p<0.01) lowered systolic (SBP), diastolic (DBP) and mean arterial pressure (MAP). Rats were two months old and 18 rats were used for this experiment.

1.3.4. Taurine causes vasorelaxation of aortic rings

Taurine has been shown to regulate the intracellular calcium homeostasis. Within the context of cardiac and smooth muscle physiology, calcium ions are very important in the regulation the contractility of these muscle cells and thus regulate both peripheral resistance and cardiac output. Taurine also has been shown to be a potent agonist of GABA, receptors and activation of these receptors has been shown to affect cardiovascular function and peripheral resistance. Thus, we used aortic rings to further elucidate the mechanisms by which taurine mediates its vasoactive properties. Freshly prepared aortic rings from the thoracic aorta were equilibrated for 45 min and isometric contractions were monitored in the presence of bath application of taurine. We first tested the effects of epinephrine (Epi), a well established and potent vasoconstrictor on the contractibility of the aortic rings (Fig. 5). Bath
Figure 5. Pharmacological response of aortic rings to epinephrine (Epi). Addition of 1μM Epi to the tissue bath resulted in a delay and sustained contraction of smooth muscle cells of the aorta. After removal of Epi from the bath, the rings remained constricted for a long time indicating the slow onset and offset action of Epi.

The kinetics of the constriction elicited by Epi was consistent with the mechanisms of action of this hormone/neurotransmitter. Upon application of Epi, it took approximately two minutes to observe the beginning of smooth muscle cells contraction, as Epi activates adrenergic receptors that are G protein coupled receptors. The peak tension was reached 15 min post bath application of Epi (Fig. 5). Similar to its slow onset of action, the effects of Epi persisted long after its removal from the bath. The persistent vasoconstriction in the absence of extracellular Epi indicates the continual activation of intracellular pathways and presence of second messenger systems triggered by Epi long after the removal of the agonist (Fig. 5).

1.3.5. Taurine activates GABA_{A} receptors in aortic preparations

In search of the potential cellular mechanism by which taurine mediates vasodilation, we used aortic rings and pharmacologically characterized the vasoactive properties of taurine on smooth muscle cells. Addition of taurine (10μM) to the tissue bath resulted in a vasorelaxation of the aortic rings (Fig. 6). The onset and offset of taurine action were much faster than those observed with Epi application, suggesting that taurine may activate an ionotropic receptor.

Since taurine is a GABA_{A} receptor agonist, we tested the effects of taurine in the presence of GABA_{A} receptor antagonist to determine if the effects were mediated through activation of GABA_{A} receptors. Application of
Figure 6. Pharmacological response of aortic rings to taurine. Addition of 10μM taurine to the tissue bath resulted in a rapid relaxation of smooth muscle cells of the aorta. After removal of taurine from the bath, the rings regained their pre-taurine contraction state relatively quickly, indicating that the fast onset and offset action of taurine could be mediated through an ionotropic receptor.

taurine in the presence of picrotoxin resulted in a rapid vasoconstriction as measured by the increased tension developed by the aortic ring (Fig. 7). The onset of vasoconstriction was very rapid within 30 sec and reached its plateau with in 2 min. 90 % of the tension was produced within 1 min of taurine and picrotoxin application (Fig. 7). Removing picrotoxin and taurine from the bath resulted in a relatively rapid vasodilation and the tension returned to baseline levels (Fig. 7) relatively quickly.

Picrotoxin is a GABA_A receptor competitive antagonist and competes with GABA to the binding site in an open-channel state. Since taurine is a GABA_A receptor agonist, application of taurine would open a GABA_A receptor and in the presence of picrotoxin, the effects of taurine on GABA_A receptor would be antagonized. Interestingly however, application of picrotoxin alone resulted in a vasoconstriction (Fig. 8). The kinetics of tension development by the aortic ring in the presence of picrotoxin alone was different than that in combination with taurine. When picrotoxin alone was added to the bath, the tension was slow to develop (max tension was produced within 5 min) and the amount of tension was lower than when picrotoxin was combined with taurine (compare Fig. 7 to 8; 0.5 vs 0.3 g). We infer from these data the following: taurine exerts its vasoactive properties through activation of the GABA_A receptors with subsequent hyperpolarization of smooth muscle cells and relaxation. The fact that picrotoxin application
Figure 7. Pharmacological response of aortic rings to taurine in the presence of picrotoxin. Addition of 10μM taurine in the presence of 5 μM picrotoxin to the tissue bath resulted in a rapid vasoconstriction of smooth muscle cells of the aorta to reach a plateau within 2~3 min. After removal of taurine and picrotoxin from the bath, the rings regained their pre-taurine contraction state relatively quickly, indicating that taurine mediates its actions on the smooth muscle cells through activation of GABA\(_A\) receptors. Resulted in a relaxation of the muscularis and a drop in tension suggest that there is a tonic activation of GABA\(_A\) receptors that could be mediated through circulating levels of GABA or taurine. However, the aortic rings are in an incubation chamber with controlled environment. The source of taurine or GABA in such a milieu could arise from release of these substances from the smooth muscle tissue itself. Smooth muscle cells have been shown to contain taurine (Lobo et al., 2001). Therefore, taurine or potentially GABA could be released from the tissue and causes a tonic relaxation of the smooth muscle cell within the muscularis of the aorta.

1.3.6. GABA\(_A\) receptor are expressed in the aorta

As further evidence for the activation of GABA\(_A\) receptors by taurine, we examined immunohistochemically the presence of GABA\(_A\) receptors on the aortic wall. We found that the muscularis contains high levels of immunoreactivity for the β subunit of the GABA\(_A\) receptors (Fig.9). Most GABA\(_A\) immunoreactivity was localized to the outer layers of the muscularis of the aorta (Fig. 9). GABA\(_A\) immunoreactivity was found in both cerebral and extracerebral blood vessels vasculature (Fig. 9A and B). We also examined
Figure 8. Pharmacological response of aortic rings to picrotoxin. Addition of 5 μM picrotoxin to the tissue bath resulted in a rapid vasoconstriction of smooth muscle cells of the aorta to reach a plateau within 4~5 min. The tension developed by picrotoxin alone was much smaller than when taurine was present. After removal of picrotoxin from the bath, the rings regained their pre-taurine contraction state relatively quickly, indicating a tonic activation of GABA$A$ receptors in the smooth muscle cells of the aorta.

the presence of taurine transporter on the wall of blood vessels. Interestingly, we found that the localization of taurine transporter in both cerebral and extracerebral vasculature is confined mostly to the endothelium layer (Fig 9A and B). Low level of taurine transporter immunoreactivity was observed on the smooth muscle cell of blood vessels.

1.4. Discussion

GABA has been shown to play an important role in the modulation of cardiovascular function and hemodynamics. GABA mediates these actions by acting not only within the central nervous system but also within peripheral tissues. Since taurine is an agonist for GABA$A$ receptors, we sought to determine the vasoactive properties of taurine, presumably through activation of GABA$A$ receptors.
Taurine and hemodynamics

Figure 9. Representative images of GABA_A receptors and taurine transporters immuno-reactivity in the wall of the aorta (A) and middle cerebral artery (B). The image in A was reconstructed from a Z stack obtained with a confocal microscope and processed using Imaris software. B is a maximum projection of a Z stack. Images. GABA_A immunoreactivity is localized to the outer muscularis, whereas taurine transporter is expressed in the apical side, presumably within the endothelium layer. Images captures with a 60 x oil objective.

Taurine (2-aminoethanesulfonic acid) is a sulfur-containing amino acid. It is one of the most abundant free amino acids in many excitable tissues, including the brain, skeletal and cardiac muscles. Physiological actions of taurine are widespread and include bile acid conjugation, detoxification,
membrane stabilization, osmoregulation, neurotransmission and modulation of cellular calcium levels (Foos and Wu 2002; Lombardini 1985; Saransaari and Oja 2000; Schaffer et al. 2000; Solis et al. 1988). Furthermore, taurine plays an important role in modulating glutamate and GABA neurotransmission (El Idrissi and Trenkner 1999; El Idrissi and Trenkner 2004; Militante and Lombardini 1998). We have previously shown that taurine prevents excitotoxicity in vitro primarily through modulation of intracellular calcium homeostasis (El Idrissi and Trenkner 1999). In neurons, calcium plays a key role in mediating glutamate excitotoxicity.

Outside of the central nervous system, taurine also is essential during developmental processes. Taurine is added to milk formula and in solution for parenteral nutrition of premature babies to prevent retinal degeneration and cholestasis (Huxtable 1992; Lourenco and Camilo 2002). Taurine is found at high concentrations in pancreatic islets (Huxtable 1992). Taurine is able to prevent pancreatic alterations induced by gestational malnutrition especially low-protein diet (Boujendar et al. 2002; Cherif et al. 1996; Dahri et al. 1991; Merezak et al. 2001).

The antihypertensive effects of taurine have been demonstrated in several experimental models (Fujita and Sato, 1984; Harada et al., 2000, 2004; Nara et al., 1978). Studies in vitro showed that taurine relaxed pre-constricted rabbit ear artery (Franconi et al., 1982), rat aorta (Ristori and Verdetti, 1991) and rat mesenteric artery (Li et al., 1996). Thoracic aortic rings isolated from rats that were chronically given beta-alanine to deplete internal taurine showed enhanced contractile responses to norepinephrine and high potassium, and reduced relaxant responses to sodium nitroprusside and acetylcholine (Abebe and Mozaffari, 2003). Thoracic aortic rings isolated from rats that were chronically given taurine showed reduced contractile responses to norepinephrine and high potassium nonspecifically (Abebe and Mozaffari, 2000). These experiments suggest that taurine plays an important role in the maintenance and regulation of vascular tone in normal and pathological situations.

We found that acute injection of taurine (43 mg/kg) to adult rats resulted in a significant decrease in peripheral resistance with no effects on heart rate (Fig. 4). We further confirmed the vasorelaxant action of taurine using aortic ring preparations. Addition of taurine to aortic rings preparation resulted in a rapid decrease in tension attributed to the relaxation of the arterial muscularis (Fig. 6). The effects of taurine on smooth muscle were mediated through activation of GABA_\text{A} receptors. Bath application of picrotoxin, a GABA_\text{A} receptors antagonist, resulted in a vasoconstriction of the aortic rings (Fig. 7). Interestingly, picrotoxin alone induced a constriction of the aortic ring in the absence of exogenously added taurine (Fig. 8), suggesting a tonic activation
of GABA$_A$ receptors either by circulating taurine or GABA. Picrotoxin is a GABA$_A$ receptor competitive antagonist and binds to GABA$_A$ in the open state. The finding that picrotoxin caused a vasoconstriction in the absence of exogenously added agonist (GABA or taurine), coupled with the kinetic of constriction, suggest that there is a tonic low level of activation of GABA$_A$ receptors. This could be mediated by release of taurine or GABA from the aortic ring tissue under stretch conditions. Additionally, we found that the endothelial cells express high levels of taurine transporters and GABA$_A$ receptors (Fig. 9). The presence of high level expression of taurine transporter in the endothelial cells suggests a high affinity uptake mechanism for taurine by the endothelial cells. Once taurine is removed from the plasma it would activate the GABA$_A$ receptors that are abundantly expressed on smooth muscle cells of aortic wall (Fig. 9).

Peripheral resistance within the large arteries is predominantly controlled by the level of tonic activity of the sympathetic nervous system and the level of adrenergic receptors activation. Thus one could suggest an antagonistic system to the sympathetic innervation of the vasculature. While the sympathetic nervous system causes vasoconstriction proportional to the level of activation of adrenergic receptors, the GABAergic system opposes that by mediating vasodilation. The GABAergic system mediates its vasoactive properties through activation of GABA$_A$ receptors expressed throughout the length of the muscularis of the vasculature. GABA$_A$ receptors can be activated either with taurine or GABA both of which are found at relatively high levels in the plasma.

The finding that acute taurine had an opposite effect on peripheral resistance than chronic suggest that the chronic supplementation of taurine in drinking water may cause alterations to the mechanisms responsible for taurine regulation of blood pressure and peripheral resistance. Consistent with this observation, we found that the effects of taurine on the GABAergic system in the brain are dependent on the duration of treatment.

We have previously shown that taurine-fed mice have reduced expression of GABA$_A$ receptors in the hippocampus (El Idrissi 2004). We suggested that a down-regulation of GABA$_A$ receptors expression was due to the sustained interaction of taurine with GABA$_A$ receptors which causes a change in subunit composition of the GABA$_A$ receptors and concomitant decrease in the efficacy of the inhibitory system (El Idrissi, 2004). Similar observations were noted in peripheral tissues mainly the pancreas (El Idrissi, 2010). Therefore, we suggest that a potential decrease in GABA$_A$ receptor expression in the muscularis aortic wall in response to chronic treatment with taurine would result in a reduced efficiency of vasodilative properties of GABA on peripheral resistance. This would lead to hypertensive effect when
taurine is chronically supplemented to rats. However, the hypertensive properties of taurine were gender specific. Only females showed a significant decrease in blood pressure when chronically fed taurine. The gender specificity of taurine on peripheral resistance is intriguing and requires further investigation of the mechanism of action. We suggest that $\text{GABA}_A$ could mediate this gender specificity. Steroid hormones have been shown to act as allosteric modulators of $\text{GABA}_A$ receptors. Thus, the gender-specific hormonal phenotype could underlie the selective modulation of $\text{GABA}_A$ receptors conductance by taurine. This however remains to be elucidated. Alternatively, taurine may mediate its vasoactive properties, in addition to activating $\text{GABA}_A$ receptors, through other known vasoactive substances. These include vasorelaxant prostaglandins and/or nitric oxide, the opening of K\textsuperscript+ channels and facilitating K\textsuperscript+ efflux, and/or reduced Ca\textsuperscript2+ availability or other mechanism(s) may be involved in the vasorelaxant effects of a taurine (Félétou and Vanhoutte, 2006).

1.5. Conclusion

In summary, this study shows that taurine could have both hypo- and hyper-tenssive properties. If chronically administered, taurine induces hypertension in female and tachycardia in both female and male rats. Intravenous injection of taurine causes a rapid decrease in blood pressure. This hypotensive effect was mediated through activation $\text{GABA}_A$ receptors expressed on the muscularis of the aorta and cerebral blood vessels. Taurine therefore, could act as a vasorelaxant when acutely injected. Furthermore, this study shows that GABA plays an important role in the regulation of cardiovascular function both centrally and peripherally. Drugs that target $\text{GABA}_A$ in the CNS would affect peripheral resistance in addition to the intended central effects.

1.6. Acknowledgements

This study was funded by a fellowship to E.O. from CUNY Summer Undergraduate Research Program (C-SURP).

1.7. References