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## High sugar intake blunts arterial baroreflex via estrogen receptors in perinatal taurine supplemented rats

Atcharaporn Thaeomor<sup>1,2</sup>, J. Michael Wyss<sup>3</sup>, Stephen W. Schaffer<sup>4</sup>, Wiyada Punjaruk<sup>1</sup>, Krissada Vijitjaroen<sup>1</sup>, and Sanya Roysommuti<sup>1</sup>

<sup>1</sup>Department of Physiology, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand <sup>2</sup>School of Biology, Institute of Science, Suranaree University of Technology, Nakhonratchasima 30000, Thailand <sup>3</sup>Department of Cell, Developmental and Integrative Biology, School of Medicine, University of Alabama at Birmingham, Birmingham, AL 35294, USA <sup>4</sup>Department of Pharmacology, College of Medicine, University of South Alabama, Mobile, AL 36688, USA

### Abstract

In adult rats, perinatal taurine depletion followed by high sugar intake alters neural and renal control of arterial pressure via the renin-angiotensin system. This study tests the hypothesis that perinatal taurine supplementation predisposes adult female rats to the adverse arterial pressure effect of high sugar intake via the renin-angiotensin system, rather than via estrogen. Female Sprague-Dawley (SD) rats were fed normal rat chow with 3% taurine (TS) or water alone (C) from conception to weaning. Their female offspring were fed normal rat chow with either 5% glucose in tap water (TSG, CG) or tap water alone (TSW, CW). At 7-8 weeks of age, the female offspring's renin-angiotensin system or estrogen receptors were inhibited by captopril or tamoxifen, respectively. Body weight, heart weight, kidney weight, mean arterial pressures (MAP) and heart rates were not significantly different among control groups (without captopril or tamoxifen). Captopril (but not tamoxifen) decreased MAP but not heart rates in all groups. In TSG compared to TSW, CW and CG groups, baroreflex sensitivity of heart rate (BS-HR) and renal nerve activity (BS-RN) were significantly decreased. Neither captopril nor tamoxifen altered BS-HR in TSG, but tamoxifen (but not captopril) restored TSG BS-RN to CW or CG control levels. Perinatal taurine imbalance (either increase or decrease) did not disturb sympathetic and parasympathetic nerve activity in the adult rats on high or basal sugar intake. Compared to its effect in CW and CG groups, tamoxifen increased sympathetic but decreased parasympathetic activity less in TSG and TSW groups. Inhibition of the renin-angiotensin system did not affect autonomic nerve activity in any group. These data suggest that in adult female rats that are perinatally supplemented of taurine, high sugar intake after weaning blunts arterial baroreflex via an estrogen (but not renin-angiotensin) mechanism.

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**Corresponding:** Sanya Roysommuti, Ph.D., Department of Physiology, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand, sanya@kku.ac.th, Phone/Fax: 66-43-348394.

## Keywords

arterial pressure; autonomic nervous system; baroreflex; estrogen; high sugar; perinatal taurine; renal sympathetic nerve; renin-angiotensin system

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## 1.1 INTRODUCTION

The perinatal environment influences not only growth and development of the fetus and newborn, but the phenotypic expression of the adult offspring. For examples, inhibition of the renin-angiotensin system from conception throughout life, or during the perinatal period alone, attenuates or prevents hypertension and other related damage in adult spontaneously hypertensive rats (Wyss et al. 1994). However, such inhibition produces salt-sensitive hypertension in adult normotensive rats. Several lines of evidence have reported that perinatal over or under dietary exposure programs adult function and dysfunction (Barnes and Ozanne 2011; Marino et al. 2011; Zhang et al. 2011). Previous experiments indicates that either taurine depletion or supplementation in early life alters renal function in adult male and female rats (Roysommuti et al. 2009a; Roysommuti et al. 2010a; Roysommuti et al. 2010b), while perinatal taurine depletion paired with a high sugar diet after weaning blunts baroreflex function and depresses the autonomic nervous system control of arterial pressure (Roysommuti et al. 2009b; Thaeomor et al. 2010). These abnormalities are improved by acute inhibition of renin-angiotensin system (Thaeomor et al. 2010).

The effect of perinatal taurine exposure on adult function is sex dependent (Roysommuti et al. 2009c), suggesting the possible role of sex hormones particularly estrogen in these effects. Without high sugar intake after weaning, perinatal taurine depletion only slightly but significantly blunts baroreflex sensitivity in male but not female rats. In contrast, a high sugar diet markedly depresses baroreflex function and increases sympathetic nerve activity in both sexes (Roysommuti et al. 2009b; Thaeomor et al. 2010). The significant role of estrogen on arterial pressure control is also supported by studies in spontaneously hypertensive rats (Bonacasa et al. 2008) and salt-induced hypertensive and ovariectomized rats (Fang et al. 2001). The low incidence of hypertension in pre- compared to postmenopausal women also supports a role for estrogen in cardiovascular disorders (Leuzzi and Modena 2011; Yanes and Reckelhoff 2011).

Perinatal taurine supplementation is common in pregnant women and as a dietary supplement in newborns (McPherson and Hardy 2011; Wu 2009; Yamori et al. 2010). Although adverse effects of taurine excess have not been definitively demonstrated in humans, taurine supplementation during late pregnancy in rats stimulates postnatal growth and induces obesity and insulin resistance in adult offspring (Hultman et al. 2007). However, perinatal taurine supplementation's effect and possible mechanisms of action on arterial pressure control has not been established. The present study tests the hypothesis that perinatal taurine supplementation predisposes female adult rats to adverse effects of high sugar intake on arterial pressure control by a renin-angiotensin (rather than estrogen) mechanism.

## 1.2 METHODS

### 1.2.1 Experimental protocol

Sprague-Dawley (SD) rats were bred at the animal unit of Faculty of Medicine, Khon Kaen University and maintained at constant humidity ( $60 \pm 5\%$ ), temperature ( $24 \pm 1^\circ \text{C}$ ), and light cycle (06.00–18.00 h). Female SD rats were fed normal rat chow with 3% beta-alanine (taurine depletion, TD), 3% taurine (taurine supplementation, TS) or water alone (control, C) from conception to weaning. Their female offspring were fed with the normal rat chow with either 5% glucose in tap water (TD with glucose, TDG; TS with glucose, TSG; C with glucose, CG) or tap water alone (TDW, TSW, CW) throughout the experiment. All experimental procedures were pre-approved by the Universities Animal Care and Use Committee and were conducted in accordance with the National Institutes of Health guidelines.

To test the possible role of renin-angiotensin system, another six separated groups had been treated with captopril in drinking water (an angiotensin converting enzyme inhibitor, 400 mg/L) from 7 days before parameter measurements until the end of experiment (CW+Cap, CG+Cap, TDW+Cap, TDG+Cap, TSW+Cap, TSG+Cap). In addition to test the possible role of estrogen, more six separated groups had been treated with an estrogen receptor antagonist (tamoxifen, 10 mg/kg/day, oral) since 7 days before the study (CW+Tam, CG+Tam, TDW+Tam, TDG+Tam, TSW+Tam, TSG+Tam).

At 7-8 weeks of age, under thiopental anesthesia, all female rats were implanted with femoral arterial and venous catheters. Three days later, arterial pressure, heart rate, arterial baroreflex sensitivity control of heart rate (BSHR) were measured in conscious freely moving rats before and during infusion of phenylephrine (BSHR-phenylephrine) or sodium nitroprusside (BSHR-nitroprusside). After 24 hours resting, rats were anesthetized with thiopental sodium, were tracheostomized, and their arterial pressures were recorded continuously, respectively. Renal sympathetic nerve activity was continuously recorded by using stainless steel electrodes (12 M $\Omega$ , 0.01 Taper, A-M System, Sequim, Washington, USA) connected to DAM-80 amplifier (World Precision Instruments, Sarasota, Florida, USA) and BioPac Systems (Goleta, California, USA), respectively. Multiunit recording of renal nerve activity was conducted only on nerve units that responded to changes in arterial pressure following nitroprusside or phenylephrine infusion. Body temperature was servo-control at  $37 \pm 0.5^\circ \text{C}$  by a rectal probe connected to a temperature regulator controlling an overhead heating lamp. At the end of experiment, all animals were terminated by a high dose of thiopental anesthesia and kidney and heart weights were then collected.

### 1.2.2 Data analyses

All data were analyzed by Acknowledge software version 3.9.1 (BioPac Systems, Goleta, California, USA). Frequency domains of arterial pressure pulse spectrum were analyzed using the Acknowledge software to indirectly estimate the sympathetic (low frequency 0.3–0.5 Hz, LF) and the parasympathetic nerve activities (high frequency 0.5–4.0 Hz, HF). The percent power spectral densities of LF or HF to the total power of LF plus HF indicate sympathetic and parasympathetic nerve activity, respectively (Roysommuti S 2009;

Thaeomor A 2010). Baroreflex sensitivity values were calculated from changes in heart rates (BSHR) or renal nerve activity (BSRA) per changes in mean arterial pressures.

### 1.2.3 Statistical analyses

All data are expressed as mean  $\pm$  SEM and were statistically analyzed using one-way ANOVA and a *post hoc* Duncan's Multi-Range test. Statistically significant difference is *p*-values  $< 0.05$ .

## 1. 3 RESULTS

At 7-8 weeks of age, all groups displayed similar body, heart and kidney weights as previously reported (Roysommuti S 2009). Mean arterial pressures were not significantly different among untreated control groups, and acute inhibition of renin-angiotensin system by captopril significantly decreased mean arterial pressures to a similar extent (about 15 mm Hg decreases). Compared to control treatment, inhibition of the estrogen receptors by tamoxifen did not significantly alter mean arterial pressures in any group, but the values of CG and TSW were slightly and significantly higher than those of CW and TSG (Fig. 1).

Heart rates were not significantly different among groups (Fig. 2). Baroreflex sensitivity control of heart rate was not significantly different among control CW, CG and TSW, but it was impaired significantly in control TSG (Fig. 3). While tamoxifen treatment significantly decreased baroreflex sensitivity in CW, CG and TSW, captopril treatment significantly decreased only in TSW. Neither captopril nor tamoxifen altered the baroreflex sensitivity controls of heart rate in TSG. Compared to CW and TSW, baroreflex sensitivity of renal nerve activity was impaired significantly in CG and TSG rats (Fig. 4). While tamoxifen treatment (compared to control) significantly decreased baroreflex sensitivity in CW, CG and TSW, captopril treatment significantly decreased in CW and CG (only BSRA-nitroprusside). Tamoxifen but not captopril treatment restored baroreflex sensitivity of TSG compared to TSW and CG.

All groups with or without captopril treatment displayed similar sympathetic and parasympathetic nerve activity while those with tamoxifen treatment significantly increased sympathetic and decreased parasympathetic nerve activity (Fig. 5). However, the autonomic nerve activity was less in TSW+Tam and TSG+Tam, compared to CW+Tam and CG+Tam, respectively.

## 1.4 Discussion

Perinatal taurine depletion followed by high sugar intake after weaning blunts baroreceptor reflex function and increases sympathetic nerve activity in adult female rats, and this effect is abolished by short-term inhibition of the renin-angiotensin system (Thaeomor et al. 2010), but not by inhibition of estrogen receptors (Roysommuti et al. 2011). The present data indicate that in adult female rats that were prenatally taurine supplemented, estrogen (but not the renin-angiotensin system) contributes to the ability of high sugar intake to depress baroreflex renal nerve control but not baroreflex control of heart rate. In contrast, the renin-angiotensin system (but not estrogen) plays a more important on baroreflex impairments in

heart rate control in TSW when compared to control rats. This phenomenon disappears after a high sugar diet. In addition, these changes may not relate to autonomic nervous system dysregulation.

The effect of estrogen on baroreceptor function is complex. Direct infusion of phytoestrogen into isolated carotid sinus depresses the sinus nerve activity via inhibition of protein tyrosine kinase and decreased  $\text{Ca}^{2+}$  influx to stretch activated channels (Ma et al. 2005). In contrast, in rats brain estrogen enhances baroreflex sensitivity induced by phenylephrine via aortic nerve, and this baroreflex change can occur without any effect on arterial pressure (Mohamed et al. 1999). In addition, central estrogen enhances baroreceptor mediated increases in adrenal hormone secretion induced by hypotension in sheep (Purinton and Wood 2002). However, many brain areas respond differently to estrogen injection. Estrogen injection into the insular cortex increases renal sympathetic (but not vagal) nerve activity, while injection into the central nucleus of amygdala decreases sympathetic nerve activity (Saleh TM 2003). Although estrogen can modify baroreflex sensitivity and autonomic tone, its effect on arterial pressure is minimal (Saleh et al. 2005; Saleh and Connell 2003). This may explain why in the present study inhibition of estrogen receptors alters autonomic nerve activity and baroreflex sensitivity without any effect on arterial pressure and heart rate.

Perinatal taurine exposure influences brain growth and development and programs adult function and abnormalities (Aerts and Van Assche 2002; Huxtable 1992; Sturman 1993). It is likely that some brain areas in perinatal taurine supplemented rats respond to estrogen differently from control taurine treated animals, in such a manner that their estrogen-dependent baroreflex functions are depressed. This notation is confirmed by baroreflex sensitivity data in TSW+Tam (about 50% increases) compared to CW+Tam (about 30% increases) rats. This effect disappears after high sugar intake after weaning in TSG but not CG groups, suggesting that perinatal taurine supplementation changes the estrogen-mediated baroreflex interaction, making it more sensitive to some mechanisms related to glucose-insulin regulation.

The renin-angiotensin system underlies sugar-induced hypertension in many animal models (Erlich and Rosenthal 1995; Freitas et al. 2007; Rosenthal et al. 1995). High sugar intake (similar to that in the present study) induces renal dysregulation prior to its effects on hypertension and diabetes mellitus, and these changes are related to renin-angiotensin system overactivity (Roysommuti et al. 2002). The role of the renin-angiotensin system on autonomic nerve function, arterial pressure and heart rate is completely preserved in perinatal taurine supplemented rats, even with high sugar intake after weaning. Its inhibition decreased baroreflex control of heart rate in TSW but not in CW and CG, but it decreased baroreflex control of renal nerve in CW and CG but not in TSW. In addition, this effect disappears when these animals are treated with a high sugar diet after weaning. The present data suggest that perinatal taurine supplementation alters the interplay of renin-angiotensin system on baroreflex function but not autonomic tone. Angiotensin II generally affects baroreflex sensitivity by acting via the brain, especially the medulla. This study thus confirms that perinatal taurine supplementation programs baroreflex function by altering central nervous system.

## 1.5 CONCLUSION

In summary, perinatal taurine exposure programs adult health and disease. Many lines of evidence report that perinatal taurine depletion induces disorders in adult offspring, especially hypertension, renal dysfunction and metabolic disorders. In contrast, taurine supplementation, either during perinatal life or in the elderly has been accepted as beneficial for health. The present study suggests that although perinatal taurine excess alone may have minimal effect on cardiovascular control, high sugar intake after weaning can modify the baroreflex function mediated by estrogen and renin-angiotensin system. In the female, the estrogen rather than the renin-angiotensin system plays a protective role on the adverse effects of a high sugar diet.

## ACKNOWLEDGEMENTS

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## Abbreviations

<b>CW</b>	control with water intake alone
<b>CW+Cap</b>	CW plus captopril treatment
<b>CW+Tam</b>	CW plus tamoxifen treatment
<b>CG</b>	control with high sugar intake
<b>CG+Cap</b>	CG plus captopril treatment
<b>CG+Tam</b>	CG plus tamoxifen treatment
<b>TSW</b>	perinatal taurine supplementation with water intake alone
<b>TSW+Cap</b>	TSW plus captopril treatment
<b>TSW+Tam</b>	TSW plus tamoxifen treatment
<b>TSG</b>	perinatal taurine supplementation with high sugar intake
<b>TSG+Cap</b>	TSG plus captopril treatment
<b>TSG+Tam</b>	TSG plus tamoxifen treatment
<b>SD</b>	Sprague-Dawley
<b>HF</b>	high frequency
<b>LF</b>	low frequency

## 1.7 REFERENCES

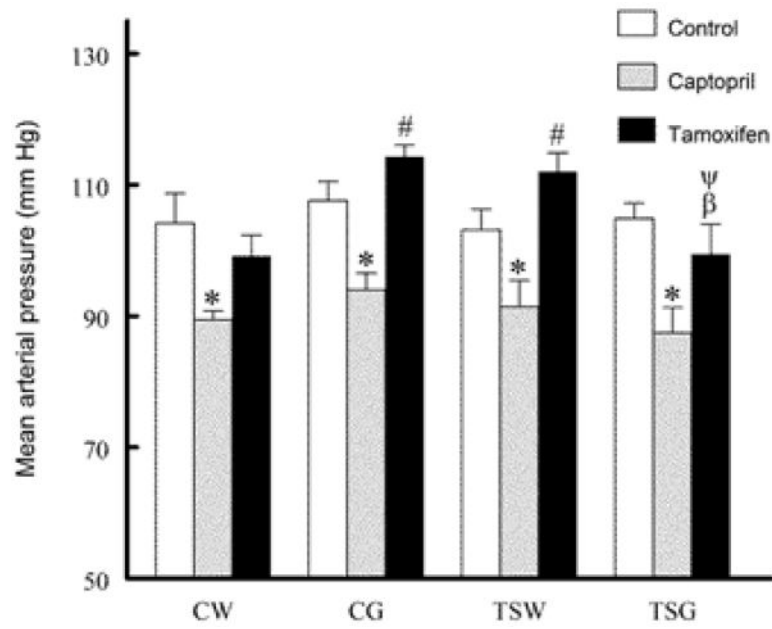
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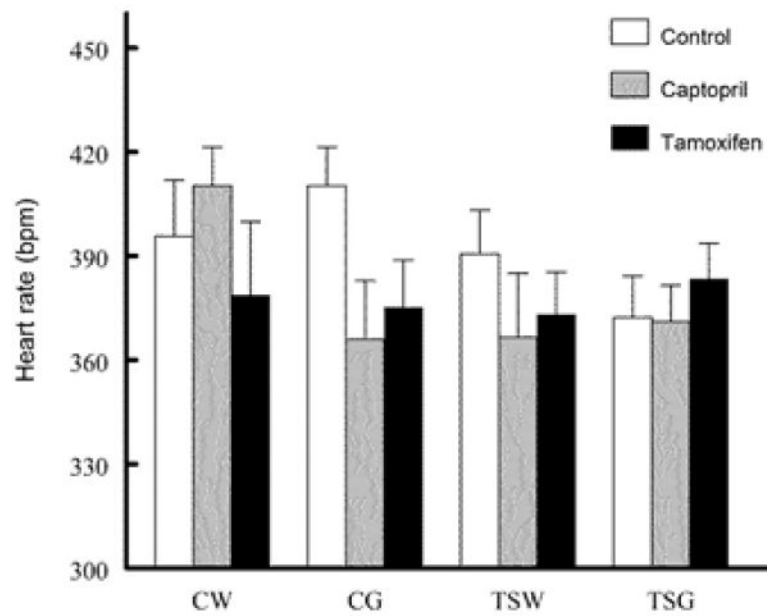
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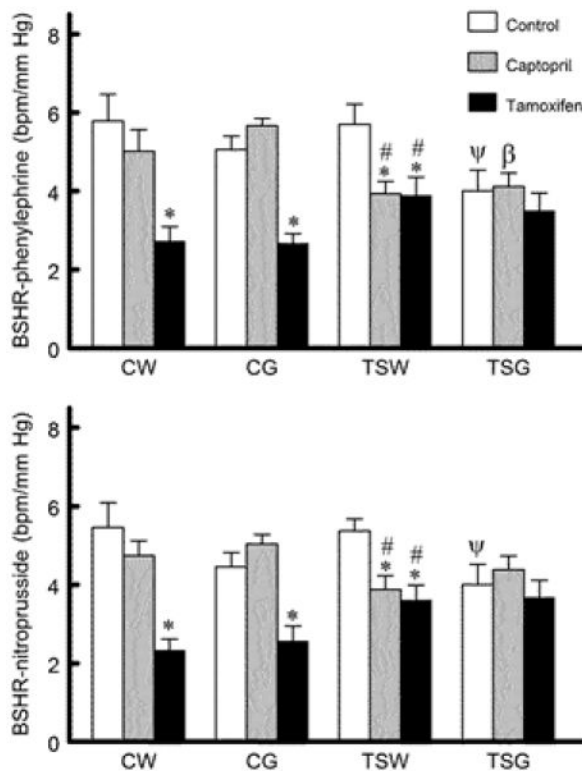
**Fig. 1.**

Comparison of mean arterial pressure among groups (CW, control with water intake alone; CW+Cap, CW plus captopril treatment; CW+Tam, CW plus tamoxifen treatment; CG, control with high sugar intake; CG+Cap, CG plus captopril treatment; CG+Tam, CG plus tamoxifen treatment; TSW, perinatal taurine supplementation with water intake alone; TSW+Cap, TSW plus captopril treatment; TSW+Tam, TSW plus tamoxifen treatment; TSG, perinatal taurine supplementation with high sugar intake; TSG+Cap, TSG plus captopril treatment; TSG+Tam, TSG plus tamoxifen treatment; \*  $p < 0.05$  vs. control; #  $p < 0.05$  vs. CW of same treatment;  $\beta$   $p < 0.05$  vs. CG of same treatment,  $\Psi$   $p < 0.05$  vs. TSW of same treatment).

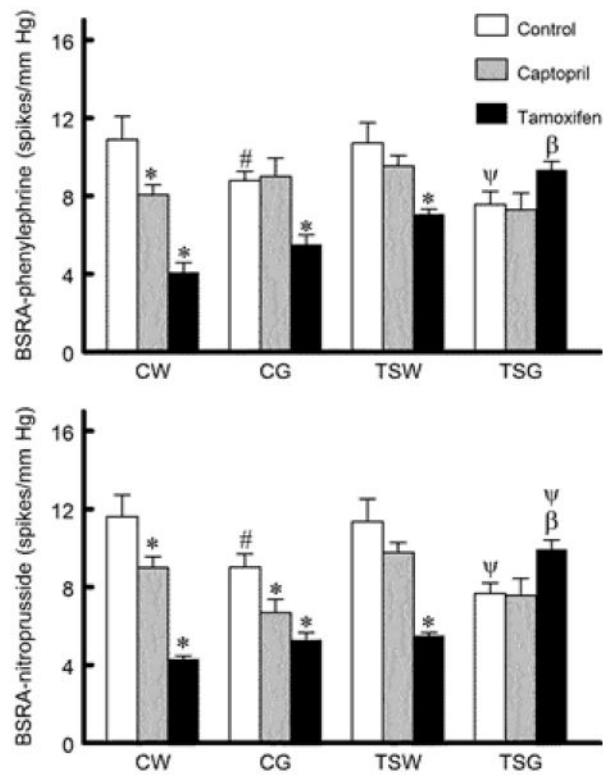


**Fig. 2.**

Comparison of heart rate among groups (CW, control with water intake alone; CW+Cap, CW plus captopril treatment; CW+Tam, CW plus tamoxifen treatment; CG, control with high sugar intake; CG+Cap, CG plus captopril treatment; CG+Tam, CG plus tamoxifen treatment; TSW, perinatal taurine supplementation with water intake alone; TSW+Cap, TSW plus captopril treatment; TSW+Tam, TSW plus tamoxifen treatment; TSG, perinatal taurine supplementation with high sugar intake; TSG+Cap, TSG plus captopril treatment; TSG+Tam, TSG plus tamoxifen treatment; no significant difference was observed among groups).

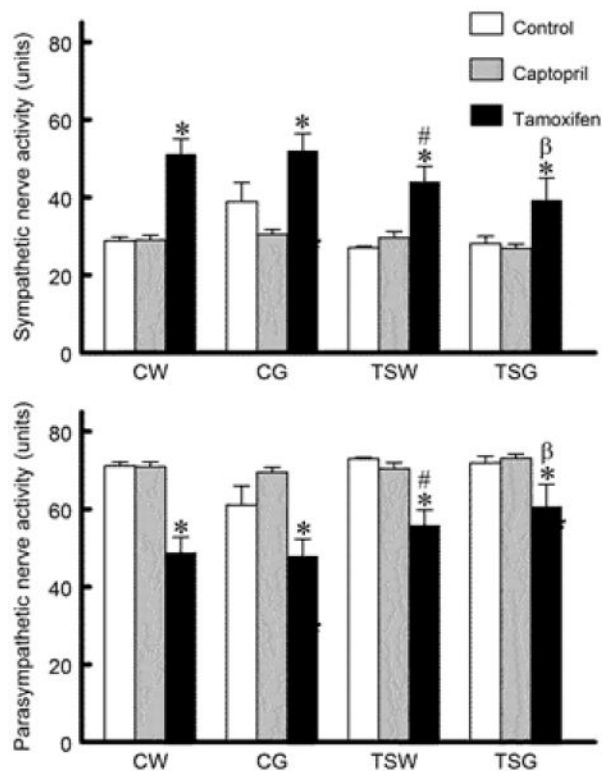


**Fig. 3.** Comparison of baroreflex sensitivity control of heart rate (BSHR) among groups (BSHR-phenylephrine, BSHR tested by phenylephrine infusion; BSHR-nitroprusside, BSHR tested by sodium nitroprusside infusion; CW, control with water intake alone; CW+Cap, CW plus captopril treatment; CW+Tam, CW plus tamoxifen treatment; CG, control with high sugar intake; CG+Cap, CG plus captopril treatment; CG+Tam, CG plus tamoxifen treatment; TSW, perinatal taurine supplementation with water intake alone; TSW+Cap, TSW plus captopril treatment; TSW+Tam, TSW plus tamoxifen treatment; TSG, perinatal taurine supplementation with high sugar intake; TSG+Cap, TSG plus captopril treatment; TSG+Tam, TSG plus tamoxifen treatment; \* p < 0.05 vs. control; # p < 0.05 vs. CW of same treatment; <sup>β</sup> p < 0.05 vs. CG of same treatment, <sup>Ψ</sup> p < 0.05 vs. TSW of same treatment).



**Fig. 4.**

Comparison of baroreflex sensitivity control of renal nerve activity (BSRA) among groups (BSRA-phenylephrine, BSRA tested by phenylephrine infusion; BSRA-nitroprusside, BSRA tested by sodium nitroprusside infusion; CW, control with water intake alone; CW +Cap, CW plus captopril treatment; CW+Tam, CW plus tamoxifen treatment; CG, control with high sugar intake; CG+Cap, CG plus captopril treatment; CG+Tam, CG plus tamoxifen treatment; TSW, perinatal taurine supplementation with water intake alone; TSW+Cap, TSW plus captopril treatment; TSW+Tam, TSW plus tamoxifen treatment; TSG, perinatal taurine supplementation with high sugar intake; TSG+Cap, TSG plus captopril treatment; TSG+Tam, TSG plus tamoxifen treatment; \*  $p < 0.05$  vs. control; #  $p < 0.05$  vs. CW of same treatment;  $\beta$   $p < 0.05$  vs. CG of same treatment,  $\Psi$   $p < 0.05$  vs. TSW of same treatment).



**Fig. 5.** Comparison of sympathetic and parasympathetic nerve activity among groups (CW, control with water intake alone; CW+Cap, CW plus captopril treatment; CW+Tam, CW plus tamoxifen treatment; CG, control with high sugar intake; CG+Cap, CG plus captopril treatment; CG+Tam, CG plus tamoxifen treatment; TSW, perinatal taurine supplementation with water intake alone; TSW+Cap, TSW plus captopril treatment; TSW+Tam, TSW plus tamoxifen treatment; TSG, perinatal taurine supplementation with high sugar intake; TSG+Cap, TSG plus captopril treatment; TSG+Tam, TSG plus tamoxifen treatment; \*  $p < 0.05$  vs. control; #  $p < 0.05$  vs. CW of same treatment; <sup>β</sup>  $p < 0.05$  vs. CG of same treatment).