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Sex dependent effects of perinatal taurine exposure on the arterial pressure control in adult offspring

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Abstract

The present study tests the sex-dependent effect of perinatal taurine exposure on arterial pressure control in adults. Female Sprague-Dawley rats were fed normal rat chow with 3% beta-alanine (taurine depletion, TD), 3% taurine (taurine supplementation, TS) or water alone (C) from conception to weaning. Their male and female offspring were then fed normal rat chow and tap water with 5% glucose (C with glucose, CG; TD with glucose, TDG; TS with glucose, TSG) or water alone (CW, TDW or TSW). At 7–8 weeks of age, they were studied in a conscious condition. Body weights were lower in male and female TDG and male TDW rats. Kidney to body weights increased in female TSW but not TSG. Plasma sodium and potassium were not significantly different among males. In the females, plasma sodium levels were lower in all glucose treated groups while plasma potassium levels were lower only in TDG. Hematocrit, fasting blood glucose, and glucose tolerance were not significantly different among sexes. Mean arterial pressures increased in male TDG, TSW, and TSG while in the females, mean arterial pressures increased in TDW, TDG, and TSG. Heart rates were not significantly different among sexes. The present data indicate that perinatal exposure alters arterial pressure control of adult rats and this effect is gender specific.

Introduction

In both human and animal models, fetal environment in utero has significant impact on adult health and disease (Harding 2001; Langley-Evans et al. 2003). Undernutrition or imbalanced food consumption (for instance low protein-high carbohydrate diets) in the prenatal period results in low birth weight and subsequently induces several cardiovascular disorders in adults, including coronary vascular diseases, hypertension, insulin resistance, diabetes mellitus, and ultimately renal damage (Barker et al. 2002; Forrester 2004). Hypertension and diabetes mellitus also appear to be related to obesity developed in the later life (Mendez et al. 2004). Epidemiologic studies indicate that African-American women have a higher prevalence of low birth weight and adult obesity (Ventura et al. 2002). Although the mechanism(s) of these effects is still unclear, abnormalities of the renin-angiotensin and sympathetic nervous systems have

been characterized in humans and animal models (Eriksson et al. 2007; Lackland et al. 2002). The perinatal programming of adult function and diseases has been recognized for a decade (Barker 2007). Low birth weight has been associated with many changes, including taurine deficiency in the perinatal period and later life (Aerts and Van Assche 2002). In adult animals, taurine supplementation decreases hypertension, likely by increased renal Na excretion, inhibition of the renin-angiotensin system, and decreased sympathetic nerve activity (Militante and Lombardini 2002).

Taurine, a 2-aminoethane sulfonic acid, is a phylogenetically ancient compound that is present in high concentration in many organs including brain, heart, kidneys, and reproductive organs. Its content is highest in these organs during fetal life and gradually decreases after birth (Aerts and Van Assche 2002). During lactation it appears to be an essential amino acid, since taurine synthesis is minimal in the organism with maternal milk as the main source. Several lines of evidence indicate that perinatal taurine status programs cells for adult function, especially organs related to the cardiovascular system. Perinatal taurine supplementation prevents hypertension in spontaneously hypertensive rats (SHR), partly by its antioxidant activity (Racasan et al. 2004). Our previous experiments indicated that either taurine depletion or supplementation in early life alters renal function (Roysommuti et al. 2004) and autonomic nervous control of arterial pressure (Roysommuti et al. 2007; Suvanich et al. 2006) in adult, male rats. Perinatal taurine depletion increased arterial pressure but not heart rate in adult, female offspring. Their renal hemodynamics and excretory function were also modified by the perinatal taurine exposure (Lerdweerapol et al. 2007). In addition, the autonomic nervous system and renal function responses to high sugar intake in young adult animals appear to be altered by perinatal taurine exposure. The protection of arterial pressure in females may be due to the putative antihypertensive effects of estrogen in female animal models, including spontaneously hypertensive and salt-induced hypertension in ovariectomized rats (Clark et al. 2004; Peng et al. 2003a). This study compares the long-term effect of perinatal taurine exposure on arterial pressure control in male and female adult offspring fed with a high sugar diet.

Materials and Methods

Sprague-Dawley (SD) rats were bred from the animal unit of Faculty of Medicine, Khon Kaen University and maintained at constant humidity (60 ± 5%), temperature (24 ± 1 °C), and light cycle (0600–1800 h). Female SD rats were fed with normal rat chow and free access to tap water alone (control, C), tap water with 3% beta-alanine (taurine depletion, TD) or tap water with 3% taurine (taurine supplementation, TS) from conception until weaning. Then, their male and 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, and CW) throughout the experiment.

At 7–8 weeks of age, under thiopental anesthesia, all male and female offspring were implanted with femoral arterial and venous catheters. Two or three days later and after an overnight fasting, arterial blood samples were obtained from conscious animals for Na, K, hematocrit, and fasting blood sugar determinations. Then, glucose tolerance tests were started by intravenous injection of glucose (2 g/kg in saline) and blood glucose levels were subsequently measured at 30, 60, and 120 minutes, respectively. Twenty-four hours later, non-fasting blood samples were collected and then arterial pressure pulses were continuously recorded (Bio-pac system, CA) in a conscious condition. At the end of experiment, all animals were sacrificed and kidney and heart weights were collected.

Experimental protocols and animal care were approved by the university animal committee. Plasma sodium and potassium concentrations were determined by a flame photometry, hematocrit by a standard technique, fresh blood sugar by a glucometer and glucostrips ((Accu-

chek®, Germany), and mean arterial pressure and heart rate by Acknowledge software version 3.8.1 (Biopac system, CA)

All data were expressed as mean ± SEM. Statistical comparisons among groups ($p < 0.05$) were done by using one-way ANOVA and Dun-can'Multi-Range.

Results

Perinatal taurine depletion caused significantly growth retardation in male offspring which could be partially recovered by a high sugar supplementation after weaning (Table 1). In contrast, growth in female rats was not retarded by that perinatal taurine depletion alone but together with a high sugar diet after weaning, it did retard growth. Perinatal taurine supplementation had no effect on body and heart weight but slightly increased kidney weight when compared to CG and CW female rats. High sugar treatment alone had no effect on growth. While plasma Na levels were not significantly different among male groups, they significantly decreased in all glucose-treated female offspring (Table 2). Both male and female offspring displayed similar plasma potassium concentrations, hematocrit, and fasting blood sugar among groups. In males, non-fasting blood sugar levels were slightly increased in CG rats, while they were significantly increased in all glucose-treated female offspring when compared to their corresponding controls (CW, TDW, and TSW). Both and female offspring displayed similar glucose tolerance (Fig. 1).

Perinatal taurine depletion alone increased mean arterial pressures in female but not male TDW while taurine supplementation alone increased them in male but not female TSW (Fig. 2). These perinatal taurine effects were not altered by the high sugar diet. The high sugar diet significantly increased mean arterial pressure in perinatal taurine depleted males (CW, 101.2 ± 2.5 mm Hg; CG, 96.0 ± 3.0 mm Hg; TDW, 97.6 ± 2.7 mm Hg; TDG, 109.6 ± 2.1 mm Hg; $P < 0.05$) and perinatal taurine-supplemented female (CW, 112.8 ± 1.8 mm Hg; CG, 117.16 ± 3.39 mm Hg; TSW, 118.0 ± 2.5 mm Hg; TSG, 121.2 ± 3.0 mm Hg; $P < 0.05$) when compared to CW or CG rats (Figure 2). Heart rates were not significantly different among male or female rats (Figure 3). Although the females displayed lower body weight than the males (Table 1), their mean arterial pressures were significantly higher in all corresponding groups (Fig. 2).

Discussion

Perinatal treatment can significantly alter adult organ function and health, including cardiovascular function. Female rats treated with testosterone during the first 4 days of life develop a male pattern of gonadotropin secretion with abnormal female sexual behavior in the mature life (BARRACLOUGH 1961; Clark et al. 2004; Peng et al. 2003a). Handling or various stressors in the neonates results in permanent changes in hypothalamic structure and abnormal stress responses in the adult period (Cella et al. 1990). Perinatal administration of angiotensin converting enzyme inhibitors attenuates hypertension in the adult SHR but does not prevent salt-induced hypertension (Wyss et al. 1994). Perinatal taurine treatment also attenuates hypertension in the adult SHR, likely via its antioxidant properties (Racasan et al. 2004). Our previous experiments indicate that pre- or postnatal (lactation) taurine supplementation increased mean arterial pressure in adult male offspring (Roysommuti et al. 2004). The present data further demonstrates that perinatal taurine supplementation can increase the mean arterial pressure in adult male rats but not female rats. Further, perinatal taurine depletion can increase arterial pressure in adult female but not male rats. This study thus demonstrates gender specific responses to perinatal taurine exposure.

It is well-known that sugar consumption is a significant risk factor for the development of hypertension. Sugar-induced hypertension is associated with hyperinsulinemia, insulin

resistance, renin-angiotensin system overactivity, sympathetic nervous system overactivity, and renal dysfunction (Johnson et al. 2007). However, previous experiments indicate that glucose supplementation induces renal dysfunction before insulin resistance and hypertension, and that these effects can be abolished by treatment with an angiotensin converting enzyme inhibitor (captopril) (Roysommuti et al. 2002). Taurine inhibits the renin-angiotensin system (Azuma et al. 2000; Schaffer et al. 2000) and prevents fructose-induced hypertension in rats (Harada et al. 2004). Moreover, in many forms of hypertension taurine supplementation in young or adult life reduces arterial pressure (Militante and Lombardini 2002), improves renal function and inhibits the sympathetic nervous system. The present study reports the interaction between perinatal taurine exposure and the subsequent effect of high sugar intake on arterial pressure in both sexes. Perinatal taurine depletion induces a pressor effect from high sugar consumption in male but not female rats and vice versa for perinatal taurine supplementation. Theses opposite effects may be due to gender differences in the body taurine content, sex hormones, autonomic nervous system, renin-angiotensin system or renal function at the adult life. The permanent changes and programming at the early life is hypothesized to be the primary factor.

Obesity, insulin resistance, hyperinsulinemia, and electrolyte disturbances are associated with the development of hypertension, and perinatal imbalances of nutrition have been reported to be a predisposing factor to these dysfunctions (Barker et al. 2002; Harding 2001; Langley-Evans 2006). Exposure to taurine in fetuses and neonates is primarily from diets through the placenta or maternal milk (Aerts and Van Assche 2002). Thus, taurine deficiency is observed in rat neonates of the pregnant mother that are fed low protein diets (Cherif et al. 1998). Though body taurine content can return to normal levels within 5–6 weeks after end of its supplementation or depletion (Pacioretty et al. 2001), permanent changes appear to continue into adult life, as shown by the present data. In the present study, the pressor effect of perinatal taurine with or without sugar supplementation did not relate to adult body weight, insulin resistance or Na-K imbalance. Periodic fluctuation of blood glucose level and hyperinsulinemia in all sugar-treated rats might play a role in sugar-induced hypertension in more aged rats. Also, sugar treatment with this dose has been reported to alter renal function without insulin resistance, glucose intolerance, and hypertension in male Sprague-Daley rats (Roysommuti et al. 2002).

Although taurine supplementation may improve or prevent hypertension in humans and animal models (Militante and Lombardini 2002), its mechanisms of action are complicated. It prevents fructose-induced hypertension but exacerbates hyperinsulinemia and hypertriglyceridemia in rats (Anuradha and Balakrishnan 1999; Harada et al. 2004). This anti-hypertensive action is likely mediated by kinins and renal fluid excretion (Gentile et al. 1994; Nandhini et al. 2004; Nandhini and Anuradha 2004). In contrast, hypertension, insulin resistance, and renal damage in adult offspring that are induced by perinatal imbalance of nutrition may be prevented or improved by taurine treatment in the early or later life (Hoet et al. 2000; Militante and Lombardini 2002). In addition, taurine may inhibit the sympathetic activity and the renin-angiotensin system in many forms of hypertension. Thus, the pressor effect of perinatal taurine exposure and its interaction with high sugar consumption at later life need further clarified.

Gender differences in pathogeneses of cardiovascular diseases have been shown in many experimental models and humans (D'Amore and Mora 2006; Meyer et al. 2006). Estrogen rather than testosterone plays a protective action for these diseases. Estrogen protects against increases in arterial pressure by acting on blood vessels and on cardiovascular centers in the brain (Ashraf and Vongpatanasin 2006; Maturana et al. 2007; Peng et al. 2003b; Wyss and Carlson 2003). Recently, it was reported that estrogen treatment improves or prevents hypertension in the female growth-restricted offspring (Ojeda et al. 2007). Taurine depletion is also observed in these animal models (Aerts and Van Assche 2002). In addition, prenatal

testosterone treatment could induce cardiovascular diseases in adult offspring, similar to prenatal malnutrition (Dumesic et al. 2007; King et al. 2007). Thus, perinatal taurine exposure likely alters the sex hormone status in the early life and programs the subsequent organ function and adult diseases.

In summary, the present study indicates a gender disparity in the long-term effects of perinatal taurine depletion and supplementation on arterial pressure control. An imbalance of taurine exposure in early life will thus predispose or program the pressor effect of high sugar consumption in the later life.

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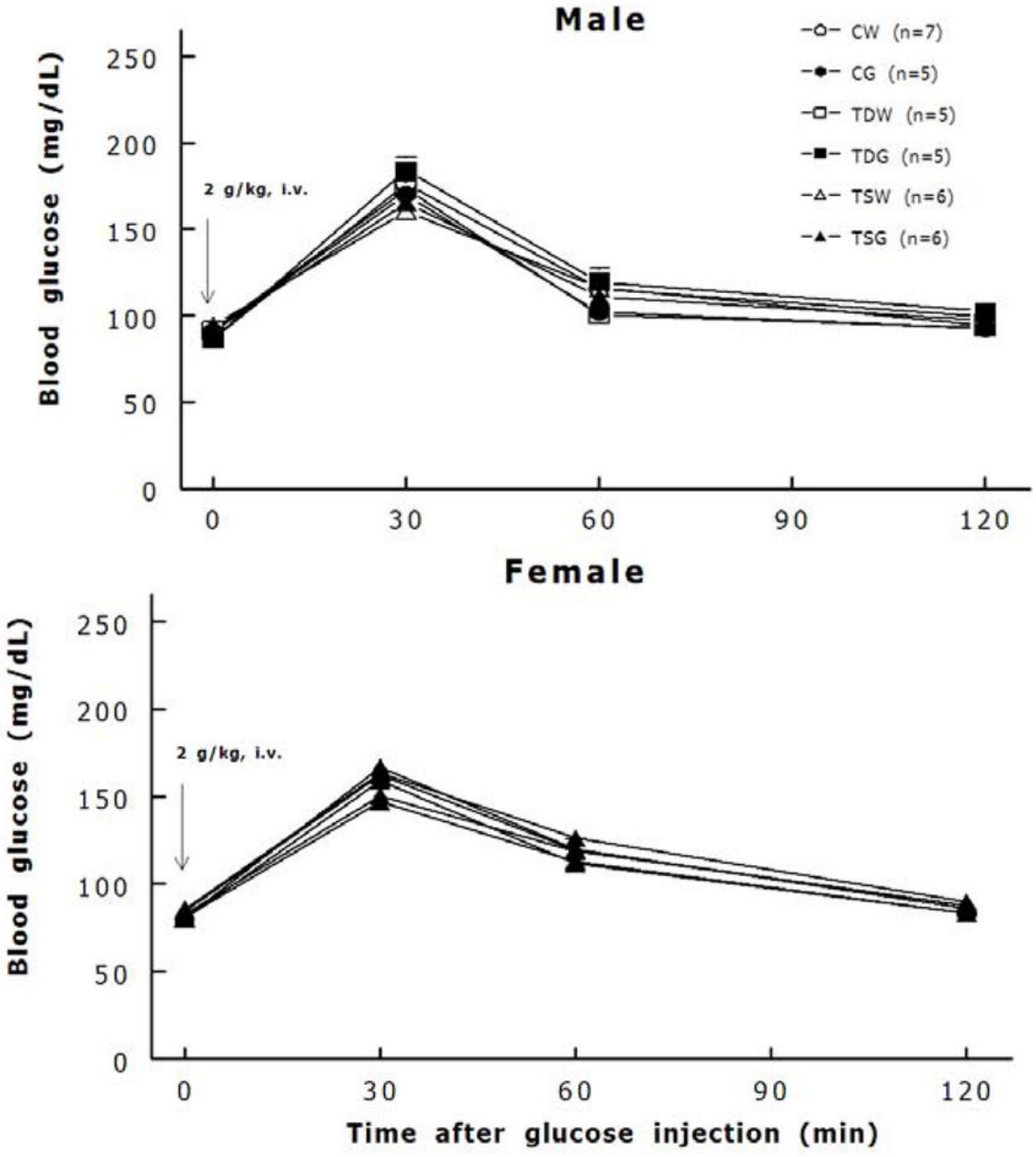

Fig. 1.
Both male and female offspring displayed well glucose tolerance.

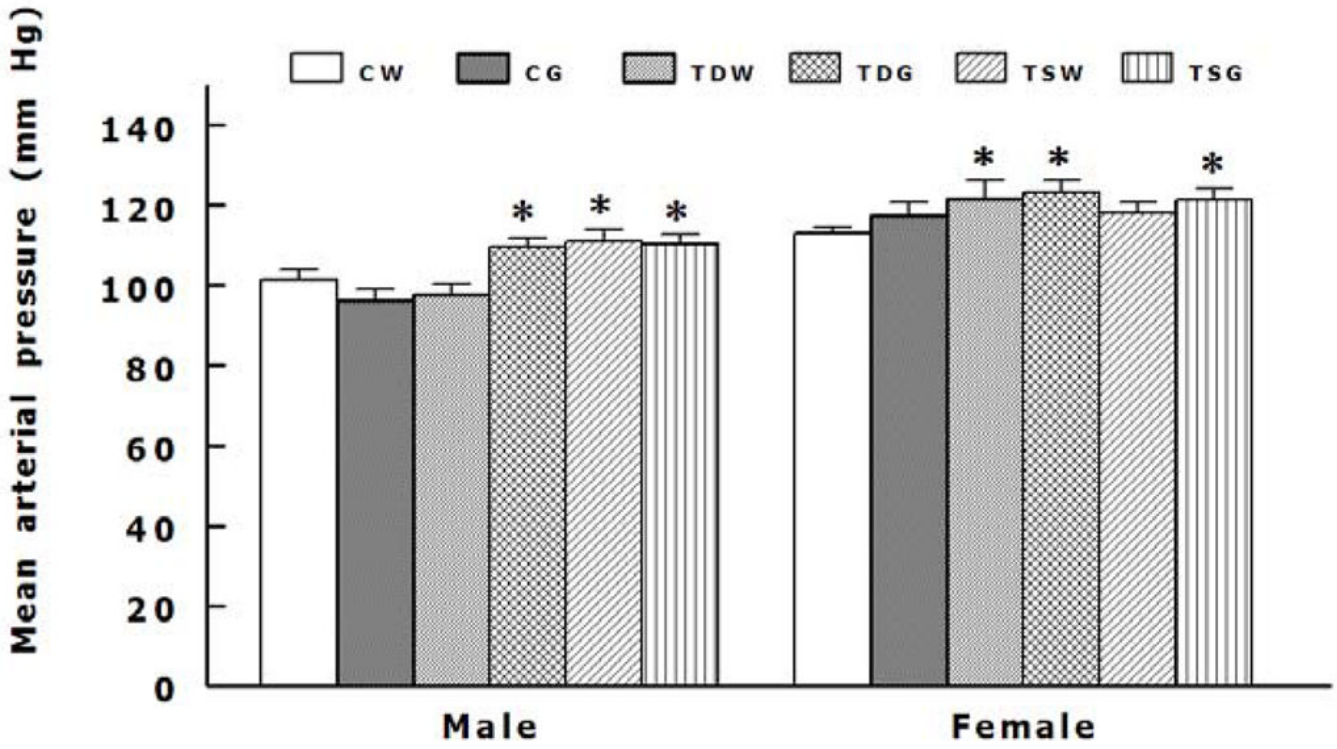

Fig. 2.

Mean arterial pressures were significantly higher in male TDG, male TSW, male TSG, female TDW, female TDG, and female TSG ($P < 0.05$ compared to CW). See text for abbreviations.

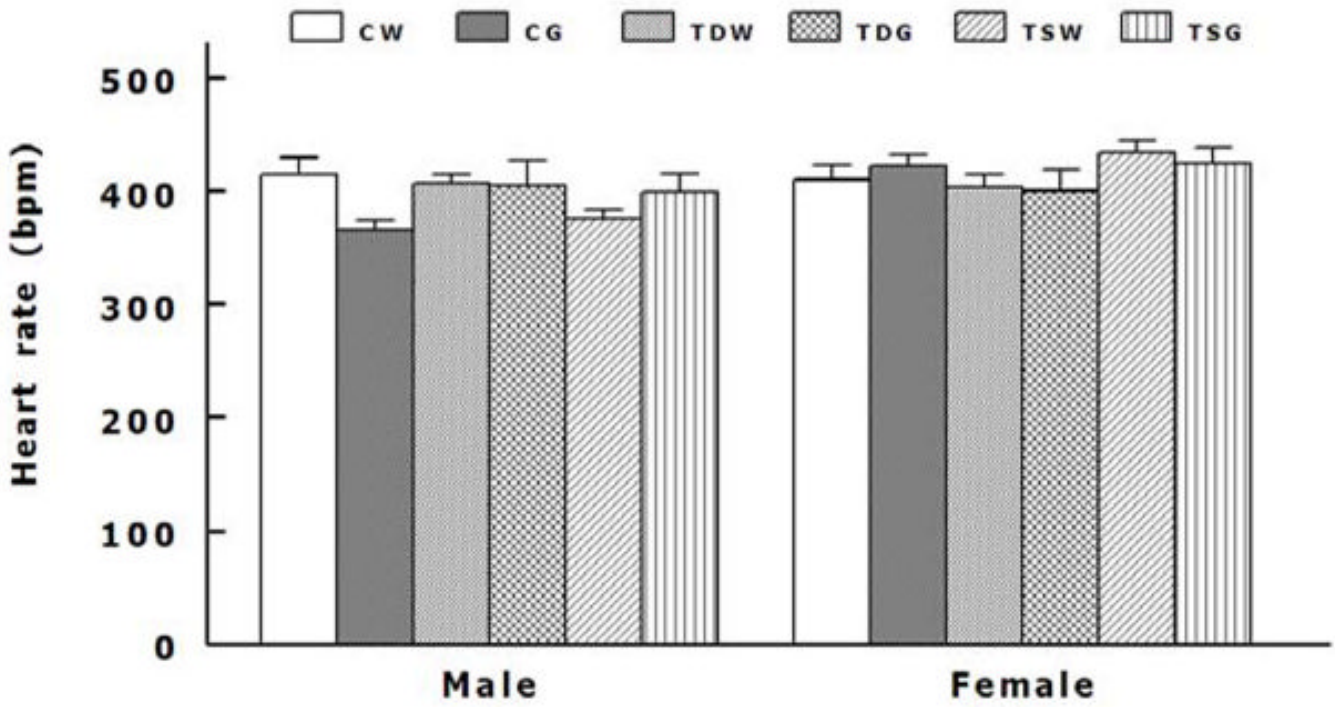

Fig. 3.
Heart rates were not significantly different among male or female offspring. See text for abbreviations.

Table 1

Body (BW), kidney (KW), and heart (HW) weights in male (M) and female (F) offspring

Treatment		BW (g)	KW (g)	HW (g)	KW/BW (%)	HW/BW (%)
CW	M (n=6)	233±4	1.12±0.02	0.90±0.02	0.48±0.01	0.39±0.01
	F (n=7)	194±5	1.66±0.04	0.6±0.02	0.85±0.03	0.36±0.01
CG	M (n=5)	234±7	1.13±0.03	0.91±0.02	0.48±0.02	0.39±0.02
	F (n=8)	196±4	1.61±0.04	0.74±0.02	0.82±0.01	0.37±0.00
TDW	M (n=5)	210±5*	1.07±0.04	0.85±0.02	0.51±0.03	0.41±0.01
	F (n=6)	196±2	1.72±0.08	0.72±0.04	0.88±0.04	0.37±0.02
TDG	M (n=5)	214±6	1.02±0.06	0.89±0.03	0.48±0.04	0.42±0.02
	F(n=10)	179±5$^{*,\alpha}$	1.59±0.02	0.67±0.03	0.89±0.02	0.37±0.01
TSW	M (n=6)	238±6	1.08±0.04	0.90±0.02	0.45±0.01	0.38±0.01
	F (n=6)	197±4	1.88±0.0$^{*,\alpha}$	0.75±0.01	0.95±0.02$^{*,\alpha}$	0.38±0.01
TSG	M (n=6)	228±7	1.11±0.05	0.93±0.02	0.49±0.02	0.41±0.01
	F (n=8)	191±5	1.67±0.04	0.73±0.02	0.88±0.04	0.38±0.01

Data were mean±SEM.

$^{*,\alpha}$denoted significant difference when compared to CW or CG, respectively. See text for abbreviations.

Table 2

Plasma sodium, plasma potassium, hematocrit, non-fasting blood sugar (NFBS), and fasting blood sugar (FBS) in male (M) and female (F) offspring

Treatment		Na (mEq/L)	K (mEq/L)	Hematocrit (%)	NFBS (mg/dl)	FBS (mg/dl)
CW	M(n=6)	139.6±1.2	3.75±0.19	42.2±0.83	83.5±2.91	80.3±3.73
	F (n=7)	132.5±3.3	4.44±2.23	41.9±1.17	115.0±5.17	86.4±3.60
CG	M(n=5)	138.6±1.5	3.82±0.04	42.2±1.02	105.6±5.28*	80.0±1.65
	F (n=8)	118.3±3.1*	4.51±0.33	40.8±0.77	129.4±3.02*	91.3±2.74
TDW	M(n=5)	139.4±0.5	3.86±0.02	41.4±0.60	89.8±5.59	81.2±4.13
	F(n=6)	122.7±2.4	4.49±0.08	40.5±0.82	125.7±2.86	91.2±2.81
TDG	M(n=5)	134.6±2.1	3.74±0.18	42.2±0.80	107.0±4.94*	84.6±3.37
	F(n=10)	117.3±2.4*	3.45±0.18	40.5±0.93*,α	120.4±5.35	86.6±2.83
TSW	M(n=6)	139.0±1.3	3.88±0.05	42.8±0.65	88.0±5.95	82.8±3.13
	F (n=6)	124.0±2.4	3.97±0.17	39.2±1.09	126.7±3.56	94.0±3.44
TSG	M(n=6)	134.8±1.8	3.80±0.15	41.2±0.79	102.5±4.40*	85.7±2.20
	F (n=8)	114.3±6.0*	4.06±0.12	41.3±1.10	121.5±3.92	90.3±1.45

Data were mean±SEM.

*,α denoted significant difference when compared to CW or CG, respectively. See text for abbreviations.