Perinatal Taurine Depletion Alters the Renal Excretory Effect of the Renin-Angiotensin System in Adult Female Rats

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Abbreviations

$AT_{1,1b,2}$ receptor	Angiotensin II receptor subtype 1, 1b or 2, respectively
ACEI	Angiotensin converting enzyme inhibitor
C	Control
Cap	Captopril
CG	Control plus high sugar intake
CW	Control without high sugar intake
ERBF	Effective renal blood flow
ERVR	Effective renal vascular resistance
$FE_{H2O, K, Na}$	Fractional water, potassium or sodium excretion, respectively
GFR	Glomerular filtration rate
HW	Heart weight
i.p.	Intraperitoneal
IUGR	Intrauterine growth restriction
KW	Kidney weight
MAP	Mean arterial pressure

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PAH	*p*-Aminohippuric acid
RAS	Renin-angiotensin system
TD	Perinatal taurine depletion
TDG	TD plus high sugar intake
TDW	TD without high sugar intake

1 Introduction

In humans, nephrogenesis starts around 5 weeks of gestation and the main renal structure is completed before birth (Dotsch et al.2009; Kett and Denton 2011). Renal growth and development include formation of blood vessels, glomeruli, tubules, hormonal networks, and innervation. In most animals particularly rodents, nephrogenesis starts prenatally and is complete before weaning; however, maturation of nephrons continues until shortly after weaning in rodents but lasts for several months after birth in humans. Thus, perinatal nutritional and hormonal imbalances would be expected to affect adult renal function and health (Roysommuti and Wyss 2014).

A clue to the role of perinatal dietary taurine and the angiotensin system in the process of renal development is suggested by studies of intrauterine growth restriction (IUGR), which decreases taurine and induces AT_{1b} receptor mRNA and protein overexpression in the adrenal gland of adult offspring, likely by epigenetic mechanisms (Bogdarina et al.2007). In contrast, IUGR reduces renin mRNA, AT_1 receptor protein in the adult kidney and increases angiotensin II levels and AT_2 receptor mRNA (Vehaskari et al.2004; Woods et al.2001). Further, IUGR decreases intrarenal renin and angiotensin II content in male but not female offspring (Woods et al.2005). This suggests that gender affects renal renin-angiotensin system (RAS) programming.

In adults following a perinatal renal insult, the kidney and related control mechanisms tend to compensate, in part depending on exposure to several environmental factors, e.g., nutritional factors, neuroendocrine status, and individual behavior (Baum 2010; Kett and Denton 2011). For example, perinatal RAS inhibition produces offspring that are sensitive to development of hypertension when placed on a high (but not basal) salt diet (Fang et al.1999). Lifetime inhibition of the RAS from conception onward prevents renal dysfunction and damage in adult SHR (Roysommuti et al.1999), but fails to prevent hypertensive responses to a high salt diet or the adverse consequences thereof (Wyss et al.1994).

Epidemiological studies suggest a negative relationship between the incidence of cardiovascular diseases and consumption of diets high in taurine, particularly fish (Yamori et al.2010). Adult consumption of high taurine diets decreases the rate of organ damage that normally accompanies advancing age. Especially protected in this process are brain, kidneys, and heart (Roysommuti and Wyss 2014). Further, hypertension in animal models can also be prevented or reduced by a taurine supplemented diet (Militante and Lombardini 2002), and our previous experiments

indicate that perinatal taurine deficiency impairs renal function in adult male and female rats (Roysommuti et al.2009a, 2010a) and impairs the autonomic nervous system in adult male (Roysommuti et al.2009b) but not female rats (Thaeomor et al.2010). Also, in both male and female rats, sympathetic nerve activity becomes hyperactive following treatment with a high sugar diet from weaning onward. Baroreflex sensitivity controls of heart rate and/or renal nerve activity are also blunted in these rats (Roysommuti et al.2009b; Thaeomor et al.2010). In adult female rats, these baroreflex abnormalities can be normalized by acute captopril, but not by tamoxifen, treatment (Thaeomor et al.2010), suggesting that RAS overactivity underlies these baroreflex abnormalities. Whether this RAS overactivity also underlies renal impairment following perinatal taurine depletion has not been tested.

Although captopril treatment decreases mean arterial pressure in control rats, control rats receiving high sugar intake after weaning, and perinatal taurine depleted rats, the treatment does not affect mean arterial pressure in the perinatal taurine depleted rats on high sugar intake (Thaeomor et al.2010). These data suggest that the effect of RAS overactivity on the autonomic nervous system and baroreflex sensitivity *per se* is not sufficient to alter arterial pressure in these rats. In addition, high sugar intake, similar to that used in the present study, impairs renal function without affecting arterial pressure and glucose tolerance and does this via RAS overactivity in adult, male rats (Roysommuti et al.2002). These different effects indicate that systemic compared to local RAS functions are differentially regulated (Ferrario et al.2014). For example, high salt intake during pregnancy induces high numbers of angiotensin II-positive cortical cells but lowers circulating angiotensin I in adult male Wistar rats (Cabral et al.2012).

The present study tests the hypothesis that perinatal taurine depletion impairs renal excretory function by increasing RAS activity in adult female rats and that this is exacerbated by a high sugar diet.

2 Methods

2.1 Animals

Sprague-Dawley rats were bred from the Northeast Laboratory Animal Center, Khon Kaen University and maintained at constant humidity (60 ± 5 %), temperature (24 ± 1 °C), and light cycle (0600–1800 h). Female and male Sprague-Dawley rats, weighing 200–250 g were randomly assigned into a mating procedure. After conception, each female rat was separated, caged individually, and fed normal rat chow and given water alone (C) or water containing 3 % beta-alanine (taurine depletion, TD) from conception until weaning. After weaning, the rats received normal rat chow and tap water with (CG, TDG) or without 5 % glucose (CW, TDW) throughout the study. Beginning a week before renal study, half of the rats in each treatment were continuously treated with an angiotensin converting enzyme inhibitor (ACEI) in tap water (captopril, 400 mg/l) throughout the experiment (CW + Cap, CG + Cap,

TDW + Cap, TDG + Cap). All experimental procedures were approved by the Khon Kaen University Animal Care and Use Committee and were conducted in accordance with the National Institutes of Health guidelines.

2.2 Experimental Protocol

At 7–8 weeks of age, under sodium pentobarbital anesthesia (Nembutal, 50 mg/kg, i.p.), all female rats were implanted with femoral arterial, venous, and bladder catheters (Roysommuti et al. 2002). Forty-eight hours later, each rat was placed in a rat restrainer in which they could move back and forth, a condition to which all rats had been acclimated 3 h per day for 1 week prior to the renal function study. After flushing the catheters, the femoral arterial catheter was connected to a pressure transducer (BIOPAC Systems, Goleta, CA, USA) for continuous measurement of arterial pressure and heart rate throughout the experiment and the femoral venous catheter was connected to an infusion pump (Harvard Apparatus, model 975, Boston, Mass, USA). After 5–10 min of rest, an isotonic saline solution containing 0.5 % inulin and 0.5 % *p*-aminohippuric acid (PAH) was intravenously infused at a rate of 0.5 ml/min for 1 min as a priming dose, followed by a basal rate of 20 μl/min for 45 min. A urine sample was collected from the bladder catheter for the last 30 min period, and an arterial blood sample (0.2 ml) was taken at the midpoint for baseline renal function, and the blood lost was replaced with an equal volume of normal saline. After baseline data collection, the isotonic saline solution was intravenously infused at a rate of 0.5 ml/min to the final volume of 5 % body weight, followed by a basal rate 20 μl/min until end of the experiment. Urine samples were collected at 15, 30, 60, and 90 min intervals after the initiation of the saline infusion, arterial blood samples were collected (0.2 ml each) at the midpoint of each urine collection interval and replaced with equal volumes of saline. At the end of the experiments, all animals were sacrificed with an overdose of sodium pentobarbital and kidney (KW) and heart weights (HW) were measured.

2.3 Data Analyses

Mean arterial pressure and heart rate were analyzed by Acknowledge software (BIOPAC Systems). Urine volumes were measured gravitationally, urine and plasma sodium and potassium were assessed by the Srinagarind Hospital Laboratory Unit (Faculty of Medicine, Khon Kaen University), and urine and plasma inulin and PAH by colorimetry. Glomerular filtration rate (GFR) was estimated by inulin clearance, effective renal blood flow (ERBF) by PAH clearance and hematocrit, effective renal vascular resistance (ERVR) by MAP/ERBF, filtration fraction by GFR/effective renal plasma flow or PAH clearance, fractional water excretion by a urine flow to GFR ratio (FE_{H2O}, %), fractional sodium excretion by the ratio of urine sodium excretion to filtered sodium load (FE_{Na}, %), and fractional potassium excretion by the ratio of urine potassium excretion to filtered potassium load (FE_K, %).

All data are expressed as means ± SEM and were statistically analyzed using one-way ANOVA and appropriate *post hoc* Tukey's test with a significant criterion of p-value less than 0.05 (Statmost version 3.5, Dataxiom Software, USA).

3 Results

At 7–8 weeks of age, body weight (CW, 194 ± 3 g; CG, 186 ± 2 g; TDW, 197 ± 3 g; TDG, 185 ± 2 g; CW + Cap, 194 ± 3 g; CG + Cap, 193 ± 5 g; TDW + Cap, 195 ± 5 g; TDG, 192 ± 3 g), kidney weight (CW, 1.60 ± 0.02 g; CG, 1.60 ± 0.04 g; TDW, 1.57 ± 0.02 g; TDG, 1.54 ± 0.02 g; CW + Cap, 1.61 ± 0.03 g; CG + Cap, 1.57 ± 0.04 g; TDW + Cap, 1.59 ± 0.05 g; TDG + Cap, 1.62 ± 0.02 g), and heart weights (data not shown) were not significantly different among the eight groups. Mean arterial pressures at rest and after a saline load were not significantly different among CW, CG, TDW, and TDG groups, but after captopril treatment, mean arterial pressures were decreased in all groups compared to their associated captopril untreated groups (Fig. 1). TDW + Cap compared to the other groups showed a much greater reduction in arterial pressure 30 min after the saline load (about 12 mm Hg below others;

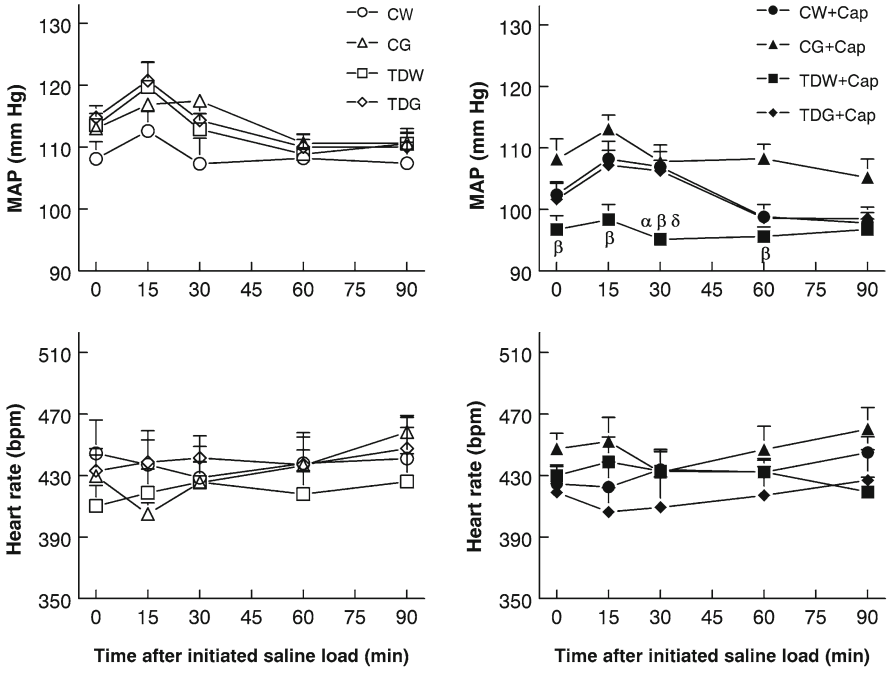

Fig. 1 Mean arterial pressure (*upper two*) and heart rate (*lower two*) at rest and in response to an acute saline load in control (CW), control plus high sugar intake (CG), perinatal taurine depletion (TDW), and perinatal taurine depletion plus high sugar intake (TDG) with (*right two*; +Cap) or without (*left two*) captopril treatment (an angiotensin converting enzyme inhibitor); α·β·δ $P < 0.05$ compared to CW or CW + Cap, CG or CG + Cap, and TDW or TDW + Cap, respectively

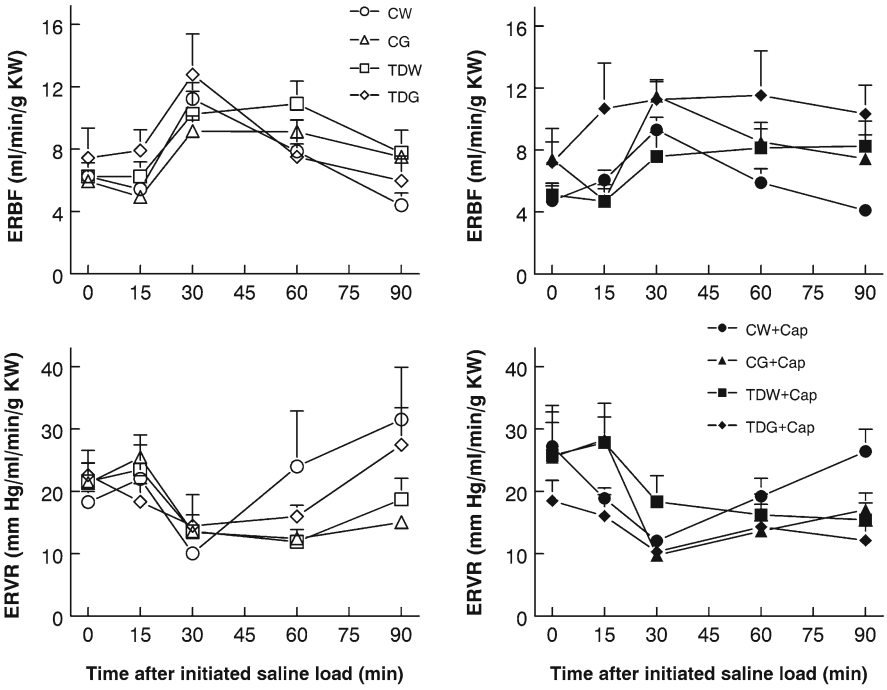

Fig. 2 Effective renal blood flow (ERBF; *upper two*) and effective renal vascular resistance (ERVR; *lower two*) at rest and in response to an acute saline load in control (CW), control plus high sugar intake (CG), perinatal taurine depletion (TDW), and perinatal taurine depletion plus high sugar intake (TDG) with (*right two*; +Cap) or without (*left two*) captopril treatment (an angiotensin converting enzyme inhibitor). No significant difference is observed among the eight groups

$p < 0.05$, Fig. 1). Heart rates before and after captopril treatments were not significantly different among the groups. Further, ERBF, ERVR (Fig. 2), GFR, filtration fraction (Fig. 3), and water (Fig. 4) and sodium excretion (Fig. 5) were not different among the groups.

Compared to control rats, fractional water excretion after a saline load (but not at rest) was significantly decreased in CG, TDW, and TDG groups. In response to captopril treatment, the control rats' fractional excretion of water decreased to the levels of the other groups, and there were no differences among the four groups of captopril treated rats at rest or during the 60 min post saline infusion (Fig. 4). At 90 min post saline load, fractional water excretion was slightly and significantly higher in the CG+Cap group compared to the CW+Cap, TDW+Cap, and TDG+Cap groups.

Compared to the CW, fractional sodium excretions after a saline load but not at rest were significantly decreased in the CG, TDW, and TDG groups. Further, except for the change in CW vs. CW+Cap rats, there were no captopril induced changes in fractional sodium excretion at any of the time points (Fig. 5).

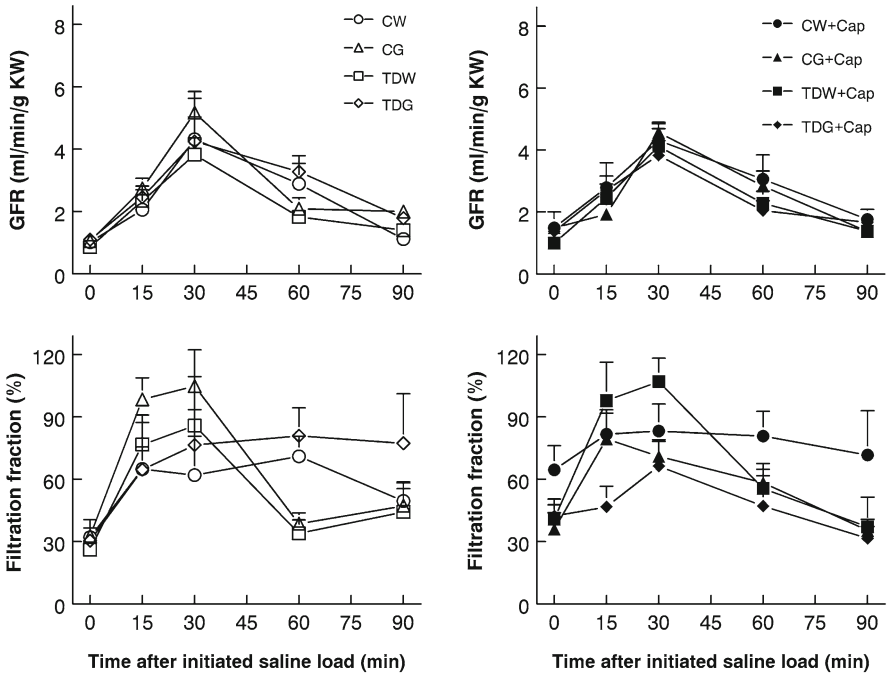

Fig. 3 Glomerular filtration rate (GFR; *upper two*) and filtration fraction (*lower two*) at rest and in response to an acute saline load in control (CW), control plus high sugar intake (CG), perinatal taurine depletion (TDW), and perinatal taurine depletion plus high sugar intake (TDG) with (*right two*; +Cap) or without (*left two*) captopril treatment (an angiotensin converting enzyme inhibitor). No significant difference is observed among the eight groups

In the controls, potassium excretion was not significantly different among the four groups throughout the study, but fractional potassium excretion was significantly different between the CG and TDW groups at 90 min post saline load (Fig.6). The captopril treatment significantly decreased potassium excretion at rest in CG + Cap compared to CW + Cap and at 60 min post saline load, in TDG + Cap compared to TDW + Cap groups, consistent with a change in fractional potassium excretion.

4 Discussion

In the prenatal and early postnatal environment, nutritional and hormonal exposures affect adult renal function and disease (Kett and Denton 2011). Previous studies report that perinatal taurine excess or deficit alters adult renal function in a sex specific manner (Roysommuti et al.2009a, 2010a). In female rats, perinatal taurine

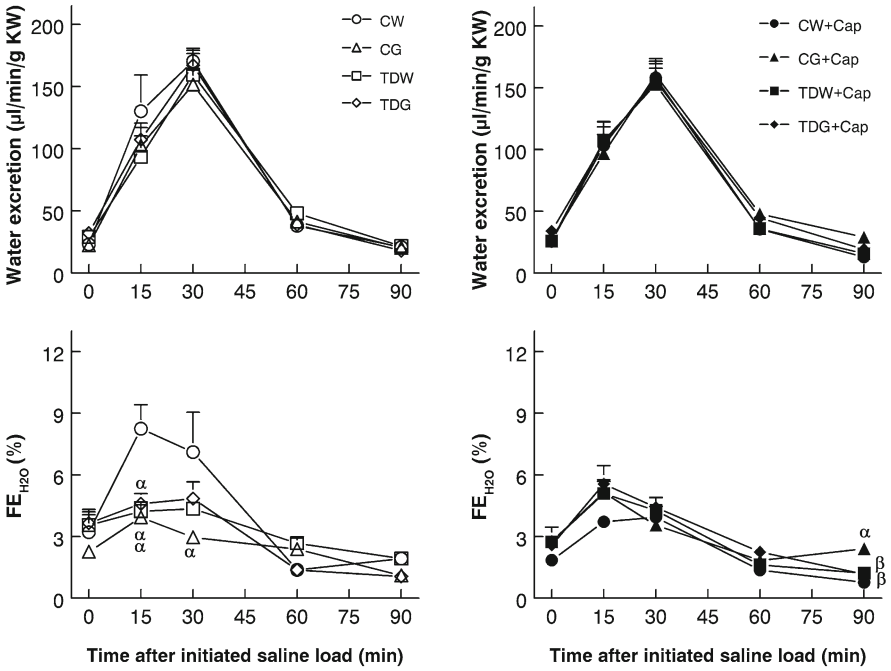

Fig. 4 Water excretion (*upper two*) and fractional water excretion (FE_{H2O}; *lower two*) at rest and in response to an acute saline load in control (CW), control plus high sugar intake (CG), perinatal taurine depletion (TDW), and perinatal taurine depletion plus high sugar intake (TDG) with (*right two*; +Cap) or without (*left two*) captopril treatment (an angiotensin converting enzyme inhibitor); $\alpha\cdot\beta P < 0.05$ compared to CW or CW + Cap and CG or CG + Cap, respectively

depletion followed by high sugar intake after weaning depresses baroreceptor reflex sensitivity (Thaeomor et al.2010) and increases sympathetic nerve activity (unpublished data) without any effect on arterial pressure (Thaeomor et al.2010). Further, inhibition of RAS by an ACEI captopril in these rats normalizes baroreflex function and autonomic nerve activity without any effect on mean arterial pressure, despite being decreased in untreated control rats. The present study indicates that the RAS does not affect renal excretory impairment in adult female rats that were perinatally depleted of taurine, irrespective of high sugar intake. Together, these data suggest that the RAS's ability to disturb the autonomic nervous system and baroreflex function following perinatal taurine depletion and a high sugar diet since weaning is system specific, and thus alters some effects, but not other closely related effects, in adult female rats.

Pressure-regulated diuresis/natriuresis is a primary mechanism that modifies arterial pressure regulation by the kidney (Brands 2012). Thus, blunted pressure-diuresis/natriuresis underlies hypertension in many human and animal models (Hall et al.2012). In SHR, lifetime inhibition of the RAS by captopril from conception

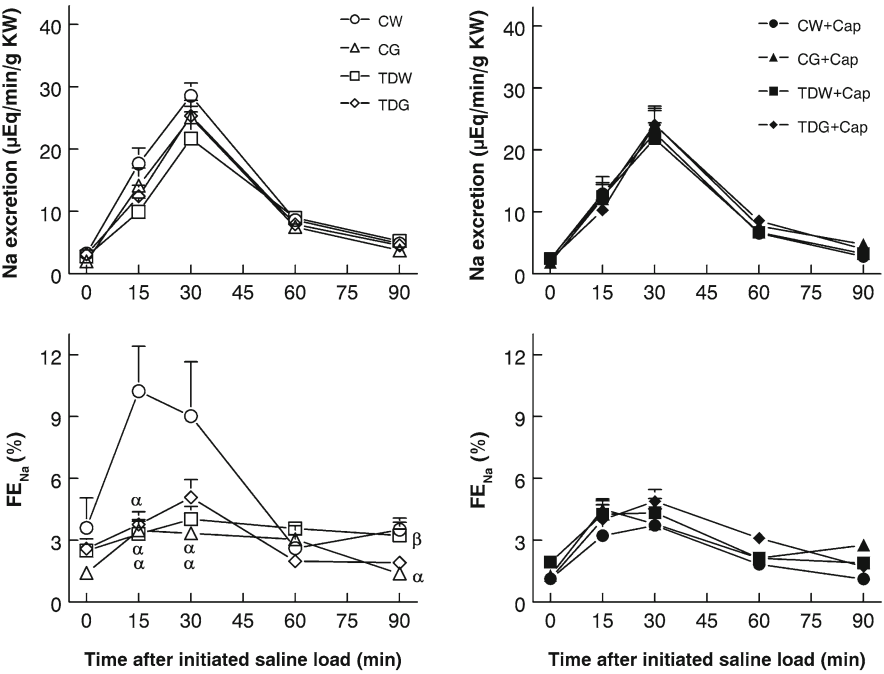

Fig. 5 Sodium excretion (*upper two*) and fractional sodium excretion (FE_{Na}; *lower two*) at rest and in response to an acute saline load in control (CW), control plus high sugar intake (CG), perinatal taurine depletion (TDW), and perinatal taurine depletion plus high sugar intake (TDG) with (*right two*; +Cap) or without (*left two*) captopril treatment (an angiotensin converting enzyme inhibitor); $\alpha\beta P < 0.05$ compared to CW or CW + Cap and CG or CG + Cap, respectively

onward normalizes arterial pressure (Wyss et al. 1994), but it does not alter the diuretic and natriuretic responses to an acute saline load (Roysommuti et al. 1999), suggesting ACEI improves pressure-diuresis/natriuresis in these animals (i.e., the renal responses are not decreased by the decreased arterial pressure). However, in SHR, the lifetime captopril treatment leads to salt-sensitive hypertension that is abolished by acute inhibition of sympathetic nervous system activity (Wyss et al. 1995). These data suggest that heightened RAS and sympathetic nerve activity in the SHR are not always linked in their effects on the kidney, but rather have specific effects that are likely related to local actions.

Diuresis and natriuresis following an acute saline load has been shown to depend on several factors particularly atrial natriuretic hormone (Andersen et al. 1998; Cowley et al. 1988), RAS (Roysommuti et al. 1999, 2002; Sandgaard et al. 2005), renal sympathetic nerve activity (Johns et al. 2011), the intrarenal dopamine system, nitric oxide (Costa et al. 2006), prostaglandins (Agnoli et al. 2001), and colloid osmotic pressure (Cowley and Skelton 1991). In dogs, this response is about 40–50 % dependent on increased atrial natriuretic hormone, which decreases tubular water

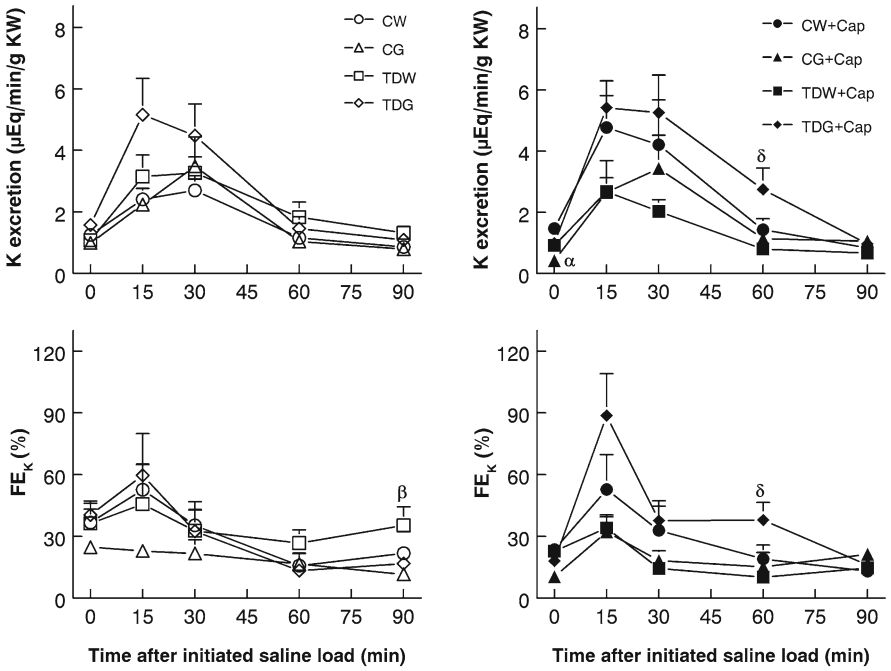

Fig. 6 Potassium excretion (*upper two*) and fractional potassium excretion (FE_K; *lower two*) at rest and in response to an acute saline load in control (CW), control plus high sugar intake (CG), perinatal taurine depletion (TDW), and perinatal taurine depletion plus high sugar intake (TDG) with (*right two*; +Cap) or without (*left two*) captopril treatment (an angiotensin converting enzyme inhibitor); β·δ $P<0.05$ compared to CG or CG + Cap and TDW or TDW + Cap, respectively

and sodium reabsorption (Cowley et al. 1988). Renal blood flow and arterial pressure also are not altered by an acute saline load (Cowley et al. 1988; Sandgaard et al. 2005), as reported in the present study for rats.

In the present data, compared to CW, perinatal taurine depletion treatment decreased fractional water and sodium excretion (indicating increased tubular water and sodium reabsorption), and this parameter was not affected by captopril treatment, except in the CW + Cap group in which inhibition of RAS caused a reduction to the responses. These data suggest that perinatal taurine depletion might depress adult RAS or alter other renal mechanisms in response to an acute saline challenge. Although captopril treatment normalizes autonomic nerve function in TDG rats (Thaeomor et al. 2010), increased renal sympathetic nerve activity following the acute saline load cannot be excluded in this study. The roles of atrial natriuretic peptide, dopamine system, nitric oxide, and prostaglandins on renal function also have to be further clarified.

Potassium excretion is less affected by perinatal taurine depletion, in agreement with previously reported studies (Roysommuti et al. 2010b). However, a significant

increase in potassium excretion consistent with fractional potassium excretion occurs in response to an acute saline load in TDW + Cap compared to TDG + Cap, suggesting that the RAS plays a significant role in potassium excretion, particularly tubular potassium transport, in adult female rats perinatally depleted of taurine. This effect is modified by high sugar intake. Nevertheless, these changes were not significantly different from CW + Cap and CG + Cap rats.

In the *in vitro* experiments, high glucose (25 mM) evokes reactive oxygen species generation and p38 MAPK phosphorylation, as well as stimulates immunoreactive rat angiotensin secretion and angiotensin mRNA expression in renal proximal tubular cells. These effects are blocked by antioxidants (taurine and tiron) (Hsieh et al. 2002). Thus, the intrarenal RAS, rather than the systemic RAS, likely plays a role in the renal excretory effect of perinatal taurine depletion. Although captopril treatment in the present dose can abolish the effect of RAS overactivity on baroreflex sensitivity and autonomic nerve activity in adult female rats that are perinatally depleted of taurine followed by high sugar intake (Thaeomor et al. 2010) and markedly prevent hypertension in SHR (Wyss et al. 1994), it might not completely block intrarenal ACE. In addition, the intrarenal RAS effect of perinatal taurine depletion may act through ACE2 pathways and affects angiotensin (1–7) rather than angiotensin II action. Angiotensin (1–7) is converted from angiotensin I and angiotensin II by ACE2 and acts via Mas receptor to increase renal excretory capacity, i.e., opposite to angiotensin II acting on AT_1 receptors (Carey and Padia 2013; Moon 2013). The key enzyme, ACE2, is not inhibited by captopril. In addition, blocking ACE results in high angiotensin I levels, which will be converted primarily to angiotensin (1–7) by ACE2. These complex intrarenal RAS mechanisms may obscure the effect of captopril in the effect of perinatal taurine depletion on renal function via the RAS.

5 Conclusion

Perinatal taurine exposure affects arterial pressure and renal function, and these effects are amplified by high sugar intake. In adult female rats perinatally depleted of taurine, baroreflex and autonomic dysfunctions are normalized by a short-term inhibition of ACEI. Although high sugar intake after weaning alters renal function before hypertension and insulin resistance development in adult male rats, the same intake fails to alter renal excretory capacity in adult female rats perinatally depleted of taurine. This suggests that sugar intake plays an early role in renal function and a later role (in adults) in arterial pressure control, but does not appreciably alter renal function in the adult, perinatally taurine depleted female rats. Further, these studies suggest that the effects of perinatal taurine depletion on the adult kidney are not primarily regulated by the RAS.

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