The Effect of Perinatal Taurine on Adult Renal Function Does Not Appear to Be Mediated by Taurine's Inhibition of the Renin-Angiotensin System

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Abbreviations

ACE	Angiotensin converting enzyme
ACEI	Angiotensin converting enzyme inhibitor
FD	Fetal or prenatal ACEI treatment
i.p.	Intraperitoneal
LD	Lactation or postnatal ACEI treatment
RAS	Renin-angiotensin system
SD	Sprague-Dawley

1 Introduction

In prenatal and early postnatal life, exposure to nutritional and hormonal elements can have long-term consequences and can affect adult function and disease (Baum 2010; Cabral et al.2012; Hogg et al.2012; Roysommuti and Wyss 2014). Like most other organs, renal function is programmed during the perinatal period by several factors (Dotsch et al.2009; Kett and Denton 2011; Woods and Rasch 1998), including dietary taurine exposure and the renin-angiotensin system (RAS), both playing a vital role in renal growth and development (Roysommuti and Wyss 2014).

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Taurine (2-aminoethanesulfonic acid) is a free beta-amino acid found abundantly in all mammalian tissues and is reported to play a vital role from prenatal to adult life (Roysommuti and Wyss 2014). Perinatal taurine deficiency induces low birth weights and these animals have a high risk of adult diseases including coronary vascular diseases, hypertension, diabetes mellitus, and renal dysfunction. In contrast, perinatal taurine supplementation has been shown to promote growth and development. Further, taurine supplementation or diets high in taurine improve congestive heart failure by inhibition of the cardiac RAS and probably also by inhibition of the systemic RAS (Ito et al.2014; Xu et al.2008). Moreover, both taurine supplementation and angiotensin converting enzyme (ACE) inhibition prevent renal damage and dysregulation with advancing age to a similar degree (Cruz et al.2000).

All components of the systemic and local RAS are present and effectively function during perinatal life, and perinatal inhibition of the RAS by either an angiotensin converting enzyme inhibitor (ACEI) or an angiotensin II receptor antagonist can induce renal damage and dysfunction in adult normotensive animals (Guron and Friberg 2000) and humans (Guron et al.2006; Tabacova et al.2003). Perinatal RAS inhibition can result in decreased nephron number, glomerular and tubular damage, reduction of glomerular filtration and renal blood flow (Woods and Rasch 1998). In addition, such perinatal RAS inhibition induces salt-sensitive hypertension in normotensive rat strains (Fang et al.1999). In contrast, lifetime inhibition of RAS improves renal function and protects against damage in spontaneously hypertensive rats (SHR) (Roysommuti et al.1999).

Our previous experiments indicate that perinatal taurine depletion or supplementation alters adult renal function, an effect that is amplified by high sugar intake after weaning (Roysommuti et al.2009, 2010a, b). In female rats that are perinatally depleted of taurine, a high sugar diet blunts baroreflex control of arterial pressure and increases sympathetic nerve activity. All of these are eliminated by acute inhibition of RAS, but not by estrogen receptor blockade (Thaeomor et al.2010). In contrast, perinatal taurine supplementation followed by high sugar intake significantly depresses baroreflex sensitivity without any effect on autonomic nerve activity, and this baroreflex dysfunction is normalized by estrogen receptor blockade but not ACE inhibition (Thaeomor et al.2013). In addition, our previous data indicate that prenatal (versus postnatal) taurine supplementation affects adult renal excretory function differentially (Roysommuti et al.2010a, b). The present study further tests the hypothesis that in male rats, the effect of perinatal taurine supplementation on adult renal function parallels, and probably is primarily mediated by, perinatal inhibition of RAS by taurine.

2 Methods

2.1 Animals

Sprague-Dawley (SD) rats from the animal unit of Faculty of Medicine, Khon Kaen University were bred and maintained at constant humidity (60±5 %), temperature (24±1 °C), and light cycle (0600–1800 h). Female Sprague-Dawley rats were fed

normal rat chow and given water alone (Control) or water containing captopril (an ACEI, 400 mg/ml) from conception until delivery (Fetal RAS depletion, FD) or from delivery until weaning (Lactation RAS depletion, LD). After weaning, the male offspring were fed normal rat chow and tap water *ad libitum*. 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 male rats were implanted with femoral arterial, venous, and bladder catheters. Forty-eight hours later, each rat was placed in a rat restrainer in which they could move back and forth, and the rats were acclimated to restraint for 1 week (3 h per day) prior to the experiment. Femoral arterial and venous catheters were flushed with 0.9 % heparinized saline (20 units of heparin/ml, 0.2–0.3 ml) to remove blood clotting. The femoral arterial catheter was connected to a pressure transducer (BIOPAC Systems, Goleta, CA, USA) for 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). The bladder catheter was then flushed with 0.9 % NaCl, 0.2–0.3 ml. 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 a 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 (via the arterial catheter). 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 of 20 μl/min until the end of the experiment. Urine samples were collected at 15, 30, 60, and 90 min intervals after the initiation of the saline infusion, 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 experiments, all animals were sacrificed with an overdose of sodium pentobarbital and kidney weight (KW) was 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 flame photometry, 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* Duncan's Multiple Range test with a significant criterion of p-value less than 0.05 (Statmost version 3.5, Dataxiom Software, USA).

3 Results

Compared to control groups, perinatal inhibition of the RAS by captopril significantly decreased body weight (Control, 200 ± 11 g; FD, 164 ± 6 g; LD, 165 ± 5 g; $P < 0.05$) but significantly increased kidney to body weight ratios (Control, 0.32 ± 0.01 g; FD, 0.40 ± 0.02 g; LD, 0.41 ± 0.03 g; $P < 0.05$). Neither prenatal nor postnatal captopril treatment significantly affected mean arterial pressure, heart rate (Fig. 1), effective renal blood flow, or effective renal vascular resistance (Fig. 2) in adult rats at rest or after isotonic saline load. Compared to Control, glomerular filtration rate significantly increased at rest and after saline load in LD and increased only after saline load in FD groups (Fig. 3). However, neither FD nor LD affected filtration fraction throughout the study.

Water excretion significantly increased at rest and 15 min after saline infusion only in FD compared to Control group, while fractional water excretion was significantly increased at rest in FD and at 30 min after a saline load in both FD and LD groups (Fig. 4). Further, sodium excretion significantly increased only after a saline load in FD compared to Control and LD groups, while both FD and LD compared to Control displayed significant decreases in fractional sodium excretion 30 min after saline load (Fig. 5). In contrast to sodium and water excretion, potassium excretion significantly increased both at rest and after saline load in both FD and LD compared to Control groups (Fig. 6). Perinatal inhibition of the RAS significantly increased fractional potassium excretion at rest, but not after saline load in FD and significantly decreased fractional potassium excretion in LD 90 min after saline load but not at rest.

We next compared whether the effects of perinatal RAS inhibition on adult renal function were parallel to those of perinatal taurine supplementation previously reported in our parallel studies (Roysommuti et al.2010a, b). Table 1 summarizes the effect of pre- and postnatal RAS inhibition or taurine supplementation on adult renal function. The data indicate that the two treatments had differing effects in 54 % of the indices measured. Prenatal treatments with captopril versus taurine differentially affected 67 % of the indices, while postnatal treatment differentially affected 42 % of indices. In no case did the two treatments cause a similar change in renal function.

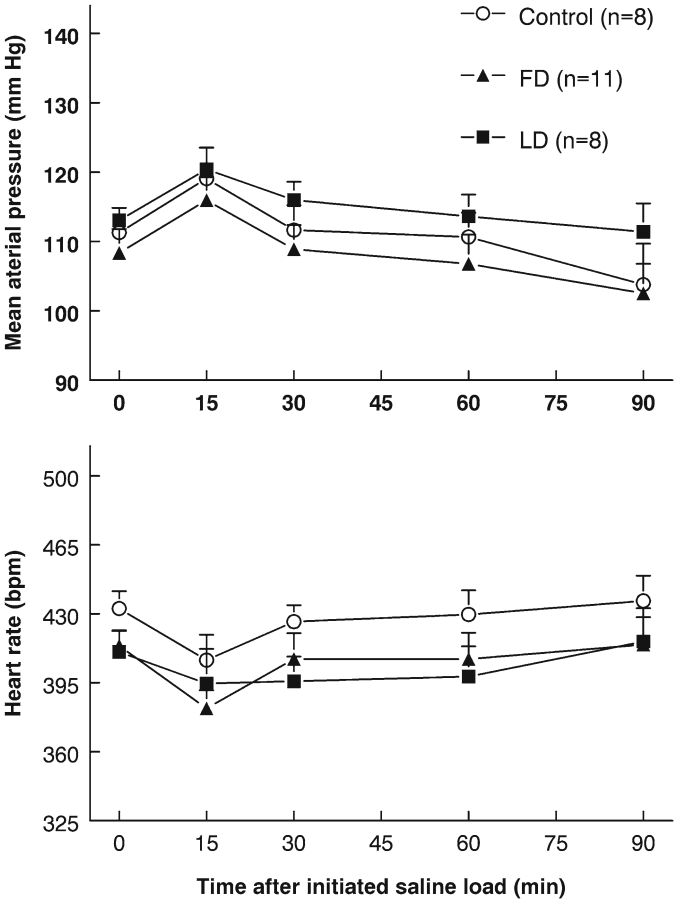

Fig. 1 Mean arterial pressure (*upper*) and heart rate (*lower*) at rest and after acute saline infusion in Control, prenatal (Fetus, FD), and postnatal (Lactation, LD) renin-angiotensin system inhibition groups. No significant difference was observed among the three groups

4 Discussion

Taurine and RAS inhibition have many similar effects on the regulation of cardiovascular and renal function, and they have both been reported to affect growth and development of the kidney (Kett and Denton 2011; Roysommuti and Wyss 2014). In adult rats, either taurine exposure or RAS inhibition prevents renal dysregulation with age (Cruz et al.2000). During perinatal life, various influences program renal excretory and hormonal function, and inappropriate regulation can lead to renal disorders in adult life (Roysommuti and Wyss 2014).

In adults, taurine supplementation can inhibit adverse RAS effects in several disorders including cardiac hypertrophy and heart failure (Ito et al.2014), and previous

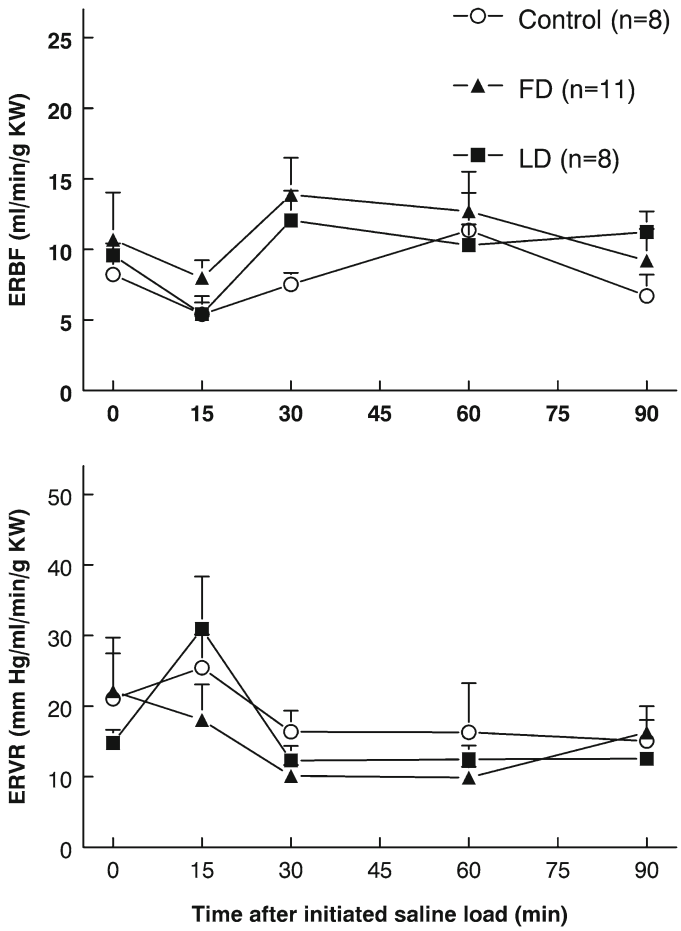

Fig. 2 Effective renal blood flow (ERBF; *upper*) and effective renal vascular resistance (ERVR; *lower*) at rest and after acute saline infusion in Control, prenatal (Fetus, FD), and postnatal (Lactation, LD) renin-angiotensin system inhibition groups. No significant difference was observed among the three groups

experiments indicate that in female rats, perinatal taurine depletion followed by high sugar intake after weaning alters adult arterial pressure control via RAS overactivity (Thaeomor et al.2010). Although the present study indicates that both perinatal taurine and RAS alter adult renal function, the majority of the changes in these parameters are different between the treatments. In the present study, not a single parameter measured was negatively or positively affected by both treatments. Thus, the data are not consistent with the hypothesis that perinatal taurine supplementation affects adult renal function primarily via perinatal inhibition of the RAS, at least in male rats. Further, this study also suggests that the RAS effects on renal function are more frequent than those following taurine supplementation.

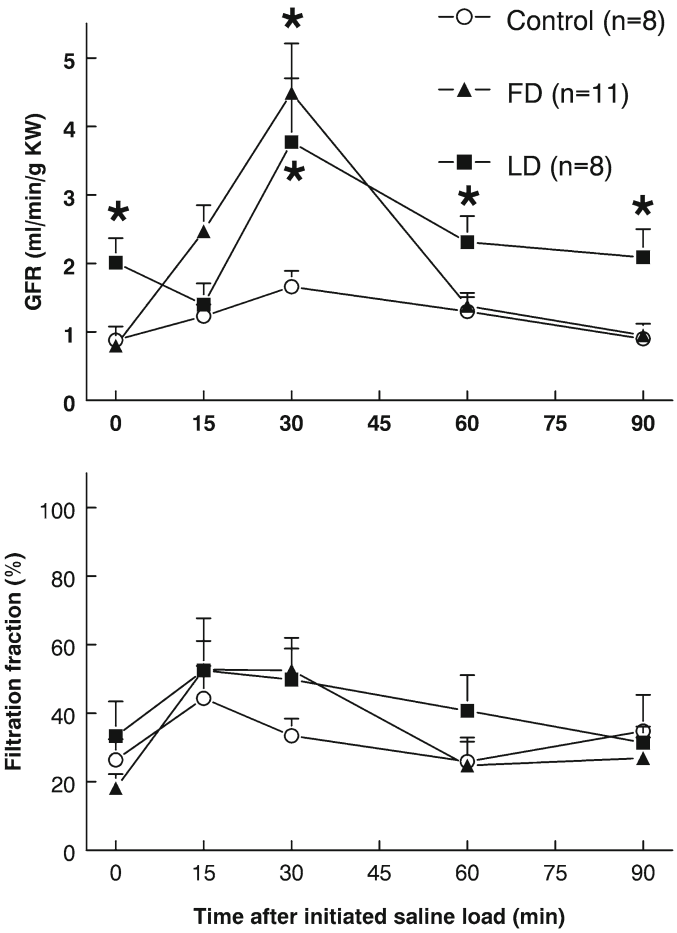

Fig. 3 Glomerular filtration rate (GFR; *upper*) and filtration fraction (*lower*) at rest and after acute saline infusion in Control, prenatal (Fetus, FD), and postnatal (Lactation, LD) renin-angiotensin system inhibition groups (*$P<0.05$ compared to Control)

In humans, nephrogenesis starts around 5 weeks of gestation and the main structure of the kidney is completed before birth (Kett and Denton 2011). This growth and development includes forming of blood vessels, glomeruli, tubules, hormonal networks, and neural innervation. In most animals and particularly in rodents, the nephrogenesis starts prenatally and is complete before weaning. However, maturation of nephrons continues several months after birth in humans, and in rodents is complete shortly after weaning. Thus, either prenatal or postnatal RAS inhibition or taurine supplementation (Roysommuti et al.2010a, b) has the potential to affect renal function in adult rats. The main perinatal effect of RAS inhibition in the present study is on alteration of glomerular and tubular function, supporting previous experiments showing that RAS affects nephrogenesis and maturation (Baum 2010;

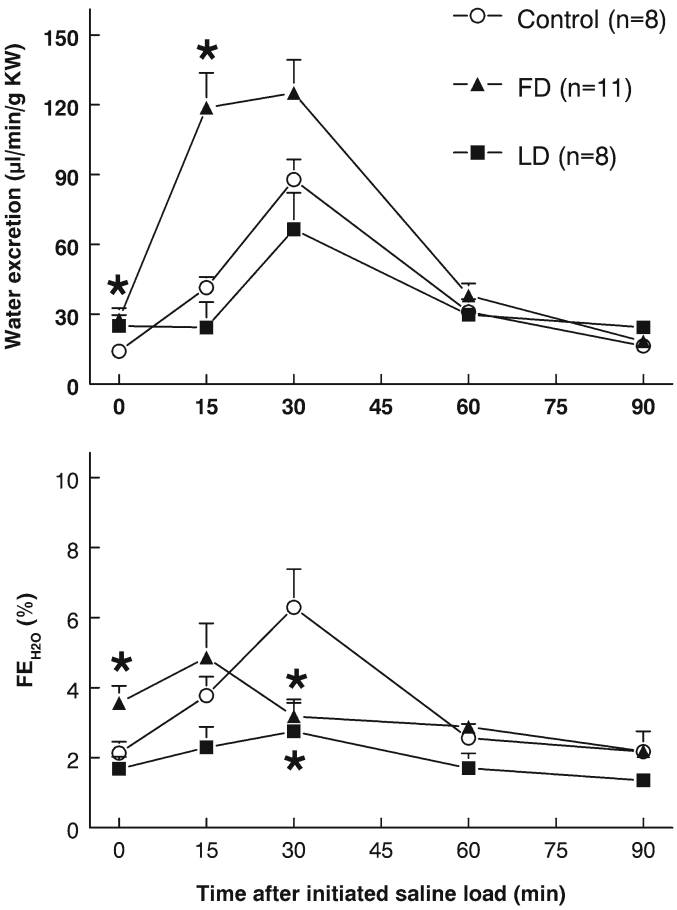

Fig. 4 Water excretion (*upper*) and fractional water excretion (FE_{H2O}; *lower*) at rest and after acute saline infusion in Control, prenatal (Fetus, FD), and postnatal (Lactation, LD) renin-angiotensin system inhibition groups (*$P < 0.05$ compared to Control)

Gubler and Antignac 2010; Guron and Friberg 2000; Spaggiari et al.2012; Woods and Rasch 1998).

Perinatal inhibition of RAS induces decreased nephron number, increased glomerular hyperfiltration, and increased tubular sodium reabsorption in adult life (Kett and Denton 2011). These changes may explain why GFR increased and fractional sodium and water excretion decreased after an isotonic saline challenge in captopril-treated rats. Under normal conditions, acute isotonic volume expansion decreases angiotensin II and renal sympathetic nerve activity, leading to decreased renal vascular resistance, increased renal blood flow, and increased glomerular filtration, respectively (see control group data). These neurohormonal responses also result in decreased tubular water and sodium reabsorption, thus producing diuresis and natriuresis. The perinatal RAS effects suggest that marked increases in GFR

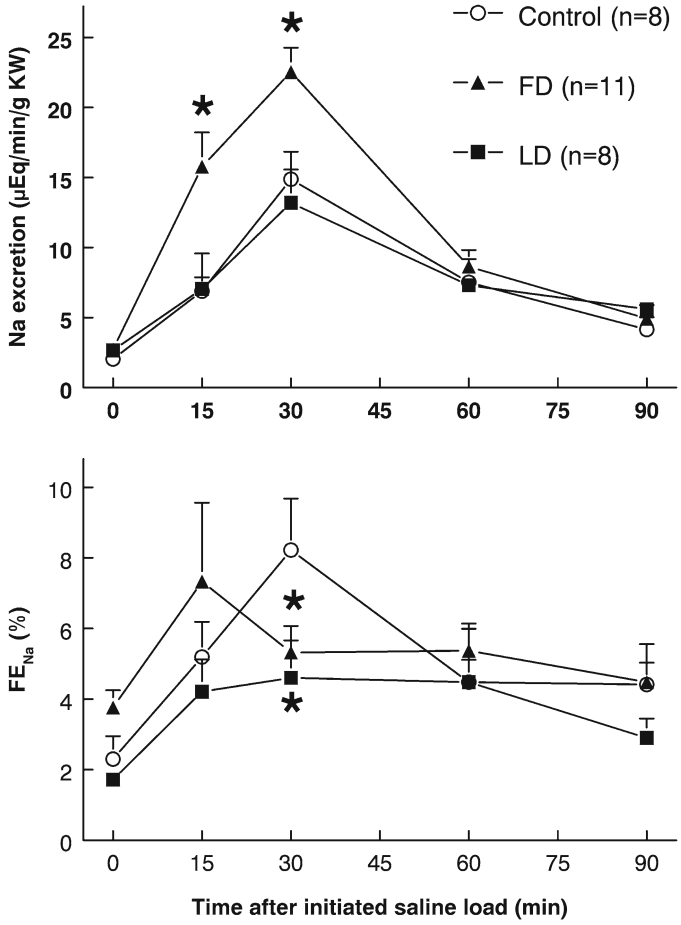

Fig. 5 Sodium excretion (*upper*) and fractional sodium excretion (FE_{Na}; *lower*) at rest and after acute saline infusion in Control, prenatal (Fetus, FD), and postnatal (Lactation, LD) renin-angiotensin system inhibition groups (*$P<0.05$ compared to Control)

and tubular water and electrolyte reabsorption may be due to an inappropriate RAS response to volume expansion in adult rats.

RAS underlies cardiac hypertrophy and heart failure in several cardiovascular disorders, and thus ACE inhibition or angiotensin II receptor antagonists are generally prescribed to treat these patients (Escobar and Barrios 2013; Ferrari and Boersma 2013; Segura et al.2013). Several lines of evidence indicate that in adults, taurine supplementation also improves cardiac ischemia/reperfusion and heart failure by inhibiting RAS activation (Ito et al.2014). In animal models, chronic taurine supplementation decreases cardiac ischemia/reperfusion injury (Sahin et al.2011), and acute treatment before (versus after) an episode of cardiac ischemia/reperfusion is less effective (Ueno et al.2007). However, taurine may more directly inhibit oxidative

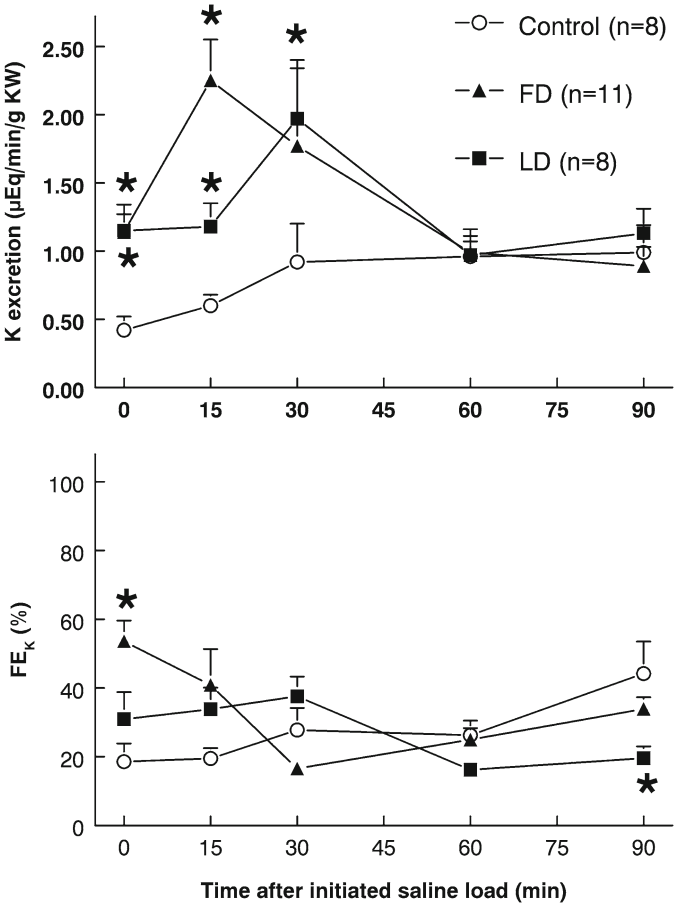

Fig. 6 Potassium excretion (*upper*) and fractional potassium excretion (FE_K; *lower*) at rest and after acute saline infusion in Control, prenatal (Fetus, FD), and postnatal (Lactation, LD) renin-angiotensin system inhibition groups (*$P<0.05$ compared to Control)

stress either through, or outside of, its RAS inhibitory action (Ueno et al.2007). Taurine is an antioxidant (Roysommuti and Wyss 2014), whereas angiotensin II increases oxidative stress (Kopkan and Cervenka 2009; Sachse and Wolf 2007). In adult kidneys, angiotensin II increases water and sodium reabsorption directly or indirectly via stimulation of aldosterone, whereas taurine supplementation decreases sodium and probably water reabsorption (Roysommuti and Wyss 2014).

These lines of evidence led us to the hypothesis that perinatal taurine supplementation could inhibit the RAS in the adult and might thereby have beneficial long-term effects. Thus, perinatal taurine supplementation might provide an alternative mechanism for RAS inhibition in the adult, particularly in heart disease (Ito et al.2014). In contrast to this hypothesis, the present data indicate that taurine sup-

Table 1 Summary of changes in renal function after prenatal (Fetus, FD) and postnatal (Lactation, LD) caused by renin-angiotensin system inhibition (Captopril) and taurine supplementation (Taurine)

	Prenatal treatment				Postnatal treatment			
	Resting		Post-infusion		Resting		Post-infusion	
Parameter	Captopril	Taurine	Captopril	Taurine	Captopril	Taurine	Captopril	Taurine
MAP	N	I	N	I	N	I	N	I
HR	N	N	N	N	N	N	N	N
ERBF	N	D	N	D	N	N	N	N
ERVR	N	I	N	N	N	N	N	I
GFR	N	N	I	N	I	N	I	N
FF	N	I	N	N	N	N	N	N
E_{H2O}	I	N	I	N	N	N	N	N
FE_{H2O}	I	N	D	I	N	N	D	N
E_{Na}	N	N	I	N	N	N	N	N
FE_{Na}	N	N	D	N	N	N	D	N
E_K	I	N	I	N	I	N	I	N
FE_K	I	N	N	N	N	N	D	N

All changes noted refer to significant changes from Control (untreated) rats
MAP mean arterial pressure, *HR* heart rate, *ERBF* effective renal blood flow, *ERVR* effective renal vascular resistance, *GFR* glomerular filtration rate, *FF* filtration fraction, E_{H2O} water excretion, FE_{H2O} fractional water excretion, E_{Na} sodium excretion, FE_{Na} fractional sodium excretion, E_K potassium excretion, FE_K fractional potassium excretion, *N* normal, *D* decrease, *I* increase (with reference to Control group)

plementation and ACE inhibition during pre- or postnatal period affect adult renal function quite differently. In addition, the most deleterious effects of either treatment on adult renal function are observed after prenatal rather than postnatal inhibition. Thus, the RAS and taurine are critical during perinatal life and alterations in their availability can predispose to adult renal dysfunction.

Our previous experiments indicate that either prenatal or postnatal taurine supplementation slightly and significantly increases mean arterial pressure but not heart rate in adult, male rats (Roysommuti et al.2010a). Further, perinatal taurine supplementation slightly blunts baroreflex control of the renal nerve in adult female rats, and this effect is abolished by an estrogen receptor blocker tamoxifen, but not captopril (Thaeomor et al.2013). In contrast to taurine, perinatal inhibition of the RAS did not affect adult arterial pressure and heart rate, an effect that is similar to previous reports (Fang et al.1999). In addition, the offspring who received perinatal RAS inhibition displayed increased salt-sensitive hypertension following 2-weeks of drinking isotonic saline (unpublished data) or eating high salt diets (Fang et al.1999). Although perinatal taurine supplementation does not induce salt-sensitive hypertension, taurine supplementation in late pregnant rats stimulates postnatal growth and induces obesity and insulin resistance in adult offspring (Hultman et al.2007). Moreover, in adult SHR, taurine supplementation accelerates the hypertensive response to a high salt diet during nighttime but not daytime (Suwanich et al.2013).

5 Conclusion

Both taurine and the renin-angiotensin system possess several important functions in humans and animals, especially during perinatal development. For instance, both perinatal taurine supplementation and RAS inhibition prevent age-related renal dysfunction and renal dysfunction in hypertensive, glucose intolerant rats. Further, perinatal taurine supplementation blunts cardiac injury and cardiac ischemia/reperfusion dysfunction and heart failure by inhibition of RAS. However, both perinatal RAS inhibition and taurine supplementation can also lead to adult renal dysfunction. The present study indicates that while perinatal taurine supplementation can alter renal function in adults, it likely does so through mechanisms other than RAS inhibition.

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