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EDUCATIONAL REVIEW

Role of renal sympathetic nerve activity in prenatal programming of hypertension

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Abstract Prenatal insults, such as maternal dietary protein deprivation and uteroplacental insufficiency, lead to small for gestational age (SGA) neonates. Epidemiological studies from many different parts of the world have shown that SGA neonates are at increased risk for hypertension and early death from cardiovascular disease as adults. Animal models, including prenatal administration of dexamethasone, uterine artery ligation and maternal dietary protein restriction, result in SGA neonates with fewer nephrons than controls. These models are discussed in this educational review, which provides evidence that prenatal insults lead to altered sodium transport in multiple nephron segments. The factors that could result in increased sodium transport are discussed, focusing on new information that there is increased renal sympathetic nerve activity that may be responsible for augmented renal tubular sodium transport. Renal denervation abrogates the hypertension in programmed rats but has no effect on control rats. Other potential factors that could cause hypertension in programmed rats, such as the renin–angiotensin system, are also discussed.

Keywords Blood pressure · Prenatal insults · Sodium absorption · Renin-angiotensin system · Programming

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Introduction

There are a number of risk factors for cardiovascular disease, including smoking, obesity, hypercholesterolemia and chronic kidney disease. What is becoming increasingly apparent is that being of low birth weight is also a risk factor for cardiovascular disease. The association between low birth weight and cardiovascular disease was proposed approximately 30 years ago by David Barker and other investigators looking at different populations around the world. For example, in one of his earliest studies Barker et al. looked at birthweight and weight at 1 year of age in Hertfordshire, England between 1911 and 1930 where excellent records were maintained [1]. They found that male infants born weighing less than 5.5 pounds had a greater risk of death from ischemic heart disease as adults. Comparable findings have been found in females as well [2]. In addition, areas of England with poor social conditions, low birth weights and a higher neonatal mortality, had higher rates of ischemic heart disease than more affluent areas of the country [3]. Several studies have shown that infants of low birth weight have higher blood pressures as adults than those of average or above average birth weight [4–7]. A difference in blood pressure between small for gestational age (SGA) and appropriate for gestational age individuals can be found in children and young adults, but the magnitude of the difference in blood pressure increases with age [8, 9]. These data are consistent with the hypothesis that an adverse intrauterine environment leading to impaired fetal growth is a risk factor for hypertension and cardiovascular disease in adult life [10]. Similar findings have been found in a number of different areas of the world and have been reviewed by others previously [6, 8, 10].

The above studies show that there is an association between SGA infants and hypertension. However, these epidemiologic studies are limited to showing an association and do

not point to the cause for the hypertension. Investigators have thus turned to animal models, predominantly sheep and rats, to investigate how a perinatal insult results in hypertension in later life. The models utilized include prenatal administration of glucocorticoids, induction of uteroplacental insufficiency, maternal caloric deprivation and maternal protein deprivation.

There are many factors that may play a role in the prenatal programming of hypertension. Prenatal programming has been shown to cause a reduction in nephron number, dysregulation of the systemic renin–angiotensin system, altered sodium transport, increased vascular tone, alterations in oxidative stress and inflammation. Each of these factors may play a role in the development and maintenance of hypertension with prenatal programming and have been reviewed in detail elsewhere [11, 12]. The purpose of this review is to discuss the contribution of sympathetic nerves in mediating the hypertension in prenatal programming. An increase in sympathetic nerve activity unifies many seemingly unrelated factors that have been proposed to increase blood pressure with prenatal programming.

Blood pressure response to stress

Adult rats that are born SGA due to maternal dietary protein deprivation or prenatal administration of dexamethasone have an increase in blood pressure when assessed using a tail cuff, which is stressful to the rats [13–15]. To assess blood pressure under non-stressful conditions, investigators have used telemetric measurements of blood pressure comparing programmed and control rats [16–19]. Male offspring of rats with intrauterine growth restriction due to maternal surgically induced placental vascular insufficiency have been shown to have a higher systolic blood pressure than controls [16, 19] and a higher peak blood pressure in response to nasal ammonia which was used to stress the rat [16]. In male rats programmed by maternal dietary protein deprivation, diastolic, but not systolic, blood pressure was increased compared to control male rats under basal conditions, but there was a greater increase in both systolic and diastolic blood pressure with the administration of nasal ammonia [18]. Both male and female offspring of mothers administered dexamethasone during the later days of gestation had lower blood pressures assessed by telemetry than controls under basal conditions [17]. However, in comparison to controls, programmed rats showed a greater increase in blood pressure in response to minor stress, such as restraint in a cylinder for 15 min [17]. Thus, while there is some variability in the effect of basal blood pressure in programmed rats, the response to minor stress results in a substantively greater increase in blood pressure in programmed rats compared to controls.

Human studies also point to an exaggerated increase in blood pressure in response to stress in adults who were of low birth weight. The Dutch famine occurred during the end of World War II when the caloric intake was reduced from about 1600 kcals to 600 kcals per day in the Netherlands by the Germans in retaliation for a railroad strike. Offspring of pregnant women who survived the Dutch famine have an increased likelihood of having the metabolic syndrome [20]. Prenatal exposure to the famine does not affect baseline blood pressure, however mild stress in the form of a mirror-drawing test, public speaking or Stroop test (a test where the brain has to deal with conflicting information, such as reading the word green written in red ink) results in an exaggerated increase in blood pressure for offspring whose mothers were exposed to the famine during the first trimester but not during mid or late gestation [21]. Other investigators have studied the effect of these same psychological stressors to examine the effect of birth weight on blood pressure in women. For every 1 kg reduction in birth weight there was an 8.7 mmHg and 4.1 mmHg increase in systolic and diastolic blood pressure, respectively, in response to minor stress [22].

An increase in blood pressure in response to stress suggests that low birth weight is associated with an increase in sympathetic nerve activity. Boguszewski et al. made direct measurements of sympathetic nerve activity in young adults who were SGA and appropriate for gestational age and found that there was an increase in peroneal nerve activity in the former and that sympathetic nerve activity was inversely related to birth length as well as adult height [23]. Weitz et al., however, found lower muscle sympathetic nerve activity in young adults born SGA compared to appropriate for gestational age young adults under resting conditions and no difference in response to stress and baroreflex stimulation [24]. The reason for this disparity in results is not clear.

Nephron endowment

Small for gestational age human neonates born after 36 weeks of gestation who died in the perinatal period have been found to have fewer nephrons than those who were appropriate weight for gestational age [25–27]. Since nephrogenesis in humans is complete by 36 weeks of gestation, these studies demonstrate that SGA neonates are born with a reduced nephron endowment. A reduction in nephron number could be a risk factor for hypertension and chronic kidney disease in later life [28, 29]. Middle-aged white patients with a history of hypertension or left ventricular hypertrophy who died as a result of an accident had 50 % fewer nephrons than age-, sex-, height- and weight-matched white controls, supporting the hypothesis that a reduced nephron number is associated with hypertension [30]. A subsequent study confirmed the relationship between low nephron number and hypertension in whites but found no association between nephron number and blood pressure in African Americans [31]. In children born with one functioning kidney due to unilateral dysplasia

or aplasia, only a small percentage develop hypertension as children; however, it is not clear what percentage will develop hypertension as adults [32–37].

Several studies have examined whether there is an association between a reduction in nephron number and elevated blood pressure in programmed rats. Whether the insult is from uteroplacental insufficiency, prenatal administration of dexamethasone or maternal dietary protein deprivation, these studies have shown about a 30 % reduction in nephron number and hypertension when the rats are studied as adults [13, 14, 38–42].

A reduction in nephron number of sufficient magnitude to cause a decrease in glomerular filtration rate (GFR) could cause an increase in sodium retention and expansion of the extracellular fluid volume, leading to hypertension. Administration of dexamethasone throughout gestation leads to a decrease in nephron number, hypertension and a reduction in GFR at 2 months of age [40]. Some studies have shown a 50 % decrease in GFR in 1.5-year-old rats that had a prenatal insult from maternal dietary food restriction and maternal low protein diets [43, 44]. Thus, a very severe prenatal insult or studies in aged rats that had caloric or protein deprivation can result in a decrease in GFR. However, most studies examining the effect of prenatal programming on GFR find either a small or no reduction in GFR compared to controls in young and middle-age rats at a time when they are hypertensive [13, 14, 42, 45].

Boubred et al. looked at the effect of increased postnatal nutrition induced by reducing the litter size to three rats on day 3 of life at a time when nephrogenesis is still occurring in the rat [46]. Compared to control rats that had ten pups in the litter, the male adult overfed group had 20 % more glomeruli than the control adults. Despite the greater nephron number, the overfed group developed hypertension, glomerulosclerosis and proteinuria as adults, demonstrating a disconnect between glomerular number and the development of hypertension and renal injury. The overfed females also had an increase in glomerular number but did not have hypertension, proteinuria or glomerulosclerosis compared to female controls.

In summary, prenatal insults can reduce glomerular number and the offspring often develop hypertension, but a reduction in nephron number alone does not appear to be the sole explanation for the increase in blood pressure. However, a decrease in nephron endowment at birth may be a risk factor for chronic kidney disease in later life.

Tubular sodium transport

The kidneys of an adult human filter 160 liters of fluid with the same electrolyte composition as that of blood. The fluid is delivered to the various segments of the nephron in a sequential fashion, which is depicted by the cartoon in Fig. 1. The proximal tubule reabsorbs all of the filtered glucose, amino acids and the vast majority of the filtered phosphate. The proximal tubule reabsorbs NaCl by both active and passive mechanisms, and by the end of the proximal tubule two-thirds of the filtered fluid and sodium is reabsorbed in an isotonic fashion. The major apical membrane sodium transporter in the proximal tubule is the Na^+/H^+ exchanger, designated NHE3. The thick ascending limb is water impermeable and reabsorbs 20–25 % of the filtered sodium chloride. Sodium enters the cell via an electroneutral sodium, potassium, 2 chloride cotransporter designated NKCC2, which is inhibited by furosemide or bumetanide. The distal convoluted tubule reabsorbs 10 % of sodium chloride via an electroneutral sodium chloride cotransporter inhibited by thiazide diuretics, which is designated NCC. The remaining fluid is delivered to the collecting duct where 1–3 % of sodium is reabsorbed. In the collecting duct sodium entry is regulated by the epithelial sodium channel which is inhibited by amiloride. The entry of sodium generates a lumen negative potential difference that provides a driving force for chloride transport across the paracellular pathway. In each nephron segment, the amount of sodium reabsorbed is tightly regulated, which will be discussed in the following sections.

While the transporters on the apical membrane of all of the segments are different, the driving force for sodium entry across the apical membrane is due to the low intracellular sodium concentration generated by the Na^+/K^+-ATPase on the basolateral membrane. The Na^+/K^+-ATPase transports three sodium ions out of the cell and two potassium ions into the cell which generates a very low intracellular sodium and a negative charge of about 70–90 mV across the membrane. An increase in Na^+/K^+-ATPase activity in the kidney would potentially increase sodium transport in all of the sodium-transporting segments described above. Na^+/K^+-ATPase activity in either the kidney or in any nephron segment has not been directly compared in programmed and control rats. However, there is evidence that there is increased Na^+/K^+-ATPase protein abundance in the kidney of programmed rats. Adult rats whose mothers were fed a low protein diet had increased renal Na^+/K^+-ATPase mRNA abundance, and offspring of mothers that received dexamethasone showed an increase in kidney Na^+/K^+-ATPase mRNA and protein abundance [47, 48]. While not a measure of Na^+/K^+-ATPase activity or sodium transport, an increase in Na^+/K^+-ATPase mRNA and protein abundance in programmed animals is consistent with an increase in sodium transport.

Proximal tubule sodium transport

Most of the sodium reabsorption in the proximal tubule occurs via the apical Na^+/H^+ exchanger designated NHE3. In parallel with a Cl^-/base exchanger, the Na^+/H^+ exchanger transports NaCl into the cell. The reabsorption of organic solutes and sodium bicarbonate in the early proximal tubule leaves a higher chloride concentration in the lumin than in the peritubular capillaries, thereby allowing for paracellular passive NaCl transport in the late proximal tubule [49]. Total

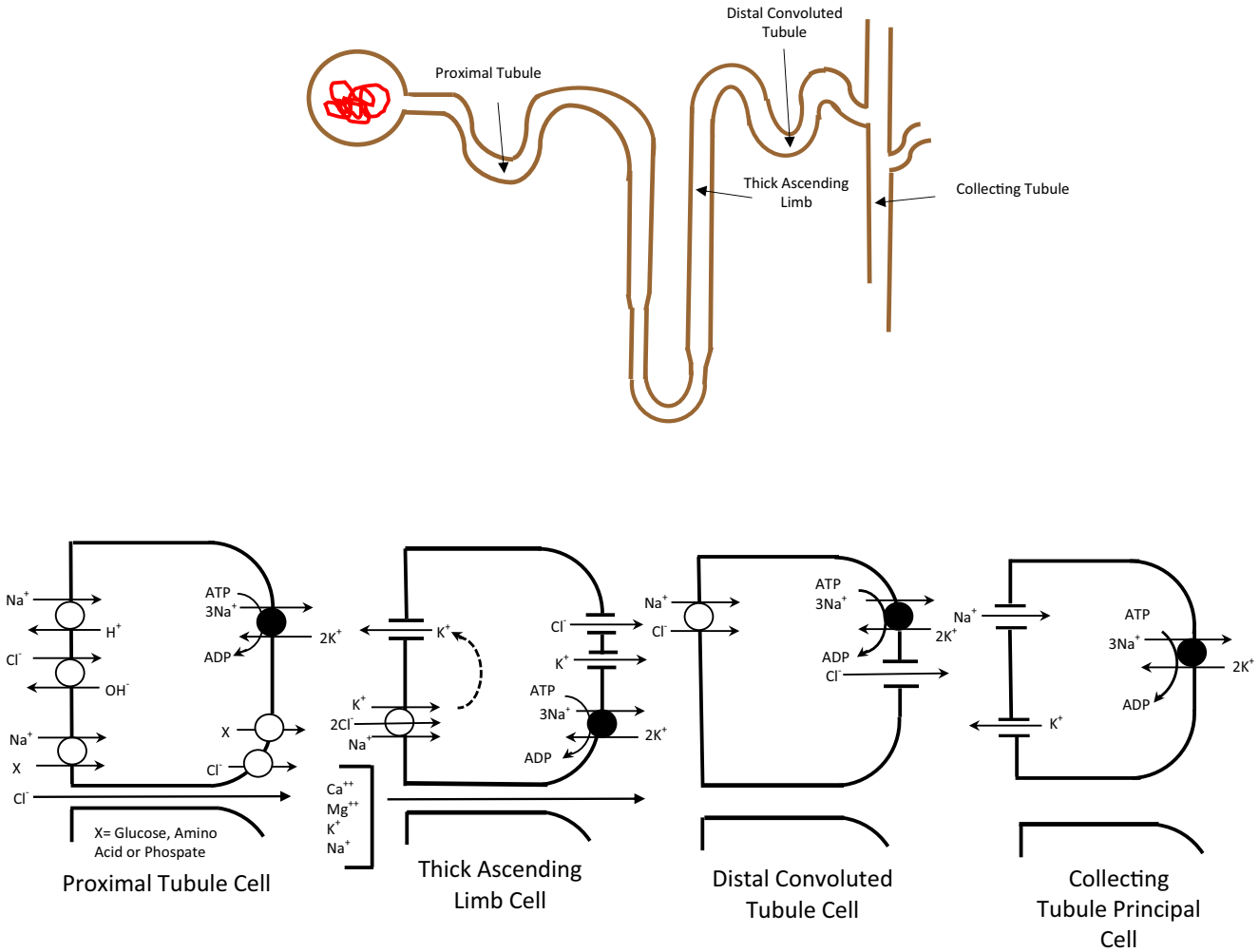

Fig. 1 The nephron (*above*) with many of the sodium transporters (*below*). There are approximately 1 million nephrons in each human kidney. The human kidneys filter 160 l of an ultrafiltrate of plasma which is reabsorbed in a sequential fashion along the length of the nephron. Shown are cells from the proximal tubule, thick ascending limb, distal convoluted tubule and cortical collecting duct with the most important apical sodium transporters depicted. There is evidence that prenatal programming increases the expression of all of the apical sodium transporters along the nephron to stimulate sodium transport which likely is an important mediator of hypertension

sodium reabsorption can be assessed using inulin as a volume marker and, as shown in Fig. 2a, there is a greater rate of volume absorption (Jv) in programmed proximal tubules from rats whose mothers were administered prenatal dexamethasone than in controls [50]. In addition, measurement of Na^+/H^+ exchanger activity by measuring the effect of luminal sodium removal on the rate of change in cell pH showed that the prenatal administration of dexamethasone stimulated the proximal tubule Na^+/H^+ exchanger [50]. Both these observations are consistent with an increase in sodium transport by the proximal tubule in programmed rats.

Thick ascending limb and distal convoluted tubule

The principal transporters on the apical membrane of the kidney in control and offspring of mothers treated with a low protein diet were compared by immunoblot, which measures the abundance of a specific protein using an antibody against that protein. While NHE3 and the ENaC subunits were comparable between the control and programmed offspring at 4 weeks of age, there was an increase in both NKCC2 and NCC protein abundance in the programmed rats [51]. The distal convoluted tubule is too short to study using in vitro microperfusion, but sodium chloride transport has been measured in the medullary thick ascending limb of programmed rats, as shown in Fig. 2b. Prenatally programmed offspring whose mothers had been administered dexamethasone or who were placed on a low protein diet were noted to have an increase in NaCl transport in the medullary thick ascending limb [51]. This study found that NKCC2 protein abundance was higher in programmed rats in the medullary but not the cortical thick ascending limb. Furthermore, administration of furosemide, which is an inhibitor of NKCC2, did not affect blood pressure in control rats, but it did normalize the blood pressure in programmed rats [52].

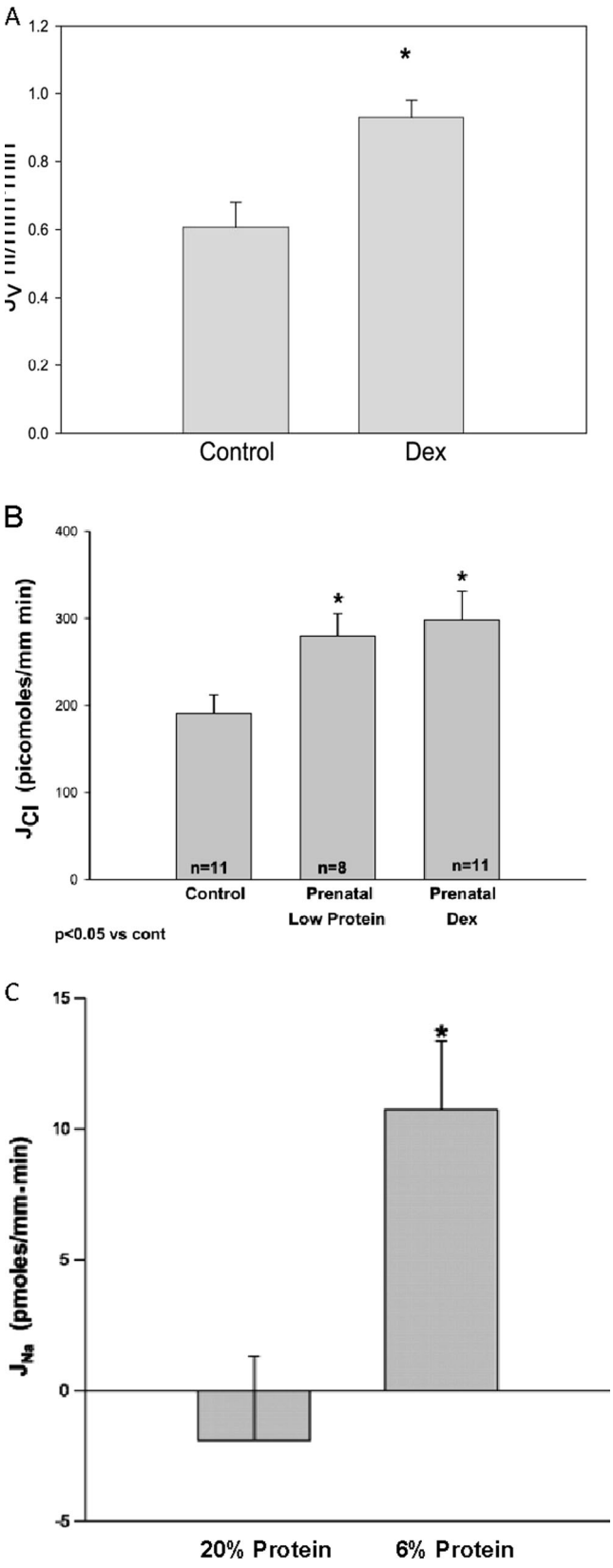

Fig. 2 Effect of prenatal programming on tubular transport. Effect of prenatal administration of dexamethasone (*Dex*) on proximal tubule transport (*Jv*, a designation for sodium transport) (**a**) (reproduced from Dagan et al. [50], used with permission), prenatal Dex and low protein diet on chloride transport (J_{Cl}) in the thick ascending limb (**b**) (reproduced from Dagan et al. [51], used with permission) and prenatal low protein diet on sodium transport (J_{Na}) in the cortical collecting tubule (**c**) (reproduced from Cheng et al. [52], used with permission). *Asterisk* (**a**, **b**) indicates significant difference at $p \leq 0.05$ compared to controls; *asterisk* (**c**) indicates significant difference at $p \leq 0.05$ compared to the other group

Sodium transport in the collecting duct

The collecting duct is responsible for only 1–3 % of sodium transport, but it is the final segment where sodium is reabsorbed and, consequently, the collecting duct plays a major role in fluid and electrolyte homeostasis. Sodium transport is mediated by ENaCs under the control of aldosterone which binds to the mineralocorticoid receptor in the collecting duct. The mineralocorticoid receptor is promiscuous, and both mineralocorticoids and glucocorticoids can bind to it. Systemic glucocorticoid levels are three orders of magnitude greater than those of mineralocorticoids, which could result in binding of glucocorticoids to the mineralocorticoid receptor in the distal nephron. However, 11-β-hydroxysteroid dehydrogenase 2 catalyzes cortisol to cortisone, an inactive metabolite, in the collecting duct. In rats, the administration of prenatal dexamethasone and a maternal low protein diet reduce renal 11-β-hydroxysteroid dehydrogenase mRNA in adult rat offspring [47, 48]. While indirect, these data suggest that glucocorticoids may have a greater mineralocorticoid action in the collecting duct in programmed rats than in control rats. Studies have also shown that plasma aldosterone levels are higher in rats whose mothers were fed a low protein diet compared to offspring fed a normal protein diet, which could potentially increase sodium transport in the distal nephron [41, 52].

While previous studies have demonstrated that prenatally programmed rats either by prenatal dexamethasone or a low protein diet did not have an increase in any of the ENaCs in the distal nephron [53, 54], there is evidence that sodium transport in the collecting duct is increased in programmed rats. The administration of benzamil, an inhibitor of the ENaC, resulted in a greater natriuresis in programmed rats than in offspring of control rats, consistent with the ENaC having higher transport rates in programmed rats [52]. More direct evidence has been obtained from microperfusion studies where collecting ducts were dissected, perfused in vitro and sodium transport measured directly using ion-specific electrodes. The adult offspring of control rats had no sodium transport while there was robust sodium transport in the collecting duct of the programmed rats (Fig. 2c) [52].

Renal nerves

Using a rat model of uteroplacental insufficiency, Alexander et al. showed that bilateral renal denervation prevented the development of hypertension in programmed rats but had no significant effect on control rats [55]. In adult rats whose mothers were administered dexamethasone, renal denervation resulted in normalization of blood pressure to levels comparable to vehicle-treated controls [54]. Similar to programming with reduced uterine perfusion, denervation did not affect the blood pressure of control rats [54, 55].

The proximal tubule and thick ascending limb are innervated, and sodium transport is increased by renal nerve stimulation or peritubular addition of norepinephrine to perfused tubules [56–60]. Renal denervation reduces blood pressure, and the mechanism for this effect is likely linked to the role of renal nerves in the regulation of sodium transport. Research from our laboratory has shown that renal denervation normalizes the protein expression of the proximal tubule Na^+/H^+ exchanger, NKCC2 expression in the thick ascending limb and NCC expression (Fig. 3) in the distal convoluted tubule of programmed rats [54]. In this same study, we found no effect of renal denervation on transporter expression in the controls, consistent with an increase in sympathetic nerve activity causing an increase in sodium transport in several nephron segments, leading to sodium-dependent hypertension.

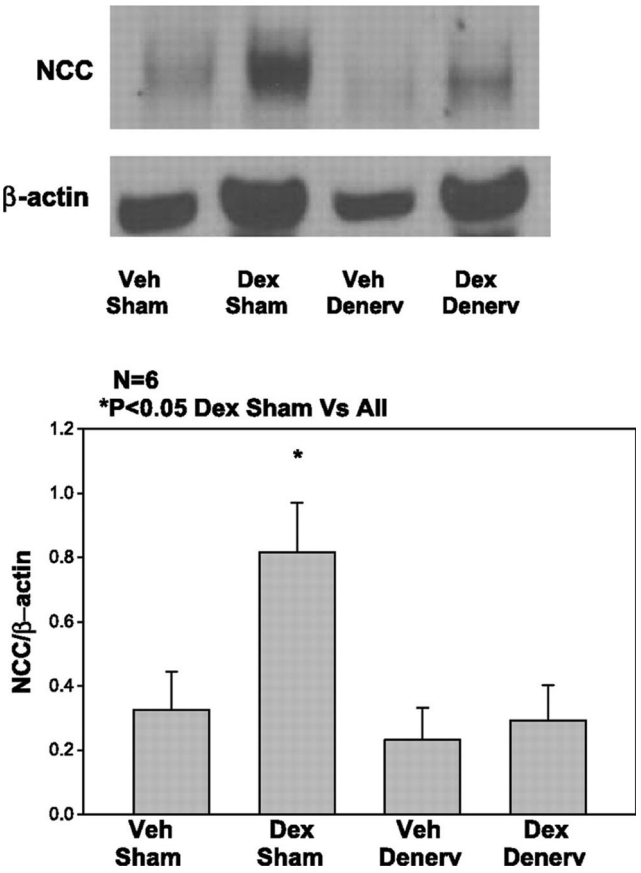

Fig. 3 Effect of prenatal dexamethasone (*Dex*) on sodium chloride cotransporter protein abundance (*NCC*) in the distal convoluted tubule. *Top* Typical immunoblot, *bottom* summary of the results of several experiments. *Veh* Vehicle, *Denerv* renal denervation. Renal denervation abolishes the increase in NCC protein abundance in programmed rats. Reproduced from Dagan et al. [54], used with permission

Our research group has directly measured renal sympathetic nerve activity in control and programmed rats [61, 62]. Interestingly, we found no difference in basal sympathetic nerve activity and blood pressure under anesthesia, but hind limb muscle contraction resulted in a significantly greater increase in blood pressure and sympathetic nerve activity in the programmed rats, as shown in Fig. 4. This coincides with the observations that blood pressure increases significantly in humans who are SGA with minor stress. We also found that treatment of rats with oral enalapril had no effect on control rats but abrogated the increase in blood pressure and increase in sympathetic nerve activity in programmed rats [62].

Renin–angiotensin–aldosterone system

The fact that every nephron segment has increased sodium transport is unlikely to be due an inherent upregulation of different transporters in each nephron segment. It makes much more sense for there to be a single system that is upregulated by programming and which regulates transport in all nephron segments. The renin–angiotensin system (RAS), either by angiotensin II or aldosterone, regulates sodium transport in every nephron segment.

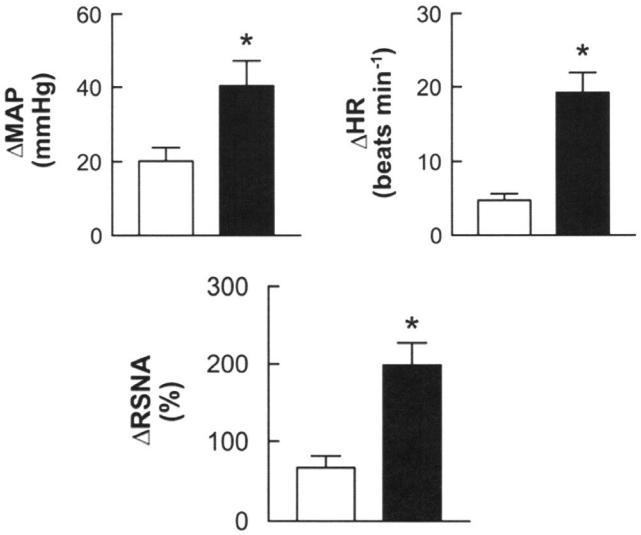

Fig. 4 Change in mean arterial pressure (*ΔMAP*), heart rate (*ΔHR*) and renal sympathetic nerve activity (*ΔRSNA*) in response to leg muscle contraction (exercise pressor reflex). *Black bars* Programmed group, *white bars* control group. There was no difference in blood pressure, heart rate or sympathetic nerve activity in anesthetized rats. However, in response to the exercise pressor reflex, there is a greater increase in blood pressure, heart rate and renal sympathetic nerve activity in the programmed rats compared to the controls. *Asterisk* indicates significance at $p < 0.05$ vs. the other group. Reproduced from Mizuno et al. [61], used with permission

As discussed above, serum aldosterone levels are elevated, which is a potential explanation for the increase in sodium transport in the collecting duct [41, 52]. Angiotensin II stimulates transport in the proximal tubule [60, 63–67], thick ascending limb [68] and distal convoluted tubule [69, 70].

While increased activity of the RAS could explain an increase in sodium transport, results from studies which have looked at the systemic RAS have been conflicting depending on the age of the animal and the type of prenatal insult. Plasma renin activity has been shown to be lower in rats whose mothers were fed a low protein diet than in controls at 4 and 8 weeks of age [41], but these same investigators found that plasma renin activity was elevated at 4, 6 and 11 months of age in programed rats compared to control rats [15, 71]. Plasma renin activity was comparable in rats whose mothers were administered prenatal dexamethasone relative to vehicle-treated rats at 4 and 8 weeks of age [72] and in 1-month-old male rats whose mothers had placental insufficiency [73]. There is no evidence that plasma angiotensin II levels are increased by prenatal programming [72, 74]; however, rats whose mothers were fed a low protein diet during the last half of pregnancy and had higher plasma angiotensin II levels while nursing than control rats [75]. In summary, while aldosterone can increase sodium transport in the distal nephron, prenatal insults alone do not cause an increase in plasma angiotensin II to account for the increase in blood pressure or increase in tubular sodium transport.

All of the components of the RAS are present in the kidney [76–80], and there is substantive evidence that the intrarenal RAS is modified by prenatal programming. Angiotensinogen is present in the proximal tubule and has been shown to be increased in 16-week-old rats programmed by placental insufficiency [73]. In the same study, renin mRNA expression and angiotensin-converting enzyme (ACE) activity were also increased in 16-week-old rats that were the offspring of rats with surgically induced placental insufficiency [73]. Prenatal programming due to dietary protein deprivation has been shown to increase the expression of type 1 renal angiotensin II receptor (AT1) [81]. Placental insufficiency did not affect AT1 receptor binding in 4-week-old rats assessed by quantitative radioligand autoradiography [73], but the offspring of mothers fed a low protein diet did show an increase in AT1 receptor mRNA and protein abundance at this age [74]. Renal angiotensin II content has been found to be comparable in 4-week-old rats whose mothers were fed a low protein diet and in 4- and 8-week-old rats programmed with prenatal dexamethasone [72, 74]. However, the prenatal administration of dexamethasone increased urinary angiotensin II levels, a reflection of renally produced angiotensin II, in programmed rats compared to control rats at 4 and 8 weeks of age [72]. ACE inhibitors and AT1 blockers have been shown to be effective in normalizing the blood pressure in programmed rats, consistent with a role of renin–angiotensin activation in the pathogenesis of hypertension with prenatal programming [19, 41, 71, 72].

In addition to the systemic RAS, there are several tissues which are able to produce angiotensin II from endogenously synthesized angiotensinogen, including the kidney. The proximal tubule produces angiotensinogen and generates and secretes angiotensin II at levels that are approximately 100- to 1000-fold higher than those in blood [77–80, 82–90]. A marker for the activity of the intrarenal RAS is urinary angiotensinogen, which correlates with renal but not serum angiotensin II levels [91, 92]. Recent studies have demonstrated that prenatal programming in rats, either by inducing uteroplacental insufficiency or feeding a pregnant mother a low protein diet, resulted in an increase in urinary angiotensinogen and angiotensin II levels in adult offspring of programmed rats [93, 94]. Our research group has shown that while prenatal administration of a low protein diet had no effect on systemic renin–angiotensin levels, programmed

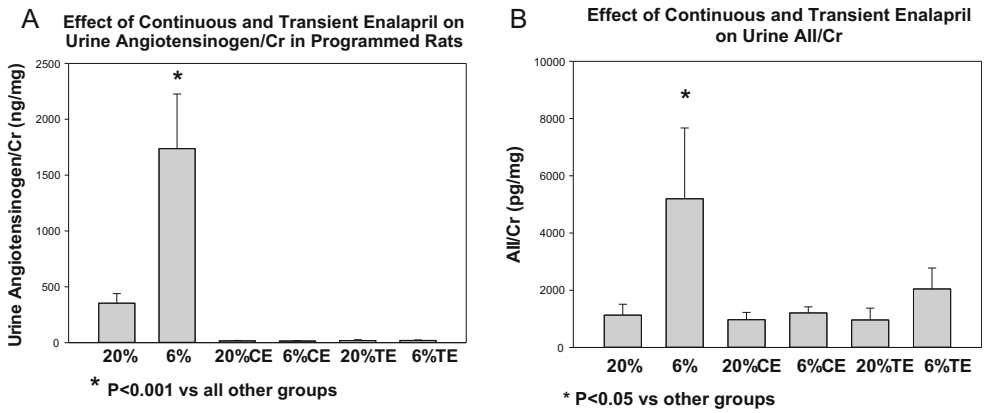

Fig. 5 Urine angiotensinogen and angiotensin II, both markers of the intrarenal renin–angiotensin system, in 6-month-old offspring of mothers fed a control diet (*20 %* protein) and those on a low protein diets during last half of pregnancy (*6 %*). The 20 % group and 6 % groups were administered either continuous enalapril from 3 weeks until time of study at 6 months (*CE*) or transient enalapril [enalapril in the drinking water from 3–6 weeks of age (*TE*)]. The 6 % group showed upregulation of the intrarenal renin–angiotensin system, as shown by increased urinary angiotensinogen/creatinine (*Cr*; **a**) and angiotensin II (*AII*)/Cr (**b**) compared to the 20 % group that was abrogated by both continuous and transient enalapril. Reproduced from Mansuri et al. [94], used with permission

rats had an increase in both urinary angiotensinogen and angiotensin II [93, 94]. Administration of enalapril to programmed rats for 3 weeks after the rats were weaned at 21 days of age resulted in normalization in blood pressure at 6 months of age [93, 94]. While transient administration of enalapril had no effect on the systemic RAS, it normalized the increase in urinary angiotensinogen and angiotensin II in programmed rats (Fig. 5) [94].

Renal sympathetic nerve activity and the intrarenal RAS are intimately linked. The effect of renal nerve stimulation to decrease urinary sodium excretion is blocked by administration of captopril in rats [95, 96]. Furthermore, the effect of renal nerves to augment sodium absorption is potentiated by intravenous administration of angiotensin II [96]. A recent study showed that renal nerve stimulation had no effect on plasma angiotensinogen levels but that it did increase both renal cortical angiotensin II levels and urinary angiotensinogen excretion [97]. Renal nerve stimulation has also been shown to decrease urinary sodium excretion and increased proximal tubule Na^+/H^+ exchanger activity and protein abundance, an effect blocked by pretreatment of the rats with losartan [97]. Thus, it is possible that the increase in renal sympathetic nerve activity in programmed rats leading to stimulation in sodium absorption occurs via a stimulation of the intrarenal RAS. If this is the case, the increase in sodium transport could be mediated by local angiotensin II production and would be abrogated by ACE inhibition or the administration of an AT1 blocker. This is yet to be determined.

Key summary points

- Prenatal insults resulting in SGA neonates result in hypertension, premature cardiovascular disease, chronic kidney disease, obesity and type II diabetes.
- Infants born SGA have a reduction in nephron number which may be a factor causing chronic kidney disease in later life.
- The cause for the hypertension with prenatal programming is multifactorial, but an increase in sodium transport in several nephron segments has been demonstrated in animal studies.
- Prenatal insults resulting in SGA rodents result in an increase in renal sympathetic nerve activity and an increase in the renal RAS that likely contribute to the increase in sodium transport in the proximal tubule, thick ascending limb and distal convoluted tubule.

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Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest.

Multiple choice questions

1. Which transporter generates the driving force for transport of sodium along the nephron.
   a) H^+-ATPase
   b) Na^+/H^+ Exchanger
   c) Na^+/K^+-ATPase
   d) NKCC2
   e) Carbonic anhydrase

2. Prenatal insults have been shown to:
   a) Decrease sodium transport in the renal tubules
   b) Reduce nephron number
   c) Reduce the size of glomeruli
   d) Increase glomerular filtration rate
   e) Cause a pressure natriuresis

3. Which prenatal insult has been shown to program hypertension?
   a) A high fat diet
   b) A low fat diet
   c) Uterine artery ligation
   d) A high protein diet
   e) A high phosphate diet

4. Offspring of the Dutch famine have an increased likelihood of which of the following problems except?
   a) Increased tubular glomerular feedback
   b) Diabetes
   c) Altered stress response
   d) Hyperlipidemia
   e) Early death from cardiovascular disease

5. Renal denervation has been shown to:
   a) Reduce ENaC expression in programmed rats
   b) Increase ENaC expression in control rats
   c) Normalize blood pressure in programmed rats
   d) Has no effect on transport
   e) Cause an increase glomerular number in programmed rats to control levels.

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Answers:

1: c
2: b
3: c
4: a
5: c