BANTAO Journal 2012; 10 (1): 1-5

BJ
BANTAO Journal

Editorial Comment

Developmental Programming –Importance for Nephrologists

Sanja Simic-Ogrizovic[1,2]

[1]Clinic of Nephrology, Clinical Center of Serbia, Belgrade, [2]School of Medicine, Belgrade University, Belgrade, Serbia

Introduction

The term "developmental programming" means the concept that many adult conditions or disease can have origins traced back to fetal and early postnatal life. Namely, developmental programming is the response by the developing mammalian organism to a specific challenge during a critical fetal time that alters the route of organ and tissue development with resulting persistent effects on the phenotype. Mammals pass more biological milestones before birth than any other time later in their lives. Each individual's phenotype is influenced by the developmental environment as much as by their genes [1].

The developmental origin of the disease hypothesis was first proposed by Barker and Osmond in The Lancet in 1986 [2]. This study was followed later by some human epidemiological and numerous animal investigations involving fetal undernutrition and/or low birth weight (LBW) and associated epigenetic influences in the development of common chronic diseases, such as hypertension, kidney disease, cardiovascular disease, liver disease, diabetes, and other metabolic abnormalities [3].

The two major topics of interest to nephrologists-hypertension and chronic kidney disease (CKD), commonly exist together and in everyday nephrological practice it is well known that the influence of one upon the other is difficult to elucidate. Moreover, hypertension is the number-two cause of end-stage renal disease (ESRD) after diabetes in the United States and Western countries. It is also a comorbid condition in approximately 61-66% of patients with an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m 2 [4].

In a historical article Brenner and Chertow [5] hypothesized that retardation of renal development, as occurs in individuals of low birth weight (LBW), gives rise to increased postnatal risks for systemic and glomerular hypertension, as well as an enhanced risk of expression of renal disease.

The mechanisms involved in developmental programming and hypertension include nutrition, oxidative stress and inflammation, glucocorticoids, transgenerational programmming and epigenetic changes.

This review article will try to converge the mechanisms involved in developmental programming for the nephrologist population through animal studies.

Animal models

With the aim of finding out how fetal insults result in hypertension and chronic kidney disease, investigators have used animal models, primarily experiments performed in rats and sheep that mimic the adverse events occuring in some pregnant women, such as maternal malnutrition, prenatal administration of glucocorticoids and uteroplacental insufficiency [6,7]. The most interesting experiments concerned:

a) possible pathways of maternal malnutrition and glucocorticoids leading to prenatal programming;
b) timing of adverse effects;
c) sex differences in response to an adverse maternal event;
d) nephron number, renal sodium transport, RAS and renal nerves in mechanisms causing hypertension and kidney disease by fetal programming;
e) effect of the postnatal environment on glomerular number and blood pressure.

a. Possible pathways of maternal malnutrition and glucocorticoids leading to prenatal programming

The fetus is protected from the relatively high concentration of maternal glucocorticoids by placental 11β-hydroxysteroid dehydrogenase type 2 (11β-hsd -2) that converts physiological maternal glucocorticoids to inactive metabolites. Rats fed a low-protein diet during pregnancy had lower placental 11β-hsd-2 activity [8-10]. Also dexamethasone can cause similar insults as dietary protein deprivation, because it is able to cross the placenta intact and is a poor substrate for 11β-hsd-2. In humans, placental 11β-hsd-2 activity was shown not to change substantively during gestation but was significantly reduced in placentas of small-for-gestational-age infants [11]. In an elegant experiment Langley-Evans [12] showed that exposure to a maternal low-protein diet in utero programmed hypertension in the offspring and the data are consistent with the hypothesis that corticosteroids of maternal origin play a role in this programming effect.

b. Timing of adverse effects

Depending on the timing and severity, each of these insults is associated with small-for-gestational weight infants. However, Moritz *et al.* [13] recently pointed out that prenatal

Correspondence to: Sanja Simic-Ogrizovic, Clinic of Nephrology, Clinical Center of Serbia, Pasterova 2, 11 000 Belgrade, Serbia; Phone: +381 64 167 58 25; E-mail: ssogrizovic@gmail.com

insults can result in programming a reduced nephron number and renal dysfunction in later life independent of LBW. From this point of view the question of the timing of the prenatal insult arises, which can determine programmed changes that affect the kidney. Woods *et al*. [14] found a reduction in glomerular number and elevated blood pressure in adult male offspring of pregnant rats that were fed a low-protein diet in the second half but not in the first half of pregnancy. They concluded that the window of sensitivity of adult blood pressure to prenatal protein restrictiton falls within the period of nephrogenesis in the rat. On the other hand glucocorticoids are often administered to pregnant women to accelerate fetal lung maturation and studies in vitro have shown that dexamethasone inhibited branching morphogenesis and reduced glomerular number when added to media of day 14.5 and day 15.5 embryonic rat metanephrons [15]. In an elegant animal experiment Ortiz *et al.* [16], showed that prenatal dexamethasone resulted in hypertension and a reduction in nephron number in adult offspring of pregnant rats when administered daily on days 15 and 16 or 17 and 18 of gestation but not before or after this time.
Nephrogenesis in the rat occurs during the last third of gestation and continues for a few days after delivery. It is obvious that the period of active nephrogenesis is the point when the kidney is most susceptible to injury, resulting in a reduction in nephron number and programming for hypertension in the adult offspring.

c. Sex differences in response to an adverse maternal event

In an animal study prenatal insults were found to affect males and females differently. In the previous mentioned study where dexamethasone was administered on days 14 and 15 of gestation, Oritz *et al*. [16] concluded that both male and female rats develop increased blood pressure with severe prenatal insults. However, milder maternal insults either affect only males or have only a transient effect on blood pressure in females. Other studies also showed that in response to moderate protein restriction during gestation in the rat, a reduction in nephron number associated with hypertension is observed only in male offspring [17] and that only male offspring exhibit vascular dysfunction in response to fetal hypoxia [18]. Therefore, the relative protection of females and the vulnerability of males to prenatal insults is probably associated with estrogen and testosterone.

d. Nephron number, renal sodium transport, RAS and renal nerves in the mechanism of hypertension and kidney disease by fetal programming

It is well known that the kidney is extremely sensitive to the effects of an adverse environment during critical windows of early development. In humans LBW is directly associated with oligonephronia [19] and the famous Brenner hypothesis [5,20,21] concerned infants with a small number of nephrons at birth who developed an impaired ability to excrete sodium leading to systemic and glomerular hypertension and eventually to glomerular sclerosis and impaired renal function. This has been demonstrated in most animal models of prenatal programming [16,22-24,] and also in clinical studies [19,25]. Nephron loss occuring in response to fetal insult is probably due to alterations in the expression of genes and growth factors critical for proper nephrogenesis [26]. Furthermore, as already pointed out, timing of the insult during development is critical for nephron balance. However in some animal models there is a no association between a reduction in nephron number and the development of hypertension [27]. Moreover, some of them demonstrate that compensatory hyperfiltration occurs in response to the reduction in nephron number leading to preservation of glomerular filtration rate [28]. Thus, a reduction in nephron number may not be a key mechanism in the developmental programming of hypertension but may be critical for the increased susceptibility to renal injury and disease observed in response to fetal insult [29].
On the other hand there is significant evidence that prenatal insults program increases in *renal tubular sodium transport*. In the animal models of Betratam *et al.* [9] adult rats whose dams were fed a low-protein diet or administered prenatal glucocorticoids had an increase in renal Na/K-ATPase mRNA loads. In another experiment Manning *et al*. [30] demonstrated increases in renal bumetanide-sensitive cotransporter (BSC2) and thiazide-sensitive cotransporter (TSC) but not the the apical proximal tubule Na/H exchanger-3 (NHE3), or any of the epithelial sodium channel (ENaC) subunits in offspring of females that had received restricted dietary protein compared with controls.
Sodium transport via ENaC in the distal convoluted tubule and collecting tubule is regulated by aldosterone. Glucocorticoids bind to the mineralocorticoid receptor with equal affinity to aldosterone but are prevented from having an effect because 11β-hsd 2 in the distal nephron converts cortisol to cortisone in humans and corticosterone to inactive 11-dehydrocorticosterone in the rat. Renal mRNA expression of 11β-hsd 2 was lower in adult rat kidneys that had undergone a prenatal insult than in controls [9]. Therefore, while whole kidney ENaC protein loads may not differ between controls and rats with prenatal insults, there still may be increased surface ENaC expression leading to higher rates of sodium absorption. Thus, critical alterations in the morphology and pathophysiology of the kidney occur in response to fetal insult. Developmental programmming of renal structure and function leads to marked changes in the renal pressure-natriuresis relationship resulting in salt-sensitive hypertension associated with diminished resistance to renal injury and disease. However, the mechanism by which the fetal environment programs sensitivity and an increased susceptibility to renal injury remains unknown and may involve either intrinsic or extrinsic renal mechanisms or both [7].
The renin-angiotensin system plays a fundamental role in nephrogenesis [31,32], in body fluid balance through systemic and intrarenal action of angiotensin and is also an importmant regulator of arterial pressure [33,34]. Pregnant women treated with an ACE inhibitor during the first trimester are at increased risk of having children with central nervous system and cardiovascular disorders [35], while ACE administered after the first trimester resulted in se-

vere renal damage leading to anuria and oligohydramnios [36]. In an animal model where rats received an AT blocker during the time when nephrogenesis was still occurring, had a reduced nephron number as well as a lower glomerular filtration rate, impaired renal concentrating ability and increased blood pressure compared with controls [37]. In another animal study maternal dietary protein deprivation resulted in offspring with lower renal renin mRNA, renal AT1-receptor protein, mRNA abundance and renal angiotensin II levels, but higher AT2-receptor mRNA levels [38-40]. Nevertheless, there are conflicting data concerning the association of plasma levels of angiotensin II with blood pressure. Thus, it could be concluded that prenatal insults probably result in renal injury by disturbing the renin-angiotensin system, but it is unlikely that RAS plays the primary role in generating or mediating the hypertension seen in neonates or adults that were small for gestational age.

Changes in *renal sympathetic nerve* activation have constant effects on natriuresis leading to long term alterations in blood pressure [41] but whether the sympathetic nervous system contributes to hypertension in LBW is controversial [42]. However, Johansson et al. [43] showed that elevations in circulating levels of catecholamines were greater in LBW children relative to their normal birth weight counterparts. Some animal studies demonstrated that chronic hypoxia during fetal development programmed by placental insufficiency [44,45] or fetal exposure to glucocorticoids [46] leads to sympathetic hyperinnervation. Increased sympathetic flow may be followed by upregulation of renal sodium transporters, increased sodium reabsorption, and hypertension [46]. Furthermore, in the experimental model of hypertension programmed by gestational malnutrition of Playdes *et al.* [47], expression of angiotensin II receptors was elevated in the low-protein offspring in regions of the brain critical for cardiovascular regulation. They pointed out a critical role for central angiotensin II in the etiology of programmed hypertension. Consequently, the pathogenesis of programmed hypertension may involve central activation of the RAS that leads to an increase in renal sympathetic nerve activity which in turn up-regulates sodium reabsorption resulting in hypertension.

Several animal studies [16,49,50] have demonstrated that a prenatal insult in rats results in pups that develop *progressive renal injury* over time. Thus, Oritz *et al.* [16] found that, subsequent to administration of dexamethasone on *days 15* and *16* of gestation, the offspring exhibited renal interstitial fibrosis, tubular atrophy, and glomerular sclerosis at 8 months of age.

e. Effect of the postnatal environment on glomerular number and blood pressure

As mentioned before nephrogenesis continues in humans until 34-36 weeks gestation, so premature human neonates born before this time still have new nephrons forming after birth. Also in rats, nephrogenesis continues for a few days after delivery. The postnatal environment can have a negative impact on renal development and may program changes in blood pressure. Recent evidence shows that postnatal nutrition and drugs can modulate prenatal programming of hypertension as well as the number of glomeruli. Schreuder *et al.* [51] demonstrated that postnatal food restriction in the rat is associated with growth retardation, with a 25% reduction in nephron number and a concomitant increase in glomerular volume compared with controls. On the other hand Yzydorczyk *et al.* [52] verified that neonatal oxygen exposure in rats leads to cardiovascular and renal alterations in adulthood. These findings have relevance to premature human neonates kept in a neonatal intensive care unit where, even under the best circumstances, neonates are not in an environment comparable to the intrauterine one. It also interesting that perinatal caloric excess can be harmful as well. Boubred *et al.* [53] showed that rats fed excess milk gained more weight and both males and females had significantly more glomeruli than the control offspring. Nonetheless, male offspring that were overfed had higher blood pressure at 2 months, proteinuria at 12 months and glomerulosclerosis at 22 months of age.

Regarding preventive measurements, the experimental study of Manning *et al.* [54] is very important. They demonstrated that administration of either a low-salt diet or an ACE inhibitor to offspring of mothers fed a low-protein diet at the time of weaning for 3 weeks prevented the development of hypertension. Blood pressure remained at control levels even though the low-salt diet and enalapril were discontinued weeks before the final measurement. Thus, there are critical times during postnatal development where one can potentially intervene and prevent hypertension. Whether this is true in humans has not yet been determined.

Lastly, all mentioned animal studies have revealed that prenatal programming of hypertension and renal injury is not definitive and can be adjust by postnatal environment.

Conclusions

In conclusion, in the last decade the structural and physiological alterations involved in the complex mechanisms of fetal programming were almost elucidated through numerous animal studies and some of them are pointed in this article. However, associations between hypertension and kidney injury in adults and events that occur in the early fetal milieu are need to be definitive approved in humans.

Conflict of interest statement. None declared.

References

1. Nijland MJ, Ford SP, Nathanielsz PW. Prenatal origins of adult disease. *Curr Opin Obstet Gynecol* 2008; 20(2): 132-138.
2. Barker DJ, Osmond C. Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. *Lancet* 1986; 1:1077-1081.
3. Nistala,R, Hayden M, DeMarco, *et al.* Prenatal Programming and Epigenetics in the Genesis of the Cardiorenal Syndrome. *Cardiorenal Med* 2011; 1(4): 243-254.
4. U.S. Renal Data System, USRDS 2010 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage RenalDisease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2010.

5. Brenner BM, Chertow GM. Congenital oligonephropathy and the etiology of adult hypertension and progressive renal injury. *Am J Kidney Dis* 1994; 23 (2): 171-175.
6. Baum M. Role of the kidney in the prenatal and early postnatal programming of hypertension. *Am J Physiol Renal Physiol* 2010; 298: F235-F247.
7. Nuyt AM, Alexander B. Developmental programming and hypertension. *Curr Opin Nephrol Hypertens* 2009; 18(2): 144-152.
8. Benediktsson R, Lindsay RS, Noble J, *et al*. Glucocorticoid exposure in utero: new model for adult hypertension. *Lancet* 1993; 41: 339-341.
9. Bertram C, Trowern AR, Copin N, *et al*. The maternal diet during pregnancy programs altered expression of the glucocorticoid receptor and type 2 11β-hydroxysteroid dehydrogenase: potential molecular mechanisms underlying the programming of hypertension in utero. *Endocrinology* 2001; 142: 2841-2853.
10. Langley-Evans SC, Phillips GJ, Benediktsson R, *et al*. Protein intake in pregnancy, placental glucocorticoid metabolism and the programming of hypertension in the rat. *Placenta* 1996; 17: 169-172.
11. Kajantie E, Dunkel L, Turpeinen U, *et al*. Placental 11_-hydroxysteroid dehydrogenase-2 and fetal cortisol/cortisone shuttle in small preterm infants. *J Clin Endocrinol Metab* 2003; 88: 493-500.
12. Langley-Evans SC. Hypertension induced by foetal exposure to a maternal low-protein diet, in the rat, is prevented by pharmacological blockade of maternal glucocorticoid synthesis. *J Hypertens* 1997; 15: 537-544.
13. Moritz KM, Singh RR, Probyn ME, Denton KM. Developmental programming of a reduced nephron endowment: more than just a baby's birth weight. *Am J Physiol Renal Physiol* 2009; 296: F1-F9.
14. Woods LL, Weeks DA, Rasch R. Programming of adult blood pressure by maternal protein restriction: role of nephrogenesis. *Kidney Int* 2004; 65: 1339-1348.
15. Singh RR, Moritz KM, Bertram JF, Cullen-McEwen LA. Effects of dexamethasone exposure on rat metanephric development: in vitro and in vivo studies. *Am J Physiol Renal Physiol* 2003; 293: F548-F554.
16. Ortiz LA, Quan A, Zarzar F, *et al*. Prenatal dexamethasone programs hypertension and renal injury in the rat. *Hypertension* 2003; 41: 328-334.
17. Ozaki T, Nishina H, Hanson MA, Poston L. Dietary restriction in pregnant rats causes gender-related hypertension and vascular dysfunction in offspring. *J Physiol* 2001; 530: 141-152.
18. Hemmings DG, Williams SJ, Davidge ST. Increased myogenic tone in 7-month-old adult male but not female offspring from rat dams exposed to hypoxia during pregnancy. *Am J Physiol Heart Circ Physiol* 2005; 289: H674-H682.
19. Hoy WE, Hughson MD, Bertram JF, *et al*. Nephron number, hypertension, renal disease, and renal failure. *J Am Soc Nephrol* 2005; 16: 2557-2564.
20. Brenner BM, Chertow GM. Congenital oligonephropathy: an inborn cause of adult hypertension and progressive renal injury? *Curr Opin Nephrol Hypertens* 1993; 2: 691-695.
21. Brenner BM, Garcia DL, Anderson S. Glomeruli and blood pressure. Less of one, more the other? *Am J Hypertens* 1988; 1: 335-347.
22. Celsi G, Kistner A, Aizman R, *et al*. Prenatal dexamethasone causes oligonephronia, sodium retention, and higher blood pressure in the offspring. *Pediatr Res* 1998; 44: 317-322.
23. Wintour EM, Moritz KM, Johnson K, *et al*. Reduced nephron number in adult sheep, hypertensive as a result of prenatal glucocorticoid treatment. *J Physiol* 2003; 549: 929-935.
24. Wlodek ME, Westcott K, Siebel AL, *et al*. Growth restriction before or after birth reduces nephron number and increases blood pressure in male rats. *Kidney Int* 2008; 74: 187-195.
25. Mackenzie HS, Lawler EV, Brenner BM. Congenital oligonephropathy: The fetal flaw in essential hypertension? *Kidney Int* (Suppl) 1996; 55: S30-S34.
26. Abdel-Hakeem AK, Henry TQ, Magee TR, *et al*. Mechanisms of impaired nephrogenesis with fetal growth restriction: altered renal transcription and growth factor expression. *Am J Obstet Gynecol* 2008; 199: 252-257.
27. Wlodek ME, Mibus A, Tan A, *et al*. Normal lactational environment restores nephron endowment and prevents hypertension after placental restriction in the rat. *J Am Soc Nephrol* 2007; 18: 1688-1696.
28. Woods LL, Ingelfinger JR, Nyengaard JR, Rasch R. Maternal protein restriction suppresses thenewborn renin-angiotensin system and programs adult hypertension in rats. *Pediatr Res* 2001; 49: 460-467.
29. Ojeda NB, Grigore D, Alexander BT. Developmental programming of hypertension: insight from animal models of nutritional manipulation. *Hypertension* 2008; 52: 44-50.
30. Manning J, Beutler K, Knepper MA, Vehaskari VM. Upregulation of renal BSC1 and TSC in prenatally programmed hypertension. *Am J Physiol Renal Physiol* 2002; 283: F202-F206.
31. Friberg P, Sundelin B, Bohman SO, *et al*. Renin-angiotensin system in neonatal rats-induction of a renal abnormality in response to aceinhibition or angiotensin-ii antagonism. *Kidney Int* 1994; 45: 485-492.
32. Guron G, Friberg P. An intact renin-angiotensin system is a prerequisit for normal renal development. *J Hypertens* 2000; 18: 123-137.
33. Hall JE, Guyton AC, and Mizelle HL. Role of the renin-angiotensin system in control of sodium excretion and arterial pressure. *Acta Physiol Scand Suppl* 1990; 591: 48-62.
34. Carey RM and Siragy HM. Newly recognized components of the renin-angiotensin system: potential roles in cardiovascular and renal regulation. *Endocr Rev* 2003; 24: 261-271.
35. Cooper WO, Hernandez-Diaz S, Arbogast PG, *et al*. Major congenital malformations after first-trimester exposure to ACE inhibitors. *N Engl J Med* 2006; 354: 2443-2451.
36. Tabacova S, Little R, Tsong Y, *et al*. Adverse pregnancy outcomes associated with maternal enalapril antihypertensive treatment. *Pharmacoepidemiol Drug Saf* 2003; 12: 633-646.
37. Woods LL, Rasch R. Perinatal ANG II programs adult blood pressure, glomerular number, and renal function in rats. *Am J Physiol Regul Integr Comp Physiol* 1998; 275: R1593-R1599.
38. Vehaskari VM, Stewart T, Lafont D, *et al*. Kidney angiotensin and angiotensin receptor expression in prenatally programmed hypertension. *Am J Physiol Renal Physiol* 2004; 287: F262-F267.
39. Woods LL, Ingelfinger JR, Nyengaard JR, Rasch R. Maternal protein restriction suppresses the newborn renin-angiotensin system and programs adult hypertension in rats. *Pediatr Res* 2001; 49: 460-467.
40. Woods LL, Ingelfinger JR, Rasch R. Modest maternal protein restriction fails to program adult hypertension in female rats. *Am J Physiol Regul Integr Comp Physiol* 2005; 289: R1131-R1136.
41. Lohmeier TE. The sympathetic nervous system and long-term blood pressure regulation. *Am J Hypertens* 2001; 14: 147S-154S.
42. Weitz G, Deckert P, Heindl S, *et al*. Evidence for lower sympathetic nerve activity in young adults with low birth weight. *J Hypertens* 2003; 21: 943-950.

43. Johansson S, Norman M, Legnevall L, *et al*. Increased catecholamines and heart rate in children with low birth weight: perinatal contributions to sympathoadrenal overactivity. *J Intern Med* 2007; 261: 480-487.
44. Tintu AN, Noble FA, Rouwet EV. Hypoxia disturbs fetal hemodynamics and growth. *Endothelium* 2007; 14: 353-360.
45. Alexander BT, Hendon AE, Ferril G, Dwyer TM. Renal denervation abolishes hypertension in lowbirth-weight offspring from pregnant rats with reduced uterine perfusion. *Hypertension* 2005; 45: 754-758.
46. Dagan A, Kwon HM, Dwarakanath V, Baum M. Effect of renal denervation on prenatal programming of hypertension and renal tubular transporter abundance. *Am J Physiol Renal Physiol* 2008; 295: F29-F34.
47. Pladys P, Lahaie I, Cambonie G, *et al*. Role of brain and peripheral angiotensin II in hypertension and altered arterial baroreflex programmed during fetal fife in rat. *Pediatr Res* 2004; 55: 1042-1049.
48. Alexander BT. Fetal programming of hypertension. *Am J Physiol Regul Integr Comp Physiol* 2006; 290: R1-R10.
49. Lucas SRR, Miraglia SM, Gil FZ, Coimbra TM. Intrauterine food restriction as a determinant of nephrosclerosis. *Am J Kidney Dis* 2001; 37: 467-476.
50. Regina S, Lucas R, Miraglia SM, *et al.* Intrauterine food restriction as a determinant of nephrosclerosis. *Am J Kidney Dis* 2001; 37: 467–476.
51. Schreuder MF, Nyengaard JR, Remmers F, *et al*. Postnatal food restriction in the rat as a model for a low nephron endowment. *Am J Physiol Renal Physiol* 2006; 291: F1104-F1107.
52. Yzydorczyk C, Comte B, Cambonie G, *et al*. Neonatal oxygen exposure in rats leads to cardiovascular and renal alterations in adulthood. *Hypertension* 2008; 52: 889-895.
53. Boubred F, Buffat C, Feuerstein JM, *et al.* Effects of early postnatal hypernutrition on nephron number and long-term renal function and structure in rats. *Am J Physiol Renal Physiol* 2007; 293: F1944-F1949.
54. Manning J, Vehaskari VM. Postnatal modulation of prenatally programmed hypertension by dietary Na and ACE inhibition. *Am J Physiol Regul Integr Comp Physiol* 2005; 288: R80-R84.