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Developmental programming and hypertension

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Abstract

Purpose of review—There is a growing body of evidence linking adverse events or exposures during early life and adult-onset diseases. After important epidemiological studies from many parts of the world, research now focuses on mechanisms of organ dysfunction and on refining the understanding of the interaction between common elements of adverse perinatal conditions, such as nutrition, oxidants, and toxins exposures. This review will focus on advances in our comprehension of developmental programming of hypertension.

Recent findings—Recent studies have unraveled important mechanisms of oligonephronia and impaired renal function, altered vascular function and structure as well as sympathetic regulation of the cardiovascular system. Furthermore, interactions between prenatal insults and postnatal conditions are the subject of intensive research. Prematurity vs. intrauterine growth restriction modulate differently programming of high blood pressure. Along with antenatal exposure to glucocorticoids and imbalanced nutrition, a critical role for perinatal oxidative stress is emerging.

Summary—While the complexity of the interactions between antenatal and postnatal influences on adult blood pressure is increasingly recognized, the importance of postnatal life in (positively) modulating developmental programming offers the hope of a critical window of opportunity to reverse programming and prevent or reduce related adult-onset diseases.

Keywords

gender difference; kidneys; oxidative stress; sympathetic nervous system; vascular function; vascular structure

Introduction

In 1964, Rose [1] reported the association of ischemic heart disease and infant mortality within the same families. Then Forsdahl in 1977 [2] showed that incidence of atherosclerotic heart disease in a certain age group could be correlated with the infant mortality rate of that same population. Interest in these types of association rose dramatically following extensive observations by Professor Barker and collaborators of a well documented population in England and Wales [3,4].

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The concept that many adult conditions or diseases can have their origins traced back to fetal and early postnatal life has been termed ‘developmental programming’. Principles underlying this concept are elegantly summarized by Nijland *et al.* [5].

Many studies have examined the impact of perturbations during gestation and neonatal life on long-term metabolic homeostasis (weight, food intake, serum lipids, and insulin resistance). The authors realize that ‘programmed’ obesity or insulin resistance can have an impact on the incidence of hypertension; nevertheless, the current review will focus on programming of elevated blood pressure itself.

Human studies: growth trajectories, prematurity, and twin studies

In epidemiological studies, the main variable examined has been (low) birth weight (LBW) and its relation with adult blood pressure and the incidence of cardiovascular-related morbidities and mortality. However, birth weight should be considered not as a triggering element in itself, but rather as the crude measure of a more global process resulting in altered development of organ structure or function or both and later life diseases. In fact, the true triggering exposures or elements, before and beyond LBW, are not yet fully determined.

Altered programming resulting in hypertension can begin *in utero*, but can also occur in postnatal life through modulation of nutrition composition [6,7], growth trajectories [8,9,10, 11], and premature birth [12–14]. Among light and thin newborns, those who grow rapidly after 2 years of age have a higher risk of hypertension and cardiovascular-related events as adults than those who remain short and thin throughout childhood [10,15]. Small babies who show catch-up growth before 2 years of age have a decreased risk of stroke in late adulthood [16]. In younger adults (~25 years), diastolic blood pressure is related to rapid weight gain in the first months of life (0–5), whereas systolic blood pressure is related to growth in the toddler years [11]. These studies suggest that growth trajectories after LBW result from differing prenatal insults and can differentially modulate cardiovascular morbidities.

Considering that the 50th percentile birth weight at 36 weeks was 2.6 kg (or 5.7 lbs) 40 years ago [17], it is plausible that a significant number of newborns have been labeled small for gestational age (SGA) [or ‘intra uterine growth restricted’ (IUGR)] in large epidemiological studies when in fact they were mildly premature. In 6-year-old children, both birth weight and gestational age are inversely associated with blood pressure; however, when modeled together, only birth weight remains significantly associated with blood pressure [18]. Gestational age at birth can influence cardiovascular reactivity to psychological stress, but with opposite effect in males vs. females [19].

Twin studies are very relevant to examine the respective roles of genetic factor, birth weight and prematurity on developmental programming (see thorough review by Davies [20]). Even though twin weights are on average significantly less than their singleton counterparts, twins do not show an increased incidence of hypertension and mortality from cardiovascular causes [21,22]. In a recent very large study of monozygotic and dizygotic twins born between 1926 and 1958, Bergvall *et al* [23••] showed that birth weight is inversely related to blood pressure independently of genetic and environmental factors.

Animal models

Many animal models have been used to study developmental programming of hypertension utilizing mostly rodents, but also sheep, swine, and guinea pigs. A majority of the studies have used nutritional intervention during gestation such as isocaloric protein-restricted diet, globally restricted or a contrario cafeteria-like diet, iron or other micronutrient-restricted or depleted diet (see [24,25] and reviews [26–28]). Elevated blood pressure in offspring has also been

triggered by antenatal administration of glucocorticoids, hypoxia, impaired placental perfusion or diabetes during gestation [29,30,31••], as well as neonatal hyperoxia or modifications of nutritional regimens [32••]. Programming can also be modulated by the genetic background of the animal studied [33•].

The kidney: nephron number, susceptibility to renal injury and disease, and salt sensitivity

The kidney is extremely sensitive to the effects of an adverse environment during critical windows of early development [34]. In humans LBW is directly correlated with a reduction in nephron number [35]; in animal models of developmental programming, whether characterized by normal or LBW, reduction in nephron number is often reported [36]. Nephron loss that occurs in response to fetal insult is likely due to alterations in the expression of genes and growth factors critical for proper nephrogenesis [37•,38] such as matrix metalloproteinase MMP-2 and MMP-9 metanephric expressions and activities which are reduced in pups of diabetic dams [39], with a critical role implicated for the renin-angiotensin system (RAS) [40], inducible enzyme cyclooxygenase-2 [41], glucocorticoids [41,42], and alterations in genes key to fetal renal apoptosis [43]. Furthermore, timing of the insult during development is critical to nephron complement [44,45]. Although a reduction in nephron number induced by uninephrectomy during the nephrogenic period in the rat leads to a marked decrease in glomerular filtration rate associated with hypertension in the adult animal [46], whether a reduction in nephron number plays a critical role in the developmental programming of hypertension is not clear. Birth weight is inversely correlated with blood pressure [47]; however, hypertension that occurs in response to fetal insult is not always associated with a reduction in nephron number [48,49]. Moreover, experimental studies demonstrate that compensatory hyperfiltration occurs in response to the reduction in nephron number leading to preservation of glomerular filtration rate [40]. Thus, a reduction in nephron number may not be a key mechanism in the developmental programming of hypertension [28,50]. A reduction in nephron number may be critical to the increased susceptibility to renal injury and disease observed in response to fetal insult [28,51]. Significant proteinuria and impaired renal function occur with aging in growth-restricted rats [52] and offspring of diabetic dams [31••], and susceptibility to a secondary renal insult is increased in rats developmentally programmed for a nephron deficit [53]. LBW also has an adverse effect on the progression and severity of renal disease in children [54] and adults [55,56], supporting the hypothesis proposed by Luyckx and Brenner [57] that hyperfiltration in LBW may lead to glomerular hypertension and a more severe course of renal disease and injury. Salt-sensitive hypertension is a critical contributor to the progression of chronic kidney disease. Birth weight is also inversely associated with salt sensitivity; a finding observed in LBW children [58], LBW adults [59•], and in animal models of developmental programming [45,60]. Independently of birth weight, offspring of diabetic dams have congenital nephron deficit, increased blood pressure as adults and salt-sensitive hypertension with altered renal sodium handling [31••]. Thus, critical alterations in the morphology and pathophysiology of the kidney occur in response to fetal insult. Developmental programming of renal structure and function leads to marked changes in the renal pressure–natriuresis relationship resulting in salt-sensitive hypertension associated with a diminished resistance to renal injury and disease. However, the mechanism by which the fetal environment programs salt sensitivity and an increased susceptibility to renal injury remains unknown and may involve both intrinsic or extrinsic renal mechanisms or both.

Renal nerves

Changes in sympathetic activity leading to reductions in pressure natriuresis result in long-term changes in arterial pressure [61]. Whether the sympathetic nervous system contributes to hypertension in LBW is controversial [62,63]. However, elevations in circulating levels of

catecholamines, neurotransmitters that serve as an indirect marker for sympathetic nerve outflow, are greater in LBW children relative to their normal birth weight counterparts [64, 65]. In addition, increased levels of plasma catecholamines are also reported in numerous experimental models of fetal programming [66,67]. In experimental studies chronic hypoxia during fetal development leads to sympathetic hyperinnervation [68] and the importance of the renal nerves, the critical link between changes in central output and alterations in renal excretory function [61], is demonstrated in the etiology of hypertension programmed by placental insufficiency [69,70] and fetal exposure to glucocorticoids [71]. The mechanism by which the renal nerves contribute to hypertension programmed in response to fetal insult was recently demonstrated to involve modulation of sodium transporter abundance [71], suggesting that increased sympathetic outflow may lead to upregulation of renal sodium transporters, increased sodium reabsorption, and hypertension. Upregulation of sodium transporters is also reported in offspring of protein-restricted dams [72], indicating common pathways programmed in response to different methods of fetal insult. The genesis of increased sympathetic activation is not known. However, the central actions of angiotensin II (ANGII) in regions of the brain critical for cardiovascular regulation can lead to an increase in sympathetic outflow including sustained increases in renal sympathetic nerve activity [73]. In an experimental model of hypertension programmed by gestational undernutrition expression of ANGII receptors is elevated in the low-protein offspring in regions of the brain critical to cardiovascular regulation; furthermore, blockade of the RAS via intracerebroventricular administration of an ACE inhibitor abolishes hypertension in low-protein offspring demonstrating a critical role for central ANGII in the etiology of programmed hypertension [74]. Thus, 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.

Vascular function

Endothelium-dependent vasodilatation is a well recognized precursor of elevated blood pressure and atherosclerosis. Several studies demonstrate that endothelial-dependent and endothelial-independent vasodilatation can be impaired and that flow-mediated dilation is decreased in LBW individuals at birth, at 3 months of age, in later childhood and in early adult life [75–77].

Vascular function in experimental animal models of programmed hypertension with exposure to a low-protein diet, globally restricted diet, uterine insufficiency and the antenatal glucocorticoid models has been recently reviewed [75,78]. *In vivo*, programmed hypertension is associated with unchanged or enhanced responses to vasoconstrictive agents such as ANGII, phenylephrine and endothelin, and is dependent on the vascular bed studied (conductance vs. resistance; cerebral vs. femoral vs. coronary arteries), the triggering insult, its timing and the age at which the offspring are studied; vascular dysfunction is often amplified with aging and males seem more affected than females [32•,49,79–83]. Increased myogenic tone is reported in offspring of dams maintained in hypoxia during gestation and seems also to amplify with age [84].

The enhanced vasomotor tone is often secondary at least in part to attenuated endothelium-mediated vasodilatation [27,85] with or without impaired vascular smooth muscle relaxation [86,87]. Reduced eNOS [88] and prostaglandin [84] participate in impaired vasodilatation. Vascular dysfunction can be associated with an enhanced generation of superoxide anion and decreased expression of soluble guanylate cyclase in the presence or not of decreased eNOS expression and nitric oxide production [29,32•,75,89,90]. The mechanisms and cascade of events linking perinatal adverse conditions and adult vascular dysfunction are not completely unraveled and, importantly, studies have not established so far whether vascular dysfunction

and enhanced vascular generation of reactive oxygen species are primary or secondary to elevated blood pressure.

Vascular structure

In addition to vascular dysfunction, perinatal conditions can alter the development of vascular structure. Remodeling of the aorta and mesenteric arteries is reported in 1-day-old and 2-month-old offspring of globally food-restricted dams [91], but not in other experimental models [49, 92]. The proportion of elastin vs. rigid collagen is a major determinant of arterial stiffness [93]. Arterial stiffness of large central arteries naturally occurs with aging and is also well established as an independent marker of cardiovascular risk in hypertension [94]. Elastin synthesis in the vessels peaks in the prenatal period and is minimal in the adult aorta [95]. IUGR rats and offspring of globally nutrient-restricted dams have lower elastin content, increased MMP-9 and MMP-2 (involved in extracellular matrix deposition), increased arterial stiffness, and remodeling of the extracellular matrix in conduit and resistance vessels [91,96, 97].

In humans, premature birth and LBW are correlated with increased arterial stiffness in children, adolescents, and adults [98]. Collagen I and III mRNA are increased in IUGR cord blood [99]. LBW is also associated with increased stiffness of large arteries, reduced aortic size and compliance [100], and increased aortic wall thickening [101], narrowing of coronary arteries [102] and carotid arteriosclerosis [103,104].

Structural anomalies of smaller arteries and capillary rarefaction are also reported in humans and in experimental studies. Narrower retinal arterioles in 51–72-year-old individuals are associated with self-recalled LBW [18•]. In adults, retinal narrowing is a reliable marker of future hypertension and cardiovascular risks [105,106]. Retinal vascularization is found altered in young adults born pre-term (without a history of retinopathy of prematurity) [107] or born at term but SGA [108]. More recently, Mitchell *et al.* [109••] reported, in a study of 1369 6-year-old children, a significant correlation between retinal arteriolar narrowing and LBW, birth length and head circumference; interestingly, the correlation is linear over the whole spectrum of birth weight.

In animal studies, rat offspring of low-protein-fed dams or of globally nutrient-restricted dams have reduced capillary density in striated muscle, mesenteric bed and renal medulla, impaired angiogenic capacity and reduced vascular endothelial growth factor expression [49,110]. Capillary rarefaction is prevented by administration of a lipid peroxidation inhibitor to pregnant low-protein-fed dams [111], suggesting a role for perinatal oxidative stress. Indeed, capillary rarefaction is present and precedes elevation of blood pressure (BP) in rats subjected to a hyperoxic stress in the newborn period [32••].

Sex hormones

An inverse association is observed between birth weight and BP in both men and women [112,113]. However, LBW is associated with sex-specific responses to fetal insult. The inverse relationship between birth weight and cardiovascular disease is greater for the lower percentile of birth weight in women [112]; low-normal kidney function is observed in LBW men and women, but the association is weaker and less consistent in women [114]. Importantly, associations between chronic kidney disease and LBW are observed in men, but not in women [115]. Sex differences in developmental programming are also observed in children. LBW in boys is associated with higher BP and vascular resistance in response to stress; whereas LBW in girls is associated with marked alterations in cardiovascular physiology [116]. Sex-specific differences in response to fetal insult are also observed in experimental studies with a protective status observed in the female gender [117]. In response to moderate protein restriction

administered during gestation in the rat, a reduction in nephron number associated with hypertension is observed only in male offspring [40,118]; severe protein restriction is required to induce adverse programming effects in female offspring [45]. Only male offspring exhibit vascular dysfunction in response to fetal hypoxia [84]; vascular dysfunction is enhanced in male offspring of nutrient-restricted dams [83]. Hypertension programmed in response to placental insufficiency in the rat results in hypertension in adult male, but not in female, growth-restricted offspring [119•,120•]. In sheep BP is higher in male offspring after fetal exposure to glucocorticoids [121]. Therefore, sex differences in developmental programming are observed with female offspring exhibiting a protected status regardless of the species or specific fetal insult. Only a few studies have begun to elucidate the mechanisms leading to sex differences in the developmental programming of adult disease. A critical role for sex hormones is indicated to contribute to sex differences in hypertension programmed in response to placental insufficiency in the rat. Testosterone is demonstrated to be a key factor in hypertension programmed in adult male growth-restricted offspring [119•]; estradiol is implicated to play a protective role against hypertension in adult female growth-restricted offspring [120•]. The mechanism by which sex hormones contribute to sex differences in this model of developmental programming may involve modulation of regulatory systems critical to long-term control of BP. In the RAS, the ACE2-dependent pathway generates the vasoactive peptide angiotensin (1–7), a negative regulator of the vasoconstrictor effects of ANGII [122]. Expression of ACE2 mRNA is enhanced in normotensive adult female growth-restricted offspring; however, ovariectomy normalizes ACE2 mRNA expression to control levels while inducing hypertension in female growth-restricted offspring [120•]. Thus, modulation of the RAS by estradiol may be one mechanism that contributes to sex differences in the developmental programming of hypertension.

Mechanisms

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

Nutrition

As the first studies which associated LBW and higher BP were carried out in poor socioeconomic milieu, nutrition was considered a probable cause of programming. Imbalances between macronutrients and in micronutrients are now considered to be critical in global nutritional restriction. The impact of poor/imbalanced nutrition in the fetal and neonatal life is particularly important in girls and women who expose their children to impaired intrauterine milieu through altered vascular function and increased incidence of type II diabetes and preeclampsia, thereby perpetuating cardiovascular programming to the subsequent generation [123] (see below).

The impact of nutrition is further unraveled through supplementation studies. Folate supplementation of low-protein-fed dams prevents elevation of BP, impaired endothelium-dependent vasodilatation and reduced nitric oxide synthase mRNA levels [90]; this study is of note as folate is a methyl donor, a key element in modulating epigenetic changes (see below). Fish oil administered to low-protein-fed dams minimizes the elevation of BP and the reduced microcirculation in the myocardium in the offspring [124]. Omega-3 supplementation of pregnant dams which receive dexamethasone prevents intrarenal ACE activation in the offspring [125]. Vitamin D supplementation in infancy is associated with a reduced incidence of preeclampsia [126]. Insufficient vitamin D intake is also incriminated in the short height and reduced pelvic diameter in mothers of LBW babies with increased risk of hypertension [127].

Oxidative stress and inflammation

Children born SGA display higher indices of lipid peroxidation and slightly higher systolic BP than appropriate for gestational age controls [128•,129•]. Many adverse fetal and neonatal conditions are associated with oxidative stress or are pro-oxidant in nature [130,131]. A recent study demonstrated the correlation between maternal C reactive protein, a marker of inflammation, and atherosclerosis lesions in children [132].

Experimental data support the hypothesis that oxidative stress may be the initiating trigger in developmental programming of hypertension. Supplementation of the spontaneously hypertensive rat during gestation and early postnatal weeks with L-arginine (which favors the formation of nitric oxide) and antioxidants results in a persistent reduction in adult BP [133]. Administration of the peroxidation inhibitor lazaroid to low-protein-fed dams prevents hypertension and vascular dysfunction in the offspring [134]. Using the opposite approach, we recently demonstrated that adult rats exposed to hyperoxic stress as newborns display elevated BP, vascular dysfunction, and microvascular rarefaction [32••].

Glucocorticoids

One of the major hypotheses in the developmental programming field postulates a key role for antenatal exposure to stress hormones (glucocorticoids) (reviewed in [78,135]). These steroids can be exogenous or endogenous (generated by maternal physiological or psychological stressors). Lower expression of 11-beta hydroxysteroid dehydrogenase type 2 (11 β -HSD2), which catalyzes the conversion of active glucocorticoids into their inactive 11-keto metabolites, and higher circulating levels of active glucocorticoids are correlated with lower birth weight in humans [136]. Glucocorticoids administered antenatally cross the placenta and reach the fetus leading to elevated BP with or without reduced birth weight in animal models [78]. In humans, the synthetic glucocorticoids betamethasone or dexamethasone (poor substrates of 11 β -HSD2) are administered to pregnant women at risk of delivering prematurely to reduce pulmonary and also renal and cerebral morbidity in the immediate neonatal period [137]. The long-term consequences of antenatal exposure to glucocorticoids in humans are not completely known, in part because premature babies exposed to glucocorticoids and who have survived are only reaching their 30s. However, studies report no change, or a slight, but significant increase in BP [138–140]; interestingly, one study did show an association with insulin resistance [141]. Antenatal exposure to excess glucocorticoids can program the hypothalamus–pituitary–adrenal axis, which also has an impact on the incidence of hypertension [78].

Elevated BP after antenatal glucocorticoid exposure probably results from impaired nephron development, vasomotor dysfunction and altered activation of the Na/K-ATPase- α 1 and the renin–angiotensin–aldosterone system with increased expression of AT1 and AT2 ANGII receptors as well as changes in noradrenergic activity in the heart and baroreflex control of the sympathetic system [78,125]. Changes in the expression of glucocorticoid metabolizing enzyme 11 β -HSD types 1 and 2 are reported in the placenta and the kidneys of offspring of nutrient-restricted ewes [42,142]. In adult rats, glucocorticoids increase AT1 mRNA and protein expression in specific brain regions implicated in central cardiovascular control as well as in vessels [143–145].

Transgenerational programming and epigenetic changes

Experimentally, transmission to the next generation of a ‘programmed’ phenotype has been demonstrated for birth weight, metabolic dysfunction [5,146,147], and recently for elevated BP and vascular dysfunction [148•]. Wild type mice born to hypertensive heterozygous NOS3 knockout mice display hypertension and enhanced vasoconstriction to phenylephrine and impaired endothelium-dependent vasodilatation [148•]. Such transmission can be attributed to

the fact that the programmed mother with vascular dysfunction will provide a deprived intrauterine environment to her offspring, thus perpetuating the cycle of fetal (mal)adaptations. An alternative possibility is that epigenetic modification of the germ line by stable DNA methylation, chromatin modification or histone acetylation caused by the prenatal exposure will transmit the prenatal experience of one generation to future generations. Nutrition, glucocorticoids, and free radicals can modulate gene methylation [149–153]. In offspring of low-protein-fed dams, the methylation status of the angiotensin II AT1b receptor in the adrenal is modified [154].

Conclusion

The magnitude of fetal and early postnatal influences on adult health and diseases, although intuitively known for centuries, is only starting to be assessed. Demonstrated and probable mechanisms underlying the altered development of organs and their functions are revealing their complexity and interactions by way of growth trajectories, the timing of the prenatal insult and the prenatal and postnatal environment [127,155]. One should not expect to find only one causal factor and, as with many complex diseases, many elements concur to result in a symptom and ultimately a disease such as hypertension. This complexity should caution the precipitous initiation of trials aiming at preventing or reversing early life programming.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 170–171).

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