Editor: Marcelo Correia

Pre-natal programming of blood pressure and hypertension

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ABSTRACT

Historically, genetics and lifestyle have been considered the primary underlying causes of hypertension. However, recent epidemiological studies indicating that size at birth is linked to increased cardiovascular risk and hypertension in later life suggest that prenatal influences contribute to the development of hypertension and cardiovascular disease. Confirmatory findings from animal studies demonstrate that prenatal programming occurs in response to an adverse fetal environment and leads to permanent alterations in the structure and pathophysiology of the fetus resulting in the disregulation of blood pressure control and an increased cardiovascular risk in later life. This review will concentrate on the common phenotypic outcomes of prenatal programming and discuss potential mechanisms that mediate these adaptive responses.

KEYWORDS

Hypertension, nephron number, glucocorticoids, renin angiotensin system, sympathetic nervous system, sex hormones.

INTRODUCTION

Historically the etiology of hypertension and cardiovascular disease has included genetic and lifestyle influences. However, based on geographical studies linking infant mortality from the early 1900's and mortality ratios from coronary heart disease 50 years later, David Barker proposed that the prenatal environment was also a major influence for later cardiovascular risk[1]. Furthermore, Barker proposed that the prenatal programming of adult disease occurs in response to an adverse influence during intrauterine life that leads to adaptations by the fetus to allow fetal survival, but results in long-term permanent changes in the physiology, endocrinology, and structure of the fetus predisposing that individual to an increased cardiovascular risk in later life[2]. To date, this hypothesis has been confirmed by numerous epidemiological studies[3,4,5] and by experimental studies utilizing animal models that mimic the condition of slow fetal growth associated with increased risk for adult disease with a strong emphasis centered on investigation into the mechanisms involved in the prenatal programming of blood pressure[6-12]. With fetal undernutrition, fetal growth is limited, resulting in a small for gestational age newborn[13]. Fetal adaptations to undernutrition in late gestation result in a redistribution of blood flow leading to an asymmetric form of intrauterine growth restriction (IUGR)[2,13] associated with an increased risk for chronic adult disease[14]. Numerous methods have been employed to induce fetal undernutrition in animal studies. Methods include maternal undernutrition during gestation[7,8,10,11], placental insufficiency[6,9], or pharmacological manipulations[12]. Despite subtle differences in the method of insult, common phenotypic outcomes are observed in these different animals models of prenatal programming and demonstrate characteristics reflective of the human condition of slow fetal growth including asymmetric fetal growth restriction[14],

Recebido: 1/11/2007 Aceito: 26/11/2007

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decreased nephron number[15,16], impaired vascular function[17,18], and marked elevations in blood pressure[3,4,5]. Although there is convincing epidemiological and experimental data to suggest that cardiovascular disease and hypertension are programmed by prenatal influences, the underlying pathophysiological mechanisms remain unclear.

REDUCED NEPHRON NUMBER

One mechanism that may contribute to the prenatal programming of hypertension may involve the ability of the kidneys to maintain normal excretory function. Total nephron number in humans is correlated with birth weight suggesting a reduction in nephron complement may limit the ability of the kidneys to maintain normal excretory function[15,16]. A reduction in nephron number is a common adaptive outcome observed in many animal models of prenatal programming induced by different methods of prenatal insult despite the different species utilized for study[7,10,11,12,19,20]. Proper renal development requires a balance of proliferative and apoptotic processes leading to the development of the permanent kidney[21]. An increase in renal apoptosis is observed in models of prenatal programming induced by placental insufficiency[19] and undernutrition [10,22] suggesting that disregulation of apoptotic factors contributes to the prenatal programming of reduced nephron complement. Alterations in the apoptosis cascade associated with a reduction in nephron number in IUGR may involve cyclooxygenase-2 (COX-2), an enzyme linked to inhibition of apoptosis[23]. Renal expression of COX-2 is decreased in the developing kidney of IUGR offspring exposed to placental insufficiency in the rat[24]. Importantly, inhibition of COX-2 during pregnancy in the rat leads to alterations in renal structure of the offspring[25] implicating an important role for COX-2 in nephrogenesis. COX-2 expression is also down-regulated in response to overexposure to glucocorticoids[26]. A decrease in 11 beta-hydroxysteroid dehydrogenase type 2 (11B-HSD2), an enzyme that inactivates cortisol, thus serving as a barrier for fetal exposure to maternal glucocorticoids, is observed in pregnancies complicated by IUGR[24] and in models of prenatal programming induced by placental insufficiency[27] or maternal undernutrition during gestation[28] in the rat. Administration of glucocorticoids during gestation in the rat and sheep leads to reduced nephron number[12,29,30,31] suggesting a causative role for glucocorticoids in the prenatal programming of reduced nephron number. Thus, exposure to glucocorticoids under conditions that mediate IUGR may lead to a reduction in COX-2 and an increase in renal apoptosis leading to a reduction in nephron compliment. Metabolites of COX-2 are also implicated in renin release[32] and down-regulation of COX-2 leading to suppression of renin may also be an intrinsic component of the mechanistic pathway involved in the prenatal programming of reduced nephron compliment. A reduction in the renal RAS is observed at birth in models of prenatal programming induced by placental insufficiency[33,34] and maternal undernutrition[11]. Furthermore, perinatal blockade of the renin angiotensin system (RAS) leads to marked reductions in nephron number associated with marked increases in blood pressure in the offspring[35,36] indicating that suppression of the RAS during nephrogenesis contributes to reduced nephron compliment. Further investigation is warranted to determine the exact integration of the COX-2 and RAS mechanistic pathways in the prenatal programming of reduced nephron number. Further investigation is also warranted to determine whether a reduction in nephron number plays an important role in the etiology of prenatal programmed hypertension.

Although numerous investigators have examined the importance of reduced nephron complement in the etiology of hypertension programmed by prenatal insult, whether a reduction in nephron number is a critical component in the etiology of prenatal programmed hypertension is unclear. Neonatal uninephrectomy is associated with hypertension in the rat[37] and genetic manipulation via conditional knockout of fibroblast growth factor receptor 2, a growth factor that is expressed in the developing kidney[38], also induces a reduced nephron complement associated with marked increases in blood pressure[39]. However, glucocorticoid exposure in the spiny mouse leads to a marked reduction in nephron number that is not associated with a marked increase in blood pressure[31] suggesting a reduction in nephron number resulting from an insult during nephrogenesis is not always sufficient to increase blood pressure. Additionally, a reduction in nephron number in animal models of prenatal programming is consistently associated with an increase in glomerular volume[40]. Thus, an increase in glomerular size may be a sign of compensatory hyperfiltration and hypertrophy in response fewer nephrons at birth. Glomerular filtration rate is not decreased in a model of prenatal programming induced by placental insufficiency[6] suggesting mechanisms that are not renal hemodynamically mediated contribute to hypertension programmed by prenatal insult. Therefore, although a reduction in nephron number may diminish resistance to mechanisms of renal damage in adult life[41,42], other systems critical to the long-term regulation of sodium and volume homeostasis such as the sympathetic nervous system (SNS) or the RAS may contribute to hypertension programmed by prenatal insult.

IMPAIRED VASCULAR FUNCTION

Vascular dysfunction is implicated in the etiology of cardiovascular disease[43] and may also contribute to hypertension programmed by prenatal insult. Impaired vascular function is observed in healthy low birth weight individuals[17] including children[18] suggesting that endothelial dysfunction is a consequence of

prenatal insult and thus, a contributor to increased cardiovascular risk. Impaired vascular function is a common phenotypic outcome in experimental models of prenatal programming. Vasoconstriction to angiotensin II (ANG II) is exacerbated in animal models of prenatal programming induced by maternal protein restriction during gestation[44,45], an effect reversed by angiotensin converting enzyme (ACE) inhibition or blockade of the angiotensin type 2 receptor (AT_1R)[44]. Although an enhanced vascular responsiveness to ANG II is not observed in response to prenatal exposure to dexamethasone, chronic ANG II does increase blood pressure[45], suggesting a role for the RAS in the prenatal programming of impaired vascular function. Reduced nitric oxide bioavailability and increased oxidative stress may also contribute to impaired vascular function observed in animal models of prenatal programming induced by maternal protein restriction during gestation[46,47,48] and placental insufficiency[49].

HIGH BLOOD PRESSURE

A marked elevation in mean arterial pressure (MAP) is another common adaptive outcome observed in animal models of prenatal programming[7-11]. Experimental studies indicate that the timing of the prenatal insult is critical to the development of hypertension[40,50]. Animal studies demonstrate that when the prenatal insult occurs during the nephrogenic period, significant increases in MAP are observed[40,50]. However, the same insult initiated prior to the nephrogenic period does not lead to an increase in blood pressure[40,50]. Changes in nephron complement follow the blood pressure response in these studies suggesting that an insult during nephrogenesis leads to 'programming' of the kidneys resulting in disregulation of the normal regulatory systems involved in blood pressure regulation.

Many regulatory mechanisms such as the SNS control sodium balance and an alteration in sympathetic activity can have sustained effects that result in long-term changes in arterial pressure[51]. In humans sympathetic activation is observed in low birth weight individuals[52,53], and is increased in response to hypoxia in animals[54]. Increased circulating catecholamines, neurotransmitters which serve as an indirect marker of sympathetic nerve outflow, are also reported in numerous models of prenatal programming[55,56,57]. Recent studies from our laboratory demonstrate that the renal nerves play a critical role in the etiology of hypertension programmed by placental insufficiency[58]. Renal denervation normalizes arterial pressure in IUGR offspring in a model of prenatal programming induced by placental insufficiency in the rat with no significant effect on blood pressure in control offspring[58]. Thus, activation of the SNS and increased sympathetic outflow to the kidney may be one mechanism involved in the prenatal programming of blood pressure and hypertension. However, the underlying mechanisms leading to SNS activation are unknown. Hypoxia is a potent stimulator of hyperinnervation[54] and hypoxia induced in response to placental insufficiency during fetal development may serve as a stimulus for increased renal sympathetic outflow. Sustained increases in renal sympathetic nerve activity can also occur as a result of the central actions of ANG II[59]. ANG II is elevated in areas of the brain critical to cardiovascular regulation in models of prenatal programmed hypertension[60] indicating that integrative actions by different regulatory systems may contribute to the programming effects on blood pressure regulation.

The RAS is also demonstrated to play a critical role in the maintenance of hypertension programmed by prenatal insult. The RAS is a major regulatory system involved in the long-term regulation of blood pressure control and volume homeostasis[61]. Blockade of the RAS prevents or abolishes hypertension in animal models of prenatal programming induced by maternal protein restriction during gestation or placental insufficiency demonstrating the importance of the RAS in the etiology of prenatal programmed hypertension[62-65]. Although suppression of the intrarenal RAS is observed at birth[11], later inappropriate activation including increased expression of angiotensin type II receptors[66,67], in addition to, increased sensitivity to angiotensin II is observed in animal models of prenatal programming induced by maternal protein restriction during gestation. A critical role for the central RAS is also implicated in mediating hypertension programmed in response to gestational protein undernutrition. AT_1R binding is elevated in areas of the brain involved in cardiovascular regulation in offspring from protein restricted dams[60]. Blockade of the RAS administered via an intracerebroventricular cannula abolishes hypertension in the low protein offspring indicating the importance of central ANG II in the maintenance of programmed hypertension[60]. Therefore, activation of the RAS occurs in response to adverse prenatal influences and contributes to the disregulation of blood pressure control. Although the exact mechanisms leading to inappropriate activation of the RAS remain unknown, prenatal exposure to glucocorticoids may contribute to the increased expression of central ANG II[68]; SNS activation may be a factor in the later inappropriate activation of the systemic RAS.

An increase in oxidative stress is indicated to play an important role in essential and experimental hypertension[69]. An increase in oxidant status is observed in animal models of prenatal programming[70,71] and in children born small for gestation[72]. Treatment with the superoxide dismutase mimetic, tempol[71], or the lipid peroxidation inhibitor, lazaroid[70], abolishes hypertension in animals models of prenatal programming induced by gestational undernutrition suggesting oxidative stress may play a critical role in the prenatal programming of hypertension. Recent studies indicate that a loss of nitric oxide bioavailability may contribute to

increased oxidative stress[73] in the disregulation of blood pressure and hypertension in addition to impaired vascular function. Vasoactive factors such as ANG II[69] or glucocorticoids[74] can stimulate production of reactive oxygen species and superoxide causing an increase in oxidative stress and disregulation of arterial pressure control. Therefore, in response to an adverse prenatal influence, overexposure to glucocorticoids and the subsequent activation of the RAS may lead to increased oxidative stress and result in the programming of hypertension.

Sex differences are observed in human essential hypertension and in experimental models of hypertension[75,76,77]. Sex differences are also observed in animal models of prenatal programming with severity of the prenatal insult critical to phenotypic outcome[78]. Moderate nutrient restriction during gestation leads to programmed hypertension in male, but not female offspring[11,40,78]; only under conditions of severe nutritional restriction do female offspring develop hypertension[40,78]. Induction of IUGR by gestational exposure to sFlt-1, an anti-angiogenic factor, also results in sex differences with hypertension observed in male, but not female offspring[79]. Sex differences are also observed in a model of prenatal programming induced by placental insufficiency[6,62,63]. Adult male IUGR offspring exhibit significant elevations in mean arterial pressure relative to their adult male control counterparts[6]. Castration abolishes hypertension in adult male IUGR suggesting a critical role for testosterone in the maintenance of hypertension in IUGR offspring[62]. Adult female IUGR offspring are normotensive relative to their adult control counterparts; however, ovariectomy leads to a marked increase in MAP in female IUGR, but not control offspring[63]. Restoration of physiological levels of estradiol in ovariectomized females normalizes blood pressure in IUGR suggesting that estradiol is protective against hypertension in this model of prenatal programming. Although this suggests that sex hormone play a mechanistic role in blood pressure control in prenatal programming of hypertension, their effects may not be direct, but may influence blood pressure via modulation of regulatory systems critical to the long-term control of blood pressure.

The RAS is one such system that may contribute to sex differences in blood pressure control via regulation by sex hormones. Renin and angiotensinogen mRNA expression are androgen dependent[80,81] and can contribute to hypertension in experimental models of hypertension[81]. In the model of prenatal programming induced by placental insufficiency, renal angiotensinogen mRNA expression is significantly increased in adult male IUGR offspring[33]. Thus, testosterone may serve as a stimulus for enhanced intrarenal angiotensinogen in adult male IUGR offspring contributing to hypertension in adulthood and sex differences in this model of prenatal programming. Modulation of the RAS by estradiol may also contribute to sex differences. Tissue expression of ACE, the enzyme critical to the formation of ANG II, is downregulated by estradiol[82]. In the model of prenatal programming induced by placental insufficiency, a significant increase in renal mRNA expression and activity of ACE2[63], an enzyme which generates ANG[1-7], a peptide that counteracts the vasoconstrictor effects of ANG II[83], is observed in adult female IUGR. Ovariectomy reduces this increase in renal ACE2 mRNA expression and activity in conjunction with the development of hypertension[63] suggesting estradiol plays a protective role and ovariectomy leads to a decrease in the vasodilator effect provided by the ACE2 pathway leading to increases in blood pressure in adult female IUGR offspring. Therefore, permanent alterations in the RAS occur in response to fetal insult; and modulation of the RAS by sex hormones is one mechanism that may contribute to sex differences in blood pressure regulation in programmed hypertension.

CONCLUSIONS

Epidemiological and experimental studies link fetal physiology to adult pathophysiology. The mechanisms whereby an adverse prenatal influence programs alterations in the fetal physiology leading to increased cardiovascular risk in later life are multifactorial and involve alterations in the regulatory systems critical to the long-term control of blood pressure regulation. Intrauterine growth restriction, indicative of fetal undernutrition, is associated with an increased exposure to glucocorticoids. Excess glucocorticoids may play a key role in the programming of adult disease due to subsequent influences on the RAS, oxidant status, and ensuing increases in sympathetic outflow. Although recent studies are beginning to examine the complex mechanisms involved in the prenatal programming of hypertension and blood pressure, additional studies are needed to elucidate the integrative interactions of these pathways. Understanding the complexity of the prenatal programming of adult disease may lead to preventive measures and early detection of cardiovascular risk.

SOURCES OF FUNDING

Dr. Alexander is supported by NIH grants HL074927 and HL51971 awarded by the National Heart, Lung, and Blood Institute. Dr. Hennington is funded by NIH grant 1P20MD002725 awarded by the National Center on Minority Health and Health Disparities.

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