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Role of fetal programming in the development of hypertension

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Abstract

Epidemiological studies have suggested that size at birth contributes to increased cardiovascular disease (CVD) risk in later life. Findings from experimental studies are providing insight into the mechanisms linking impaired fetal growth and the increased risk of CVD and hypertension in adulthood. This article summarizes potential mechanisms involved in the fetal programming of hypertension and CVD, including alterations in the organs and regulatory systems critical to long-term control of sodium and volume homeostasis.

Keywords

glucocorticoids; kidney; renin-angiotensin system; sex hormones; sympathetic nervous system; vascular function

Cardiovascular (CV) disease is a major cause of death among men and women in Western societies, with hypertension representing a major contributor [1]. However, impaired survival and increased mortality remain, following interventions to reduce blood pressure in hypertensive populations compared with normotensive populations, suggesting a reduction in blood pressure does not provide absolute cardioprotection [2,3]. Therefore, a better understanding of mechanisms underlying CV disease may aid in the cure and prevention. The early origins of CV disease may be key to understanding the complex interactions between blood pressure and CV risk. The etiology of CV disease linked to disturbances in early life was first proposed by Anders Forsdahl in 1973. Forsdahl's studies initiated the theory that poor social conditions during childhood and adolescence exerted a major influence on CV risk in adulthood [4]. David Barker expanded the concept to include the prenatal period as a major influence on later CV risk. [5] Although both noted a strong positive correlation between coronary heart disease and infant mortality, Barker was the first to report the inverse relationship between weight at birth and blood pressure [6]. Based on his observations, Barker

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proposed that fetal programming of adult disease occurs in response to an insult during intrauterine life, which leads to adaptations by the fetus to allow fetal survival, but also results in permanent structural and physiological changes with long-term consequences, such as an increased risk of CV disease in later life [7]. To date, these findings have been confirmed by numerous experimental studies that have provided insight into the mechanisms whereby influences in early life contribute to increased blood pressure and CV risk in adulthood [8–14].

Since the first reports by Barker and Forsdahl, numerous epidemiological studies have investigated the link between size at birth and blood pressure. However, many of the findings have been controversial owing to the lack of adequate methodologies to deal with multivariate cofounders within the population studies [15–19]. In many studies, a direct link between birth weight and blood pressure is not observed, suggesting birth weight may be a crude index of fetal exposure to an adverse environment *in utero* [19]. Although a reduction in weight at birth is not always observed in response to fetal insult [20,21], animal models with well-controlled variables designed to induce a suboptimal fetal environment support Barker's hypothesis that programming of adult disease is linked to an adverse fetal environment [8–14,20,21], indicating that organ growth and development may be slowed by fetal insult, leading to programming effects on adult disease outcome. Diverse techniques utilized in experimental models to induce a fetal insult include placental insufficiency, maternal exposure to stress, hypoxia or undernutrition, or fetal manipulation by genetic, surgical or pharmacological treatment [8–14,20–26]. These experimental models have been applied to various species, including rat and sheep, and report an important role for fetal life in the origin of a wide variety of diseases including the metabolic syndrome, obesity, diabetes, insulin resistance, CV disease and hypertension [8–14,20–26]. However, investigation into the mechanisms that mediate the fetal programming of hypertension is one of the most studied topics and will be the focus of this article.

Mechanisms of fetal programming of hypertension

Glucocorticoids

Fetal exposure to excess glucocorticoids (GCs) may be a critical link between an adverse fetal environment and programming of CV disease and hypertension. Experimental studies demonstrate that excess exposure to GCs during gestation, either through direct administration of GCs or by inhibition of 11 β -hydroxysteroid dehydrogenase type 2 (11 β -HSD2), an enzyme that serves as a barrier to fetal exposure to maternal GCs, leads to alterations in vascular function and blood pressure [10,27–29]. Importantly, other models of fetal programming of vascular dysfunction and hypertension, such as those induced by gestational protein restriction [30,31], maternal stress [32], hypoxia [33] or placental insufficiency [34], demonstrate a marked increase in GC expression and/or marked decrease in the expression of 11 β -HSD2. Thus, excess fetal exposure to GCs mediated via a reduction in placental 11 β -HSD2 may be a common mechanistic pathway programmed in response to fetal insult. In experimental studies whereby exposure to exogenous GCs serves as the fetal insult, a reduction in nephron number [35], vascular dysfunction [36], alterations in the renin–angiotensin system (RAS) [37], programming of the hypothalamic–pituitary–adrenal (HPA) axis [28,38–40] and hypertension [27–29] are observed in the offspring. However, programming effects mediated via direct GC excess during fetal life exhibit species- and timing-of-fetal-insult-specific differences [27–29,41]. Fetal responses to direct GC exposure leads to hypertension and a reduction in nephron number in the rat that does not always coincide, depending on the gestational age of insult and the length of exposure [28]. In addition, GC exposure during late gestation in the rat may not always result in programmed hypertension [41]. Alterations in the function of the HPA axis also appear to occur in an age-dependent manner and demonstrate sex differences in response to GC exposure [38,42]. Programming of the HPA axis is also observed in response to

gestational nutrient restriction [43,44], with the timing of the insult critical to the HPA response [44]. Therefore, exposure to GC during fetal life, whether direct or as a result of a nutritional insult, appears to play a critical role in the fetal programming of adult disease with timing and severity of the insult critical to the fetal phenotypic outcome (Box 1).

A reduction in placental 11 β -HSD2 is observed in human pregnancies and complicated by intrauterine growth restriction (IUGR) [45], suggesting a physiological importance to altered GC exposure in the fetal programming of adult disease. Thus, a causative role for GCs in the fetal programming of adult disease is strongly suggested by experimental studies, with a role for GCs linked to the programming of potential mediators of CV and blood pressure regulation, including reduced nephron number, vascular function and the RAS.

Nephron number

Marked alterations in kidney morphology, such as a decrease in nephron number, is a common phenotypic outcome observed in response to fetal insult in many different animal models of fetal programming [13,14,46–49]. Significant reductions in nephron number are also reported with low birth weight in humans [50]. However, experimental studies demonstrate that fetal programming of reduced nephron number is sensitive to the timing of fetal insult [27,46]. In the rat, nephrogenesis is initiated in midgestation and continues until 10 days postdelivery [51]. Maternal protein restriction administered during the late gestational period in the rat results in a marked reduction in nephron number and hypertensive offspring; however, the same insult initiated during early gestation has no effect on renal morphology and blood pressure [46,52]. Fetal exposure to GCs also results in a time-sensitive window of fetal exposure with administration of GCs during days 15–18 of gestation, leading to a reduction in nephron number that is not observed when GC exposure is administered prior to or after that critical time frame [28]. The kidneys play a major role in the long-term regulation of arterial pressure through pressure natriuresis, whereby changes in renal perfusion pressure leads to alterations in sodium and water balance [53]. Therefore, the reduction in nephron number that occurs in response to fetal insult during a critical period of development points to the kidney as a key target for fetal programming. Additionally, the association of reduced nephron number and increased blood pressure also suggests that a reduction in nephron number may lead to a subsequent decrease in renal excretory function, therefore, contributing to the fetal programming of hypertension. The importance of reduced nephron number and hypertension is demonstrated in studies where neonatal uninephrectomy or blockade of the RAS during nephrogenesis leads to a reduction in renal function, hypertension and greater susceptibility to renal damage [25,26,54–57]. However, fetal exposure to GCs does not always result in a reduction in nephron number in hypertensive offspring [28], indicating that a reduction in nephron number is not always involved in the programming of hypertension. In addition, a reduction in nephron number can also be associated with an increase in glomerular volume [46]. Since an increase in glomerular size may be a sign of compensatory hyperfiltration and hypertrophy in response to fewer nephrons at birth, a reduction in nephron number may diminish resistance to mechanisms of renal damage in adult life [58,59], but other systems critical to the long-term control of blood pressure may contribute to hypertension that is programmed by fetal insult.

Box 1. Phenotypic outcomes that can occur in response to fetal insult in experimental models of fetal programming

- Slowed organ growth and maturation
- Excess fetal exposure to glucocorticoids
- Vascular dysfunction

- Reduced nephron number
- Alterations in the renin–angiotensin system, renal sympathetic nerve activity and oxidative stress
- Disregulation of blood pressure control

Vascular function

Many animal models of fetal programming report that impaired vascular function occurs in response to fetal insult [21,60–62]. Vascular dysfunction plays a critical role in the development of CV disease [63] and is implicated in the pathophysiology of hypertension [64]. Impaired vascular function is observed in clinical studies including healthy children with low birth weight [65,66], suggesting that vascular consequences of fetal programming may precede the development of adult CV disease. In animal models of fetal programming, fetal insult by nutritional restriction, placental insufficiency or hypoxia, lead to vascular dysfunction associated with impaired endothelium-dependent nitric oxide (NO) availability [61,67,68]. *L*-arginine supplementation restores vascular function and attenuates hypertension in offspring from undernourished dams [69], demonstrating that abnormalities in the NO pathway may contribute to impaired vascular function and hypertension in these models of fetal programming. Increased sensitivity to vasoconstrictors is also observed in response to fetal insult. Enhanced sensitivity to endothelin is observed in response to fetal dexamethasone exposure in sheep [60]; enhanced sensitivity to Ang II is increased in offspring from undernourished dams [70,71], an effect reversed by angiotensin-converting enzyme (ACE) inhibition or blockade of the angiotensin type 2 receptor [70]. Although an enhanced vascular responsiveness to Ang II is not observed in response to fetal exposure to dexamethasone in the rat, chronic Ang II does increase blood pressure [36]. However, exposure to dexamethasone in early gestation in the sheep enhances coronary arterial responsiveness to Ang II, indicating the heart as a target organ for programming in response to fetal insult [29]. Thus, tissue- and species-specific differences are observed in the fetal response to excess GC exposure. Additionally, enhanced responsiveness to Ang II suggests a causative role for the RAS in the vascular dysfunction programmed by fetal insult. Therefore, an imbalance in potent vasoactive factors produced by endothelial cells may contribute to impaired vascular function, leading to an increase in total peripheral resistance and contributing to the development of hypertension programmed in response to fetal insult. Importantly, alterations in vascular function may precede the development of hypertension, indicating a role for impaired endothelial function in the programming of hypertension.

Cardiovascular development

Vascular endothelial cells contribute to CV regulation by producing a collection of vasoactive agents whose functions include vasodilatation, vasoconstriction and vascular growth [66], with normal vascular function depending on a fine balance between these vasoactive agents. Fetal influences leading to alterations in these vasoactive factors may increase vascular angiogenesis, reactivity and peripheral vascular resistance and contribute to elevations in blood pressure and CV disease. Alterations in CV development and cardiomyocyte cell cycle are observed in animal models of fetal programming induced by placental insufficiency [72–74], chronic hypoxia [23,75], low salt [76] and nutrient restriction [75,77,78]. Altered cardiac β -adrenergic responses and signaling [79], increased cardiac fibrosis [80] and a decrease in the ability of the heart to recover from ischemic events [76] may also contribute to increased risk for CV disease programmed by fetal insult. Moreover, significant elevations in blood pressure [8,13,14] are commonly observed in different models of fetal programming and indicate an important role for the dysregulation of blood pressure control in mediating the increased risk for CV disease programmed by fetal insult.

Renin–angiotensin system

The RAS is another regulatory system strongly involved in CV and blood pressure regulation [81]. Alterations in the RAS induced in response to fetal insult may serve as a potential mechanism critical to the fetal programming of hypertension. Late gestational exposure to GCs in sheep leads to an increase in fetal pulmonary ACE expression associated with an increase in blood pressure [82]. However, placental insufficiency in the sheep leads to suppression of the fetal renal RAS [83], indicating that programming of the fetal RAS may exhibit tissue-specific effects. The RAS is highly expressed in the developing kidney [51]. Blockade of the RAS during the nephrogenic period in the rat leads to a marked reduction in nephron number associated with hypertension in adulthood [54,84]. Suppression of the RAS is also observed at birth in rat models of fetal programming induced by gestational protein restriction [13] and placental insufficiency [85]. Therefore, a reduction in nephron number and a subsequent decrease in renal excretory function is one potential mechanism that may contribute to the fetal programming of hypertension, and suppression of the renal RAS during a critical window of nephrogenesis may be a key component in this programming cascade. Although suppression of the RAS is observed at birth in models of fetal programming induced by gestational protein restriction, later, inappropriate activation of the RAS appears to be associated with established hypertension [85–87]. Blockade of the RAS abolishes hypertension in models of fetal programming induced by gestational protein restriction [86] and placental insufficiency (Figure 1) [88], indicating a critical role for RAS involvement in adult hypertension programmed in response to fetal insult in the rat. However, activation of the RAS does not occur in response to placental insufficiency [85], suggesting increased sensitivity to Ang II may contribute to hypertension in this model of programmed hypertension. Interestingly, a role for the renal RAS in mediating hypertension programmed by early fetal exposure to GCs is not indicated [89]. Thus, alterations in the RAS appear to contribute to hypertension programmed in response to certain fetal insults, highlighting the complexity of the mechanistic pathways involved in the fetal programming of hypertension and blood pressure control.

Sympathetic nervous system

Findings from animal studies indicate that alterations in the regulatory systems critical to the long-term control of blood pressure occur in response to an adverse fetal environment. Adaptive changes are triggered in response to *in utero* insult to allow fetal survival. However, in response to suboptimal fetal conditions, blood flow redistribution to critical organs such as the brain and heart occurs at the expense of other organs such as the liver, kidney, muscles and skin, resulting in exposure to hypoxia, with modifications in the hypoxia inducible factor (HIF) pathway [90]. HIF, a transcription factor, influences several regulatory pathways, including the sympathetic nervous system, via stimulation of tyrosine hydroxylase [91]. In humans, sympathetic activation is observed in low birth weight individuals; and sympathetic activation is increased in response to hypoxia in animals [92–96]. Increased circulating catecholamines are also reported in numerous models of fetal programming induced by placental insufficiency as well as gestational protein restriction [97–99]. The renal nerves play a critical role in the etiology of hypertension programmed by placental insufficiency in the rat [100,101]. Renal denervation delays the development of hypertension in prepubertal offspring [101] and abolishes hypertension in adult male IUGR offspring [100], suggesting a critical role for the renal nerves in the etiology of fetal-programmed hypertension. Therefore, hypoxia may serve as a stimulus for increased renal sympathetic nerve activity leading to hypertension programmed in response to fetal insult.

Oxidative stress

Increased levels of reactive oxygen species or oxidative stress are associated with CV diseases such as hypertension [102]. Treatment with the superoxide dismutase mimetic, tempol [103],

or the lipid peroxidation inhibitor, lazaroid [104], abolishes hypertension that is prenatally programmed in response to maternal protein undernutrition. Although the exact mechanism(s) linking oxidative stress and fetal programming remains unknown, some studies indicate that the loss of NO bioavailability linked to increased oxidative stress contributes to endothelial dysfunction programmed by fetal insult [105].

Postnatal factors & sex hormones

Postnatal factors can exacerbate the effects of programming initiated *in utero*. In humans, accelerated weight gain in early childhood exacerbates the risk of adult hypertension programmed in fetal life [106]. In animal models, when undernutrition *in utero* is followed by accelerated or extreme catch-up growth, male offspring are more prone to develop altered lipid metabolism [107], increased susceptibility to myocardial ischemia-reperfusion injury [77], insulin resistance and obesity [108,109]. Prenatal exposure to sex steroids such as testosterone also leads to postnatal catch-up growth in a sex-dependent manner, since postnatal growth is increased in female sheep but not male sheep [110]. Importantly, prenatal testosterone exposure in female sheep is associated with mild hypertension [111], indicating a role for sex hormones in the fetal programming of adult disease. Sex differences in phenotypic outcome are observed in response to fetal insult with the severity of the fetal insult playing a critical role in setting the programming response of adult blood pressure control. Moderate maternal protein restriction during gestation results in marked elevations in blood pressure in male offspring, but not female offspring [13,112]; whereas severe maternal protein restriction during gestation increases blood pressure in both male and female offspring [46]. Therefore, the fetal response to fetal insult can be sex specific, leading to sex differences in adult phenotypic outcome. Sex differences in response to fetal programming are dependent not only on the severity of insult [112], but vary in response to different dietary insults [113] and variations in postnatal growth [107,108] with the female gender more resistant to programming in response to moderate nutritional insults [112], yet more responsive to insults of excess fat diet [113] or GC exposure [42,114]. However, diet-induced maternal obesity is not always related to sex differences in adult disease outcome [115], indicating species differences may occur in response to fetal insult – rat [113] versus mouse [115] – or that differences in phenotypic outcome may be related to variations in the composition of the maternal diet. Although experimental studies are providing insight into the mechanisms and factors involved in the fetal programming of hypertension, the complexity of the fetal response to an adverse fetal environment or insult is complex and may reflect the heterogeneity of human programming of adult disease.

Sex hormones

Sex differences are observed in the blood pressure response to fetal insult and recent findings indicate that the sex hormones play a critical role in mediating the sex differences in blood pressure regulation in a model of fetal programming induced by placental insufficiency. Adult male IUGR offspring in this model exhibit marked increases in mean arterial pressure whereas female IUGR offspring remain normotensive relative to their control counterparts (Figure 2) [8]. Castration abolishes hypertension in adult male IUGR offspring [88]; ovariectomy induces a significant increase in mean arterial pressure in adult female IUGR offspring with no effect on blood pressure in adult female control [116]. Estradiol replacement to restore estradiol to levels observed in adult female rats [117] abolishes hypertension induced by ovariectomy in adult female IUGR offspring [116]. Thus, these data suggest that testosterone contributes to the exacerbation of hypertension in adult male IUGR offspring, and that estradiol plays a protective role in the normalization of blood pressure in adult female IUGR offspring. However, the mechanisms by which sex hormones contribute to hypertension in IUGR offspring may not be direct, but may involve modulation of the regulatory systems important in sodium and water homeostasis and arterial pressure control.

The RAS may be one such system modulated by sex hormones leading to sex differences in hypertension programmed by fetal insult. The ACE-dependent pathway of the RAS generates the potent vasoconstrictor peptide, Ang II [118]. However, the ACE2-dependent pathway generates the vasodilatory peptide Ang-(1–7), which provides a counter-regulatory balance to ACE [118]. Estradiol influences the vasoconstrictor–vasodilator actions of the RAS by altering the ACE and ACE2 pathways [119,120]. In a model of fetal programming induced by placental insufficiency, marked increases in renal ACE2 mRNA expression are observed in normotensive adult female IUGR offspring [116]. However, hypertension induced by ovariectomy in adult female IUGR offspring is associated with a significant decrease in renal mRNA expression of ACE2, with no effect in adult female control offspring [116]. Thus, loss of ovarian function may decrease the vasodilator effect provided by the ACE2 pathway, leading to increases in blood pressure in postpubertal female IUGR offspring. Alterations in the RAS by testosterone may also contribute to sex differences in adult blood pressure in this model of fetal programming. A role for testosterone modulation of the RAS is indicated in studies whereby angiotensinogen mRNA expression in the kidney and liver is reported to be testosterone dependent [121]. Furthermore, testosterone is reported to augment renal proximal tubule transport by stimulation of the local RAS, thus, contributing to higher blood pressure [122]. In a model of fetal programming induced by placental insufficiency, renal angiotensinogen and renin mRNA expression is significantly increased in adult male IUGR offspring [85]. Therefore, testosterone may serve as a stimulus for enhanced intrarenal angiotensinogen in this model of fetal programming, resulting in exacerbation of hypertension in adulthood in male IUGR offspring. Loss of ovarian function may result in abnormal blood pressure regulation in adult female IUGR offspring, therefore, leading to sex differences in blood pressure regulation in response to fetal insult.

Conclusion

Human studies and experimental animal models report that hypertension is programmed in response to an insult during fetal life. Fetal programming of hypertension includes a wide range of alterations in the regulatory systems as well as modification in organs such as the heart, vasculature and kidneys involved in the long-term control of blood pressure regulation (Figure 3). Better understanding of the complex and intrinsic mechanisms involved in the fetal programming of hypertension will aid in the design of realistic approaches to treat or prevent these adverse adaptive phenotypic outcomes to fetal insult, and may lead to a decreased CV risk in individuals with a low birth weight.

Future perspective

The incidence of babies born with low birth weight is increasing within the USA, indicating that the relationship between size at birth and increased CV risk is a major health concern. Insights from animal studies that are elucidating the mechanisms of adult disease programmed by exposure to fetal insult will aid in the development of effective diagnostic tools and interventions to prevent or decrease the risk of CV disease in later life.

Executive summary

Introduction to fetal programming

- Fetal programming of hypertension occurs in response to an insult during intrauterine life, which leads to adaptations by the fetus to allow fetal survival, but also results in permanent structural and physiological changes with long-term consequences such as an increased risk for cardiovascular disease and hypertension.

- Diverse techniques utilized in experimental models to induce a fetal insult include placental insufficiency, maternal exposure to stress, hypoxia, undernutrition or fetal manipulation by surgical or pharmacological treatment.

Mechanisms of fetal programming

- Findings from experimental studies demonstrate that the intensity, timing and nature of the fetal insult are critical to the phenotypic outcome.
- Alterations in the regulatory systems critical for the long-term control of blood pressure occur in response to an adverse fetal environment and indicate an important role for the vasculature, heart, kidney, sympathetic nervous system, renin–angiotensin system, oxidative stress and sex hormones, in addition to postnatal influences in the fetal programming of hypertension.

Conclusion

- A better understanding of the complex and intrinsic mechanisms involved in the fetal programming of hypertension will aid in the design of realistic approaches to treat or prevent these adverse phenotypic outcomes to fetal insult, and may lead to a decreased cardiovascular risk in individuals with a low birth weight.

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Figure 1. Mean arterial pressure is abolished by blockade of renin–angiotensin system in adult male growth-restricted offspring in a model of fetal programming induced by placental insufficiency in the rat.

Figure 2.

Mean arterial pressure is significantly elevated in adult male growth-restricted offspring in a model of fetal programming induced by placental insufficiency in the rat.

Figure 3.
Possible mechanisms involved in the fetal programming of hypertension.