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Intrauterine Growth Restriction: Fetal programming of hypertension and kidney disease.

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Abstract

The etiology of hypertension historically includes two components, genetics and lifestyle. However, recent epidemiological studies report an inverse relationship between birth weight and hypertension suggesting that a suboptimal fetal environment may also contribute to increased disease in later life. Experimental studies support this observation and indicate that cardiovascular/kidney disease originates in response to fetal adaptations to adverse conditions during prenatal life.

Keywords

fetal programming; hypertension; kidney; experimental models

INTRODUCTION TO FETAL PROGRAMMING

The fetal environment is considered a key factor in the etiology of cardiovascular disease later in life. The theory that experiences in early life exert a major influence on cardiovascular risk was first reported by Dr Anders Forsdahl in 1973. Dr. Forsdahl's studies initiated the theory that poor social conditions could serve as an adverse stimulus during childhood and adolescence leading to increased risk for cardiovascular disease in adulthood (1). Dr. David Barker advanced the concept by suggesting that the influences that lead to increased cardiovascular risk may have their origins in prenatal life. Both of these original observations noted a strong positive correlation between coronary heart disease and infant mortality. However, Dr. Barker first noted the inverse relationship between weight at birth and risk of cardiovascular disease (2), formulating the fetal environment as a new component in the etiology of cardiovascular disease. Based on his observations, Barker hypothesized that developmental programming of adult disease occurs in response to an imbalance during fetal life between fetal demands and nutrient supply resulting in fetal undernutrition (3). Impairment in fetal development, which can be marked by intrauterine growth restriction (IUGR) and low birth weight, results from these fetal adaptations to an adverse fetal environment leading to molecular and physiological adaptive changes (4). Although these fetal adaptations allow fetal survival, they also results in long-term consequences such as marked alterations in the physiology and structure of the cardiovascular, renal, metabolic, respiratory, endocrine, and nervous systems (4-6). Acceptance of the theory of fetal programming has met with skepticism due to the inability of many epidemiological studies to separate the contribution of confounding variables including socioeconomic and social factors, in addition to, genetic factors, catch-up

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growth, and current BMI (7). However, experimental approaches using animal models that initiate an insult during a crucial period of fetal life provide critical support for Barker's initial hypothesis and importantly, insight into the mechanisms linking birth weight and blood pressure (8-12). Thus, the theory of fetal programming has emerged as a very new and exiting field for investigation, due to not only to its novelty, but also due to controversy surrounding the interpretation of epidemiological studies.

ANIMAL MODELS OF FETAL PROGRAMMING OF ADULT DISEASE

Investigators utilizing animal models to induce an adverse fetal environment and mimic the human condition of slow fetal growth are elucidating the mechanistic pathways implicated in the developmental programming of adult disease (5,13-16). Different methods have been utilized to induce a suboptimal fetal environment in experimental studies. Despite subtle differences in the method of insult, common outcomes are observed (FIGURE 1) and demonstrate characteristics reflective of the human condition of slow fetal growth including asymmetric fetal growth restriction (4), decreased nephron number (17), impaired vascular function (18), and significant elevations in blood pressure (3).

MANIPULATION OF MATERNAL CONDITIONS

I. Models of dietary manipulation

Fetal programming as hypothesized by Barker involves adaptive responses by the fetus to undernutrition. One of the most common models, dietary manipulation, involves global nutritional or isocaloric protein undernutrition administered during gestation (8-10,12). Common adaptive outcomes include IUGR associated with reduced nephron number (8-10, 12), altered vascular function (19), and increased blood pressure (8-10,12), an effect that is not species specific.

Investigators utilizing models of gestational protein undernutrition demonstrate that the timing of the insult during gestation is critical to the fetal adaptive response. In the rat, marked changes in kidney morphology and increases in blood pressure are observed when the nutritional insult coincides with nephrogenesis. However, the same insult initiated prior to the nephrogenic period does not alter kidney structure or blood pressure regulation (8,20). Since the kidneys are known to play a major role in the long-term regulation of arterial pressure (21), these studies suggest that an insult during kidney development leads to 'programming' of the kidneys resulting in an abnormal outcome in the complex mechanisms associated with blood pressure regulation.

II. Models of reduced utero-placental perfusion

Fetal nutrition induced by impairment of utero-placental perfusion is a model of fetal programming utilized to mimic the human condition of IUGR marked by asymmetric fetal growth restriction (22). Placental insufficiency is the common consequence in these models which results in deprivation of nutrient and oxygen delivery to the fetus (11,23,24). Common adaptive outcomes observed in response to placental insufficiency include reduced nephron number (23), altered vascular reactivity (25), cardiovascular remodeling (24), and marked increases in blood pressure (11).

IV. Models of hypoxia

Exposure during gestation to acute or chronic hypoxia is also used to mimic conditions leading to slow fetal growth (26-28). Reduced litter size and birth weight are common features of this model and hypoxia, as an insult during fetal development, leads to cardiovascular and cerebrovascular remodeling (26,27). Findings from this model have provided insight into the

importance of suppression of growth related genes and induction of inflammation related genes in the etiology of IUGR (28,29).

V. Models of pharmacological manipulation

Pharmacological manipulation during pregnancy is another model used to induce an adverse fetal environment to mimic the pathophysiological conditions linked to IUGR. 11 beta-hydroxysteroid dehydrogenase type 2 (11B-HSD2), an enzyme which inactivates cortisol thus serving as a barrier for fetal exposure to maternal glucocorticoids, is decreased in pregnancies complicated by IUGR (30). Pre-natal exposure to glucocorticoids or the 11B-HSD2 inhibitor, carbenoxolone, leads to reductions in birth weight (31-34), reduced nephron number (33), glucose intolerance (34), and programmed hypertension (32,33). Interestingly, these effects are transmitted to the next generation despite further exposure to glucocorticoids suggesting the potential involvement of epigenetic mechanisms (34).

MANIPULATION OF THE FETUS

I. Models of uninephrectomy

Uninephrectomy in an adult does not normally lead to changes in kidney function and blood pressure (35). However, uninephrectomy during the nephrogenic period leads to marked elevations in blood pressure and greater severity of kidney damage in later life (36-38).

II. Models of pharmacological blockade

The renin angiotensin system (RAS) is highly expressed in the kidney during development and plays a critical role in mediating proper nephrogenesis (39). RAS blockade during nephrogenesis in the rat leads to permanent alterations in kidney function and structure associated with significant increases in blood pressure (40-42).

III. Models of genetic manipulation

Gene deletion is another method utilized to induce a sub-optimal fetal environment and IUGR. Genetic mouse models are used to study mechanisms associated with metabolic disorders related to growth restriction, and alterations related to altered nitric oxide (NO) synthesis and metabolism (43-46).

COMMON MECHANISTIC PATHWAYS IN FETAL PROGRAMMING

Although the methods used to induce a fetal insult may vary in animal studies, common fetal adaptive responses are observed. These include not only common adult disease outcomes, but also similar alterations in the mechanistic pathways that lead to chronic adult disease.

I. Fetal programming of the sympathetic nervous system

Blood flow re-distribution is one of the first adaptative changes observed in response to fetal insult. Blood flow to critical organs such as the brain and heart is spared at the expense of other organs such as liver, kidney, muscles and skin (47) resulting in fetal hypoxia with alterations in the hypoxia inducible factor (HIF) pathway (48). HIF, a transcription factor, influences several regulatory pathways including the sympathetic nervous system (SNS) via stimulation of tyrosine hydroxylase (48). In humans sympathetic activation is observed in low birth weight individuals, and is increased in response to hypoxia in animals (49-52). Increased circulating catecholamines are also reported in numerous models of fetal programming induced by placental insufficiency as well as gestational protein restriction (53-55). Recent studies demonstrate that the renal nerves play a critical role in the etiology of hypertension programmed

by placental insufficiency (56). Therefore, hypoxia may serve as a stimulus for increased renal sympathetic nerve activity leading to hypertension.

II. Fetal programming of the renin angiotensin system

Animals models of fetal programming induced by gestational protein undernutrition and placental insufficiency report common temporal alterations in the RAS (9,57,58). Suppression of the intrarenal RAS at birth (9,57) is followed by later activation of the RAS including increased expression of renal AT₁ receptors (59,60) and renal ACE (12,57). Importantly, blockade of the RAS prevents or abolishes hypertension in offspring of protein restricted or reduced uterine perfusion dams, thus demonstrating the importance of the RAS in the etiology of programmed hypertension (57,61-63).

III. Fetal programming of nephron number

Impairment in nephrogenesis resulting in reduced nephron number is a common outcome of fetal programming observed in many different animal models, and also in human studies associated with IUGR (9,10,16,17,24,64,65). Increases in renal apoptosis and expression of key apoptosis genes may contribute to reduced nephron number programmed by fetal insult (10,24). These adaptive changes during fetal programming point to the kidney as a critical target for fetal programming, and emphasize the importance of the kidney in the long-term regulation of blood pressure control.

IV. Fetal programming of vascular dysfunction

Vascular dysfunction plays a critical role in the development of cardiovascular disease (65). Impaired endothelial function is observed in clinical studies of low birth weight including studies performed in healthy children (18) suggesting that vascular consequences of fetal programming precede the development of adult cardiovascular disease. Animal models of fetal programming induced by nutritional restriction, placental insufficiency, and hypoxia report endothelial dysfunction associated with reduced NO availability (19,25,67-69). Treatment with the antioxidants, vitamins C and E, improve vascular function (70) suggesting altered NO bioavailability linked to increased oxidative stress contributes to vascular dysfunction programmed by fetal insult.

CONCLUSIONS

Human studies indicate that slow fetal growth is linked to increased risk for adult disease. Animal studies demonstrate that adverse conditions during fetal development lead to permanent alterations in the structure and physiology of the fetus influencing disease outcome in later life. Furthermore, animal studies are beginning to elucidate alterations in common mechanistic pathways intrinsic in the fetal programming of adult disease.

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Fetal Programming of hypertension and adult disease

FIGURE 1.

An adverse fetal environment due to either maternal or fetal influences leads to impaired kidney development and common adaptive alterations in systems critical to the long-term control of blood pressure resulting in hypertension and increased risk for kidney disease later in life.