Hypertension, a multifactorial disorder thought to result from both genetic and environmental factor interactions, is a major risk factor for the development of cardiovascular (CV) disease. Recent epidemiological studies suggest that hypertension and CV disease may be programmed by factors initiated in utero (27, 46, 61). David Barker and colleagues (6–9), on the basis of evidence from geographical studies, were the first to implicate in utero factor involvement in the development of CV disease. Specifically, Barker noted that the geographical distribution of neonatal mortality in England and Wales at the beginning of the 1900s was found to closely resemble the distribution of death rates from CV disease 70 years later. Because most neonatal deaths in the early 1900s were attributed to low birth weight (LBW), Barker hypothesized that influences during fetal life that slow fetal growth could program or permanently alter the body’s structure and physiology in ways linked to CV disease in the adult (7, 8). In addition, on the basis of the association between birth weight and adult blood pressure reported by Wadsworth et al. (111), Barker proposed that influences in the fetal environment could also affect blood pressure in adult life (10). Numerous epidemiological studies now support this inverse relationship between LBW and hypertension (46, 61), an observation further supported by elevations in blood pressure also found in LBW children (62, 68, 122). Thus on the basis of Barker’s hypothesis, adverse conditions in utero may lead to LBW and fetal programming of hypertension and CV disease.

WHAT IS FETAL PROGRAMMING OF HYPERTENSION?

The inverse relationship observed between LBW and hypertension may be due to a suboptimal fetal environment initiated during the gestational period (7). Fetal growth and development are determined by both the fetal genome and by maternal and placental capacities to supply nutrients to the fetus (21, 108, 116). During fetal life, tissues and organs go through critical periods of development that may coincide with periods of rapid cell division (76). Thus when an insult, such as undernutrition, occurs in utero at a critical or sensitive period of development, the resulting adaptive changes may be permanent and lead to long-term changes in structure and function. Furthermore, that timing of the insult in utero is critical and mediates the severity or nature of the adaptive response (7). Thus programming during fetal life occurs in response to an adverse fetal environment and results in permanent adaptive responses that may alter organ growth, structure, physiology, and metabolism leading to increased risk for development of adult hypertension and CV disease (7).

WHAT ARE THE MECHANISMS LINKING LBW AND HYPERTENSION?

Nutrient and oxygen supply limitations are the components of the intrauterine environment that limit fetal growth and development.
Invited Review

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result in small for gestational age (SGA) newborns. Fetal adaptations to oxygen and nutrient restriction that occur during a critical period of fetal development may result in long-term effects and increased risk for development of CV disease and hypertension. To date, human-based studies and studies using animal models have begun to examine the mechanisms linking LBW and hypertension.

INSIGHT PROVIDED BY HUMAN STUDIES

Numerous epidemiological studies have provided the basis for the investigation into fetal programming of hypertension and adult disease. However, some clinical studies have begun to address the mechanism(s) mediating the link between LBW and hypertension.

Role of nephron number. In 1988, Brenner et al. (19) postulated that a reduction in nephron number might be linked to the development of essential hypertension. Keller et al. (50) using three-dimensional stereology from autopsy kidneys noted fewer glomeruli per kidney from patients with hypertension compared with normotensive controls. On the basis of this concept, if a reduction in nephron number is initiated in utero due to an adverse fetal environment, this may lead to hypertension. Because African Americans in the Southeast United States have a significantly greater risk for LBW (75) and the development of hypertension compared with Caucasians (38), Hughson et al. (45) investigated the link between birth weight and glomerular number. Using the physical dissector/fractionator combination for autopsy kidneys, birth weight was found to be a strong predictor of total glomerular number and mean glomerular volume in both African Americans and Caucasians (45), an observation also observed in autopsy kidneys from Hispanic infants (70). Thus these studies support the hypothesis that permanent changes in structure may result from fetal programming and also suggest that LBW as a risk factor for hypertension may due to impaired glomerular number.

Role of endothelial dysfunction. Vascular endothelial dysfunction plays an important role in the development of CV disease including hypertension (87). Fetal programming may result in both structural and physiological changes in the vasculature and contribute to increased risk for development of hypertension and CV disease associated with LBW. Impaired endothelial function is observed in LBW individuals, including children, suggesting that an adverse fetal environment due to fetal undernutrition may have severe and long-term effects on angiogenesis and vascular function in the developing fetus (35, 63, 74, 87). In addition, because impaired endothelial function is observed in healthy LBW children, this suggests that vascular consequences of fetal programming associated with LBW may precede and contribute to the development of adult hypertension and CV disease. Thus clinical studies suggest that LBW is associated with both structural and physiological changes, including hypertension and endothelial dysfunction, as well as a reduction in glomerular number.

INSIGHT PROVIDED BY ANIMAL STUDIES

Intrauterine growth restriction (IUGR) occurs when a fetus fails to achieve its genetically determined growth potential (21) and results in LBW or SGA newborns. Numerous factors regulate fetal growth and include nutrient and oxygen bioavailability, genetic factors, and hormones (21, 116). Investigators use many different animal models to induce an adverse fetal environment and mimic the human condition of IUGR. Manipulations by investigators include global food restriction (25, 117) or protein restriction administered during gestation (16, 33, 59, 92, 109, 119), chronic hypoxia administered to the mother during the gestational period (42, 67), placental insufficiency (1, 11, 44, 78, 123), and prenatal glucocorticoid treatment (85, 114). Animal species used for fetal programming studies vary and include the rat (1, 16, 42, 59, 78, 92, 109, 119), sheep (25, 33, 114, 123), rabbit (11), guinea pig (90), and a naturally occurring model of asymmetric IUGR in newborn piglets (13). These animal models of fetal programming demonstrate that exposure to an adverse environment in utero results in offspring that exhibit marked structural and physiological alterations. In addition, studies based on animal models of fetal programming support the theory that timing of the insult in utero is critical and the severity of the insult can mediate the extent of the adaptive response. Furthermore, as discussed below, results from these studies provide insight into the mechanisms linking LBW and hypertension.

LBW and hypertension. Support for the inverse relationship observed in epidemiological studies between LBW and hypertension is also provided by animal models of fetal programming. Introduction of an insult, such as maternal undernutrition in the rat (117) or maternal protein restriction in the rat (16, 59, 109, 119) or sheep (33), results in LBW offspring that later develop marked elevations in blood pressure. Because LBW within the Western world is more likely the result of impaired uteroplacental perfusion rather than maternal malnutrition (15, 43), we used a unique model of in vivo placental insufficiency to examine the association between LBW and hypertension (1). In this model of fetal programming, reduced uterine perfusion initiated at day 14 of gestation in the rat results in a 12% reduction in weight at birth in both male and female offspring (1). Male and female growth-restricted offspring exhibit a marked increase in mean arterial pressure (MAP) at 4 wk of age, but only male growth-restricted offspring remain hypertensive at 12 wk of age (Ref. 1; Fig. 1). Thus as discussed in

![Fig. 1. Measure of mean arterial pressure in a rat model of intrauterine growth restriction induced by reduced uterine perfusion. Data shown is for both male and female growth restricted (IUGR) vs. control offspring, at 4, 8, and 12 wk of age. *P < 0.05 vs. male control; †P < 0.05 vs. female control; ‡P < 0.01 vs. control; §P < 0.01 vs. control. All data are expressed as means ± SE. (Reprinted with permission from Alexander, Ref. 1).](http://ajpregu.physiology.org/DownloadedFrom/102.20.33.6/2017)
greater detail later, gender-specific differences are observed in this model of fetal programming. Adverse consequences of programming can be altered by the severity and timing of the insult as shown by Langley and colleagues, whereby the magnitude of the blood pressure response observed in the offspring is significantly related to the degree of protein restriction administered during gestation (55) and the period of gestation when administered (58). Thus initiation of an insult during the gestational period leading to LBW in animal models of fetal programming is associated with an increase in blood pressure supporting epidemiological studies linking LBW with hypertension in humans.

Role of nephron number. Kidneys are known to play a major role in the long-term regulation of arterial pressure through pressure natriuresis, whereby changes in renal perfusion pressure lead to alterations in sodium and water balance (37). A role for renal involvement in mediating hypertension in LBW individuals is provided by clinical studies (45, 50, 70) and is further supported by animal models of fetal programming. Specifically, reductions in nephron number are observed in offspring from protein-restricted dams (59, 109, 119) and ewes (33), IUGR offspring induced by placental insufficiency in the rat (78) and rabbit (11), animal models using prenatal glucocorticoid treatment in the rat (85) and sheep (114), and in a naturally occurring model of IUGR in the pig (12). Therefore, a marked reduction in nephron number is associated with a significant elevation in blood pressure in many different animal species using different methods to induce an adverse fetal environment (33, 59, 85, 109, 114, 117, 119). However, whether a reduction in nephron number serves as a link between LBW and hypertension is unclear.

Further support for Barker’s hypothesis is also provided by animal models regarding the timing of the insult. Nephrogenesis in the rat occurs during the last third of gestation and continues for several days postdelivery (60). Maternal protein restriction administered during the last third of gestation or during the period of nephrogenesis, results in offspring that exhibit a marked reduction in glomerular or nephron number and develop hypertension (59, 121). However, protein restriction administered in early gestation during preimplantation and before the nephrogenic period, results in offspring that exhibit normal renal morphology (58, 121) and remain either normotensive (121) or become moderately hypertensive (54, 58). Thus as predicted by Barker, timing of the insult in utero may be critical in the fetal programming of adult disease. However, because hypertension in animal models of fetal programming may occur despite normal glomerular content, this data suggests that alterations in renal morphology may not be the only causative factor mediating LBW-associated hypertension.

Investigators have begun to examine what mediates the reduction in nephron number observed in animal models of fetal programming. Apoptosis plays an important role in normal nephrogenesis (105, 115). The reduction in glomerular (nephron) number observed by Vehaskari et al. (109) in offspring from protein-restricted dams is associated with an increase in renal apoptosis and cell proliferation. In a model of placental insufficiency Pham et al. (93) also found that a reduction in nephron number is associated with an increase in renal apoptosis in addition to significant alterations in key components of the apoptosis cascade. Thus reductions in nephron number are associated with increased renal apoptosis, suggesting a possible molecular mechanism whereby fetal programming leads to permanent changes in renal morphology.

To summarize, a reduction in nephron number is observed in many animal models of fetal programming, an observation that provides evidence that an adverse fetal environment, when initiated at a critical stage of development, can lead to permanent structural alterations. However, a reduction in nephron number may not be the definitive link between LBW and hypertension because not all hypertension in the protein restriction model of fetal programming is associated with reduced nephron number (54, 58). Further evidence for this is suggested in a study whereby protein-restricted dams supplemented with glycine, an amino acid that may become inadequate during fetal development in this model, results in offspring that remain normotensive (48). Thus alterations in the normal regulatory systems involved in the long-term control of blood pressure may contribute to the fetal programming of hypertension.

Role of renal hemodynamics. Pressure natriuresis plays an important role in long-term blood pressure regulation (37). A hypertensive shift in the pressure natriuresis relationship is observed in all forms of hypertension including human essential, genetic, and experimental animal models. Numerous factors including intrarenal defects and/or abnormalities in the extrarenal regulatory control systems that control kidney function may mediate the reduction in renal sodium excretory function observed in hypertension (39). Uninephrectomy during nephrogenesis results in reduced glomerular filtration rate (GFR) and hypertension in both the rat (118) and sheep (79). These studies suggest that a significant reduction in nephron number occurring during renal development may lead to permanent alterations in both renal function and blood pressure control. Thus in fetal programming, a reduction in nephron number during nephrogenesis may lead to a decrease in GFR and a subsequent reduction in pressure natriuresis and hypertension. However, the precise role a reduction in nephron number and GFR may play in mediating a reduction in pressure natriuresis and hypertension in fetal programming is unclear. In a naturally occurring model of IUGR in piglets, a reduction in nephron number was associated with a reduction in absolute GFR (12). Woods et al. (119), using unbiased stereologic techniques determined that a reduction in glomerular (nephron) number in offspring from protein-restricted dams was associated with a reduction in GFR adjusted per kidney weight. However, average individual glomerular volume and total glomerular volume were not reduced, nor was absolute GFR. In this study, Woods and colleagues used a moderate restriction of protein (8.5% protein vs. 19%) administered throughout the gestational period. In similar studies using a comparable degree of protein restriction administered throughout gestation (9% vs. 18%) absolute GFR was also not reduced (59, 98). However, in this study by Langley-Evans et al. (59), GFR was measured only in female offspring from protein-restricted dams. As discussed later, gender-specific differences are observed in animal models of fetal programming, since greater severity of the adaptive response to adverse fetal conditions is observed in programmed male offspring relative to programmed female offspring. In a rat model of fetal programming induced by placental insufficiency, Merlet-Benichou et al. (78) noted that a decrease in nephron number was associated with a significant reduction in GFR adjusted per kidney weight.
weight at 2 wk of age. However, using a similar method of reduced uterine perfusion, we did not find a significant reduction in absolute GFR (1). Thus glomerular (nephron) number may be decreased in animal models of fetal programming; however, this reduction in glomerular number may not be associated with a reduction in glomerular volume and/or a reduction in absolute GFR, at least not within the initial stages of hypertension. To summarize, reductions in nephron number and alterations in GFR may contribute to the marked elevations in blood pressure observed in animal models of fetal programming. However, alterations in the normal regulatory systems involved in the long-term control of blood pressure may also be important contributors to the etiology of fetal programming of hypertension.

Role of the renin angiotensin system. The renin angiotensin system (RAS) is an important regulator of arterial pressure and body fluid balance through both the systemic and intrarenal actions of angiotensin (20, 40). In the developing kidney, constituents of the RAS are highly expressed and play a critical role in mediating proper nephrogenesis (36, 120). Woods and Rasch (120) illustrated the importance of the RAS in mediating development of proper renal morphology and physiological function of the kidney. Specifically, Woods and Rasch observed that blockade of the angiotensin type 1 receptor (AT1R) during the nephrogenic period after birth in the rat was associated with a decrease in nephron number, a reduction in renal function, and an increase in arterial pressure. Woods et al. (119) also suggested a role for involvement of the RAS in fetal programming because maternal protein restriction during gestation in the rat was associated with a reduction in renal renin mRNA and tissue ANG II levels in the offspring at birth. Suppression of the RAS at birth in this model of fetal programming was also associated with reduction in glomerular number, increase in arterial pressure, and decrease in GFR normalized to kidney weight (119). Suppression of fetal RAS was also observed in a model of fetal programming induced by placental insufficiency because removal of caruncles in pregnant sheep resulted in a marked reduction in fetal renal renin and angiotensinogen mRNA and fetal kidney weight (123). Therefore, suppression of the RAS during fetal development may play a key role in mediating the structural and physiological changes observed in models of fetal programming. Evidence for RAS suppression in offspring from protein-restricted dams was also observed by Manning and Vehaskari (71) because plasma renin activity (PRA) remained significantly reduced before the development of hypertension; however, PRA was markedly increased after establishment of hypertension in these offspring. In 10-mo-old lambs from protein-restricted ewes, a twofold increase in renal protein expression of the angiotensin-converting enzyme (ACE) was associated with marked elevations in MAP (33). Therefore, evidence from these studies suggests that the reduction in nephron number observed in models of fetal programming induced by maternal protein restriction may be due to suppression of the fetal RAS. However, later inappropriate activation of the RAS appears to be associated with established hypertension suggesting that significant alterations in the RAS may contribute to the etiology of hypertension observed in models of fetal programming.

Investigators have quantitated the importance of the RAS in the evolution of the hypertension in animal models of fetal programming. Early administration of ACE inhibitors enalapril (72) and captopril (102) prevented development of hypertension in offspring from protein-restricted dams; use of an AT1R blocker exhibited a similar result (103). In all of these studies, early short-term blockade of the RAS in offspring from protein-restricted dams resulted in long-term antihypertensive effects because blood pressure in treated offspring from protein-restricted dams remained comparable to that observed in control offspring for 8 to 16 wk following treatment. Thus results from these studies suggest a role for RAS involvement in the early etiology of hypertension in this model of fetal programming. However, the contribution of the RAS to the etiology of hypertension in this model remains unclear.

Recent studies suggest that intrarenal ANG II can contribute to the development of hypertension despite the absence of an increase in components of the systemic RAS. Within the kidney, all components of the RAS are present, including angiotensinogen (34). Recent studies suggest that the majority of intrarenal ANG II may be formed within the kidney (20) because concentrations of ANG II located within the renal interstitial fluid greatly exceed plasma concentrations of ANG II (81). The importance of intrarenal effects on the regulation of blood pressure was demonstrated when tissue-specific overexpression of renal angiotensinogen in transgenic mice resulted in marked elevations in blood pressure despite unchanged levels of circulating ANG II (22). This study demonstrated that intrarenal ANG II could be an important regulator of arterial pressure. Recent reports now indicate a role for enhanced intrarenal angiotensinogen production leading to increased intrarenal ANG II in the Dahl salt sensitive rat (52), spontaneously hypertensive rat (53), and polycystic kidney disease (64). What role the intrarenal RAS plays in the etiology of hypertension in animal models of fetal programming is unclear. Hypertension in lambs exposed to low protein in utero is associated with enhanced renal ACE protein expression (33). In a model of fetal programming induced by early dexamethasone exposure in the sheep, elevations in blood pressure are not associated with elevations in peripheral components of the RAS (89). Whether intrarenal ANG II levels are elevated in this model remains unknown. Thus the intrarenal RAS independent of systemic RAS may play a role in some models of fetal programming by contributing to impaired sodium reabsorption and the development of hypertension. What role the RAS plays in the etiology of hypertension in the low protein model of fetal programming is unclear. Development of hypertension in offspring from protein-restricted dams is prevented by early blockade of the RAS (72, 102, 103). However, in this model of fetal programming, systemic (71) and intrarenal components of the RAS (99, 110) are not elevated at this time. However, increased sensitivity to ANG II (77, 98) and alterations in ANG II receptor expression (77, 98, 99, 110) are observed in offspring from protein-restricted dams.

Whether renal AT1R mRNA is increased (110) or unchanged (77) at 4 wk of age in offspring exposed to low protein in utero is unclear. However, at 4 wk of age, renal AT1R protein expression is significantly increased (98, 99, 110). Because the hypertensive effects of angiotensin are mediated via the AT1R (20, 40), upregulation of the AT1R could contribute to the development of hypertension in the low-protein model of hypertension. However, sodium excretory function is not altered at 4 wk of age in offspring from protein-restricted dams (72, 99), suggesting that angiotensin-mediated sodium
retention does not contribute to the development of hypertension in this model of fetal programming.

At birth, a significant decrease in renal AT₁R protein expression is observed in offspring from protein-restricted dams (110). The AT₁R is necessary for normal renal development in the rat (107), and nephrogenesis in the rat continues until ~10 to 12 days after birth. Therefore, the reduction in renal AT₁R expression noted at birth may play a role in mediating the reduction in nephron number observed in offspring from protein-restricted dams.

Alterations in renal expression of the AT₂R are also noted in the protein restriction model of fetal programming. AT₂R are highly expressed in fetal life, but expression decreases significantly after birth (20). In offspring from protein-restricted dams, renal AT₂R protein expression is decreased at birth despite an observed increase in renal AT₂R mRNA expression (110). Because the AT₂R is not thought to play an important role in nephrogenesis (107), reduced expression of this receptor at birth may not impact renal development. At 4 wk of age, Vehaskari et al. (110) report renal AT₂R protein expression is slightly higher in low-protein-exposed offspring, but Sahajpal and Ashton (99) found renal AT₂R protein expression is reduced at 4 wk of age. Discrepancies also exist as to whether renal AT₂R mRNA expression is decreased (77) or unchanged (110). Because low protein diets can differ greatly in composition, discrepancies in observed outcomes may be due to different programming effects induced by different dietary content. Thus the role of the renal AT₁R in the etiology of hypertension is yet to be elucidated.

To summarize, alterations in renal ANG II receptors may play an important role in mediating the structural alterations observed in the protein restriction model of fetal programming. However, because no alteration in renal sodium excretory function in observed in conjunction with the development of hypertension in low-protein offspring, renal ANG II receptors may not directly contribute to the development of hypertension in this model of fetal programming.

The role of the RAS in the maintenance of hypertension has also been investigated. Hypertension was attenuated in adult offspring from protein-restricted dams by administration of either the ACE inhibitor enalapril (71) or captopril (56). We observed a similar response in adult LBW offspring from dams with reduced uterine perfusion using either ACE inhibition or AT₁R blockade (2, 3). Thus on the basis of a common observation noted from two models with the use of different methods to induce an adverse fetal environment, the RAS is suggested to play an important role in the maintenance of hypertension in fetal programming of hypertension.

To summarize, these studies provide support that in utero programming of hypertension due to fetal exposure to an adverse environment may be critically linked to abnormalities in the RAS. Upregulation of renal AT₁R expression at birth may mediate structural changes induced in response to an adverse fetal environment. Maintenance of hypertension in fetal programming may be sustained through inappropriate activation of systemic RAS leading to enhanced sodium reabsorption. Although numerous studies have examined the role of the RAS in linking LBW with hypertension, other mechanisms may be involved in the fetal programming of hypertension in addition to mediating intrarenal alterations in the RAS or later inappropriate activation of systemic RAS in fetal programming. Upregulation of components of the RAS including the ANG II receptors may be due to inappropriate exposure to glucocorticoids (16, 57), as well as activation of the RAS by increased renal sympathetic nerve activity (4).

**Role of the sympathetic nervous system.** Alterations in sympathetic activity have sustained effects on pressure natriuresis that result in long-term changes in arterial pressure. Indeed, increased sympathetic activity is believed to play an important role in the pathogenesis of essential hypertension (24, 65, 66). Regarding LBW in humans, however, there is little information on sympathetic function in adult life. Some studies (17, 47, 94), but not all (112), support the notion that the sympathetic nervous system may contribute to hypertension in adulthood. In contrast to the paucity of information from human studies, increased circulating levels of norepinephrine have been reported in a number of animal models of fetal programming. These models include IUGR induced by maternal protein restriction in the rat (92) and placental insufficiency in both the rat (44) and sheep (49, 104). Increased circulating levels of norepinephrine also occur in spontaneous LBW piglets (13). In addition, chronic prenatal hypoxia is associated with sympathetic hyperinnervation (96, 97) and an increase in adrenal medullary norepinephrine content and tyrosine hydroxylase activity (69), the rate-limiting enzyme in the synthesis of norepinephrine.

Because the renal nerves are believed to be the critical link that transduces changes in central output to alterations in renal excretory function (24, 65, 66), we examined the role of the renal nerves in mediating hypertension in a model of LBW induced by placental insufficiency (4). Although chronic bilateral renal denervation at 10 wk of age had minimal effects on arterial pressure in sham control offspring, it completely abolished the hypertension in growth-restricted offspring when measured 2 wk later (at 12 wk of age)(Fig. 2). Thus this study supports the hypothesis that the sympathetic nervous system may play an important role in the pathogenesis of LBW hypertension.

![Fig. 2](http://ajpregu.physiology.org/10.220.33.6.pdf)
Role of sodium transporters. Inappropriate tubular sodium reabsorption may also play an important role in mediating adult hypertension induced by an adverse fetal environment. Upregulation of renal sodium transporters may serve as an intrinsic renal defect contributing to altered renal sodium reabsorption and subsequent hypertension in fetal programming of hypertension. Alterations in expression of specific sodium transporters are observed in the model of fetal programming induced by maternal protein restriction during gestation (16, 73). Specifically, Bertram et al. (16) observed an increase in mRNA expression of the α- and β-subunits for the apical Na\(^{+}\)-K\(^{+}\)-ATPase sodium transporter in low-protein-exposed offspring. In another study by Vehaskari et al. (73), transcriptional upregulation and protein abundance of two specific sodium transporters were observed in low-protein-exposed offspring. In this study, two critical sodium transporters, the thick ascending limb bumetanide-sensitive Na\(^{+}\)-K\(^{+}\)-2Cl cotransporter and the distal convoluted tubule thiazide-sensitive Na\(^{+}\)-Cl cotransporter, were upregulated before development of hypertension, suggesting that changes in sodium handling mediated by alterations in the expression of sodium transporters may play a role in the etiology of hypertension in fetal programming. However, hypertension in low-protein-exposed offspring is not associated with alterations in renal excretory function under basal conditions (72, 98). Thus because renal excretory function is not altered in conjunction with upregulation of specific renal sodium transporters, what role upregulation of renal sodium transporters may play in the fetal programming of hypertension in offspring from protein-restricted dams remains unclear.

Role of glucocorticoids. Glucocorticoids serve as potent regulators of fetal growth and development by altering the expression of many proteins at both the molecular and cellular level (30). During normal development, circulating levels of glucocorticoids in the fetus are relatively low compared with maternal levels (101). 11β-dehydroxysteroid dehydrogenase 2 (11β-HSD2), an enzyme that converts active corticosterone in the rat and cortisol in humans into their inactive counterparts, is highly expressed in the placenta and is thought to serve as a barrier to protect the fetus from overexposure of glucocorticoids (101). Thus as glucocorticoids mediate a significant impact on the expression of numerous genes and proteins, exposure of the fetus to excess glucocorticoids may play an important role in the fetal origins of adult disease.

Support for this hypothesis is suggested by numerous studies (14, 82, 85) whereby exogenous exposure to glucocorticoids during gestation in the rat leads to hypertension in adult offspring. In the model of fetal programming, induced by maternal protein restriction in the rat, a reduction in placental 11β-HSD2 gene expression was noted during fetal life and was associated with increased glucocorticoid expression in fetal tissues, including brain and kidney (16, 57). Maternal stress during gestation in the rat was also associated with stress-induced elevations in plasma cortisol in the fetus (106). Hypoxia is shown to reduce 11β-HSD2 protein and activity in cultured cytotrophoblast cells (41). Whether this response is observed in vivo is unknown, but suggests a reduction in placental 11β-HSD2 and subsequent fetal exposure to excess glucocorticoids may be present in animal models of fetal programming induced by hypoxia or placental insufficiency and in human IUGR. Thus excess fetal exposure to glucocorticoids mediated via a reduction in placental 11β-HSD2 may be a common component in models of fetal programming.

A role for excess fetal exposure in mediating structural and physiological alterations in the fetus is suggested in animal studies because fetal exposure to exogenous glucocorticoids is associated with a reduction in nephron number in both the rat (85) and sheep (114) and increased renal expression of AT\(_1\)R and AT\(_2\)R in the ovine fetus (80). Because prenatal treatment with cortisol alters renal cortical Na\(^{+}\)-K\(^{+}\)-ATPase activity (91), inappropriate glucocorticoid exposure in utero may also lead to alterations in sodium transporters with subsequent effects on sodium and water balance leading to a reduction in pressure natriuresis and hypertension. Thus fetal exposure to inappropriate levels of glucocorticoids is associated with both structural and physiological alterations. This suggests that inappropriate glucocorticoid exposure in utero may also play a role in animal models of fetal programming and human IUGR by contributing to reduced nephron number, activation of the RAS, altered expression of renal sodium transporters, and the subsequent development of hypertension.

Role of endothelial dysfunction. Impaired endothelial function has been observed in clinical studies of LBW, an observation that extends to animal models of fetal programming. Brawley et al. (18) noted that hypertension in low-protein exposed rat offspring was associated with impaired endothelium-dependent and -independent nitric oxide (NO)-mediated vascular relaxation. We also noted that NO-mediated, endothelium-dependent vascular relaxation was inhibited in hypertensive offspring from dams with reduced uterine perfusion (88). In a study from Franco et al. (32), hypertension and impaired endothelium-dependent vascular function in offspring from undernourished dams was associated with decreased vascular endothelial NO synthase (eNOS) expression and activity. The role for impaired endothelial NO in mediating vascular dysfunction and hypertension in fetal programming is further supported because L-arginine supplementation restored vascular function and attenuated the observed hypertension in offspring from undernourished dams (5). Williams et al. (113) observed that maternal hypoxia during gestation also resulted...

![Fig. 3. Potential mechanisms leading to a reduction in pressure natriuresis and hypertension in animal models of fetal programming. AT\(_1\) and AT\(_2\) angiotensin type 1 and type 2 receptor, respectively; GFR, glomerular filtration rate; RAS, renin angiotensin system; RSNA, renal sympathetic nerve activity.](image-url)
in impaired NO-mediated endothelial function in adult offspring, an effect mediated by reduced NO bioavailability. Thus abnormalities in the NO pathway may contribute to impaired vascular relaxation and hypertension in fetal programming.

Hypertension is associated with decreases in endothelial NO bioavailability and increases in oxidative stress, both of which lead to endothelial dysfunction (100). As mentioned above, a role for reduced NO bioavailability is suggested in mediating hypertension and vascular dysfunction in animal models of fetal programming. A role for oxidative stress is also suggested because antioxidant treatment with vitamins C and E resulted in attenuation of hypertension in offspring from undernourished dams, as well as improved vascular function (31). Thus exposure to an adverse environment in utero results in altered NO bioavailability linked to increased oxidative stress and subsequent vascular dysfunction, which in turn, may contribute to the etiology of fetal programming of hypertension.

Gender differences in fetal programming of hypertension. The role of gender has not been addressed in epidemiological studies regarding LBW and hypertension. However, in many animal models of fetal programming, gender-specific differences are noted. Vascular responses in some models of fetal programming exhibit gender-specific differences because only male offspring from hypoxic dams exhibit vascular dysfunction (42), as do male offspring from dams with moderate global undernutrition (84). Severity of the model appears to play a role in mediating gender-specific differences in fetal programming because moderate levels of maternal protein restriction administered during gestation in the rat results in reductions in nephron number, suppression of fetal intrarenal RAS, and hypertension in male offspring only (121). Only more severe levels of protein restriction lead to a reduction in nephron number and hypertension in female offspring (121). In addition, timing of the insult in utero appears to be gender specific because maternal protein restriction administered in early gestation during the preimplantation period results in hypertension in male offspring only (54). In a model of fetal programming induced by placental insufficiency, hypertension is maintained in male offspring only after passage through puberty (Ref. 1; Fig. 1), suggesting a role for sex hormones in modulating the response to an adverse fetal environment. Gender-specific differences are also observed in the lard-fed model of programming whereby maternal exposure to excess intake of dietary fat is associated with hypertension in female offspring only, yet endothelial dysfunction is observed in both male and female offspring (51). Therefore, what sex-specific mechanisms are involved in utero in the programming of hypertension is unclear; and whether sex steroids play a protective or proactive role in hypertension after birth has also yet to be elucidated.

Catch-up growth. Programming effects initiated in utero due to fetal undernutrition may be potentiated by events occurring after birth (83). In humans, small size at birth followed by accelerated growth in childhood is associated with increased risk of death from coronary heart disease (26, 27, 95) and development of the metabolic syndrome (28, 29). In animal models of fetal programming, LBW, due to maternal protein restriction followed by rapid growth after birth, in mice leads to a reduction in maximum longevity (86). In addition, accelerated catch-up growth following maternal protein restriction in the rat is associated with increased body weight and body fat, and leptin resistance in the adult (23). Thus although an unfavorable environment in utero may be a main determinant for the development of adult disease, environmental influences after birth, such as accelerated or catch-up growth may increase the severity or risk for development of adult disease.

In conclusion, on the basis of the geographical association between neonatal mortality and mortality from CV disease, Barker (7) hypothesized that undernutrition in utero promotes IUGR as evidenced by low weight at birth and fetal programming of CV disease, such as hypertension. The pathogenesis of hypertension is multifactorial and involves both intrinsic intra-renal defects and neurohumoral factors (39). Evidence from animal studies of fetal programming suggests that factors mediating the development and maintenance of hypertension programmed in utero are numerous and involve both structural and physiological alterations leading to permanent changes in the regulatory systems involved in the long-term control of arterial pressure (Fig. 3). Thus animal studies have provided insight into the mechanisms mediating fetal programming of hypertension. Although common observations are noted for the different models of programming, these studies highlight the complexities involved in mediating the relationship between LBW and hypertension.

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