Sex Differences in the Developmental Origins of Cardiovascular Disease

The Developmental Origins of Health and Disease (DOHaD) proposes that adverse events during early life program an increased risk for cardiovascular disease. Experimental models provide proof of concept but also indicate that insults during early life program sex differences in adult blood pressure and cardiovascular risk. This review will highlight the potential mechanisms that contribute to the etiology of sex differences in the developmental programming of cardiovascular disease.

Historical Perspective: Developmental Origins of Health and Disease

Published in 1986, the origins of the hypothesis that nutrition during early life influences later cardiovascular health was based on the noted resemblance of the geographical distribution of mortality from ischemic heart disease with infant mortality (7). An inverse relationship between birth weight and blood pressure in children at 10 years of age was published in 1988, leading Barker to postulate that hypertension was the link between an adverse fetal environment and the increased risk of cardiovascular disease in later life (8). Based on these assumptions, Barker proposed that influences during fetal life that slow growth alter the structure and physiology of the fetus, programming an increase in blood pressure and risk for cardiovascular disease (8). Barker’s hypothesis was followed by experimental studies utilizing models of undernutrition (49) that demonstrated proof of concept and initiated investigation in the cause and effect of the Developmental Origins of Health and Disease (DOHaD).

Epidemiological Studies

Low Birth Weight and Blood Pressure

Within the general population, men have higher blood pressure than age-matched women during early adulthood (58). Aging reduces this sex difference (47) and significantly increases the risk for cardiovascular disease in women (42). Low birth weight (5.5 pounds or 2.5 kilograms or less) serves as a crude indicator of slow fetal growth. Numerous studies indicate that birth weight is inversely related to blood pressure (8, 15, 16, 22, 50). Furthermore, this inverse relationship between birth weight and blood pressure is observed during childhood or before the confounding effects of adult cardiovascular and lifestyle risk factors (8, 23, 51, 56). Hypertension serves as a risk factor for cardiovascular disease, and numerous population studies indicate that birth weight is inversely related to coronary heart disease (4, 6, 52, 55, 82). Studies that directly address whether sex impacts programmed cardiovascular risk are limited. Thus whether men and women differ in their risk for increased blood pressure and coronary heart disease that has its origins during early life is not clear. Whether age alters the effect of sex on programmed cardiovascular risk in men and women has also not been clearly elucidated.

Few studies have investigated whether a sex difference in the relationship between birth weight and blood pressure is present during childhood or adolescence. In a study of 600 children 3–6 yr of age in China, the inverse relationship between birth weight and systolic blood pressure (SBP) was stronger in boys than in girls (12). However, a study of over 4,000 youth in Sweden noted a stronger effect of birth weight on SBP at 15 yr of age in girls than in boys (43). Both studies utilized birth weight data extracted from medical birth records and two separate measures of ambulatory SBP. Variation in age may contribute to this disparate finding. In a study of 1,000 children in the U.K. that was specifically designed to address sex differences in the relationship between birth weight and blood pressure, no relationship was noted for ambulatory measurements in children below 11 yr of age or 11 yr or older (70). However, there was a significant negative correlation between birth weight and 24-h mean SBP in girls but not boys below 11 yr of age; both sexes exhibited a significant negative correlation between birth weight and blood pressure at 11 yr and older (70). Over 600 birth weights were confirmed by medical birth records in this study (70), but, based on reliability of infant birth weight by maternal recall (14), this study suggests that a sex difference in the inverse association between birth weight and blood pressure exists before puberty. Sex differences in the developmental
programming of blood pressure during childhood and adolescence may be due to sex-specific programming of the microvasculature. An increase in systemic vascular resistance is associated with an increase in SBP in a study of boys born small at birth (41). This study did not report an increase in SBP in girls born small; however, small size at birth in girls was associated with an increase in cardiac sympathetic activation, indicating that females are not exempt from the adverse impact of programmed alterations in their cardiac physiology (41). Therefore, additional studies are needed to fully address the influence of sex on enhanced programmed cardiovascular risk during childhood and adolescence and to determine the impact these alterations in physiology and blood pressure that originate in early life have on cardiovascular health with age.

Numerous studies indicate that birth weight and blood pressure are inversely associated in both men and women in adulthood (4, 15, 16, 27, 33, 53); however, whether men and women differ in programmed cardiovascular risk is not clear. A systematic review and meta-regression analysis of the literature from 1999 to 2001 conducted by Lawlor et al. did not detect a sex difference in the inverse relationship between birth weight and blood pressure in adulthood (53). However, this study did note a stronger inverse relationship in adults relative to children, suggesting that age acts as a secondary insult to exacerbate the impact of slow growth during fetal life on later cardiovascular risk. Gamburg and colleagues also noted that the inverse relationship between birth weight and SBP increased with age (27). Their analyses, which involved a reevaluation of data from over 190,000 individuals in 20 Nordic cohorts, indicated that an inverse relationship between birth weight and SBP was present in men and women, but this association was stronger in women for birth weights of <4 kg (27). However, evaluation of over 5,000 participants in northern Finland noted that the association for birth weight and SBP remained significant in females only when current body mass index was included (39). Women also exhibited a stronger inverse association between birth weight and cardiovascular end points such as coronary heart disease and stroke in another cohort of over 10,000 individuals (55). Nonetheless, calculation of the overall 10-yr risk for coronary heart disease derived from a number of risk factors, including age, blood pressure, cholesterol, diabetes, and smoking, was greater in low-birth-weight men relative to their low-birth-weight female counterparts when assessed in young adulthood (93). Thus low-birth-weight men and women exhibit a greater risk for higher blood pressure and coronary heart disease relative to their normal-birth-weight counterparts.

Whether there is a sex difference in the development of cardiovascular risk that has its origins in fetal life is not clear. Age amplifies the inverse relationship between birth weight and blood pressure (50), suggesting that differences in the age of the cohorts examined and/or differences in study parameters may contribute to these discrepancies. However, few studies have directly examined the impact of sex and age on programmed cardiovascular risk.

In a Swedish cohort of over 400 women examined at two different ages, the prevalence and risk of hypertension was significantly elevated in low-birth-weight women at 60 yr of age compared with their prevalence and risk of hypertension at 50 yr of age (5). A cross-sectional survey of over 1,000 women noted that the risk for coronary heart disease was inversely related to low birth weight in postmenopausal women (52). A strong inverse relationship between birth weight and ambulatory blood pressure was observed in a cohort of 500 men and women at 70 yr or older (108). Thus several studies indicate that the strong relationship between birth weight and cardiovascular risk persists in later life in men and women. Furthermore, these studies suggest that age may augment the adverse programming of high blood pressure and coronary heart disease in later life.

**Low Birth Weight and Risk Factors for Cardiovascular Disease**

Sex differences in cardiovascular risk factors such as cholesterol contribute to sex differences in the incidence of coronary heart disease that is greater in men relative to women within the general population (42). Birth weight is also inversely related to a number of cardiovascular risk factors. Total cholesterol is inversely correlated with birth weight (91). The incidence of diabetes is also increased in low-birth-weight individuals (16). However, few studies have directly tested whether men and women differ in the association of birth weight and other cardiovascular risk factors besides blood pressure. A meta-analysis of 30 studies published in 2006 noted that birth weight was more strongly correlated to total cholesterol in men but not in women (54). However, a recent study utilizing a British cohort of over 6,000 individuals at 45 yr of age reported an inverse association between birth weight and total cholesterol that was present only in women (79). Both men and women exhibited an inverse correlation between birth weight and triglycerides in this British cohort (79). Findings from the Dutch Hunger Winter Families Studies noted an elevation in total cholesterol and triglycerides at 58 yr of age in women but not in their age-matched male counterparts (62). Therefore, the impact of sex on the developmental programming of lipids is not clear.
Differences in age and the type or severity of the early life insult may contribute to discrepancies in these findings, and overall these studies highlight the complexity of the developmental origins of cardiovascular health. Slow growth during fetal life also exerts sex-specific programming of cardiac hemodynamics in adulthood. An increase in SBP and wave reflections were observed in low-birth-weight men; however, cardiac output and stroke volume were increased in low-birth-weight women (68).

**Low Birth Weight, Renal Function, and Renal Disease**

Nephron number is reduced in low-birth-weight men and women (37). However, one study indicated that small for gestational age (SGA) was associated with a reduction in renal function that was stronger in men than in women (32), whereas another study reported that an increase in SBP was associated with normal renal function in SGA women (45). Both of these studies examined renal hemodynamics in young adulthood (32, 45). Hyperfiltration occurs in individuals with reduced nephron number to maintain normal renal function, thus contributing to the progression of renal disease (63). A significant correlation was observed between low birth weight and chronic kidney disease (CKD) in men but not in women when CKD was assessed based on estimated glomerular filtration rate or the urine albumin-to-creatinine ratio (57). However, low birth weight was associated with a greater risk of end-stage renal disease (ESRD) in both low-birth-weight men and women relative to their normal-birth-weight counterparts when ESRD was defined by patients on renal dialysis (48). Discrepancies in these findings may be related to assessment of early (57) vs. late (48) markers of kidney disease. Thus low-birth-weight women may be protected to some degree in the early development of impaired renal function, but low birth weight ultimately contributes to the development of ESRD in both men and women. Additional studies are needed to clarify the exact impact that sex and age have on the progression of renal disease in low-birth-weight men and women.

**Summary**

To conclude, whether men and women differ in their risk for cardiovascular and renal disease that has its origins during early life is not clear. Numerous studies indicate that age augments the severity of programmed cardiovascular and renal risk. However, additional studies are needed to directly determine the impact of age on programmed cardiovascular and renal risk and to test whether a sex difference in programmed cardiovascular and renal risk persists in the elderly. In addition, longitudinal studies are needed to determine the long-term impact of an increase in blood pressure and other risk factors for coronary heart disease in low-birth-weight individuals that may adversely influence cardiovascular and renal health across the lifespan.

**Animal Models of Developmental Insult**

Although numerous epidemiological studies imply an inverse association between birth weight and blood pressure, experimental models provide proof-of-concept and allow investigation into the mechanistic pathways that mediate the developmental programming of cardiovascular risk. Experimental models of developmental programming demonstrate sex differences that differ in their response to the severity of developmental insult (102) or exhibit age-dependent changes in cardiovascular risk (2, 38, 83). Models utilized to induce developmental insults to impact later cardiovascular health derive from the known causes of impaired fetal growth. These include models of undernutrition induced by manipulation of the maternal diet (64, 99) or models of placental insufficiency induced by reduced uterine perfusion (2) or bilateral uterine ligation (98). Placental insufficiency also mimics the initiating event in the etiology of preeclampsia, and prenatal exposure to a restriction in delivery of nutrients and hypoxygen can limit fetal growth (30). Prenatal exposure to hypoxia is also utilized to induce IUGR (83) and examine mechanisms related to the developmental programming of increased cardiovascular risk. Prenatal exposure to nicotine (105) or dexamethasone (77) also programs an increase in cardiovascular risk and mimics major risk factors for low birth weight, including maternal smoking during pregnancy (46) or inappropriate exposure of the fetus to maternal glucocorticoids as observed in pregnancies complicated by fetal growth restriction and hypertension (67). Severe stress during early life is linked to increased cardiovascular disease in later life (1), and maternal separation during lactation in the rat provides a model of early life stress that programs increased cardiovascular risk in the adult offspring (60). Importantly, this model indicates that the postnatal period is a window of early development that is sensitive to the programming of increased cardiovascular risk. Over one-third of adults in the U.S. are obese, and experimental models of maternal obesity or overfeeding (44, 86) are utilized to investigate the impact of overnutrition on later cardiovascular health of the offspring. Sex differences in adult blood pressure and cardiovascular risk are observed in experimental models of developmental insult (2, 44, 61, 100, 105), and age impacts the developmental programming of
cardiovascular risk (38, 83) (Table 1). Sex hormones are implicated as potential mediators of sex-specific programming of cardiovascular risk. Furthermore, sex hormones may exert their influence via modulation of the regulatory systems key to the long-term control of blood pressure. Investigation into the mechanisms that program an increase in blood pressure in response to an adverse insult during early life implies a key role for the renin angiotensin system (RAS), oxidative stress, and the renal nerves. This review will focus on the current insight into how these factors contribute to sex differences in programmed cardiovascular risk.

Sex Differences and the Role of Sex Steroids

Numerous epidemiological studies indicate that offspring of a preeclamptic pregnancy exhibit a marked increase in blood pressure in later life, as reviewed in Davis et al. (19). Placental ischemia is indicated to be the initiating event in pregnancies complicated by preeclampsia (30), and a reduction in uterine perfusion initiated at day 14 of gestation in the rat leads to intrauterine growth restriction (IUGR) and hypertension in male offspring (2) (Table 1). Hypertension in male IUGR offspring is associated with a twofold increase in circulating testosterone (72). Castration abolishes hypertension in adult male IUGR offspring (72), implicating the importance of testosterone in the etiology of IUGR-induced hypertension in this model of developmental insult. Male IUGR rats also exhibit an enhanced increase in blood pressure in response to acute Ang II relative to the Ang II-induced increase in blood pressure observed in their male control counterparts (76); castration abolishes hypersensitivity to acute Ang II in male IUGR rats (76). Thus these studies suggest that testosterone acts as a pro-hypertensive factor in male IUGR rats exposed to placental insufficiency during fetal life (FIGURE 1). Female IUGR offspring in this model of placental insufficiency are normotensive after puberty (2) (Table 1). Estradiol levels do not differ in the female IUGR rat relative to its female control counterpart during development or after puberty (71). However, ovariectomy induces hypertension (Table 1), whereas estradiol replacement in ovariectomized female IUGR offspring reverses the increase in blood pressure that occurs after a loss of ovarian hormones in the female IUGR rat (71). Ovariectomy also enhances blood pressure

<table>
<thead>
<tr>
<th>Model of Developmental Insult</th>
<th>Age</th>
<th>Blood Pressure</th>
<th>Ang II Sensitivity</th>
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<tbody>
<tr>
<td>Placental insufficiency (reduced uterine perfusion) E14–E21</td>
<td>4 mo</td>
<td>Increased (telemetry) (72)</td>
<td>Enhanced (acute, catheter) (76)</td>
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<tr>
<td></td>
<td>12 mo</td>
<td>Not yet reported</td>
<td>Not yet reported</td>
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<tr>
<td>Placental Insufficiency (bilateral uterine ligation) E18–E21</td>
<td>8, 12, or 20 wk</td>
<td>Increased (tail cuff) (98)</td>
<td>Not yet reported</td>
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<td></td>
<td>18 mo</td>
<td>Not yet reported</td>
<td>Not yet reported</td>
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<tr>
<td>Prenatal dexamethasone (0.2 mg/kg) E14, E15–E16, or E17–E18</td>
<td>6 mo</td>
<td>Increased (tail cuff) (77)</td>
<td>Not yet reported</td>
</tr>
<tr>
<td></td>
<td>21–22 wk</td>
<td>Increased (catheter) (99)</td>
<td>Not yet reported</td>
</tr>
<tr>
<td>Prenatal protein restriction (5% vs. 19%) E0–E21</td>
<td>22 wk</td>
<td>Increased (catheter) (102)</td>
<td>Not yet reported</td>
</tr>
<tr>
<td>Early life stress (3 h of maternal separation per day) P2–P14</td>
<td>12 wk</td>
<td>No change (telemetry) (60)</td>
<td>Enhanced (chronic, telemetry) (61)</td>
</tr>
<tr>
<td>Prenatal nicotine (102 mg/ml nicotine) E4–E21</td>
<td>5 mo</td>
<td>No change (catheter) (105)</td>
<td>Enhanced (acute, catheter) (105)</td>
</tr>
<tr>
<td></td>
<td>22 mo</td>
<td>Increased (catheter) (92)</td>
<td>Enhanced (acute, catheter) (92)</td>
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Note that an increase in blood pressure or enhanced sensitivity to angiotensin II (Ang II) represents the change relative to the same-sex control counterpart. OVX, ovariectomy; E, gestational life; P, postnatal life; ELS, early life stress.
sensitivity to acute Ang II in female IUGR offspring relative to their ovariectomized female control counterparts (74) (Table 1), indicating that estrogen status is linked to cardiovascular risk programmed in response to reduced uterine perfusion in the female IUGR rat (FIGURE 2). Offspring exposed to early life stress do not exhibit an increase in blood pressure relative to age-matched controls under baseline conditions (Table 1). However, chronic Ang II elicits a greater degree of Ang II-induced hypertension in male rats exposed to early life stress relative to male control counterparts (60) (Table 1). Although chronic Ang II is associated with a marked reduction in circulating levels of testosterone in male control and male early life stress rats, plasma testosterone remains significantly increased in the early life stress male rats relative to control counterparts during chronic Ang II (61). Castration abolishes the heightened blood pressure in response to chronic Ang II in early life stress male rats (61), suggesting that testosterone plays a permissive role in the programming of enhanced cardiovascular risk following exposure to stress during early life. Female rats exposed to early life stress also develop a greater increase in blood pressure in response to chronic Ang II compared with female control counterparts (61). However, the increase in blood pressure in response to chronic Ang II is blunted in female rats exposed to early life stress relative to their early life stress male counterparts (Table 1). Furthermore, the development of chronic Ang II-induced hypertension in female rats exposed to early life stress is delayed relative to their male counterparts (61) (Table 1). Whether ovarian hormones confer protection against programmed cardiovascular risk in female rats exposed to early life stress has not yet been investigated, but testosterone is implicated as a pro-hypertensive agent in male rats in this model of developmental insult (FIGURE 1).

Prenatal exposure to nicotine does not program hypertension in young adult rats at baseline; however, male but not female offspring in this model exhibit enhanced sensitivity to acute Ang II in young adulthood (105) (Table 1). Ovariectomy induces enhanced sensitivity to acute Ang II in young adult female rats exposed to prenatal nicotine (104) (Table 1). Estrogen replacement ameliorates the enhanced acute Ang II-mediated increase in blood pressure in ovariectomized female prenatal nicotine rats, indicating that estradiol may serve as an anti-hypertensive factor in this model of prenatal insult (104) (FIGURE 2).

Moderate maternal protein restriction (9% vs. 20%) programs hypertension in male offspring (99), although female offspring of moderate protein-restricted dams remain normotensive (100) (Table 1). Circulating levels of testosterone do not differ in male controls relative to male offspring exposed to this level of maternal protein restriction (101). Furthermore, castration fails to ameliorate hypertension programmed by prenatal exposure to maternal protein restriction (101), indicating that hypertension programmed by a 50% reduction in maternal protein intake is not testosterone dependent. More severe protein restriction (5% vs. 20%) is required to program hypertension in female offspring (102) (Table 1). However, the importance of sex hormones in the etiology of hypertension induced by severe protein restriction during fetal life has not yet been investigated.

To summarize, numerous models of developmental insult exhibit sex differences in blood pressure under baseline conditions and in response to the vasoactive factor Ang II. Additionally, a greater risk for higher blood pressure is observed in male offspring relative to their female counterparts, despite the timing of the developmental insult (prenatal vs. postnatal) or the method of insult (prenatal nicotine, undernutrition, or glucocorticoid exposure). In many models of developmental insult, testosterone is indicated to provide a pro-hypertensive effect, whereas estrogen is suggested to contribute an anti-hypertensive influence (FIGURES 1 AND 2). However, a role for sex hormones in the etiology of sex differences in hypertension and increased cardiovascular risk programmed in response to a developmental insult is not implicated in all.
experimental models, highlighting the complexity of programmed chronic disease.

**Sex Differences and the RAS**

The RAS is a key mediator of blood pressure and volume homeostasis. Recent studies suggest that the “nonclassical” or vasodilatory arm of the RAS is enhanced in female rats relative to males (84) and that modulation of the RAS via sex steroids contributes to sex differences in the RAS and blood pressure control (34, 35). Density of the renal angiotensin type 1 receptor (AT1R), the receptor, which mediates the “classic” vasoconstrictor actions of angiotensin II (Ang II), is greater in the male relative to the female rat (87), whereas renal expression of the angiotensin type 2 receptor (AT2R), which opposes the classic actions of the AT1R, is increased in the female rat relative to the male rat (85). Recent studies indicate a role for sex hormones in the modulation of RAS components. Expression of the “classic RAS pathway” is greater in males in a manner that is testosterone dependent (107); estrogen enhances production of the “nonclassical” angiotensin-(1–7) [Ang-(1–7)] peptide to act as an anti-hypertensive hormone in the female (13). Male and female rodents exhibit a sex difference in the blood pressure response to Ang II (106). Estrogen enhances expression of the renal AT2R and ACE2 in the female rat in response to chronic Ang II (13), suggesting that estrogen exerts a protective effect in response to chronic Ang II by altering the vasoconstrictor/vasodilator balance (13). Female offspring in experimental models of developmental insult are protected to a greater degree in young adulthood from increases in blood pressure under baseline conditions and in response to Ang II relative to male counterparts (61, 71, 100, 105). Recent experimental studies implicate an important role for the classical and nonclassical RAS as potential mediators in the sex-specific developmental programming of blood pressure and cardiovascular risk.

A marked increase in systolic blood pressure is observed in SGA boys that is associated with a marked increase in Ang II and angiotensin-converting enzyme (ACE) (24). Although this association implicates a role for the RAS in mediating the inverse relationship between size at birth and blood pressure, the importance of the RAS in mediating hypertension programmed by developmental insult and the sex-specific developmental programming of blood pressure and cardiovascular risk.

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FIGURE 2. Sex differences in the developmental origins of hypertension

Numerous studies indicate that the ovarian hormones contribute to sex differences in programmed cardiovascular risk. Upregulation of compensatory mechanisms, including the ACE2/AT2R pathways and anti-oxidants, may be estrogen dependent. Yet, increases in oxidative stress may program cardiovascular risk in female offspring impacted by an insult during early life. In addition, age leads to an increase in visceral adiposity, circulating leptin, and involvement of the renal nerves in the development of age-dependent hypertension.
expression is increased by moderate maternal protein restriction (9% vs. 18%) in female offspring, with no effect on renal AT1R expression in the low protein male counterpart (65, 66). However, more severe maternal protein restriction (6% vs. 20%) programs hypertension associated with upregulation of vascular AT1R expression in the male offspring by 3 mo of age, whereas hypertension and upregulation of the vascular AT1R expression is delayed until 6 mo of age in the female offspring (89). To summarize, these studies suggest that upregulation of the classic or vasoconstrictor arm of the renal RAS contributes to increased blood pressure programmed in response to a developmental insult in male offspring, whereas female counterparts exhibit counterregulatory programming of the nonclassical or vasodilatory components of the RAS that ameliorates or delays the development of programmed hypertension (FIGURES 1 AND 2). In addition, these studies indicate that developmental insults program a sex difference in blood pressure that is associated with sex-specific expression of the RAS in a manner that may be age-dependent in female offspring.

**Sex Differences and Oxidative Stress**

Increased levels of reactive oxygen species (ROS) or an increase in oxidative stress is associated with cardiovascular diseases such as hypertension (97). Markers of oxidative stress are increased in children born SGA (25). However, SGA children also exhibit an elevation in SOD activity, suggesting that compensatory mechanisms may be upregulated to oppose programmed hypertension and cardiovascular risk (25). Numerous experimental studies implicate the importance of oxidative stress in the developmental programming of hypertension (26, 28, 73, 90, 103) and indicate that modulation of oxidant status by sex steroids may contribute to the differential programming of cardiovascular risk in male offspring relative to female offspring (25, 73, 104). IUGR programmed by placental insufficiency at day 14 of gestation in the rat is associated with a marked increase in renal markers of oxidative stress in hypertensive male IUGR offspring but not in normotensive female IUGR offspring (73). Chronic treatment with the SOD mimetic tempol, an antioxidant, abolishes hypertension in male IUGR offspring (73), indicating that an increase in oxidative stress contributes to the developmental programming of IUGR-induced hypertension. However, renal expression and activity of catalase, an antioxidant, is elevated in the normotensive, female IUGR rat (73), indicating that compensatory pathways may counteract the adverse programming of hypertension in female IUGR offspring. Tempol also abolishes hypertension programmed by prenatal exposure to maternal protein restriction in the rat (90), indicating that common mechanistic pathways contribute to developmental programming of increased cardiovascular risk despite subtle differences in the method of prenatal insult. Although oxidative stress appears to play a more important role in the regulation of blood pressure in males compared with females in experimental models of hypertension (18, 59), exposure to a developmental insult may program an increase in oxidative stress that contributes to increased cardiovascular risk in both male and female offspring (25). Global undernutrition programs an increase in vascular oxidative stress that can be abolished by antioxidant treatment in conjunction with restoration of vascular function in the female rat (26). Ovariectomy enhances vascular reactivity to acute Ang II in association with an increase in production of ROS in aortic segments in female rats exposed to prenatal nicotine (104). The antioxidant apocynin abolishes the heightened vascular reactivity induced by ovariectomy in prenatal nicotine female offspring, suggesting that removal of ovarian hormones unmask the adverse impact of a developmental insult (104). To conclude, oxidative stress contributes to the developmental programming of hypertension. Whether testosterone contributes to increased production of ROS in the developmental programming of hypertension is not yet known. Upregulation of compensatory antioxidant pathways are observed in female offspring. However, loss of ovarian hormones may induce production of ROS, contributing to an increase in programmed cardiovascular risk in female offspring exposed to adverse events during early life (FIGURE 2).

**Sex Differences and the Role of the Renal Nerves**

An increase in renal sympathetic nerve activity is observed in numerous experimental models of hypertension (21), indicating that the renal nerves serve as a link between activation of the central sympathetic nervous system (SNS) and impaired renal contributions to volume and electrolyte homeostasis. The importance of the SNS in low-birthweight individuals is controversial with studies indicating that low-birth-weight individuals demonstrate an increase (11, 40, 81, 88) or a decrease (96) in activation of the SNS. However, several experimental studies suggest that activation of the SNS contributes to the developmental programming of hypertension and increased cardiovascular risk. Increased circulating levels of catecholamines are noted in offspring of rats fed reduced protein content during pregnancy (78), in a naturally occurring model of IUGR in the pig (80), and in offspring exposed to placental insufficiency in the rat (36). Hypertension in the juvenile rat exposed to maternal obesity during
gestation is abolished by α1- and β-adrenergic blockade, implicating the importance of the SNS in the etiology of hypertension programmed by maternal obesity (86). The renal nerves contribute to alterations in renal function programmed by early life stress in the male rat (61). Renal denervation abolishes hypertension in male offspring exposed to glucocorticoids during fetal life (17). Renal denervation also abolishes hypertension in prepubertal (75) and young adult (3) male IUGR offspring exposed to placental insufficiency initiated at day 14 of gestation. Thus these studies indicate a key role for activation of the renal sympathetic nerves in the etiology and maintenance of hypertension programmed by a developmental insult (FIGURES 1 AND 2). In the model of placental insufficiency induced at day 14 of gestation, female IUGR offspring are normotensive in young adulthood (2) but develop age-dependent hypertension that is associated with a marked increase in total and visceral fat and elevated circulating leptin by 1 yr of age (38). Renal denervation abolishes age-dependent hypertension in the female IUGR offspring at 1 yr of age (38). Thus the contribution of the renal nerves to age-dependent hypertension in female IUGR rats may result from mechanisms related to obesity and leptin-derived renal sympathetic nerve activity (20). However, hypertension in male IUGR offspring during young adulthood is not associated with an increase in fat mass or circulating levels of leptin (Intapad S, Dasinger JH, Ojeda NB, Alexander BT, unpublished observations), suggesting that hypertension that originates in early life in male IUGR offspring develops independent of an increase in fat mass. To conclude, the renal nerves contribute to the etiology of hypertension in male offspring exposed to prenatal insults such as placental insufficiency or dexamethasone. Postnatal insults such as early life stress also involve the renal nerves in the programming of increased cardiovascular risk. However, the mechanisms that contribute to the activation of the renal nerves in the developmental programming of hypertension may be sex specific.

Developmental Programming of Cardiovascular Disease

The Impact of Age

Although numerous experimental models of developmental insult report that female offspring are protected against hypertension and programmed cardiovascular risk in young adulthood (2, 69, 105), additional studies now indicate that age modulates programmed risk in a manner whereby females develop age-dependent increases in blood pressure (38) and enhanced sensitivity to Ang II (92) that are not observed in young adulthood (2, 105) (Table 1). Female rats exposed to placental insufficiency at day 14 of gestation are normotensive at 3 mo of age (2) but exhibit hypertension by 12 mo of age when measured by radiotelemetry (38) (Table 1). Uterine weight does not differ in female IUGR offspring relative to their female control counterparts at 12 mo of age, suggesting that the age-dependent increase in blood pressure is not associated with an alteration in ovarian hormone levels (38). However, placental insufficiency induced by bilateral uterine ligation at day 18 of gestation is not associated with hypertension at 4 or 18 mo of age in female rats when measured by the tail-cuff method (69) (Table 1). Differences in the impact of age on later blood pressure in female offspring in these models of placental insufficiency may be due to variations in the severity of the model, the timing of the insult, or the method utilized for measurement of blood pressure. Female offspring exposed to prenatal nicotine exhibit an enhanced increase in the blood pressure in response to acute Ang II at 22 mo of age (92) that is not observed in young adulthood (105) (Table 1). Baseline blood pressure remains unchanged in male and female offspring in this model of prenatal exposure to nicotine relative to age-matched controls at 4 mo of age. However, systolic blood pressure is increased at 22 mo of age in prenatal nicotine-exposed males but not females relative to age-matched, same-sex controls (92), indicating that male offspring in this model of developmental insult are more susceptible to the impact of age on blood pressure. Male offspring are also more sensitive to the impact of age in a model of programming induced by prenatal exposure to hypoxia (11.5% O2 vs. 21% O2) (83). Prenatal hypoxia induces enhanced sensitivity to mild cardiac ischemia/reperfusion (I/R) injury in male and female IUGR offspring at 4 mo of age that is exacerbated by 12 mo of age in male rats only (83). Thus insults during development program long-term cardiovascular risk in a manner that is sex and age dependent. Different models exhibit differential programming of cardiovascular risk and sex-specific susceptibility to age-dependent changes in adult outcome, highlighting the complexity of developmental insults on later chronic health.

Epigenetic Processes

Adverse influences during fetal life that program an increase in blood pressure and cardiovascular risk may involve epigenetic processes (94). Epigenetic mechanisms involve chromatin-based alterations in gene expression that do not involve changes in the overall nucleotide sequence (94).
Despite the significant interest in the importance of epigenetic processes, few studies have directly investigated whether epigenetic processes contribute to the developmental programming of hypertension and enhanced cardiovascular risk (10, 29). Maternal protein restriction programs alterations in the methylation pattern of the ACE gene in the fetal brain (29) or the AT1bR gene in the adrenal gland at 4 wk of age (10). Uteroplacental insufficiency in the rat programs sex-specific changes at postnatal day 20 in the methylation pattern of 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), an enzyme involved in renal glucocorticoid sensitivity (9). Whether these alterations persist into adulthood and contribute to the development of hypertension in later life is not yet clear. However, sex-specific programming of epigenetic processes may contribute to sex differences in programmed disease. However, additional studies are needed to determine the pathophysiological importance of epigenetic processes on cardiovascular risk that originates from a developmental insult.

Translational Considerations

The blood pressure difference in low-birth-weight children and adults relative to their normal-birth-weight counterparts is minimal (50). However, small increases in blood pressure above normal that extend across the lifespan can significantly increase the risk for cardiovascular or renal disease in later life (95). Age serves as a second hit in low-birth-weight individuals, increasing susceptibility to renal injury, hypertension, and coronary heart disease (48, 50). Whether men and women differ in their degree of programmed cardiovascular risk is not clear. Impaired renal function and progression into CKD may be delayed in low-birth-weight women relative to their male counterparts (32, 45, 57). Experimental studies suggest that female offspring exposed to a developmental insult are protected to some degree relative to their age-matched counterparts in young adulthood (2, 77, 102, 105), yet age augments increased programmed cardiovascular risk in female and also male offspring (38, 83). Thus these studies suggest that birth weight as a crude marker of fetal growth should be a clinical consideration in the therapeutic approach and management of blood pressure, and cardiovascular and renal disease.

Conclusions

In closing, experimental studies indicate that sex impacts the developmental programming of blood pressure and cardiovascular risk. Testosterone appears to serve as a pro-hypertensive agent in the developmental programming of increased blood pressure and cardiovascular risk (61, 72) (FIGURE 1), whereas estrogen contributes anti-hypertensive influences against programmed increases in blood pressure and sensitivity to vasoactive factors (71, 104) (FIGURE 2). Age exacerbates the developmental programming of chronic disease (38, 83), highlighting the need for additional studies to elucidate the exact contribution of sex and age to programmed disease risk in the human population to determine how events during early life impact the management of chronic disease in low-birth-weight women and men.

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