

## Developmental Programming of Hypertension Physiological Mechanisms

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Epidemiological studies indicate that the origins of high blood pressure initiates in fetal life.<sup>1-3</sup> Recent reviews highlight a role for numerous factors in the pathogenesis of the developmental programming of hypertension including epigenetic processes, glucocorticoids, reduced nephron number, activation of the sympathetic nervous system, and the renin-angiotensin system (RAS) and endothelial dysfunction.<sup>4-7</sup> Studies published in *Hypertension* and other journals highlight the complexity of cardiovascular risk that has its origins in fetal life. The purpose of this minireview is to present an update on recent studies in *Hypertension* that investigate the underlying mechanisms that contribute to the developmental programming of hypertension and increased risk for cardiovascular disease.

### Sympathetic Nervous System and the Developmental Programming of Hypertension

Barker<sup>8</sup> first proposed the theory of the fetal origins of coronary heart disease based on the hypothesis that adaptive responses by the fetus to maternal undernutrition would enhance survival to birth at the expense of later cardiovascular health. The first animal studies to investigate the Barker hypothesis utilized rodent models to demonstrate that maternal undernutrition during gestation programs an increase in blood pressure in the offspring.<sup>9</sup> Based on previous studies indicating a role for the renal nerves in experimental models of low birth weight,<sup>10,11</sup> Mizuno et al<sup>12</sup> proposed that increased blood pressure in protein-restricted offspring would be associated with an increase in baseline measure of renal sympathetic nerve activity (SNA). Although baseline measurement of renal SNA under anesthesia did not differ in male protein-restricted offspring versus male control at 4 to 5 months of age, renal SNA was significantly elevated in response to a secondary hit of physical stress in association with a greater blood pressure response<sup>12</sup> indicating a role for an increase in renal SNA in the developmental programming of increased blood pressure and cardiovascular risk. Chronic systemic blockade of the RAS with enalapril, an angiotensin-converting enzyme inhibitor, abolishes hypertension in offspring programmed via exposure to a fetal insult such as maternal dietary protein restriction<sup>13</sup> or placental insufficiency,<sup>14</sup> suggesting a role for the peripheral RAS in the pathogenesis of increased cardiovascular risk programmed by fetal insult. Expression of the angiotensin type 1 receptor is elevated in regions of the brain

involved in cardiovascular regulation in offspring exposed to maternal dietary protein restriction.<sup>15</sup> Intracerebroventricular administration of the angiotensin type 1 receptor antagonist, losartan, at a dose 100× lower than an effective systemic dose, abolishes hypertension in rat offspring exposed to maternal dietary protein restriction<sup>15</sup> demonstrating a role for the central RAS in the pathogenesis of increased cardiovascular risk that has its origins in fetal life. Increases in renal SNA can be modulated by changes in activity of the central RAS.<sup>16</sup> Thus, in a more recent study published in *Hypertension*, Mizuno et al<sup>12</sup> expanded their investigation to elucidate the mechanism whereby sympathetic responsiveness to physical stress is enhanced in offspring exposed to maternal dietary protein restriction.<sup>17</sup> They found that chronic blockade of the RAS with enalapril not only reduced blood pressure in male protein-restricted offspring under baseline conditions but also attenuated the exaggerated increase in renal SNA and diminished the enhanced blood pressure responsiveness to physical stress in male protein-restricted offspring with no effect on renal SNA or blood pressure in male control offspring.<sup>17</sup> Thus, this study by Mizuno et al<sup>12</sup> suggests that the RAS contributes to the development of enhanced sympathetic and blood pressure responsiveness to physical stress programmed in response to a fetal insult (Figure).

Many studies demonstrate an inverse association between birth weight and blood pressure,<sup>1-3</sup> indicating birth weight as a predictor of cardiovascular risk. Although malnutrition contributes to fetal growth restriction in many developing countries,<sup>18</sup> placental insufficiency is the major cause of low birth weight within the Western world.<sup>19</sup> Placental hypoxia that occurs in response to placental insufficiency alters fetal oxygen delivery resulting in intrauterine growth restriction (IUGR).<sup>20</sup> Rook et al<sup>23</sup> recently utilized a rat model of prenatal hypoxia to examine the role of muscle SNA in the fetal origins of hypertension. Muscle SNA is elevated in healthy young adults of normal stature born small for gestational age who tend to have higher blood pressure relative to appropriate for gestational age counterparts,<sup>21</sup> suggesting that an increase in SNA may be a link between birth weight and blood pressure. Although aging in humans is associated with an increase in sympathetic outflow to the peripheral tissues, responsiveness to sympathetic stimulation decreases with aging.<sup>22</sup> Therefore, Rook et al<sup>23</sup> investigated whether temporal changes in muscle SNA were associated with increased blood pressure in male

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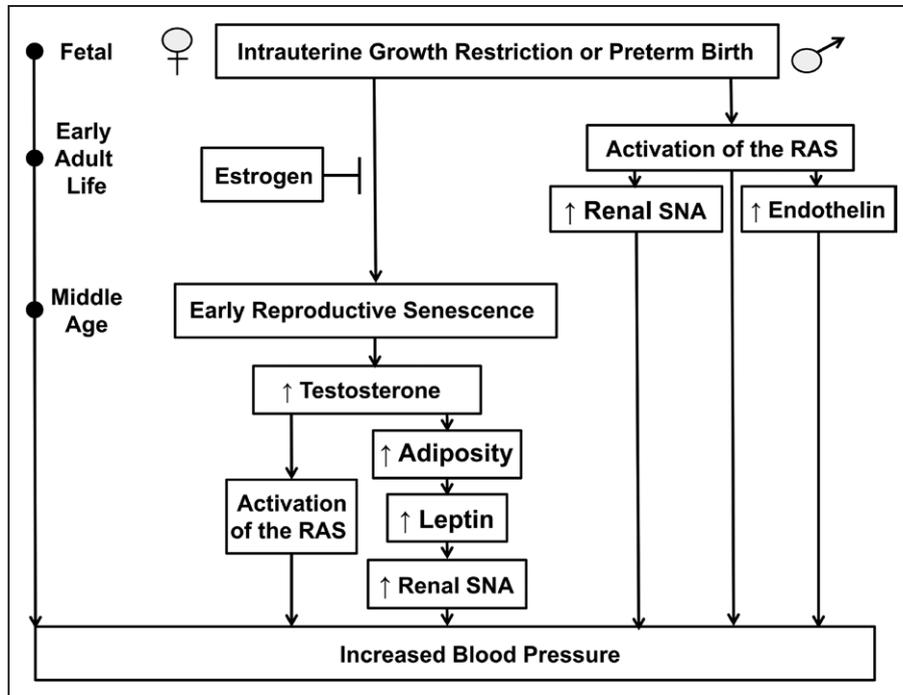
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**Figure.** A schematic representation of the proposed pathogenesis of the developmental programming of hypertension. Numerous experimental models of developmental origins including placental insufficiency, moderate maternal protein restriction, fetal exposure to exogenous glucocorticoids, and prenatal exposure to hypoxia or nicotine program a sex difference in adult cardiovascular risk. Several studies indicate that estrogen is protective against the developmental origins of increased cardiovascular risk in female offspring in early adult life. Yet, recent studies report that protection against programmed cardiovascular (CV) risk in female offspring is lost by 1 year of age. Despite the method of fetal insult, common mechanistic pathways contribute to programmed CV risk. This review highlights recent advances in the developmental origins of health and disease published in *Hypertension*. Insight from these studies indicates the importance of the renin–angiotensin system (RAS) and endothelin system, sympathetic nerve activity (SNA), and sex steroids in the cause of hypertension that has its origins in early life. Early adult life (3–5 mo of age), middle age (12 mo of age).

offspring exposed to prenatal hypoxia. This study published in *Hypertension* reported that frequency of single-unit muscle SNA and sympathetic innervation of the tibial arteries were increased at 3 months of age in male offspring exposed to prenatal hypoxia.<sup>23</sup> Blood pressure was not elevated at this age, but blood pressure was increased by 9 months of age in male offspring exposed to prenatal hypoxia relative to male control,<sup>23</sup> suggesting that exposure to hypoxia during fetal life programs an increase in basal muscle SNA that precedes the development of increased blood pressure. Despite the increase in sympathetic nerve density, vasoconstrictor responses to sympathetic nerve stimulation were blunted in male prenatal hypoxia offspring at 3 months of age relative to age-matched control counterparts.<sup>23</sup> Blockade of the neurotransmitter neuropeptide Y attenuated these responses in male control offspring at 3 months of age with no effect on vasoconstrictor responses to sympathetic nerve stimulation in prenatal hypoxia counterparts.<sup>23</sup> However, responsiveness to sympathetic stimulation was attenuated in male control offspring by 9 months of age.<sup>23</sup> Collectively, these data indicate that fetal exposure to prenatal hypoxia programs premature aging of the vasculature; yet, the quantitative importance of muscle SNA in the pathophysiology of increased cardiovascular risk after exposure to a fetal insult is not yet clear.

Many experimental models of developmental programming report a sex difference in blood pressure with males exhibiting a significant increase in blood pressure in young adulthood, whereas female counterparts remain

normotensive.<sup>24–28</sup> Yet, female offspring exposed to an insult during fetal life do not remain protected against an increase in blood pressure in later life.<sup>25,29</sup> Previous studies addressing the importance of the renal nerves and SNA in the developmental programming of hypertension involve studies performed in male offspring.<sup>10,11,17,23</sup> Although male IUGR offspring in the model of IUGR induced via placental insufficiency in the rat are smaller in size relative to control counterparts, hypertension in male IUGR offspring is abolished by bilateral renal denervation at 3 months of age.<sup>11</sup> In this model, blood pressure does not differ between female IUGR relative to female control offspring at 3 months of age.<sup>24</sup> However, Intapad et al<sup>30</sup> recently reported in a study published in *Hypertension* that female IUGR offspring exhibited a significant increase in blood pressure relative to age-matched female counterparts at 1 year of age. Visceral fat mass and circulating leptin levels were increased in conjunction with the significant increase in blood pressure in female IUGR offspring relative to control counterparts at 1 year of age; increases not present in female IUGR offspring at 6 months of age when they were still normotensive.<sup>30</sup> Based on studies by Hall et al<sup>31</sup> suggesting that obesity-related hypertension involves activation of the renal nerves, Intapad et al<sup>30</sup> demonstrated that bilateral renal denervation abolished the increase in blood pressure in female IUGR offspring at 1 year of age. It was previously reported that bilateral renal denervation abolishes hypertension in male IUGR offspring as early as 6 weeks of age, before puberty.<sup>32</sup> Taken together, data from studies in the model of IUGR

induced by placental insufficiency indicate a sex difference in the fetal programming of increased sympathetic outflow to the kidney. The importance of the renal nerves in the pathogenesis of increased blood pressure in male IUGR offspring that is present before puberty suggests that activation of the renal nerves is established in utero in male IUGR offspring, whereas an additional stimulus must contribute to the activation of the peripheral sympathetic nervous system that occurs in later life in female IUGR littermates. Leptin is associated with hypertension in women as they age.<sup>33</sup> Thus, the age-related increase in circulating leptin in female IUGR offspring at 1 year of age may serve as a secondary stimulus demonstrating sex-specific programming of increased cardiovascular risk (Figure).

Maternal prepregnancy body mass index is positively associated with blood pressure and total body fat mass in childhood<sup>34</sup> indicating that low birth weight resulting from maternal undernutrition or placental insufficiency is not the only adverse programmable influence on later cardiovascular risk. Prior et al<sup>35</sup> recently reported in *Hypertension* that fetal exposure to maternal obesity programmed an increase in blood pressure associated with a significant increase in fat mass and leptin in rabbit offspring. In this model, renal SNA was elevated in obese offspring in young adulthood relative to control counterparts.<sup>35</sup> Obese offspring also exhibited a greater rise in renal SNA in response to air jet stress or intracerebroventricular infusion of leptin relative to control counterparts.<sup>36</sup> Samuelsson et al<sup>36</sup> note a similar outcome in mice born to high-fat dams. Yet, Prior et al<sup>35</sup> also noted an enhanced increase in renal SNA in response to intracerebroventricular infusion of ghrelin, an activator of neuropeptide Y. Thus, sympathetic overactivation after a developmental insult may be influenced by increased adiposity in a manner that is not species specific.<sup>30,35,36</sup>

Collectively, studies highlighted in this section suggests that the pathogenesis of elevated sympathetic outflow programmed in response to a developmental insult may be multifactorial. Although the pathogenesis of increased SNA after a developmental insult may involve obesity or increased adiposity, the central RAS may also serve as a potential stimulus for the developmental origins of increased SNA in a manner that is sex and age dependent.

### Sex Steroids, the RAS, and the Developmental Programming of Hypertension

Onset of menopause is accelerated in low birth weight women<sup>37</sup> suggesting that the influence of an adverse fetal environment extends beyond the developmental programming of increased blood pressure and cardiovascular risk. In the model of IUGR programmed by placental insufficiency, female IUGR offspring exhibit persistent estrous at 1 year of age unlike control offspring that retain an appropriate age-related pattern of estrous cyclicity.<sup>38</sup> Early reproductive senescence in female IUGR at 1 year of age is also associated with a significant increase in circulating testosterone.<sup>38</sup> The transition into menopause is associated with an increase in testosterone in women participants who develop cardiovascular disease relative to those women who do not in a longitudinal report from the Chicago site of the Study of Women's Health Across the Nation.<sup>39</sup> Furthermore, testosterone is positively associated

with blood pressure after menopause.<sup>40</sup> To address the hypothesis that an increase in testosterone contributes to the pathogenesis of elevated blood pressure in female IUGR offspring at 1 year of age, a recent study published in *Hypertension* showed that chronic blockade of the androgen receptor with flutamide abolished the significant increase in blood pressure at 1 year of age in female IUGR rat offspring programmed by fetal exposure to placental insufficiency.<sup>41</sup> In this study by Dasinger et al,<sup>41</sup> chronic treatment with enalapril also decreased blood pressure in female IUGR offspring indicating a role for the RAS. Testosterone is implicated in the activation of the RAS in the aging female spontaneously hypertensive rat.<sup>42</sup> Thus, Dasinger et al<sup>41</sup> also demonstrated that intramedullary expression of the angiotensin type 1 receptor was increased in untreated female IUGR offspring at 1 year of age, but did not differ in female IUGR treated with flutamide relative to untreated female controls.<sup>41</sup> Based on these findings, Dasinger et al,<sup>41</sup> proposed that testosterone-mediated activation of the RAS contributes to the development of increased blood pressure in female IUGR offspring at 1 year of age (Figure). Visceral adiposity increases after menopause and is positively associated with testosterone independent of aging.<sup>39</sup> Although this relationship is correlative, these findings suggest that increases in testosterone may contribute to the development of increased visceral adiposity in female IUGR offspring at 1 year of age.<sup>30</sup> Furthermore, increases in visceral fat, and the subsequent increase in circulating leptin, may serve as a stimulus for elevated sympathetic outflow to the renal nerves in the female IUGR<sup>30</sup> (Figure).

Testosterone also contributes to the pathogenesis of hypertension in female offspring programmed in response to fetal exposure to excess maternal testosterone during prenatal life. Blesson et al<sup>43</sup> recently reported that prenatal testosterone excess programs an increase in blood pressure associated with an elevation in testosterone in female offspring mimicking the pathogenesis of polycystic ovary syndrome. This study published in *Hypertension* demonstrated that chronic blockade of the androgen receptor with flutamide abolished the programmed increase in blood pressure in the prenatal testosterone-exposed female offspring<sup>43</sup> implicating an important role for hyperandrogenism in the pathogenesis of hypertension in this model.<sup>43</sup> It is well established that protein kinase C (PKC) isoforms modulate vascular activity. Thus, Blesson et al<sup>43</sup> also examined vascular PKC expression and noted that the protein expression of the PKC $\delta$  isoform was elevated within the mesentery of the prenatal testosterone-exposed rats.<sup>43</sup> To elucidate the link between hyperandrogenemia and PKC $\delta$ , they showed that PKC $\delta$  expression was increased in a dose-dependent manner in cultured mesenteric artery smooth muscle cells exposed to testosterone. Additional studies identified a testosterone responsive enhancer element located within the PKC $\delta$  gene.<sup>43</sup> Therefore, this study demonstrated a role for PKC $\delta$  in the pathogenesis of increased blood pressure and identified a role for testosterone in the control of PKC $\delta$  expression via transcriptional regulation.

The recent study by Dasinger et al<sup>41</sup> demonstrates that testosterone contributes to the increase in blood pressure that develops in female IUGR offspring at 1 year of age.<sup>41</sup> However, previous studies using the model of IUGR induced

via placental insufficiency indicate that estrogen is protective against increased blood pressure and cardiovascular risk in female IUGR offspring in young adulthood.<sup>44,45</sup> Specifically, ovariectomy induces a significant increase in blood pressure<sup>44</sup> and enhances the blood pressure response to acute angiotensin II (Ang II) in female IUGR offspring.<sup>45</sup> A recent study by Xiao et al<sup>46</sup> in *Hypertension* provides further support that estrogen offsets the developmental programming of increased blood pressure and cardiovascular risk in female offspring using a model of prenatal nicotine exposure. Maternal smoking increases the incidence of low birth weight.<sup>47</sup> Although baseline blood pressure is not elevated in rat offspring exposed to nicotine during prenatal life, male prenatal nicotine offspring exhibit an enhanced blood pressure response to acute Ang II at 5 months of age that is not observed in age-matched female littermates.<sup>48</sup> A recent publication by Xiao et al<sup>46</sup> in *Hypertension* demonstrated that the blood pressure response to acute Ang II was enhanced by ovariectomy in female prenatal nicotine offspring at 5 months of age.<sup>46</sup> In addition, 17 $\beta$ -estradiol replacement attenuated the heightened blood pressure response to acute Ang II<sup>46</sup> (Figure).

Thus, studies in models of developmental programming indicate a sex difference in cardiovascular risk and suggest an age-specific role for sex steroids in the pathogenesis of increased blood pressure in female offspring.<sup>41,44,48</sup> Experimental studies suggest that estradiol is protective against increased cardiovascular risk in female offspring in young adulthood, whereas other studies implicate testosterone as a permissive factor in the development of increased blood pressure in female IUGR offspring in later life. Although beyond the scope of this review, testosterone also contributes to increased blood pressure and cardiovascular risk in male offspring exposed to a developmental insult.<sup>14</sup>

### Endothelin, Sex Differences, and Programmed Cardiovascular Risk

The National Institutes of Health recently mandated sex as a variable in consideration of how health and disease processes differ. As highlighted above, numerous models of developmental programming report a sex difference in blood pressure<sup>9,24,26–28</sup> with onset of increased cardiovascular risk delayed in females.<sup>24,25,29,30</sup> Although the importance of endothelin-1 (ET-1) as a potential contributor to the pathogenesis of hypertension and increased cardiovascular risk after a fetal insult has undergone limited investigation, recent studies published in *Hypertension* indicate that the ET-1 system may contribute to sex differences in increased cardiovascular risk that has its origins in early life. In a study by Bourque et al,<sup>25</sup> prenatal hypoxia programmed an age-related increase in blood pressure in male, but not in female IUGR offspring relative to same-sex counterparts by 1 year of age. Furthermore, blockade of the ET-1 system by the ET<sub>A/B</sub> receptor antagonist, tezosentan, caused a 2-fold decrease in blood pressure in male IUGR rats relative to male control with no effect on blood pressure in female control or IUGR offspring<sup>25</sup> suggesting that female rats were resistant to blockade of the ET-1 system. Another recent study in *Hypertension* by Intapad et al<sup>49</sup> also demonstrated a sex-specific response to ET-1 receptor blockade. In male IUGR rats programmed by placental insufficiency, blockade

of the ET<sub>A</sub> receptor abolished the enhanced blood pressure response to acute Ang II (Figure), whereas ET<sub>A</sub> receptor blockade exerted no effect on blood pressure in female control or IUGR offspring.<sup>49</sup> Ojeda et al<sup>45</sup> previously reported that the blood pressure response to acute Ang II is exacerbated in ovariectomized female IUGR in young adulthood. In the study by Intapad et al,<sup>49</sup> blockade of the ET<sub>A</sub> receptor had no effect on blood pressure in ovariectomized female IUGR offspring indicating that blood pressure in female offspring, regardless of birth weight, was resistant to ET-1 receptor blockade. Although the stimulus for increased production of ET-1 after a fetal insult remains unknown, Ang II is reported to increase ET-1 production.<sup>50</sup> Previous studies indicating that the RAS contributes to increased blood pressure in experimental models of fetal insult<sup>13–15</sup> suggests that activation of the RAS may serve as a potential mediator of the ET-1 pathway. However, the underlying mechanisms that contribute to the sex difference in the blood pressure response to ET-1 blockade remain to be determined.

### Concluding Remarks

Essential hypertension is a complex condition of unknown pathogenesis, and recent advances in the field of developmental origins of hypertension add a layer of complexity to our understanding of blood pressure control. Recent studies using experimental models of fetal insult demonstrate that exposure to an adverse environment during fetal life programs an increase in blood pressure via multiple pathways. Yet, despite the method of fetal insult, these experimental studies indicate that similar pathways contribute to the pathogenesis of increased blood pressure that has its origins in early life. Men and women differ in their risk for cardiovascular disease in a manner that is altered with age. Recent advances in the field of developmental origins of health and disease also suggest that the pathogenesis of increased blood pressure programmed by exposure to a fetal insult differs in men relative to that in women and in a manner that is age specific. Birth weight is a risk factor for hypertension and cardiovascular disease; but the clinical significance of birth weight is not yet a consideration in the management of an individual's cardiovascular health. Thus, additional studies are needed to clarify the most effective pharmacological therapeutic approaches for the management of blood pressure in men and women born preterm, IUGR, or high birth weight.

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### Disclosures

None.

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## Developmental Programming of Hypertension: Physiological Mechanisms

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