The Barker hypothesis or the theory of fetal programming proposes that undernutrition during fetal life slows fetal growth, leading to an increase in risk factors for cardiovascular disease (10). Numerous experimental models of undernutrition induced by protein restriction during gestation or placental insufficiency provide proof of principal for this concept (10). Yet, recent experimental studies report that environmental influences during early postnatal life can also impact later cardiovascular risk in the absence of slow fetal growth (5). Experimental studies utilizing different methods of developmental insult are demonstrating that common cardiovascular outcomes are observed despite the timing or method of developmental insult (5, 10). Importantly, these studies are providing insight into the mechanistic pathways implicated in the etiology of programmed cardiovascular risk.

Factors that alter the ability of the kidney to regulate body fluid and electrolyte homeostasis contribute to the development of hypertension (4). Activation of the sympathetic nervous system (SNS) is implicated in the etiology of hypertension and an increase in renal sympathetic nerve activity (rSNA) is suggested to serve as the link between the central SNS and the kidney (4). An increase in rSNA is observed in many experimental models of hypertension. In addition, renal denervation abolishes hypertension in numerous experimental models of hypertension including the spontaneously hypertensive rat, chronic angiotensin II or DOCA salt in the rat, or obesity in the dog (4), indicating a key role for the renal nerves.

Postnatal exposure to early life stress (ELS) induced by maternal separation during lactation in the rat programs a reduction in glomerular filtration rate (GFR) associated with enhanced sensitivity to acute angiotensin II, a marker for enhanced cardiovascular risk (9). Although overt hypertension is not observed in this model of ELS, Loria et al. (8) demonstrate in an issue of the American Journal of Physiology-Renal Physiology that renal denervation restores GFR in the offspring exposed to ELS. The importance of the renal nerves in the etiology of programmed cardiovascular risk is indicated in studies utilizing prenatal exposure to placental insufficiency (1, 7), glucocorticoids (2), diabetes (3), or maternal obesity (11). However, this study by Loria et al. is the first to demonstrate a key role for the renal nerves in the programming of cardiovascular risk in a model induced by exposure to an adverse event during postnatal life (8). In humans nephrogenesis is complete by late gestation; however, kidney development in the rat proceeds until after birth (12). Whether programming of increased rSNA induced by ELS is directly related to the impact of stress during nephrogenesis is not yet clear. Furthermore, whether exposure to ELS would program a similar response in the human is unknown. Yet, this study demonstrates that the renal nerves are a key component in the programming of cardiovascular risk in the rat despite the timing of the insult, prenatal vs. postnatal, or the method of insult, chronic stress vs. over or undernutrition.

To date, no single experimental study has provided a comprehensive in-depth investigation into the importance of increased sympathetic activity in the developmental programming of cardiovascular risk (Table 1). The ability to adequately address the role of the SNS is complicated by differences in risk factors that are programmed by developmental insult and that sex and age can impact later cardiovascular outcome (7). An increase in renal renin (6, 11) or an increase in rSNA (3) may be indicative of a role for the sympathetic origins of programmed cardiovascular risk. Yet, whether rSNA is elevated in these different models of developmental programming is not well-defined (Table 1). Direct measure of renal nerve activity is reported in only one study (3); however, measurement of this parameter is significantly limited by investigator expertise. Renal norepinephrine (NE) content and/or tyrosine hydroxylase (TH) expression, the rate-limiting enzyme in the synthesis of catecholamines and NE, are often stated as indirect markers of elevated rSNA (2, 8, 11) but, an increase in renal NE or TH is not observed in conjunction with an increase in rSNA in offspring exposed to maternal diabetes (3). Nonetheless, renal denervation restores GFR (3, 8) or normalizes blood pressure (1, 2, 3, 7) in all programming models studied to date including the sex- and age-dependent increase in blood pres-

**Table 1. Summary of current data related to the role of renal sympathetic activation in the etiology of hypertension programmed in response to a developmental insult**

<table>
<thead>
<tr>
<th>Developmental Insult</th>
<th>Sex</th>
<th>BP</th>
<th>Age</th>
<th>GFR</th>
<th>Renal NE or TH</th>
<th>Renal Renin</th>
<th>rSNA</th>
<th>RDX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placental insufficiency</td>
<td>M</td>
<td>↑</td>
<td>16 wk</td>
<td>No change</td>
<td>No change in NE or TH</td>
<td>↑</td>
<td>Not reported</td>
<td>↓ BP</td>
</tr>
<tr>
<td>Prenatal dexamethasone</td>
<td>M</td>
<td>↑</td>
<td>8 wk</td>
<td>Not reported</td>
<td>↑ NE</td>
<td>Not reported</td>
<td>↑</td>
<td>Not reported</td>
</tr>
<tr>
<td>Maternal diabetes</td>
<td>M</td>
<td>↑</td>
<td>12 wk</td>
<td>No change in NE</td>
<td>↑ NE</td>
<td>Not reported</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Early life stress</td>
<td>M &amp; F</td>
<td>↑</td>
<td>12–14 wk</td>
<td>↓</td>
<td>↑ NE</td>
<td>Not reported</td>
<td>Not reported</td>
<td>↑ Restore GFR</td>
</tr>
<tr>
<td>Maternal high-fat diet</td>
<td>M</td>
<td>↑</td>
<td>90 days</td>
<td>Not reported</td>
<td>↑ NE</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

BP, blood pressure; GFR, glomerular filtration rate; NE, norepinephrine; TH, tyrosine hydroxylase; rSNA, renal sympathetic nerve activity; RDX, renal denervation.
sure that occurs in female offspring exposed to placental insufficiency (7).

In conclusion, the study by Loria et al. in an issue of the *American Journal of Physiology-Renal Physiology* implicates a key role for the renal nerves in the developmental programming of cardiovascular risk induced by an adverse environmental influence during early postnatal life. This study highlights the need for further investigation into the mechanisms that initiate increased SNS activity following a developmental insult. Importantly, this study emphasizes the need to clarify the importance of increased sympathetic outflow to all organs and determine whether the SNS is a key component of enhanced cardiovascular risk that originates in early life.

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**DISCLOSURES**

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**REFERENCES**


