Activation of the sympathetic nervous system, is it key to the developmental origins of enhanced cardiovascular risk?

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THE BARKER HYPOTHESIS OR THE theory of fetal programming proposes that undernutrition during fetal life slows fetal growth programming 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 increased rSNA (2, 8, 11) but, an increase in 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 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 pressure.

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>Placental insufficiency</td>
<td>F</td>
<td>↑</td>
<td>1 yr</td>
<td>No change</td>
<td>No change in NE</td>
<td>Not reported</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>Not reported</td>
<td>↓ BP</td>
</tr>
<tr>
<td>Maternal diabetes</td>
<td>M</td>
<td>↑</td>
<td>12 wk</td>
<td>No change in TH</td>
<td>↑ NE</td>
<td>↑</td>
<td>BP restore GFR</td>
<td></td>
</tr>
<tr>
<td>Early life stress</td>
<td>M</td>
<td>No change</td>
<td>12–14 wk</td>
<td>↑ NE</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Nearest GFR</td>
<td></td>
</tr>
<tr>
<td>Maternal high-fat diet</td>
<td>M &amp; F</td>
<td>↑</td>
<td>90 days</td>
<td>Not reported</td>
<td>↑ NE</td>
<td>Not reported</td>
<td>Not reported</td>
<td></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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