Divergent pathways of programming: prenatal vs. postnatal protein undernutrition

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As first proposed by David Barker (2) and now supported by numerous epidemiological and experimental studies (1, 12, 21), fetal undernutrition leads to permanent structural and physiological alterations resulting in the development of hypertension and cardiovascular disease. Although epidemiological studies provide the basis for investigation into mechanisms linking birth weight and adult disease (1, 2, 12, 21), investigators utilizing animal models to mimic the human condition of slow fetal growth are elucidating the mechanistic pathways implicated in the increased risk for cardiovascular disease. Experimental studies demonstrate that undernutrition during gestation in the rat leads to marked increases in blood pressure associated with significant reductions in nephron number, impaired vascular function, and temporal and tissue-specific alterations in the renin angiotensin system (RAS) (1, 12, 21). The RAS, in addition to the renal nerves, contributes to the etiology of hypertension programmed by exposure to an adverse fetal environment, and recent studies indicate inflammation and oxidative stress may also play an important role (1, 12, 21).

As predicated by Barker (2), timing of the prenatal insult is critical for the severity of the postnatal response (1, 13, 21). Animal models of fetal programming demonstrate that increased cardiovascular risk is greatest in animals exposed to a nutritional insult that includes the nephrogenic period in late gestation (13, 21). Thus, manipulation of nutritional status during prenatal periods critical to nephrogenesis can lead to reductions in nephron number, hypertension, and reduced lifespan.

Postnatal influences can also modulate the programming effects of an adverse fetal environment (1, 3, 5). Rapid growth during lactation leads to reduced longevity in intrauterine growth-restricted mice (16). However, appropriate nutritional status during lactation in the rat can alleviate the response to fetal undernutrition on nephron number and blood pressure (22). Postnatal influences can also alter the cardiovascular risk in humans. Accelerated catch-up growth during infancy and childhood in low-birth-weight individuals leads to detrimental effects on cardiovascular health (5, 18); however, slow growth in early infancy has beneficial effects on cardiovascular risk (19). Thus, modulation of postnatal growth can alter the cardiovascular risk associated with slow fetal growth.

Although nephrogenesis initiates during the last third of gestation in the rat, renal development continues for 2 wk after birth (10). Recent studies by Jennings et al. (11) demonstrate that protein undernutrition administered during different windows of nephrogenesis, whether during the prenatal or the postnatal period, leads to opposing effects. Protein undernutrition during prenatal life in the rat leads to reduced longevity associated with shorter renal telomeres (11). However, protein undernutrition during lactation in the rat leads to protection against age-related loss of renal function associated with longer renal telomeres, slower growth, and increased longevity (11, 17). Thus, timing of the nutritional deficient during the nephrogenic period, either prenatal or postnatal, leads to divergent outcomes.

Shortening of telomeres occurs with aging in the kidney, and telomere dysfunction is linked with increased risk of cardiovascular disease (8, 15). Oxidative stress is also implicated in aging and longevity in conjunction with telomere dysfunction (8, 9). Nutritional restriction during adulthood leads to longevity in many animal models and one mechanism hypothesized involves attenuation of oxidative damage (14). In this issue of the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, Tarry-Adkins et al. (20) report that reduced age-dependent shortening of renal telomeres in rats exposed to protein undernutrition during lactation is associated with increased renal antioxidant expression. However, reduced antioxidant capacity is observed in fetuses exposed to protein undernutrition during fetal life (4) and oxidative stress contributes to the etiology of cardiovascular risk induced by prenatal insult (4, 21). Therefore, divergent outcomes for oxidant status occur in response to prenatal vs. postnatal protein undernutrition (Fig. 1).

In summary, critical windows of developmental programming influence different adult outcomes. Insight provided by Jennings et al. (11) and Tarry-Adkins et al. (20) demonstrates

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<thead>
<tr>
<th>Environment</th>
<th>Pre-natal</th>
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<tbody>
<tr>
<td>Anti-oxidant Capacity</td>
<td>↓</td>
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<tr>
<td>Renal Telomere Length</td>
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<td>Longevity</td>
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Fig. 1. Divergent outcomes programmed by prenatal vs. postnatal protein undernutrition. Numerous investigators utilizing models of prenatal programming induced by protein undernutrition during gestation in the rat report common outcomes including hypertension, decreased nephron number, and temporal and tissue-specific alterations in the renin angiotensin system (RAS) (1, 12, 21). Additional outcomes reported by Jennings et al. (11) and O’Toole and Hales (16) include shorter renal telomere length and reduced longevity, and as demonstrated by Cambonie et al. (4), decreased renal antioxidant capacity. However, studies by Jennings et al. (11) demonstrate that postnatal protein undernutrition during lactation leads to increased renal telomere length and increased longevity; and as reported in this issue of the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, increased antioxidant status (20). Therefore, divergent outcomes occur in response to prenatal vs. postnatal protein undernutrition.

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that nutrition in early postnatal life has major biological effects on antioxidant status and adult lifespan. Although numerous studies indicate that adult nutritional status is linked to longevity (14), an important caveat to the renoprotective effects of protein undernutrition during lactation includes consideration of other programming effects that may be induced by postnatal nutritional restriction. Animal studies suggest glucose metabolism and insulin resistance are also susceptible to modulation of protein undernutrition during lactation (23). In addition, although slow fetal growth provides a beneficial influence on cardiovascular risk in low birth weight individuals (19), observational studies in humans implicate slow infant growth with cardiovascular risk in low birth weight individuals (19), observational studies in humans implicate slow infant growth with cardiovascular risk in low birth weight individuals (19), observational studies in humans implicate slow infant growth with cardiovascular risk in low birth weight individuals (19). Therefore, the effects of postnatal protein restriction may not be all beneficial.

GRANTS

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REFERENCES