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Developmental programming of the kidney: does sex matter?

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The 'Developmental Origins of Health and Disease' proposes that early life events may, in part, determine the risk of many chronic diseases in later life. Two key features of this concept that are highlighted in a recent study by Moritz *et al.* (Moritz *et al.* 2009) in *The Journal of Physiology* are the existence of critical windows of susceptibility and the different adaptive responses to developmental insults observed between male and female offspring (Gilbert & Nijland, 2008). Depending upon the species studied, critical windows of sensitivity have been identified from conception through the neonatal period. This is particularly relevant with respect to the programming of cardiorenal function, as renal development extends into the postnatal period in laboratory species, such as the rat. Hence, it is important to recognize that it is not only the fetus that may be at risk for developmental programming but also the neonate. Moreover, recent studies have shown that the extent to which an insult may affect the offspring also depends upon the sex of the fetus/neonate (Zambrano *et al.* 2005). Nevertheless, the manner in which critical windows of susceptibility and sex differences interact to result in developmental programming remains unclear.

Whilst the developmental programming of cardiovascular disease and chronic kidney disease have long been linked with low birth weight, it is important to recognize that this may be more of an indicator of a predisposition towards, rather than a causal marker, of later disease. Additionally, it should be noted that low birth weight is a proxy indicator of poor fetal growth and it is the underlying cause of poor fetal growth rather than the birth weight that is the predisposing factor. Moreover, since birth weight is a discrete measurement that lies on a continuum across populations, apparently normal birth weight offspring may in fact be growth restricted if they did not attain their genetic potential.

The mechanisms by which male and female fetuses differ in their respective responses to sub-optimal intrauterine environments are not yet known. Furthermore, the developmental windows in which nutrient restriction and/or over-nutrition have the largest impact on male and female offspring have yet to be elucidated. Two hypotheses proposed to explain these differences in developmental programming that are associated with biological sex are (1) male and female offspring adapt differently to developmental stressors (Zambrano *et al.* 2005); and (2) that male sex hormones (such as testosterone) interact with the developmentally challenged organism to have a profound influence on the progression of developmentally programmed disease states (Ojeda *et al.* 2007*a*,*b*). Recently, Gilbert & Nijland proposed a third possibility to explain sex differences in developmental programming of cardiovascular and renal function, and postulated that innate differences between the sexes that are independent of sex hormones may play a significant role in developmental programming and later disease development (Gilbert & Nijland, 2008).

Moritz *et al.* report on the long-term effects of intrauterine growth restriction (IUGR) and postnatal nutritional restraint in female rats and how these differ from what they previously observed in similarly treated male rats (Moritz *et al.* 2009). Moritz and colleagues report that uteroplacental insufficiency and associated, impaired maternal lactation result in growth restriction and reduced nephron number in female offspring, similar to previously reported male offspring (Wlodek *et al.* 2007). In contrast to previous experiments with restricted male offspring who exhibited reduced nephron number and elevated blood pressure at 5–6 months of age, restricted female offspring with fewer nephrons did not develop hypertension as late as 18 months of age. Indeed it has long been observed that IUGR and nutrient-restricted male offspring tend to develop more exaggerated disease states than female littermates (Gilbert & Nijland, 2008). Despite the considerable evidence linking altered renal development with subsequent increases in blood pressure (Woods *et al.* 2001; Ojeda *et al.* 2007*a*,*b*; Gilbert & Nijland, 2008), the present study suggests that a developmental compromise in nephrogenesis may not result in hypertension, particularly in females. Nevertheless, further studies are needed to confirm these results.

Previous studies have generally supported the notion that a developmental deficit in nephron endowment associates with increased blood pressure in adulthood (Gilbert & Nijland, 2008). In particular, Woods *et al.* found that uninephrectomy in newborn male rats reduced nephron number and increased glomerular volume which resulted in decreased renal function and increased salt-sensitive development of hypertension (Woods *et al.* 2001). Importantly, the authors noted that hypertension precedes glomerular damage and proteinuria in their study, an interesting contrast to the present findings in which glomerular hypertrophy and renal gene expression are changed without the onset of hypertension. The obvious difference between the present study (Moritz *et al.* 2009) and the earlier work (Woods *et al.* 2001) is the sex of the animals investigated. Nevertheless, the present findings by Moritz and colleagues suggest that the development of hypertension in females may not depend upon the generation of a renal nephron deficit. Moreover, these findings indicate that insults during the latter part of renal development by way of postnatal growth restraint may not be a causal factor in the development of hypertension in females. Further studies are clearly needed to delineate the respective roles of intrinsic biological sex differences vis-à-vis the contributions of sex hormones during and after adolescence.

Despite the lack of overt hypertension in these animals, the authors do report indications of early renal insufficiency as demonstrated by elevated levels of plasma creatinine. Moreover, Moritz *et al.* show alterations in renal structure with the emergence of glomerular hypertrophy and alterations in a variety of extracellular

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markers of renal damage. The changes observed in transforming growth factor-β_1 (TGF-β_1) and collagen IV suggest the initiation of extracellular matrix turnover, and may presage later renal damage. Hence, further studies investigating the ability of these female rats to respond to renal stressors such as partial nephrectomy or high salt diets may provide interesting information regarding susceptibility to renal disease in the offspring of complicated pregnancies.

The authors further investigated the impact of the neonatal lactational environment on nephrogenesis, hypothesizing that improvement of neonatal nutrition during the latter portion of renal development would rescue nephrogenesis as previously observed in male offspring. Although Wlodek *et al.* have previously reported mammary growth reduction associated with uterine restriction, the mechanisms underlying this remain unknown (Wlodek *et al.* 2007). Thus, it is possible that factors released by the ischaemic placenta such as the vascular endothelial growth factor (VEGF) antagonist soluble fms-like tyrosine kinase-1 (sFlt-1) or the TGF-β antagonist soluble endoglin (sEng), both of which are induced by placental ischaemia in the rat (Gilbert *et al.* 2009), could alter the development of the mammary gland; thereby reducing milk quality and quantity and further restricting offspring nutrient uptake during the latter phases of renal development. Moreover, VEGF has long been recognized as an important factor in renal development that is susceptible to perturbations in the fetal environment. However, it remains unclear whether or not there are sex-related differences in VEGF action or expression during compromised fetal development.

Whilst Moritz and colleagues discuss the sexual dimorphism observed in the programming of disease, they implicate the action of sex steroids in the differences in the degree of renal dysfunction and lack of hypertension observed in female offspring. Interestingly, the IUGR female offspring developed glomerular hypertrophy in the absence of elevated testosterone levels, which has been implicated in the exaggerated male susceptibility to both chronic kidney disease and cardiovascular disease. To further address this observation, experiments utilizing ovariectomy and hormone replacement would provide an informative addition to elucidate the roles of sex hormones on renal injury and subsequent development of, or protection against, hypertension.

In summary, the recent paper (Moritz *et al.* 2009) provides important new insights regarding the contribution of placental insufficiency to the trajectory of fetal and postnatal development and provides further evidence of the differences between the developmental cardiorenal outcomes of male and female growth-restricted offspring. Lastly, the present work of Moritz and colleagues highlights the importance of different critical windows of susceptibility and that these periods may vary based on biological sex.

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