Editorial Commentary

Sex, Salt, and Senescence
Sorting Out Mechanisms of the Developmental Origins of Hypertension

Jeffrey S. Gilbert

The developmental origins of health and disease hypothesis derives from clinical observations indicating long-term health consequences, such as hypertension, for persons of low birth weight.1 Considering that the kidneys hold such a prominent role in the long-term control of blood pressure, it is not surprising that subsequent observations from human and animal studies have found associations between nephron deficit (of fetal origin) and adult hypertension, although these observations have not been without controversy.1 Numerous experimental models have been developed that support this hypothesis and seek to elucidate the mechanisms by which perinatal stressors affect fetal development to generate persistent elevations in the blood pressure of the offspring and of the subsequent hypertension during later life.1–4 Throughout this body of work investigating the developmental origins of hypertension and regardless of the type of experimental insult, several common themes have emerged: the necessary involvement of the kidney,1–5 dysregulation of the renin-angiotensin system (RAS),1–3,5 and gender differences in response to the various stimuli.1,2,5

Although it has long been observed that a variety of endocrine and nutritional insults during renal development result in developmental deficits in the kidney (reviewed elsewhere1), abnormalities in the RAS appear to be a central common pathway.6 The importance of the intrarenal RAS in renal development has been recognized for over a decade, when initial studies, such as those by Friberg et al,7 recognized that angiotensin II type 1 (AT1) receptor antagonism during nephrogenesis leads to development deficits in the kidney. Hence, experimental studies using AT1 receptor antagonism during renal organogenesis provide a robust model for interrogation of the mechanisms underlying these developmental deficits in renal function. Despite the observation that previous studies consistently show that AT1 blockade during nephrogenesis compromises renal development, the precise mechanisms by which this developmental insult results in adult hypertension remain vague. This question has come under increased scrutiny as of late, as recent studies have begun to unravel these mechanisms.2,8,9 In this issue of Hypertension, Salazar et al9 have contributed further to this body of knowledge by testing the roles of sex, age and sodium in mediating hypertension resulting from early exposure to AT1 antagonism that results in decreased nephron endowment.

Although the role of angiotensin II in the developmental programming of hypertension has received much attention, the contribution of salt sensitivity to the progression and maintenance of programmed hypertension has largely remained undefined. This is especially intriguing considering that all forms of chronic hypertension observed to date demonstrate, to some extent, impaired renal sodium excretory capacity. Thus, it is surprising that only recently have studies such the current contribution by Salazar et al9 come to the fore. In the present work, the authors show that both male and female rats with a developmentally derived nephron deficit exhibit salt-sensitive hypertension at 11 to 12 months of age but not at 3 to 4 months of age. This was not entirely unexpected based on the authors’ previous report that AT1 antagonism during the nephrogenic period impairs the ability to eliminate an acute sodium load in both male and female rats.3 Interestingly, only the male rats suffered a deterioration of renal hemodynamic function during exposure to a prolonged high-salt diet.5 Furthermore, because an inability to suppress the RAS plays an important role in the development of salt-sensitive hypertension, measurement of plasma renin activity or angiotensin II concentrations at various levels of sodium intake would have been an interesting addition to the present study. Although the link between developmental nephron deficit and impaired sodium excretory capacity remains unclear, it is likely due to more than simply reduced glomerulus number and may also include alterations in renovascular and tubular morphology, along with disrupted tubular sodium transporter expression.6 Despite the compelling findings in the present study by Salazar et al,9 much remains unclear regarding the potential renoprotective effects of sex or sex hormones in this model of hypertension.

Recent work has suggested that estrogens confer a protective effect on intrauterine growth-restricted females that prevents the development of programmed hypertension.10 Interestingly, this does not appear to be the case with respect to blood pressure in the work of Salazar et al.5 The authors report the observation that during exposure to a high-salt diet at 11 to 12 months of age, the putative renoprotective effect of female sex hormones observed in their model to prevent proteinuria despite elevated systolic blood pressure seems to be exceeded.6 Despite considerable differences between the models used by Ojeda et al10 and those of Salazar et al,9 it appears that the magnitude of the insult to the kidney during

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From the Department of Physiology and Center for Excellence in Cardiovascular-Renal Research, University of Mississippi Medical Center, Jackson, Miss.

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Correspondence to Jeffrey S. Gilbert, Department of Physiology and Biophysics, University of Mississippi Medical Center, 2500 N State St, Jackson, MS 39216-4505. E-mail jsgilbert@physiology.umsmed.edu

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development has an influence on the extent of protection that may be afforded by female sex hormones in later life.

Although the contribution of gender to the developmental origins of disease is widely recognized, it seems that sex may exert distinctly different influences during fetal and adult life. It appears that, whereas male fetuses may be more susceptible to in utero nutrient privation, female fetuses may have increased susceptibility to gestational overnutrition. The reasons for this remain nebulous; however, 1 clue may be held in the long-observed differences in growth rates exhibited by male and female fetuses in utero. Hence, a faster growing male fetus may experience greater or lesser degrees of these nutritional insults compared with a female counterpart. In contrast, when faced with a robust stressor, such as the AT1 antagonism used by Salazar et al in the present study, both male and female fetuses are affected similarly in utero, although the latter are affected less in later life. Effects such as these during early life are largely independent of the influence of the sexually dimorphic postpubescent endocrine milieu and suggest the existence of an alternate sex-based mechanism.

It is widely recognized that differences in sex hormones contribute to considerable sexual dimorphism in the transcriptome of a variety of mammalian tissues and organs; however, it has only recently been recognized that androgen/estrogen-independent mechanisms may operate at the transcriptional level to regulate sex differences. This possibility represents an alternate pathway that may be at work contributing to the observations that the relationship between sex hormones and blood pressure is far more complex than simply the balance of estrogen versus testosterone. Taken together, it appears that the influence of sex on the developmental origins of disease may reach far beyond the widely recognized role of sex hormones. Clearly, further studies are needed to evaluate these potential alternative mechanisms for sex differences in hypertension.

The study by Salazar et al further illustrates the importance of examining the mechanisms whereby developmental deficits in the kidney contribute to both the progression and the maintenance of hypertension in adulthood. The Figure illustrates a possible pathway by which perinatal RAS inhibition may interact with these other factors and work in concert to result in adult hypertension. Although it is clear that research in this area will have to work toward a better understanding of the complexities of the early life origins of salt sensitivity, these findings illuminate the complexities of the relationship among blood pressure, sex hormones, and aging. Furthermore, these studies provide groundwork for further investigations into the renal mechanisms of developmentally programmed hypertension.

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Jeffrey S. Gilbert

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