Mechanisms of Fetal Programming of Adult Hypertension
Role of Sex Hormones
Christine Maric

Epidemiological and experimental studies suggest that the in utero environment plays a critical role in the development of adult disease, including cardiovascular disease and hypertension. Intrauterine growth retardation produced by maternal undernutrition or exposure to maternal glucocorticoids during critical periods of organogenesis impairs fetal growth and produces offspring that develop hypertension early in life. This concept of “fetal programming” was first proposed by Barker et al to describe the relationship between low birth weight and subsequent risk for the development of cardiovascular disease and hypertension, insulin resistance, and type 2 diabetes mellitus in adult life. Several studies have confirmed and extended the Barker et al hypothesis to fetal programming of Parkinson’s disease, dementia, osteoporosis, and polycystic ovary syndrome.

Although most clinical and experimental studies support the role for fetal programming of adult hypertension, there is still controversy regarding the cause and mechanisms underlying this phenomenon. Studies to date implicate reduced nephron endowment, factors that affect endothelial and arterial compliance, alterations in the function of renin-angiotensin system (RAS), and programming of the major organs and endocrine/neural systems involved in long-term blood pressure regulation. Despite intense investigation into the mechanisms underlying fetal programming of adult hypertension, there is still no unifying hypothesis on how these different mechanisms and pathways are programmed in utero and how they ultimately result in dysregulation of blood pressure later in life.

It is well documented that premenopausal women exhibit a lower incidence of cardiovascular disease and hypertension compared with age-matched men. After menopause, the risk for development and the rate of progression of hypertension in women become comparable to those seen in age-matched men. These observations indicate that female sex hormones may protect against the development of hypertension premnopaussally and that their absence after menopause may create a stage for the development of hypertension. Alternatively, the fact that the male sex is a risk for the development of hypertension suggests that male sex hormones may adversely regulate blood pressure. Indeed, absence of testosterone in experimental models abolishes hypertension, most likely through interaction with the RAS. These observations suggest that both male and female sex hormones, via interaction with other regulatory pathways, including the RAS, contribute to the development and progression of hypertension. However, few studies to date have examined the contribution of sex hormones in fetal programming of adult hypertension.

In the present issue of Hypertension, Ojeda et al describe the contribution of estradiol in the regulation of postpubertal blood pressure in the intrauterine growth-restricted (IUGR) offspring. Previous studies from this laboratory showed that placental insufficiency in the rat results in development of hypertension in both prepubertal male and female offspring. This study also showed that, after puberty, only male offspring remain hypertensive, whereas females become normotensive by 10 weeks of age, coinciding with increased levels of estradiol associated with puberty. Based on these findings, Ojeda et al hypothesized in the current study that estradiol may stabilize blood pressure. To test this hypothesis, Ojeda et al ovarioctomized female control and IUGR offspring at 10 weeks of age and implanted them with radiotelemeters for monitoring systemic blood pressure. A subgroup of ovarioctomized animals received 17β-estradiol replacement and/or an angiotensin-converting enzyme inhibitor, enalapril, for 14 days. The major findings of this study are as follows: (1) ovarioctomized IUGR females have increased blood pressure compared with intact IUGR females; (2) 17β-estradiol replacement attenuates this ovarioctomy-induced increase in blood pressure; and (3) angiotensin-converting enzyme inhibition also attenuates the ovarioctomy-induced increase in blood pressure. Ojeda et al conclude that hypertension in the female IUGR offspring is RAS mediated and that estradiol contributes to the normalization of blood pressure in these animals.

Previous studies by Ojeda et al showed that testosterone plays a role in modulating hypertension in adult male IUGR offspring by regulating the RAS. These observations, in addition to the finding of the current study that estradiol is protective against the development of hypertension in adult female IUGR offspring, suggest an important role for sex hormones in regulating blood pressure in adulthood. Studies by Ojeda et al and others have shown that, in addition to modulating the RAS, other regulatory pathways, including NO, are targets for sex hormones in regulating blood pressure in IUGR offspring. These findings suggest that sex hormones are unlikely to regulate blood pressure directly but rather modulate the activity of other blood pressure regula-
tory pathways. Further supporting the notion that the effect of sex hormones on blood pressure is not direct is the lack of correlation between sex hormone levels and the incidence of hypertension. There is strong evidence to suggest that the incidence of hypertension increases after menopause and, thus, low levels of estradiol. Interestingly, there is also an age-related increase in the incidence of hypertension that coincides with andropause and, thus, low levels of testosterone. In the present study, Ojeda et al did not observe any difference in estradiol levels between the control and offspring of IUGR animals, suggesting that absolute levels of sex hormones, at least in these studies, do not correlate with the development of hypertension. Furthermore, these observations oppose the general belief that androgens are “bad” and estrogens are “good” for blood pressure and suggest that the relationship between sex hormone levels and hypertension is likely to be far more complex.

Ojeda et al report that both male and female IUGR offspring develop hypertension early in life and that only females stabilize their blood pressure by 10 weeks of age. This finding is not universal. In rats fed a high-fat diet during pregnancy, hypertension develops only in female offspring. Although these conflicting findings may simply be related to differences in experimental models, they raise an interesting question: could fetal programming be sex specific? Another interesting question relating to sex differences in fetal programming is whether differences in growth rates play a role in the development of adult hypertension. Evidence suggests that the most adverse blood pressure outcomes occur among individuals who were small at birth but relatively large as adults, suggesting an adverse effect of accelerated postnatal growth on the development of hypertension. It is well documented that the onset of puberty is associated with higher growth rates in males versus females, suggesting that accelerated growth may contribute to the increased risk for the development of adult hypertension in males. Also interesting is the aspect of life expectancy. In addition to predisposing to the development of cardiovascular disease and hypertension, fetal undernutrition seems to be associated with reduced life span. Although women generally have a longer life expectancy than men, it is unclear whether there are sex differences in the life expectancy of progeny that were undernourished in utero.

In conclusion, the study by Ojeda et al confirm previous reports that predisposition to adult hypertension may be programmed in utero. Although mechanisms linking low birth weight to hypertension in later life are likely to be complex, the present study underscores the importance of the interaction between sex hormones and the RAS. Future studies are warranted to dissect out the mechanisms involved in initiating programming events in utero, as well as events secondary to the development of hypertension. Understanding these mechanisms is of pivotal importance for the development of novel, potentially sex-specific strategies for prevention and treatment of hypertension.

Disclosures

None.

References

6. Ojeda NB, Grigore D, Robertson EB, Alexander BT. Estrogen protects against increased blood pressure in postpubertal female growth restricted offspring. *Hypertension*. 2007;50:
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