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COMMENTARY

Renal Development and Adult Hypertension

Commentary on the article by Woods *et al.* on page 460

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Thanks to decades of study, we are now all aware that certain lifestyles, alone or in combination with genetic predisposition, put adults at increased risk for a variety of diseases including hypertension. However, over the last ten years a new idea has received increasing attention regarding the existence of additional determinants for adult cardiovascular disease. This new idea has been vigorously championed by Dr. DJP Barker. He and his colleagues, on the basis of multiple epidemiologic studies demonstrating inverse associations between birth weight and cardiovascular disease have suggested that disorders such as coronary heart disease and hypertension in adulthood have at least a part of their origin in fetal life (1). They propose that "in utero programming" contributes to cardiovascular disease found in adults (2). "Programming" in this context means that an event *in utero* has permanent effects on the physiology, structure and metabolism of the individual (2). Barker suggests that adaptations made by the fetus in response to under nutrition result in the increased rate of cardiovascular disease and hypertension found in adults born with low birth weights and short body lengths. Thus, the programming stimulus is relative fetal under nutrition which results in impaired intrauterine growth.

It is within this context that the paper by Woods and coworkers in this volume of the journal is both significant and exciting. In their paper, Woods *et al.* make several observations in groups of animals studied under identical conditions. They show that a reduction in protein intake by female rats during pregnancy causes lasting changes in their male offspring. These changes include reductions in birth weight, increases in arterial blood pressure, reductions in nephron number and impairments in renal function in adulthood. While similar observations have been made in the past (3–7), the work by Woods *et al.* is unique because it implicates an alteration in the maturation of the renin-angiotensin system at a critical time (the perinatal period) in development as causative for the hypertension observed in adulthood. They show that in male newborn pups of mothers fed a low protein diet during pregnancy the expression of renin mRNA and the tissue concentration of angiotensin are suppressed in the kidney. The link between the suppression of renin expression in the perinatal period and hypertension in the adult is established by several observations that have as their final common pathway, reduced nephron number and impaired renal function in the adult. Thus, we know that there is an increase in renin expression in the perinatal period (8, 9) in normal pregnancy and there is also evidence that the renin angiotensin system is essential for normal kidney growth and development (10–13). If pharmacological or gene targeting approaches are used to block the production or action of angiotensin in early development, then kidney growth and nephrogenesis are impaired, kidney to body weight ratio is reduced, and renal function is compromised (11, 14, 15). This constellation of changes is similar to that found by Woods *et al.* in the present study. Reduction in nephron complement early in life has been hypothesized to play a role in the genesis of hypertension later in adults (16, 17) and previously Woods (18) showed that unilateral nephrectomy (reduced nephron number) in neonates produces hypertension in adulthood. All these findings are consistent with the global hypothesis detailed by Woods *et al.* in the present paper, *i.e.* that protein restriction in pregnancy suppresses renin expression in the perinatal period which in turn suppresses nephron development and this results in hypertension in adult life. This global hypothesis is well supported by their simultaneous demonstration of alterations in renin expression, nephron number and blood pressure in animals derived from mothers that consumed reduced protein diets during pregnancy. It is noteworthy that the results of the present study are also consistent with the long-held view of Guyton and coworkers regarding the importance of reductions in renal function in the development of hypertension (19).

As with any good study, the present work brings up several questions. Among them is the role of gender. This assumes importance because the present observations indicate prenatal protein restriction produces hypertension in males. But, it has been noted that overall caloric restriction (50% reduction in normal food intake) during the last half of pregnancy while producing pups of reduced birth weight has no effect on blood pressure in the female offspring when they become adults (20). On the other hand, protein restriction in pregnancy has been reported to increase blood pressure equally in male and female

offspring (21). In addition, there are other reports that prenatal stimuli have gender specific consequences in postnatal life on endocrine systems which could have an impact on blood pressure (22, 23). If the effect of protein restriction in this animal model is gender dependent, it will be very important to define the mechanisms involved in creating the gender dependency. Also, the existence of gender specific effects would have some implications relative to the epidemiologic findings mentioned earlier.

Another question which arises is whether or not the effects observed in the present study are a consequence of reduction of protein intake during pregnancy or of a change in the relative proportions of protein to other dietary constituents consumed during pregnancy. There is some evidence that changing the proportion of dietary constituents in early development does result in hypertension later. For example, substituting coconut oil for corn oil in a protein replete diet results in hypertension (24). Also, it has been reported that a low protein, high glucose diet during pregnancy does not produce hypertension in offspring, while a low protein, high starch diet does (24, 25). These observations suggest that there can be highly complex interactions between the composition of a diet consumed during pregnancy and its effects upon offspring. Clearly, the implications of this issue are significant when considering nutritional supplementation for pregnant individuals suffering from malnutrition.

Finally, a general question of interpretation is worth mentioning. In the present study, blood pressure was determined after removing the animals from their own cages and placing them in wire restrainers. Moving a rodent from its home cage and restraining it are generally thought to represent stress to the animal. Although Woods *et al.* attempted to acclimate the animals by placing them in the restrainers several times, repeated restraint has been shown to cause repeated elevations in plasma corticosterone which is a stress hormone in rats (26). Therefore, one wonders if some of the hypertension observed in the animals subjected to protein restriction *in utero* is the result of an enhanced response to stress. This would also be an exciting finding which, it should be emphasized, would not diminish the importance of the observations of Woods *et al.* and their possible significance relative to the "Barker hypothesis of fetal origins of adult disease".

In summary, the paper by Woods *et al.* is quite interesting because it shows that a reduction in protein consumption during pregnancy can cause an alteration in the maturation of the renin angiotensin system at a critical period which subsequently is associated with impaired kidney development and hypertension in adulthood. Consequently, it provides a mechanism for the impact of protein restriction *in utero* on hypertension in adulthood.

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