Glycemic control in the growth-restricted kidney: the sweet taste of success

Jeffrey S. Gilbert
Department of Physiology and Pharmacology, University of Minnesota Medical School, Duluth, Minnesota

There has been growing interest in the widely recognized and robust associations between alterations in the trajectory of fetal development and increased incidence of a number of chronic adult diseases (1, 2, 6, 14). Pregnancy is a significant physiological stress requiring a variety of carefully synchronized physiological adaptations to maintain both maternal and fetal homeostasis. Disruption of the maternal-fetal balance by stressors such as fetal undernutrition and placental insufficiency creates a suboptimal intrauterine environment with both near- and long-term consequences for maternal and fetal health and well-being.

Although a number of alterations to the fetal environment, ranging from nutrient deficits (5, 7), dietary excesses (9), and exogenous substances (11) are recognized to affect renal organogenesis (2, 14), the exact links between the disruption in the renal development and the manifestations of renal disease and hypertension in later life remain unclear. To this end, a number of questions continue to perplex researchers in this area. How critical is nephron endowment with respect to eventual onset of hypertension? Does a shift in the relative populations of the nephron population play a role (i.e., cortical vs. juxtamedullary) in programmed renal function? How and when does biological sex influence the developmental programming of renal function? Does altered fetal renal development render the kidney more susceptible to subsequent insults such as renal insufficiency, a high-salt diet, or hyperglycemia? The latter question is the topic of a recent inquiry by Lim et al. (10) in an issue of the American Journal of Physiology-Renal Physiology.

It has been previously proposed that a secondary (i.e., postnatal) insult superimposed upon a developmental deficit of the kidney (e.g., impaired nephron endowment) would accelerate the presentation of, or in some cases, reveal the hypertensive phenotype (2, 3, 12, 14). Moreover, with the considerable increase observed with respect to the incidence of metabolic disease worldwide, determining the roles of early vs. later life influences is taking on increasing importance. To this end, several recent studies (3, 10, 16) have begun work toward identifying the respective contributions of renal nephron endowment vs. postnatal influences on the generation of hypertension.

Although it has been recognized for many years that chronic hyperglycemia has deleterious effects on the kidney and renal function (13), it remained unclear whether hyperglycemia was a sufficient “second hit” that would accelerate or trigger a decline in renal function in intrauterine growth-restricted (IUGR) offspring. In the present study, Lim et al. (10) report that moderate hyperglycemia has similar effects on renal function in both IUGR offspring from dams fed low-protein diets (LPD) and normal pregnant controls. While it is not surprising that high blood glucose levels would have deleterious effects on renal function, it is intriguing that LPD offspring were not affected by hyperglycemia more than the control group. Unfortunately, the focus of this study was on male offspring, so it remains unclear whether sex differences play a prominent role in this model as reported in other models (3, 11, 13).

In contrast to the present findings of Lim et al. (10), recent work utilizing an IUGR-LPD model in which the offspring have fewer nephrons and develop high blood pressure by 8 wk of age reported that males fed high-fat diets developed hypertension sooner and suffered from more rapid deterioration of renal function (3). Interestingly, the authors also observed that the female IUGR-LPD rats were not susceptible to either the prenatal or postnatal interventions. Furthermore, a recent study employing a genetic model of reduced nephron endowment (glial cell line-derived neurotrophic factor wild-type mice) suggests the reduction in nephron number may only be a prelude to hypertension and not the sole underlying cause (16). Hypertension and impaired renal function did not manifest until a secondary insult of a high-salt diet was superimposed on nephron deficit present in these mice (16). Viewed in concert with the recent findings of Lim et al. (10), these findings clearly show that postnatal insults are not all equivalent with respect to accelerating the onset of renal dysfunction in IUGR offspring.

Another question that has not received as much attention is which specific nutrient(s) results in impaired nephrogenesis and is responsible for generating the hypertensive phenotype observed in models of developmentally programmed hypertension. While a number of studies have demonstrated links between size at birth, increased blood pressure, and nephron endowment, the findings have not all been consistent (6) and clearly demonstrate unresolved issues regarding the variety of responses to the dietary manipulations (LPD in particular). In contrast to a large number of studies reporting that LPD results in hypertensive offspring with impaired nephron endowment, several groups (including the authors of the present study) have found that LPD does not generate a hypertensive phenotype. This has remained an intriguing question without much progress toward identifying an answer. One possibility that may be considered is the role specific amino acids may play in mitigating the effects of LPD during pregnancy. Amino acid supplementation with glycine (8) has been shown to alleviate the LPD-induced changes in blood pressure in the offspring; hence it is possible that differences in the gut flora generate region-specific responses to dietary challenges. In the case of LPD, varied populations of gut microflora may alter the availability of amino acids to the mother and contribute at least in part to these observations (4). Indeed, there has been a considerable increase in the number of studies addressing this very issue in recent years (15).

While the study by Lim et al. (10) provides intriguing new insights regarding the role of glycemic control in offspring following both normal and IUGR pregnancies, it also provides important validation of a noninvasive method to evaluate renal blood flow. If this method can be repeated in the hands of
others, it will undoubtedly provide important new information regarding the ontogeny of renal disease in a number of animal models. In summary, the present study by Lim et al. provides key insights regarding the importance of managing blood glucose levels in IUGR offspring with an impaired nephron endowment and in normal-weight offspring. Moreover, it also reinforces the multiplicity of factors that may play important roles in the progression of renal disease. Nevertheless, further studies are needed to examine possibilities such as the role of microflora as mediating or mitigating (depending upon the setting) nutritional stress as well as the potential role of biological sex and/or sex hormones in the developmental programming of adult health.

GRANTS

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REFERENCES