Unraveling perinatal programming of the kidney

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TO THE EDITOR: I read with great interest the paper of Baserga et al. (1), which describes the effect of uterine artery ligation in the pregnant rat on fetal cyclooxygenase-2 (COX-2) expression and blood pressure. This is an important subject and the study presents interesting results, but I would like to comment on some parts of their study.

As nephrogenesis in the rat is a process that continues until around day 8 after birth, the newborn rat is indeed a good model for studying the effect of insults during active nephrogenesis. Previously, we have shown postnatal food restriction in the rat by increasing litter size to 20 pups to lead to a 25% decrease in nephron number with a high correlation between body weight at day 10, i.e., at the end of nephrogenesis, and nephron number (7). Recently, Wlodek et al. (9) showed that cross-fostering an intrauterine growth restricted (IUGR) pup onto a control dam, a normal nephron number and tail cuff systolic blood pressure at the age of 20 wk was achieved. This underlines the fact that the postnatal period in which the majority of nephrons are being formed is very important in determining final nephron number. Of interest, dams after uterine artery ligation do not provide a normal lactational environment in combination with a low number of pups per litter, as this leads to a less stimulated milk production and therefore to postnatal growth restriction (9). Baserga et al. (1) culled litters to six pups only, which would have been of influence on the milk quantity and/or quality. As no data on the body weight were provided, the influence of the postnatal environment on the results cannot be determined.

However, the influence of the intrauterine environment is also not completely clear. Even though there is a difference in the timing of uterine artery ligation between the above-mentioned studies [Baserga et al. (1) on day 19, Wlodek et al. (9) on day 18, and Schreuder et al. (6) on day 17 of pregnancy], it has been shown that the position of the pup in the uterus is of influence on the degree of growth restriction (4). Using only 6 pups at day 1 and picking them at random, thereby allowing for a varying degree of IUGR, makes it very difficult to distinguish between pre- and postnatal insults (1). As the degree of influence on final nephron endowment is based on the timing, the nature and the severity of the insult that disturbs nephrogenesis, such information is vital to improve our understanding of renal programming.

My second comment concerns the blood pressure data presented in the paper that are based on the tail cuff method. This method is known to cause stress to the animals (2), and IUGR rats have been shown to have an altered stress response (8). It is recommended to use the tail cuff method only when studying blood pressure in large groups of animals and screening for large differences (3). However, six animals were studied per group, and the results are confusing. For instance, mean blood pressure is lower than diastolic blood pressure in female IUGR rats at day 140 of life (113 and 129 mmHg, respectively). Whether this is due to a ‘falling’ method, which was a limitation of the study according to the authors, or a typing error even though the graphic display shows the same results, cannot be determined. It would therefore be interesting to repeat such a study by using appropriate methods, which, using a longitudinal set up, also allows for the detection of the timing of blood pressure increase.

In conclusion, the study of Baserga et al. (1) allows for speculations on the role of COX-2 in the programming of kidney, but future study with specific attention to the timing of programming and the appropriateness of the methods is needed to shed more light on this issue.

REFERENCES