Editorial Commentary

How Safe Is Unilateral Nephrectomy?

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See related article, pp 1458–1463

In this issue of Hypertension, Rodríguez-Gómez et al report on their studies of the long-term consequences of unilateral nephrectomy (UNx) in male and female rats. This is an excellent study with very interesting implications to science, as well as clinical practice. The investigators studied the effects of UNx over 18 months, a long period of time given the relatively short life span of the rat. They noted that the males appeared to be more sensitive to the UNx as evidenced by earlier salt-sensitive hypertension, as well as greater pathological changes when animals were studied at the 18-month time point. We point out that the methods used by the authors to determine salt sensitivity were quite clever. Both acute and chronic salt loading were used to assess the relationships between blood pressure and natriuresis, the Guytonian renal function curves. Interestingly but not surprisingly, the authors observed that the presence of salt-sensitive hypertension corresponded quite well with renal pathology in the rats studied at 18 months.

The major finding reported by Rodríguez-Gómez et al was that the males seemed to adapt less well to UNx than the female rats. This observation is consistent with a body of work addressing sex differences. Using micropuncture and other physiological measurements, Baylis and Wilson demonstrated that glomerular capillary hydrostatic pressure was substantially higher in male rats compared with female rats subjected to UNx and a high-protein diet. Mulroney et al demonstrated considerably less hypertrophy after UNx in female when compared with male rats. This group also observed that testosterone appeared to be the driving force in this differential hypertrophy. Unfortunately, the current study was not able to address the role that hormones play in the observed differences in salt sensitivity.

The findings of this article force one to reflect on the relationship between salt and hypertension in clinical subjects. First and foremost, there has been some debate as to whether the kidney is truly the controller of blood pressure as proposed by Crawford et al some years ago. Although a detailed review of this debate is well beyond the scope of this commentary, most have concluded that the concepts developed by Guyton are applicable to a considerable portion of both experimental and human hypertension. However, the relationship between salt and blood pressure is certainly more complex than predicted by these concepts. This has been demonstrated, perhaps best, in the famous Intersalt study. In this landmark article, a rather weak correlation was seen between dietary salt intake and systolic blood pressure, which was, in fact, lost when the centers representative of the very lowest salt intakes were dropped from the analysis. However, the increases in systolic blood pressure that occurred with age were closely related to dietary salt intake. In short, increasing dietary salt intake does appear to result in salt sensitivity over long periods of time. The tacit assumption is that, clinically, salt sensitivity corresponds with pathological changes in the kidney. The molecular mechanisms underlying this are topics of intense investigation. Whether and how sex differences might weigh in on the relationship between dietary salt and progressive increases in salt sensitivity are still opaque.

One obvious and important clinical implication of UNx is kidney transplant donation. For many years, we have understood that, provided extensive screening is performed on the donor, kidney donation can be considered safe. That said, it has been clearly established that, even with appropriate screening, kidney donation appears to lead to increases in the incidence of hypertension and proteinuria. If the data from Rodríguez-Gómez et al is applicable in humans, this would suggest that female sex might confer additional safety to the prospective donors. Fortunately, the risk of renal donors developing end-stage renal disease with currently accepted screening criteria is extremely small, although some degrees of proteinuria and increased risk of hypertension have been noted in several series. Although it is difficult to exclude any difference between female and male donors, these differences are less than one might anticipate if we extrapolate the findings of the article under discussion. One reason for this may be age. Typically, human donors are mature, whereas the animals studied by Rodríguez-Gómez et al were quite young. It has been clearly established that renal hypertrophy after UNx decreases in both experimental animals and humans with age, and this hypertrophy does appear closely linked to the processes that lead to salt-sensitive hypertension, proteinuria, and progressive renal failure.

In summary, Rodríguez-Gómez et al provide us with an interesting study of how sex differences produce considerable variance in the physiological response to UNx. Further work will be necessary to fully understand the hormonal and molecular mechanisms operant in these differences, as well as the clinical implications of their findings.

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