Nephron Number and Renal Risk in Hypertension and Diabetes

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It has been proposed that “nephron underdosing,” i.e., a low number of nephrons at the time of birth, is linked to essential hypertension and a greater propensity to develop progressive loss of renal function after renal injury. This hypothesis was confirmed recently by examining the number of glomeruli in patients with essential hypertension. The mechanisms through which a low number of nephrons causes hypertension have not been clarified, but it is likely that functional changes in postglomerular segments of the nephron, e.g., handling of sodium, play an important role. Neonatal uninephrectomy increases BP, renders BP salt sensitive, and renders the kidney more susceptible to damage. Apart from genetic factors, fetal/maternal malnutrition during pregnancy seems to play an important role in the pathogenesis of nephron underdosing. Furthermore, intrauterine programming during organogenesis, e.g., by hyperglycemia, seems to be important: In animal experiments, offspring of either hyperglycemic or diabetic mothers have fewer nephrons.


More than a decade ago, Brenner (1) proposed the hypothesis that a low number of glomeruli at birth (“nephron underdosing”) causes hypertension and after injury renders the kidney more susceptible to renal damage and progressive loss of renal function. This hypothesis was tested recently by comparing the kidneys of 10 matched control subjects with those of 10 white victims of accidents who had a history of hypertension and left ventricular hypertrophy. Stereologic analysis documented that in hypertensive individuals, the number of glomeruli was diminished and (presumably as a compensatory effort to minimize the deviation of filtration surface) the volume of glomeruli was increased (2). Although it is currently unclear to what extent the findings in this small sample can be extrapolated to essential hypertension in general, the observation is of considerable interest because it opens new perspectives.

First, genes that operate in organogenesis (e.g., PAX, WT1) may be involved in the genesis of hypertension. In this context, it is of interest that a structural abnormality (brachydactyly) has been shown in a genetic form of hypertension closely resembling essential hypertension (3); furthermore, rarefaction of skin capillaries has been documented both in patients with essential hypertension (4) and even in offspring of patients with essential hypertension (5). Second, numerous findings point to a role of intrauterine factors in the development of “nephron underdosing,” so to some extent, essential hypertension may also be the consequence of intrauterine problems.

It has been argued that it is unlikely that nephron underdosing causes hypertension because uninephrectomy for live kidney donation is not associated with hypertension in the donor (6). This objection certainly does not disprove the hypothesis of Brenner (1). First, long-term follow-up of live kidney donor showed that some hypertension may be seen (7,8). Furthermore, experimental data indicate that neonatal and adult nephrectomy differ with respect to effects on BP (9), potentially suggesting that the hypertensinogenic effect is demonstrable only during a sensitive phase.

It is perhaps also a simplifying assumption that the low glomerular number per se accounts for the increase in BP. Such an explanation is not satisfactory, because rough estimates of the total filtering surface indicate that glomerular enlargement almost completely compensates for the low number of glomeruli, thus ensuring an almost normal filtration surface. Preliminary experimental data also suggest that it is potentially not a low glomerular number per se but associated developmentally programmed changes in the function, particularly sodium re-absorption of postglomerular nephron segments that are involved in the genesis of hypertension (10).

Potential Causes of Nephron Underdosing: Maternal/Fetal Malnutrition

There is ample evidence that essential hypertension is to a large extent explained by genetic factors. In this context, it is also of interest that nephron numbers are low in hypertension-prone rat strains such as hypertension prone Milan rats and spontaneously hypertensive rats (11).

Environmental factors that operate during the intrauterine phase, particularly during organogenesis, seem to play an additional role (12,13). Such factors include the action of toxins such as gentamycin, cyclosporin A, vitamin A/retinoid deficiency, and smoking. Of particular interest in the context of the present communication are findings indicating that intrauterine malnutrition because of placental dysfunction or poor ma-
ternal health as well as hyperglycemia/diabetes cause lower numbers of nephrons (14).

Manalich et al. (15) examined 35 neonates and counted the glomeruli in coronal sections of the renal cortex. They found fewer and bigger nephrons in the kidney of newborns with low birth weight. They also found an almost four-fold increase in glomerular volume in newborns with low birth weight. The correlation between birth weight and glomerular number was very tight (r = 0.87). In a recent autopsy study on adults, Hughson et al. (16) found a linear relationship between glomerular number and birth weight as well. Again, a strong inverse relation was noted between glomerular number and glomerular volume.

Although the relation between low birth weight and glomerular numbers has been well documented (15,16), its relation to hypertension (and high cardiovascular risk profile) in adults, that had been proposed by Barker et al. (17), has not been confirmed consistently. Nevertheless, in the study by Hardy et al. (18) on 3634 individuals who were born in 1946, those with a birth weight >4000 g had at 53 yr a mean systolic pressure of 136.5 mmHg, whereas those with a birth weight <2500 g had a systolic pressure of 143 mmHg.

Nephron Underdosing and Maternal Diabetes

In experimental animals, streptozotocin-induced diabetes causes a highly significant reduction of glomerular numbers in the offspring of diabetic mothers (13,19). Insulin plays an important role in glomerulogenesis as suggested by the observation that reduced bioavailability of IGF, e.g., by overexpression of IGF binding proteins or conditional transgene expression of IGFbp in pups, led to lower nephron numbers. Furthermore, in culture experiments, addition of IGF2 or IGF2-receptor sense or antisense oligonucleotides stimulated and inhibited in vitro nephrogenesis, respectively (19,20). In a rat strain with inborn reduction of nephron numbers, the MWF strain, the nephron number was less by 31% compared with Wistar rats, and this was associated with diminished IGF2-receptor expression, underlining the important role of IGF in nephrogenesis.

Nephron Underdosing and Propensity to Glomerular Injury

It has been proposed that fewer numbers of glomeruli lead to a higher single nephron GFR so that eventually such hyperfiltering glomeruli develop focal glomerulosclerosis spontaneously and particularly after injury (21,22). This concept is supported by the results of animal experiments. Neonatal uninephrectomy in Sprague-Dawley rats caused an increase in glomerular volume, development of salt-sensitive hypertension, proteinuria, and glomerular scarring (9). The concept is also plausible in view of the fact that postmitotic podocytes are the main, although not only, target cells of glomerular injury. In large glomeruli, each podocyte has to cover an ever-enlarging domain so that the podocyte eventually covers an excessively large domain. The podocyte is no longer able to prevent the sequence of denudation of the basal membrane, synchexy for-

Nephron Underdosing and Salt Sensitivity

In a number of minorities, e.g., Australian aborigines (23), Pima Indians (24), and blacks (although the last has remained controversial [16,25]), larger glomeruli have been found. This finding was interpreted as an indication of reduced nephron numbers and linked to the high predisposition to salt-sensitive hypertension in these minorities. There may be an analogy to animal experiments in which neonatal uninephrectomy rendered BP more salt sensitive (9).

Conclusion

Both experimental and clinical observations indicate that low nephron numbers are a risk factor for hypertension and cardiovascular disease. Recently, some potentially remediable factors that operate during the intrauterine period and determine pathology in adult life have been identified and will hopefully lead ultimately to rational strategies of intervention.

References

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