Nephron Number, Uric Acid, and Renal Microvascular Disease in the Pathogenesis of Essential Hypertension

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One of the world’s greatest epidemics is the epidemic of essential hypertension, which during the last 100 years has increased from a prevalence of 5% to 10% in the European and American population to >30% today. Hypertension was nonexistent in other places of the world but has risen to similar frequencies with the introduction of Western diet and culture. As a major cause of stroke, heart disease, and kidney disease, hypertension is a major underlying cause of morbidity and mortality, and therefore understanding its underlying etiology is critically important.

The groundbreaking studies of Dahl and Guyton led to the recognition of the key role for the kidney in the pathogenesis, but controversy remains on the precise mechanism. The observations that several hereditary causes of hypertension result from genetic mutations that lead to increased sodium reabsorption in the nephron (particularly in the collecting duct) has led to a search for genetic causes.1 However, although genetic polymorphisms are clearly important, most studies suggest genetic mechanisms may only have a modest (20%) influence on the hypertensive phenotype.2

A congenital mechanism, or fetal programming, has also been proposed (the “Barker-Brenner hypothesis”).3,4 Low birth weights (LBWs) predispose to the later development of hypertension as well as other cardiovascular diseases, including obesity and diabetes. LBW infants often have impaired kidney development, resulting in a reduced nephron endowment. Following birth, the children have an increased risk for developing endothelial dysfunction and obesity, and by adulthood they have a relatively increased frequency of hypertension, obesity, and diabetes.3,4

Although LBW is a predisposing factor, it can only account for a modest 20% of the variation. Small infants have a 29% risk of developing hypertension as adults, whereas the risk for large infants is 24%.5 The evidence for low nephron number is more compelling,6 but it remains unclear how a reduction in nephron number causes hypertension. The observation that kidney donation in adults only increases the risk for hypertension slightly has suggested that there may be something unique about the fetal environment that may be critical for the later phenotype.

A third major hypothesis is that subtle renal microvascular and inflammatory injury to the kidney may result in increased salt-sensitivity and hypertension.7 The injury can develop via a variety of mechanisms that all have in common renal vasoconstriction and that lead to the development of microvascular disease and interstitial inflammation with the local generation of oxidants and angiotensin II. A central pathway that can drive the process is endothelial dysfunction with a reduction in local endothelial NO levels, and evidence has been provided that elevated uric acid may be one of the major causes of endothelial dysfunction, linking hyperuricemia with hypertension, metabolic syndrome, and kidney disease.8–10 These associations are supported by preliminary studies in humans.11,12 More definitive studies in humans are ongoing.

The observation that uric acid may have a pathogenic role in essential hypertension led to a hypothesis to account for how a LBW and a low nephron number might predispose to hypertension later in life.11 Specifically, it is known that mothers at risk for having LBW babies are frequently hypertensive, obese, or preeclamptic, which are all conditions associated with elevated uric acid levels. In turn, elevated uric acid in the mother is a major risk factor for a LBW infant.13,14 Uric acid is a small molecular weight substance that passes freely into the fetal circulation13 where it has the potential for inhibiting glomerular endothelial cell proliferation.11 A rise in uric acid in the third trimester would preferentially affect nephron development since kidney development occurs late in pregnancy. The child would then be born with a low nephron number. Over time the child would also be predisposed to developing hyperuricemia, for the child would likely have similar dietary and hereditary predispositions to the mother, and hence would be at risk for the early development of hypertension. This hypothesis has support in in vitro studies and animal models in which reduction in nephron number in adult rats has also been shown to predispose to pregglomerular arteriolar disease,15 which engages the cycle of microvascular injury and interstitial inflammation.

Epidemiological evidence is now accruing to support this latter hypothesis. In this issue of Hypertension, Franco et al evaluated 78 children who were born at full term: 42 with LBW (<2500 g) and 36 with birth weight >3000 g.16 At 8 to 13 years old, children with a history of LBW had higher systolic blood pressure (albeit still in the normal range), markedly higher serum uric acid, and altered endothelial function as assessed by flow-mediated dilation studies. Because patients with birth weight between 2500 g and 3000 g were excluded from analysis it is not possible to know whether these patients fall between the 2 extreme groups.
The link between LBW and future hypertension has been challenged by Falkner and colleagues, who evaluated 250 children, 36% of whom were LBW and found no inverse correlation with adolescent blood pressure or body mass index at 11 to 14 years old. In contrast, we found adolescents with newly diagnosed essential hypertension were hyperuricemiac in nearly 90% of cases, and the uric acid levels correlated both with the severity of the systolic and diastolic hypertension and inversely with the birth weight.11,18 Children with normal blood pressure, white coat hypertension, and secondary hypertension did not have similar correlations.11

Evidence is also accruing that it is the presence of renal microvascular disease and not nephron number that is the critical determinant of whether hypertension will develop. Hence, in the spontaneously hypertensive rat, cross-breeding with progeny that had small renal arterioles as opposed to low nephron number,19,20 low-protein diet feeding to pregnant rats also results in LBW pups that subsequently develop hypertension. However, recent studies show that these pups develop renal microvascular disease and interstitial inflammation early in life, and that if these structural changes are blocked with mycophenolate the subsequent development of hypertension can be prevented.21

In conclusion, the ability of uric acid to induce endothelial dysfunction and inhibit angiogenesis makes it an attractive mechanism for preventing the linkage between birth weight and future cardiovascular disease. The observation that Western diet, particularly fructose-containing sugars and purine-rich meats, can markedly raise uric acid levels also provides a mechanism to explain the rapid development of obesity and hypertension throughout the world.22 Of course, there is the alternative possibility that uric acid remains a secondary phenomenon and simply reflects early vascular dysfunction, as proposed by the authors in the accompanying article. It will thus be important to perform further experimental and clinical studies to determine the mechanistic pathways that are driving this epidemic of hypertension and cardiorenal disease.

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