Editorial Commentary

Angiotensinogen Genotype and Blood Pressure Responses to Reduced Dietary NaCl and to Weight Loss

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With the human genome project nearing completion and with the increasing availability of genotyping technology, there is considerable interest in identifying genes that contribute to hypertension and to physiological determinants of hypertension. In a number of relatively rare hypertensive disorders, specific genetic polymorphisms resulting in elevated arterial pressure have recently been described, eg, glucocorticoid-remediable primary aldosteronism, Liddle’s syndrome, and the syndrome of apparent mineralocorticoid excess. In several but not all of these disorders, hypertension is the consequence of alterations of either adrenal steroid metabolism or direct renal tubular function resulting in antinatriuresis. Conversely, specific polymorphisms have been identified that result in alterations of renal tubular function that promote natriuresis and consequently relatively low blood pressure levels.

What relevance, if any, these or similar polymorphisms may have to blood pressure regulation or hypertension in the general population remains to be determined. Despite evidence for heritability, essential hypertension is a complex trait that does not exhibit classic mendelian modes of inheritance attributable to a single gene locus. Multiple genetic loci may be involved in blood pressure regulation, and hypertension may be related to the interaction of susceptible genes with environmental stressors, such as dietary sodium chloride (NaCl) consumption.

Trials of Hypertension Prevention (TOHP) is a longitudinal study designed to evaluate the efficacy of reduction of dietary NaCl and of weight loss on blood pressure in a cohort of moderately overweight adults with diastolic blood pressures of 83 to 89 mm Hg. In this issue of Hypertension, Hunt et al report that different polymorphisms of the angiotensinogen gene are associated with different levels of blood pressure in white subjects participating in the trial. Furthermore, over the 36 months of study, in response to both a reduced NaCl intake and weight loss, reduction of diastolic blood pressure was greater and incidence of hypertension was less in persons with the AA angiotensinogen genotype compared with those with the GG genotype. Blood pressure responses in persons with the AG genotype were intermediate.

This study is important for several reasons. To have 3-year follow-up data on 1509 subjects who have been randomized to a successful NaCl and/or weight reduction intervention is a remarkable achievement. The results highlight the limited contribution of a single polymorphism of the angiotensinogen gene to blood pressure level and to blood pressure responses to NaCl reduction and weight loss. Although different blood pressure responses to NaCl reduction and weight loss were observed by angiotensinogen genotype at 36 months, there were no differences at 6 or 18 months. Furthermore, although angiotensinogen genotype was associated with blood pressure responses to NaCl reduction alone and to weight loss alone, it was not associated with blood pressure responses to the combined NaCl reduction–weight loss intervention. The results would be more credible if they had been consistent over time and if an effect of angiotensinogen genotype had also been observed in the combined intervention group.

Individuals with the AA genotype are homozygous for the T235 allele of the M235T polymorphism of angiotensinogen (substitution of threonine for methionine at codon 235). In other populations, linkage of this allele with essential hypertension has not been consistently observed, reflecting either genetic diversity among populations, the limited contribution of this locus to hypertension, and/or methodological problems with several of the studies. This is in stark contrast to the monogenic hypertensive disorders in which a single mutation has a profound effect on blood pressure. Cross-breeding experiments in the rat (F2 progeny from a cross between normotensive Brown Norway rats and spontaneously hypertensive rats) document that each of a number of putative hypertensive alleles contribute to blood pressure and that the height of the blood pressure is dependent on the number of such alleles. Similarly, a number of susceptibility genes may contribute to essential hypertension and, as documented for the angiotensinogen gene, any single polymorphism by itself may have a relatively small impact on blood pressure level.

Within a population, there is considerable variability of blood pressure responsiveness to NaCl intake, and salt sensitivity of blood pressure should be considered a quantitative rather than a qualitative trait. Heritability of salt sensitivity and salt resistance of blood pressure is most convincingly documented in animal models. Family studies, including twin studies, suggest that there is a heritable contribution to salt sensitivity of blood pressure in humans, and there is limited evidence for heritability of NaCl excretion and levels of hormones that regulate NaCl excretion. The study of Hunt et al suggests that angiotensinogen genotype has, at best, a modest influence on the blood pressure responses to NaCl reduction and to weight loss. It is likely that additional genetic markers of salt sensitivity will
be identified, and similar to blood pressure level itself, in any individual the magnitude of the effect of dietary NaCl on blood pressure will reflect the culmination of a variable number of genetic polymorphisms.

Hunt et al speculate that higher blood pressure levels and greater blood pressure responses to reduced NaCl intake and to weight loss in persons with the AA genotype are related to increased angiotensinogen concentrations and failure to reduce plasma angiotensin II concentrations in response to a high NaCl intake. However, no measurements of angiotensinogen or other components of the renin-angiotensin-aldosterone system are provided, and salt sensitivity of blood pressure is generally associated with low rather than with high plasma renin levels. It is clear that additional studies are required to determine whether the angiotensinogen genotype is simply a marker for hypertension and salt sensitivity of blood pressure or whether these hemodynamic responses are in some way causally related to altered products of gene expression in persons with the AA genotype.

We can expect that future studies will not only uncover specific genetic linkages with hypertension but will also provide information about mechanisms by which genetic polymorphisms affect physiological mechanisms that contribute to the development of hypertension. From a clinical perspective, identification of genetic markers for hypertension and for salt sensitivity of blood pressure may have important implications for the prevention and treatment of hypertension.

References


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