Genes and environment in blood pressure control—salt intake again shows its importance¹,²

Paul R Conlin

Our patients constantly struggle with uncertainty as they estimate their health risks across the continuum from having total control over their destiny (ie, “you are what you eat”) to complete capitulation (ie, “it’s all in your genes”). So it is with the risk of hypertension—is it affected most by environmental influences, such as excess salt and calorie intake and a dearth of physical activity, or by our genetic make-up?

Hypertension is a complex and common disease, and, therefore, understanding the genetic underpinnings will be similarly complicated. There was great hope when single gene mutations were identified as the causes of rare, heritable hypertensive syndromes, such as glucocorticoid-remediable aldosteronism and Liddle’s syndrome (1). Whereas these gene defects elegantly explained the causes of hypertension affecting a few people, they led many to believe that other candidate genes may also be abnormal in subsets of the population with hypertension.

One of the earliest and best-studied genes is the angiotensinogen (AGT) gene, in which a polymorphism in the noncoding region at codon 235 [methionine (M) to threonine (T) substitution] was associated with a greater risk of hypertension (2). It was later shown that this variant was not a functional mutation but was in linkage disequilibrium with a guanine (G) to arginine (A) substitution in the −6 position of the promoter region (G→6A polymorphism). A number of studies have shown an association between these polymorphisms and hypertension. The presence of the AA (or TT) genotype is associated with a family history of hypertension (2), higher concentrations of AGT (3), favorable blood pressure response to the inhibition of angiotensin-converting enzyme (4), and salt-sensitive blood pressure (5).

Not surprisingly, the frequency of these AGT gene variants differs significantly across populations. For example, among those of Northern European descent, the prevalence of the T235 allele is ≈30%, whereas, among African Americans, the prevalence is ≈98% (6). Asians and those of Middle Eastern and Eastern European descent have intermediate frequencies. Speculation about the marked differences in gene frequency relates to selective forces that are at play through evolution. One hypothesis is that the T235 allele represents a “thrifty” genotype that afforded protection through its effects on enhancing sodium conservation via the renin-angiotensin-aldosterone system. Whereas sodium retention is favorable to survival, it may become deleterious when salt is no longer scarce, by contributing to elevated blood pressure (7). A number of investigators have studied links between this genotype and the salt sensitivity of blood pressure.

In this issue of the Journal, Norat et al (8) report on an association between blood pressure and sodium excretion in a cross-sectional study of >11 000 persons of Northern European descent. Study participants were phenotyped for blood pressure and urinary electrolyte excretion on a single occasion and genotyped at the AGT M235T position. Technical issues did not allow study of the G→6A variant. Study participants were between the ages of 45 and 79 y, and all were white. Average blood pressure for the study population was at prehypertension levels, but ≈20% were taking antihypertensive medications, presumably with a diagnosis of hypertension. The major advantages of this study are its large size and the ability to link blood pressure, sodium intake, and AGT genotype; the major drawbacks include its cross-sectional design, its limitation to whites, and its dependence on a single measurement of the variables of interest.

The investigators found a significant relation between increasing levels of sodium excretion and both systolic and diastolic blood pressure, regardless of AGT genotype. Across quintiles of sodium excretion and separated by AGT genotype, those in the highest quintile of sodium excretion had a systolic blood pressure 5–8 mm Hg higher than that of those in the lowest quintile. Diastolic blood pressure was similarly and significantly different, although the magnitude of the difference was less (2–3 mm Hg). Norat et al clearly confirmed a cross-sectional relation between sodium intake (as estimated by excretion) and blood pressure, regardless of genotype.

With respect to the effect of AGT genotype per se, the data were not as robust. Across the spectrum of sodium excretion, those carrying the T235 allele had a significantly greater slope in the relation between urinary sodium and systolic blood pressure than did those with other alleles. Among women but not men, there was a slightly but significantly higher blood pressure in those with the TT genotype than in those with the MT or MM genotype. It is not clear whether this difference between the male and female subjects represents a true sexual dimorphism, because a similar genotype × sex interaction was not seen in a more diverse population (9). Thus, there was a very small effect of the
T235 allele on blood pressure, and it was evident only at higher levels of sodium excretion.

These results provide further clear evidence for a cross-sectional relation between greater sodium intake and elevated blood pressure and, to a lesser extent, an effect of AGT genotype on this relation. We must be cautious not to interpret these results as if they came from an intervention trial in which sodium intake was varied. We do not know whether these same persons would have lower blood pressure with restricted sodium intake. Evidence for an association between AGT genotype and blood pressure response to sodium restriction was noted in the Trials of Hypertension Prevention, Phase II (10). It is also unfortunate that the study by Norat et al does not contribute any new knowledge with respect to persons of African descent, in whom there is much greater prevalence of the T235 allele.

Major focuses in clinical research are to develop personalized treatment strategies that are preemptive and to allow persons to be proactive. With regard to preventing hypertension, there is overwhelming evidence that sodium restriction lowers blood pressure (ie, is a successful preemptive strategy). As a result, nutrition guidelines continue to strongly recommend sodium restriction across the population (ie, a proactive strategy) (11). However, implementation of and adherence to such nonpharmacologic treatments remain challenging. Clinicians are often stymied by poor patient acceptance and by not knowing how aggressively to advocate for such interventions. It is with respect to this issue that a personalization strategy would be most helpful. But we are not yet at the stage where tools such as genotyping can help us reliably identify those persons who will benefit most from sodium restriction.

It is unrealistic to think that complex physiologic processes, such as blood pressure regulation or its response to sodium intake, will be affected by just one or even a few major genes. It is more likely that genetic profiles (eg, genotypes at multiple loci) will be more informative. We are still some distance from having this type of information. Our present knowledge suggests that polymorphisms in the genes known to affect blood pressure, including AGT, are only minor effect modifiers.

While we await new studies that allow us to tailor such interventions and treatments, we must not lose sight of the wealth of information already accumulated on the effects of lifestyle modifications on blood pressure. Reduced sodium intake, the Dietary Approaches to Stop Hypertension (DASH) diet, weight loss, and exercise have substantial effects in almost all subgroups of the population and should continue to be widely and broadly promoted.

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REFERENCES