Genetics of hypertension with its disappointing results may evoke reactions ranging from enthusiasm and hope to suspicion and skepticism. A variety of reasons may account for these contrasting results that cannot be discussed here. However, in our opinion, 2 of these reasons are the most important ones: First, there is clear contradiction between the well-established notion of the enormous heterogeneity of hypertension (in terms of molecular, biological, and clinical mechanisms) and the demand that a gene variant must be active across different populations, race, age, gender, etc. Second, the probability models of frequentist statisticians, based on randomness, trivialize the ordered complexity of biological systems based on natural laws. In fact, all the available statistical genetic guidelines for defining causation of a single gene in a complex disease, like hypertension, are unable to fully account for genetic or environmental interactions.

More than 50 years of pathophysiological, clinical, and epidemiological studies have clearly shown that these interactions are of paramount importance for the elevation of blood pressure. In fact, it is highly unlikely that the same molecular mechanism may account for a disease that affects up to 40% of the adult population of the industrialized countries. Interactions among these factor varieties can only be inferred from empirical observations and not from deductive mathematical logic.

Along this line, studies trying to correlate genotypes with intermediate phenotypes, that are along biologically plausible pathways linking the genes of interest to blood pressure, may reduce this complexity and, therefore, provide more consistent data across the different studies. Intermediate phenotypes are also indispensable to dissect the heterogeneity of this human condition into subsets of patients with more homogeneous pathophysiological profiles, particularly when the genetic findings in animal models have to be evaluated for their relevance to the genetics of human hypertension. For instance, renal function studies in 3 genetic animal models revealed clear-cut differences in the renal hemodynamic profile despite the fact that hypertension (or a portion of it) could be transplanted with the kidney in all these models. We are clearly dealing with different genetic mechanisms, all acting through the kidney. To prove their relevance in humans, it is desirable to define the subset of patients sharing the corresponding pathophysiological profile.

Whichever is the triggering mechanism of hypertension, the relationship between kidney perfusion pressure and Na excretion must be reset to maintain hypertension. Therefore, renal hemodynamics, with the related hormones at different levels of Na intake, are among the most relevant intermediate phenotypes to be considered. In this issue of Hypertension, Beeks et al. describe the effects of the 3 α-adducin genotypes on renal hemodynamics in 117 hypertensive patients. Previous studies, showing an enhancement of the constitutive capacity of tubular cells to reabsorb Na by the mutated Trp α-adducin, led these investigators to test the hypothesis that the adducin polymorphism could be associated with variations in renal hemodynamics at different Na intakes. Indeed, in homozygous carriers of the mutated Trp α-adducin, a reduction in renal blood flow and glomerular filtration rate (GFR) was detected in a low-salt diet. The same trend, although not significant, was also observed at a normal salt diet. These results agree with previous data showing, in carriers of this genotype, a faster progression of renal diseases or the association to Na sensitivity.

For an intermediate phenotype to be used as a tool to classify patients according to their pathophysiological profiles, the extent of its variability throughout the lifespan needs to be known, together with the context influence. For instance, data, both in genetic rat model of hypertension or in human hypertension, demonstrate that, at least in some rat strains (MHS) or subsets of patients, GFR or renal blood flow (RBF) may be higher, similar, or lower than that of appropriate controls, according to the hypertension phase or age. Therefore, the lack of difference in slope among the 3 genotypes when RBF was plotted against age may also be due to a lack of statistical power, because of the relatively small number of subjects in the homozygous Trp α-adducin genotype and of the relevant number of variables affecting renal hemodynamics, including the persistence of the influence of previous antihypertensive therapy. It has recently been shown that the relation between the magnitude of the response to angiotensin I and the angiotensin-converting enzyme insertion/deletion polymorphism is affected by variations in Na intake similar to those applied by Beeks et al. The response to angiotensin I is greater in the DD carriers than in II carriers at a sodium intake of 200 mmol/d, but such a difference disappears after 1 week at 50 mmol/d Na intake. The response to angiotensin II is not affected by the angiotensin-converting enzyme insertion/deletion polymorphism or by variation in Na intake. These findings suggest that a low level of Na intake may, per se, activate the renin-angiotensin system, thus blunting the underlying genetic mechanism modulating the production of angiotensin II from angiotensin I. Therefore, any abrupt change in dietary Na may be associated to modification in the genotype-phenotype relationship present at normal Na intake. It is likely that the inconsistency among the published data on the genotype-phenotype relationships after variation of the dietary Na may also be due to this type of
interference. On the other hand, the variations in the dietary Na observed in the clinical practice are much less than those applied in the experimental protocols. Therefore, the clinical significance of the data obtained with these protocols must be evaluated with caution.

The increase of ANP in Trp α-adducin carriers 6 has been interpreted as a compensatory mechanism aimed at counteracting the renal Na retaining effect of this allele. Probably, other compensatory mechanisms are at work 11 when the constitutive capacity of tubular cells to reabsorb Na is modified by one allele or a combination of alleles. For this reason, the more comprehensive the physiological profile of the intermediate phenotypes related to a given renal function modification, the more precise is our definition of the clinical impact of the alleles of interest.

All the results so far obtained 7 on adducin point to an effect at the tubular level resulting in an increase of constitutive Na reabsorption in carriers of the mutated Trp allele. Therefore, a higher level of GFR and RBF may be consistent with this notion. Indeed, such a pattern has been shown in rats 5 at the prehypertensive stage. Unfortunately, a longitudinal study on patients carrying this allele is not available. Thus, the hypothesis that initial hyperfiltration may be followed by a faster rate of decline of filtration and renal blood flow with age remains unproved in human.

Which are the blood pressure levels in the 3 α-adducin genotypes? In all the 6 studies on white populations 12–17 where it has been reported, blood pressure of the Trp/Trp homozygous genotype tends to be slightly lower than that of the heterozygous or even of the homozygous Gly/Gly genotype. These findings have been generally overlooked because of the low frequency of the homozygous mutated genotype. Moreover, an excess of the Trp/Trp genotype in normotensives (P < 0.00001), but not in hypertensives (P = 0.554), was demonstrated as a deviation from Hardy Weinberg equilibrium. We carried out this analysis by pooling the data from 12 studies 13,15–25 for a total of 5381 normotensives and 3784 hypertensives. One way to reconcile the above illustrated findings is to postulate that an initial increase in GFR and RBF may compensate for the increased tubular reabsorption and limit the increase of blood pressure. In the long run, this hyperfiltration may accelerate the already known steeper decrease of RBF with age of hypertensives compared with normotensives. Again, this speculation must be proved with appropriate longitudinal studies.

We may conclude that variations in renal function are associated to the α-adducin genotypes. However, the precise time-course of these changes and their modulatory factors, either genetic or environmental, must be properly evaluated in humans to measure the clinical impact of these findings.

References


Adducin, Renal Intermediate Phenotypes, and Hypertension
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Hypertension. 2004;44:394-395; originally published online August 16, 2004;
doi: 10.1161/01.HYP.0000141413.91223.2c

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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