EDITORIAL FOCUS

An experimentum crucis in salt sensitivity

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“Instead of a multitude of things, try only the Experimentum Crucis: for it is not number of experiments, but weight to be regarded.”


ELUCIDATION OF THE GENETIC BASIS of essential hypertension is a challenging endeavor. Remarkable progress has been made studying families affected by rare Mendelian forms of high or low blood pressure. This approach has been successful because it identifies mutations with large effect sizes on single genes that regulate renal sodium (Na+) handling and Na+ balance. However, essential hypertension is not a Mendelian trait but a complex one that is incompletely penetrant and likely governed by a mixture of genetic, environmental, and stochastic factors. Nonetheless, a candidate gene approach, informed by studies of Mendelian forms of low blood pressure (8–10), has demonstrated that rare genetic variants within a large background of neutral variants can account for a large fraction of blood pressure variation (4).

In an issue of the American Journal of Physiology-Renal Physiology, Ray et al. (6) adopt a similar candidate gene approach with participants of the Genetic Epidemiology Network of Salt-Sensitivity (GenSalt) study and evaluate whether epithelial Na+ channel (ENaC) variants underlie salt sensitivity. Salt sensitivity can identify individuals who are at high risk for hypertension, cardiovascular disease, and overall mortality (5, 11). Moreover, salt sensitivity may reflect more directly on the mechanisms by which each individual variant changes ENaC activity. Two ENaC variants are notable from this study. αV481M variant also carry one of the loss-of-function ENaC variants. Contrary to their hypotheses, the investigators found no statistically significant associations among ENaC variants and salt sensitivity. There are several possible reasons for these null results, many of which are acknowledged by the investigators. First, it is possible that a single ENaC variant may not have an effect size large enough to alter salt sensitivity in a clinically detectable way. Similar to essential hypertension, salt sensitivity is not a Mendelian trait, so the effect of an allele at one gene locus could be diluted by competing alleles at other loci. For example, in the present study, the four salt-sensitive participants carrying the gain-of-function αV481M variant also carry one of the loss-of-function ENaC variants.

Second, the investigators excluded participants whose gene variants could have increased the frequency of those that might associate with salt sensitivity. The investigators identified 16 nonsynonymous gene variants of α, β, and γ subunits of ENaC. They examined how these variants affect ENaC activity by generating human αβγ−ENaC DNAs with individual variants and measuring the activity of resultant channels in the Xenopus laevis oocyte expression system. Furthermore, they assiduously characterized the mechanisms by which each individual variant changes ENaC activity. Two ENaC variants are notable from this study. αV481Mβγ−ENaC exhibited a 2.7-fold increase in current, which was associated with a decrease in ENaC cell surface expression and a decrease in Na+ self-inhibition. Conversely, αA334Tβγ−ENaC exhibited a decrease in current, which was associated with a decrease in ENaC cell surface expression and an increase in Na+ self-inhibition. In addition to functional characterization of ENaC variants, the investigators searched for clinical correlations by asking if gain-of-function variants associate with salt-sensitive patients and, conversely, if loss-of-function variants associate with salt-resistant participants.

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DISCLOSURES

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REFERENCES


