Study of molecular genetics of salt sensitivity with reference to ethnic diversity

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"Salt sensitivity" could constitute candidate biological mechanisms underlying susceptibility for essential hypertension. In general, salt-sensitive people tend to develop hypertension more often than salt-resistant people; however, the incidence appears varied among different ethnic groups. We take notice of such ethnic diversity to unravel genetic aspects of salt-sensitivity. Although a large-scale database has to be constructed prior to comparing different ethnic groups, several points need to be considered; for example, how can the degree of salt-sensitivity be appropriately evaluated apart from blood pressure, and what kind of physiological components can be tested as potential genetic susceptibility.

In order to address these issues, we conducted preliminary investigations regarding salt sensitivity. First, several circulatory hormones were monitored in 7 healthy volunteers during the acute salt loading experiment, where 2-liter of saline solution was infused over 2-hour periods. Second, the distribution of principal circulatory hormones, such as the renin-angiotensin system, was examined in 102 healthy (normotensive) subjects to see whether they can be used as parameters reflecting salt sensitivity. Third, an extensive search for gene polymorphisms was carried out in the atrial natriuretic peptide locus (*ANP*), one of candidate genes for salt sensitivity.

Our results demonstrate that both hypertensive and normotensive hormones substantially changed during the acute salt loading. This observation should be taken into account when dissecting a complex genetic basis of salt sensitivity. Also a detailed exploration of individual hormone profile in the general population appears to be useful for the selection of phenotypic variables in a large-scale genetic analysis. (Study panels with 200-300 individuals are currently being or will be collected in Africans, Japanese, and Brazilians, respectively.) Five polymorphisms were detected in the *ANP* locus, and categorized into three classes based on the pattern of linkage disequilibrium. Association analyses were further performed between three selected *ANP* polymorphisms and plasma ANP levels or hypertension status, resulting in the lack of association.

It remains unknown whether or not genetic determinants of salt sensitivity actually contribute to the development of "essential" hypertension. However, it is very likely that findings on molecular genetics of salt sensitivity enable us to screen patients who will have the most benefit from salt reduction.