

Dissection and functional analysis of salt-sensitivity genes in rats
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Summary

Recent progress in the Human Genome Project is exploring the etiology of hypertension from the aspect of salt-sensitivity. As a first approach to identify the salt-sensitivity genes, we carried out a rat cross experiment. Crosses were made between 3 male spontaneously hypertensive rats and 3 female Wistar-Kyoto rats to make F1 hybrid. F1 hybrid were intercrossed for the study of F2 segregating generation. The other cross between Dahl's salt-sensitive and Dahl's salt-resistant rats was also made. Using 213 microsatellite markers, we found several candidate loci responsible for blood pressure. The arterial natriuretic peptide receptor locus, guanylate cyclase A on chromosome 2, neuropeptide Y locus on chromosome 4, and gamma crystallin locus on chromosome 9 were associated with high blood pressure. Peroxisomal ketoacyl-coA thiolase locus on chromosome 8 was associated with low blood pressure. However, there is a big difference in physiological state between rat and human, suggesting that rat results are not equal to human results. We then performed a genetic epidemiological study on a cohort in Ohazama, to investigate the relationship between the dipping phenomenon in 24-hour blood pressure and angiotensinogen genotype. It has been reported that there is a relation between the non-dipper type of 24-hour blood pressure profile and salt sensitivity. In this study, the 235T allele is presented as +31C. In the non-dipper type, which is common in patients with salt sensitivity, the incidence of CC genotype was significantly higher than in the dipper type. In the reverse-dipper type, in which the night-time blood pressure is higher than the daytime pressure, the incidence of CC was even higher. On the other hand, in extreme dippers, in whom there was an extreme blood pressure fall at night, the incidence of CC was lowest. These data suggest that the higher frequency of non-dipper type, which is possibly related to salt sensitivity, in CC carriers suggested the genetic involvement of angiotensinogen polymorphism in the risk for cardiovascular disease.