Role of Na^+/Ca^{2+} exchanger type 1 in the development and maintenance of salt-sensitive hypertension

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Summary

It is widely known that excessive dietary salt may cause hypertension. However, the mechanism and target genes of salt-sensitive hypertension are not yet clear. In this study, we aim at clarifying the role of Na^+/Ca^{2+} exchanger (NCX) type 1 in the development and maintenance of salt-sensitive hypertension by using genetically NCX-engineered mice and specific NCX inhibitors. We first evaluated the pathological role of NCX1 in deoxycorticosterone acetate (DOCA)-salt-induced hypertension by using heterozygous NCX1-knockout mice, which are useful as a low NCX1-expressing animal model. There was no significant difference in blood pressure between heterozygous and wild-type mice. After treatment with DOCA-salt for 4 weeks, wild-type mice showed the significant increases in the systolic blood pressure (change: 27±1 mmHg), but heterozygous did not. Moreover, we examined the effects of NCX inhibitors on several hypertensive animal models. Specific NCX inhibitor SEA0400 (1-10mg/kg, p.o.) reduced the blood pressure in DOCA-salt hypertensive rats and Dahl salt-sensitive rats, whereas it did not significantly affect the blood pressure in WKY, SHR, Dahl salt-insensitive rats, and 2K1C hypertensive rats. Furthermore, chronic treatment with SEA0400 markedly suppressed DOCA-salt-induced hypertension, secondary renal dysfunction, and vascular hypertrophy. When the low-dose SEA0400 (10 μg/kg/min) was infused into femoral artery of DOCA-salt hypertensive rats in order to evaluate the vasodilation effect of SEA0400, the blood flow markedly increased. In contrast, SEA0400 did not affect the femoral blood flow of normal rats (sham). These results suggest that NCX1 participates in the development and maintenance of salt-sensitive hypertension.