No. 0634

Changes in Molecular Functions and Expressions of Two-Pore-Domain Potassium Channels in Salt-Sensitive Hypertension

Yuji Imaizumi, Susumu Ohya, Hisao Yamamura

Nagoya City University

Summary

Excess salt-intake is one of the major risks of hypertension, and salt-sensitivity is associated with the increased incidence of cardiovascular disease complications. K^+ channels are important regulators of vascular tone. Activation of K^+ channels in vascular smooth muscle leads to membrane hyperpolarization, and thereby results in vasodilation. A newly discovered, two-pore domain K^+ (K_{2P}) channel family has around 15 members, however, little is known about the contribution of K_{2P} channels to vascular tone regulation and changes in expression of the related subtypes in salt-sensitive hypertension.

In this study, we first examined the expression of 11 members of K_{2P} channels in several vascular smooth muscles of salt-sensitive Dahl (DS) rat by real-time PCR. In aorta, mesenteric artery, renal artery, and femoral artery, TWIK-like Acid Sensitive K^+ channel subtype 1 (TASK1) was significantly expressed. We next compared the expression levels of TASK1 between DS rats fed low-salt (0.4 %) (DS-L) or high-salt (8 %) (DS-H) diet. Significant hypertension and hypertrophy were observed in DS-H rats. In abdominal aorta, the expression of TASK1 transcripts was significantly down-regulated in DS-H, whereas in renal artery significantly down-regulated in DS-H. We have previously shown the similar results in aorta of spontaneous hypertensive rats (SHR) (Kiyoshi *et al., Am. J. Physiol.*, 2006). These suggest that TASK1 may be responsible for the pH-sensitive and voltage-insensitive K^+ conductance that sets the resting membrane potential in these vascular smooth muscles. However, significant functional differences were not detected between their arteries of DS-H and DS-L using both whole-cell patch clamp and measurement of contractile responses. We isolated novel two spliced isoforms of TASK1 with different N-terminal sequences in rat aorta.

In order to construct high-throughput screening system of TASK1 using voltage-sensitive oxonol dye assay, we prepared human TASK1-stably expressed HEK293 cell lines (HEK-hTASK1) using Geneticin-containing culture medium. Functional characterization of hTASK1 was then performed by whole-cell patch clamp and voltage-sensitive dye assay. HEK-hTASK1 transfectants may be a useful tool for screening TASK1 channel modulators.