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Molecular Pharmacological Studies on Potassium Channels and Their Regulatory Molecules

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K^+ channels play important roles in the control of a large variety of physiological functions such as muscle contraction, neurotransmitter release, secretion and cell proliferation. Over 100 of cloned K^+ channel pore-forming α and accessory β subunits have been identified so far. Here, a series of molecular pharmacological and physiological studies on some types of voltage-dependent K^+ channels and Ca^{2+}-activated K^+ channels, which we have done recently, will be introduced.

1. Physiological Roles and Molecular Basis of Voltage-Dependent K^+ Channel

Voltage-dependent K^+ channels are classified as kinetically distinct two types, 1) a fast-inactivating A-type and 2) a slowly-activating delayed rectifier-type. We have cloned novel A-type K^+ channel α (Kv4.3L) and β (KChIP2S) subunits predominantly expressed in mammalian heart, and found the sites in Kv4 channels for 1) the regulation of the voltage dependency and 2) the CaMKII phosphorylation in the C-terminal cytoplasmic domain. We have also revealed the findings that delayed rectifier-type ERG1 and KCNQ channels contribute to the resting membrane conductance in vascular and gastrointestinal smooth muscles.

2. Physiological Roles and Molecular Basis of Ca^{2+} -Activated K^+ Channel

Large-conductance Ca^{2+}-activated K^+ (BK) channel is ubiquitously expressed, and also contributes to diverse physiological processes. Recently, O'Rourke's group has been suggested that BK-like channel ($mitoK_{Ca}$) is expressed in the mitochondrial inner membrane of cardiac ventricular cells, and BK channel openers protect mammalian hearts against ischemic injury presumably via $mitoK_{Ca}$ opening (Science, 2002). Our findings have revealed that BKβ1 interacts with cytochrome c oxidase I (Cco1) in cardiac mitochondria, and the activation of BK channels by 17β-estradiol results in significant increase in survival rate of ventricular myocytes. These suggest that BKβ1 may play an important role for the regulation of cell respiration in cardiac myocytes and be a target for the modulation by female gonadal hormonal.