Renal Potassium (K) Channels : Lessons from Molecular Cloning and Genetics

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Potassium (K) channels provide diverse functions in cells including setting the membrane potential, generating electrical signals in excitable cells, regulating cell volume and cell movement as well as K secretion in specialized epithelia. Since K channels play such an important role in kidney function, understanding the structure and regulation of renal K^+ channels is essential to gaining insights into the molecular mechanisms of kidney potassium handling. The movement of K ions through these channels is governed by protein conformational changes resulting in channel opening or closing, also referred to as gating. K channels have evolved an array of gating sensors that respond to membrane voltage and/or a variety of extra- and intracellular molecules or ligands. All K channels are characterized by a tetrameric structure of membrane-spanning subunits with a central pore containing a selectivity filter that determines cation specificity. The pore architecture is conserved among K channels and is represented by the bacterial KcsA K channel structure. The outer half of the pore provides the selectivity filter while the inner (cytosolic) half provides the channel gate.

Inward rectifiers (Kir) form a distinct subfamily of K channels characterized by their ability to conduct K ions more easily in the outside-to-inside direction. Rectification results from blocking of the outward movement of K ions by impermeant intracellular cations like Mg and polyamines. These blocking cations interact with a unique extended cytoplasmic pore composed of C-terminal β strands reminiscent of bacterial porins. There are seven subgroups of Kir channels, Kir1-Kir7, that share a similar subunit topology of a single membrane-spanning helix on either side of a highly conserved K^+-selective filter. Kir channels are gated by the binding of intracellular ligands, like the $\beta\gamma$ G protein subunits, ATP and protons, to the cytosolic N- and C-termini. ATP-gated (K_{ATP}) K channels couple metabolism to cell excitability and provide therapeutic targets for diseases including tissue ischemia, diabetes, and hypertension.

In the mammalian kidney, the Kir1.1 (ROMK) potassium channel provides for the apical recycling of K in the thick ascending limb and for K secretion by collecting duct cells. ROMK is a K_{ATP} channel that is believed to be formed by heteromeric association of 4 Kir1.1 pore-forming subunits with CFTR, the cystic fibrosis transmembrane conductance regulator that belong to the ATP-Binding Cassette (ABC) family. CFTR is a Cl channel that exhibits a high affinity binding to sulfonylureas, like glibenclamide, that close K_{ATP} channels. Loss-of-function mutations in ROMK have been shown to produce Bartter's syndrome, an autosomal recessive renal tubulopathies characterized by hypokalemic metabolic alkalosis, salt wasting, hyperreninemia and hyperaldosteronsim. Bartter's syndrome is genetically heterogeneous set of disorders also resulting from

(1) loss-of function mutations in the genes encoding the apical Na-K-2Cl cotransporter *SLC12A1* and the basolateral Cl^- channel, *ClC-Kb*, and its regulator, *Barttin*, and (2) gain-of function mutations in the extracellular Ca (nutrient)-sensing receptor, *CaSR*. The location of the amino acid residue altered with certain KCNJ1 mutations, the resultant ROMK channels would be expected to exhibit altered gating. These issues will be in detail. Elucidation of these mechanisms provides important insights to K handling by distal nephron segments including the collecting duct. Selective breeding of ROMK (*Kcnj1*) knockout mice has produced a model of Bartter's syndrome with good postnatal survival that is providing important insights into the pathophysiology of this disorder.