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Focused issue on K_{ATP} channels

Function and distribution of the SUR isoforms and splice variants

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Abstract

Alternative splicing allows multiple mRNAs to be generated from a single gene, which in turn can be translated into a group of diverse proteins with different roles and structures. The outcome of alternative splicing leads to the co-existence of multiple splice variants of a gene at different concentrations in different tissues. The pore-forming subunit of the K_{ATP} channel ($K_{IR}6.x$) and the regulatory sulfonylurea receptor (SUR_x) subunits exist in a 4:4 stoichiometry to form hetero-octameric ATP-sensitive potassium channel (K_{ATP}) channels, which are widely distributed in various types of tissues at either the plasma membrane (cellK_{ATP}) or mitochondrial inner membrane (the mitochondrial form of K_{ATP} channel, mitoK_{ATP}). They perform important physiological functions in regulating insulin secretion in pancreatic β-cells, providing ischemic protection in heart and brain, and regulating vascular tone in smooth muscles. Two separate genes, the regulatory subunit protein I (SUR1) and the regulatory subunit protein II (SUR2) encode the high- and low-affinity SUR, respectively. This review summarizes the current studies on the function and distribution of the SUR isoforms and alternative splice variants, and to a lesser extent the $K_{IR}6.x$ subunits. The different isoforms and splice variants allow for many K_{ATP} channel combinations, and therefore, increases the channel diversity and the possibility of complexity in function.

Keywords: K_{ATP} channels; SUR isoforms; Splice variant; Gene

1. Introduction

Since Noma [1] first described a new type of potassium channel inhibited by intracellular ATP but stimulated by MgADP in isolated ventricular myocytes of guinea pig, intensive research efforts have been made to understand the composition and physiological function of ATP-sensitive potassium channels (K_{ATP}). It has been reported that K_{ATP} channels are widely distributed in various types of tissues and play important physiological roles, i.e. in regulating insulin secretion in pancreatic β-cells [2], providing ischemic protections in heart [3] and brain [4] and regulating vascular tone in smooth muscles [5]. K_{ATP} channels that are located either at the plasma membrane (cellK_{ATP}) or at the inner mitochondrial membrane (the mitochondrial form of K_{ATP} channel, mitoK_{ATP}), have been reported based on the pharmacological and biochemical evidence. Although the molecular nature of mitoK_{ATP} remains to be elucidated, it is known that the cellK_{ATP} channel consists of at least two distinct subunits [6,7]: a pore-forming subunit, which belongs to the K^+ inward rectifier family ($K_{IR}6.x$) and a regulatory subunit, the sulfonylurea receptor (SUR_x). More recent discoveries of isoforms and alternative splice variants for the K_{ATP} channel subunits have increased the channel diversity and complexity. The scope of this review covers recent breakthroughs in the

Abbreviations: ABC proteins, ATP-binding cassette transporter proteins; K_{ATP}, ATP-sensitive potassium channel; K_{IR}, K^+ inward rectifier family; $K_{IR}6.x$, the pore-forming subunit of the K_{ATP} channel; $K_{IR}6.1$, the pore-forming subunit 6.1; *KIR6.1*, isoform I coding by the pore-forming subunit gene; $K_{IR}6.2$, the pore-forming subunit 6.2; *KIR6.2*, isoform II coding by the pore-forming subunit gene; mitoK_{ATP}, the mitochondrial form of K_{ATP} channel; NBF, nucleotide-binding fold; cellK_{ATP}, the plasma membrane form of K_{ATP} channel; SUR, sulfonylurea receptor; SUR1, the regulatory subunit protein I; *SUR1*, isoform I coding by the sulfonylurea receptor gene; SUR2, the regulatory subunit protein II; *SUR2*, isoform II coding by the sulfonylurea receptor gene; SUR2A, the splice variant that uses exon 39 as its C-terminus exon; SUR2B, the splice variant that uses exon 40 as its C-terminus exon; TM, transmembrane spanning helices; TMD, transmembrane domain.

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K_{ATP} channel field with the major focus on the roles and distributions of the *SUR* isoforms and alternative splice variants.

2. Composition of the K_{ATP} channels and subunits

2.1. Configuration of the K_{ATP} channels

It is generally agreed that the pore-forming $K_{IR}6.x$ and the regulatory SUR_x subunits exist in a 4:4 stoichiometry to form a hetero-octameric K_{ATP} channel. The topology of the two subunits is illustrated in Fig. 1. The pore-forming subunit, $K_{IR}6.x$, is a weak rectifier of the K^+ inward rectifier family, which contains seven members ($K_{IR}1$–7). K_{IR} channels are commonly present as tetramers using either homomeric or heteromeric subunits. Each monomer contains a pore loop (P) flanked by two transmembrane segments (M1 and M2) and by the cytoplasmic domains located at the N- and C- termini. It is believed that ATP can directly inhibit $K_{IR}6.x$ by acting through these cytoplasmic domains. $K_{IR}6.x$ or SUR_x has an endoplasmic reticulum (ER) retention signal motif [8], RKR, which can block the individual cell surface expression of each subunit. The RKR motif of the pore-forming subunit 6.2 ($K_{IR}6.2$) is located at the last 26 amino acids of the C-terminus [9,10] while for the regulatory subunit protein I (SUR1), it is located in front of the first nucleotide-binding fold (NBF1).

Compared to $K_{IR}6.x$, the regulatory subunit of the K_{ATP} channel, SUR_x, is much bigger in size and more complicated in structure. SUR, a receptor for sulfonylureas, is a member of the ATP-binding cassette (ABC) protein superfamily. ABC proteins are relatively large transporter proteins that are responsible for transporting a wide variety of substrates ranging from ions, lipids, and secondary metabolites to drug molecules across the cell membrane [11]. To date, approximately 65 human ABC transporter proteins have been identified, which are divided into seven subgroups, ABC1, MDR/TAP, MRP, ALD, OABP, GLN20 and White [12]. Like a typical ABC transporter, SUR_x has multiple transmembrane spanning segments forming two transmembrane domains, TMD1 and TMD2. Each TMD has an intracellular nucleotide-binding fold (NBF1 or NBF2) which contains two Walker motifs (A and B). The Walker regions are involved in catalyzing the hydrolysis of ATP, which is used as energy to facilitate the uptake of substrates via the TMDs. It has been previously reported that a conserved aspartate residue in the Walker B region coordinates the Mg^{2+} ion of MgATP while a conserved lysine residue in Walker A mediates the binding of ATP [13] in MDR1 [14], CFTR [15] and SUR_x [16]. Moreover, the SUR proteins display the closest phylogenetic relationship to the MRP1-6 proteins and CFTR in structure due to the presence of an additional N-terminal transmembrane domain (TMD0). This TMD0 links to TMD1 by a cytoplasmic loop, L0. The role of TMD0 in certain MRPs, CFTR and SUR1 is different as reported before. TMD0 seems to have important function in CFTR and MRP2 but not in MRP1. However, evidence from a study of TMD0 in SUR1 indicates that the TMD0 and L0 of SUR1 are involved in controlling the gating of the SUR1-based K_{ATP} channels [17].

2.2. The physical association between the $K_{IR}6.x$ and SUR_x subunits

The K_{ATP} channel $(K_{IR}6.x/SUR_x)_4$ is believed to exist as a hetero-octamer [18] and the physical association of $K_{IR}6.x$ with SUR_x has attracted much research interest. A key point was whether SUR_x was required in forming a functional K_{ATP} channel and if so, how important SUR_x was to the channel activity and regulatory mechanisms? Several models have been established based on the SUR1/$K_{IR}6.2$ channel to address this issue. A $K_{IR}6.2$ mutant channel with its last 26 amino acids deleted from the C-terminus was able to reach the plasma membrane surface in the absence of the SUR1 subunit [9]. Because the "minimal channel" could be inhibited by ATP, the observations indicated that SUR1 might not be required to form a functional K_{ATP} channel. It was later that Babenko et al. [17] showed that the assembly of SUR1 with

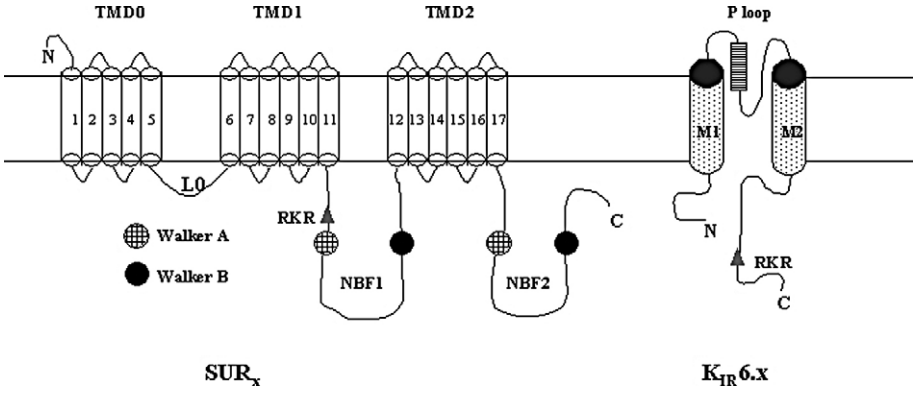

Fig. 1. Diagram of the topology of K_{ATP} channels. The pore-forming subunit $K_{IR}6.x$ is shown on the right while the regulatory subunit, SURx, is shown on on the left. The pore loop (P) and the two transmembrane segments (M1 and M2) of $K_{IR}6.x$ are marked. An endoplasmic reticulum (ER) retention signal (RKR) is labeled at the C-terminus of the $K_{IR}6.x$. The 17 transmembrane-spanning segments of the SURx are numbered in T0-T2 domains. The two nucleotide-binding fold domains (NBF1 & 2) and the Walker A and B regions are indicated. A cytoplasmic loop, L0, that links TMD1 to TMD0 is labeled. The ER retention signal motif (RKR) for SURx is also shown.