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Focused issue on K_{ATP} channels

Roles of K_{ATP} channels as metabolic sensors in acute metabolic changes

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Abstract

Physiological and pathophysiological roles of K_{ATP} channels have been clarified recently in genetically engineered mice. The Kir6.2-containing K_{ATP} channels in pancreatic ß-cells and the hypothalamus are essential in the regulation of glucose-induced insulin secretion and hypoglycemia-induced glucagon secretion, respectively, and are involved in glucose uptake in skeletal muscles, thus playing a key role in the maintenance of glucose homeostasis. Disruption of Kir6.1-containing K_{ATP} channels in mice leads to spontaneous vascular spasm mimicking vasospastic (Prinzmetal) angina in humans, indicating that the Kir6.1-containing K_{ATP} channels in vascular smooth muscles participate in the regulation of vascular tonus, especially in coronary arteries. Together with protective roles of K_{ATP} channels against cardiac ischemia and hypoxia-induced seizure propagation, it is now clear that K_{ATP} channels, as metabolic sensors, are critical in the maintenance of homeostasis against acute metabolic changes.

Keywords: SUR1; SUR2; ATP-sensitive K^+ channel; Exocytosis; Sulfonylurea; Glucose responsive neuron; Vasospasm

1. Introduction

ATP-sensitive potassium (K_{ATP}) channels are present in various tissues including pancreatic islet cells, heart, skeletal muscle, vascular smooth muscle, and brain, in which they couple the cellular metabolic state to its membrane excitability [1]. The K_{ATP} channel is a hetero-octamer comprising two subunits: the pore-forming Kir6.x (Kir6.1 or Kir6.2) and the regulatory sulfonylurea receptor SUR (SUR1 or SUR2) [2–4]. Different combinations of Kir6.1 or Kir6.2 and SUR1 or SUR2 variant (SUR2A or SUR2B) in cell lines constitute K_{ATP} channels with distinct electrophysiological and pharmacological properties that correspond to the various K_{ATP} channels in native tissues. Kir6.2 and SUR1 constitute the pancreatic ß-cell type K_{ATP} channel [5,6]; Kir6.2 and SUR2A constitute the cardiac type K_{ATP} channel [7]. Kir6.1 and SUR2B constitute the vascular smooth muscle type K_{ATP} channel, which is activated by nucleoside diphosphates (NDPs) and inhibited by glibenclamide [8]. Electrophysiological and biochemical experiments with these reconstituted K_{ATP} channels revealed various features of the channels, including the regulation of channel gating by nucleotides, drugs, and intracellular signals, the stoichiometry and membrane topology of the channels, and the membrane sorting of the channels [2–4,9]. Various physiological and pathophysiological roles of K_{ATP} channels were implied in pharmacological experiments using K_{ATP} channel blockers and K^+ channel openers (KCOs). However, such pharmacological approaches have been limited because there are few channel blockers and openers specific for each type of K_{ATP} channel.

Genetically engineered animal models have now made more detailed clarification of the physiological and pathophysiological roles of K_{ATP} channels possible. Recently, several genetically engineered mice strains lacking K_{ATP} channels or with altered K_{ATP} channel function have been generated (Table 1). These include mice lacking various K_{ATP} channels (knockout mice) [10–14] and mice expressing various mutant K_{ATP} channels (transgenic mice) [15–18]. In this review, we focus on the role of the K_{ATP} channels as metabolic sensors learned in studies of transgenic mice expressing a dominant-negative K_{ATP} channel in pancreatic ß-cells and K_{ATP} channel knockout mice made by genetic disruption of the pore-forming subunit (Kir6.2 or Kir6.1) of the K_{ATP} channels.

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Table 1
K_{ATP} channel genetically modified mice

Knockout mice
Kir6.2$^{-/-}$ [10]
SUR1$^{-/-}$ [11,13]
SUR2$^{-/-}$ [12]
Kir6.1$^{-/-}$ [14]
Transgenic mice
(1) Dominant-negative Kir6.2 in pancreatic ß-cells
Kir6.2G132S (by insulin promoter) [15]
Kir6.2^{132}*A*^{133}*A*^{134}*A* (by insulin promoter) [16]
(2) Overactive Kir6.2 in pancreatic ß-cells
Kir6.2[*ΔN2-30*] (by αMHC promoter) [17]
(3) Overactive Kir6.2 in heart
Kir6.2[*ΔN2-30, K185N*] (by αMHC promoter) [17]
(4) Overexpression of SUR1 in forebrain (by CMK promoter) [18]

2. Roles of K_{ATP} channels learned from *Kir6.2*$^{-/-}$ mice

2.1. K_{ATP} channels in pancreatic ß-cells link glucose metabolism and electrical activity

Heterologous expression of Kir6.2 with SUR1 reconstitutes K_{ATP} channel currents with electrophysiological and pharmacological properties similar to those observed in native pancreatic ß-cells [5,6]. The K_{ATP} channel in the pancreatic ß-cell has been known to be critical in both glucose-stimulated and sulfonylurea-stimulated insulin secretion. The current model of glucose-stimulated insulin secretion is illustrated in Fig. 1 [19–21]. In this model, glucose is transported into pancreatic ß-cells through glucose transporter (GLUT) (GLUT2 in rodents and GLUT1 in human), the subsequent metabolism of glucose generating various metabolic signals including ATP. A rise in the intracellular ATP concentration closes the K_{ATP} channels, depolarizing the ß-cell membrane, which opens the voltage-dependent calcium channels (VDCCs), allowing calcium influx. The resultant rise in intracellular calcium concentration ($[Ca^{2+}]_i$) in the ß-cell triggers insulin secretion. Thus, the K_{ATP} channel links metabolic alterations to the electrical activity of the ß-cells. In addition, the K_{ATP} channel of the pancreatic ß-cell is the target of sulfonylureas such as glibenclamide and tolbutamide, widely used in

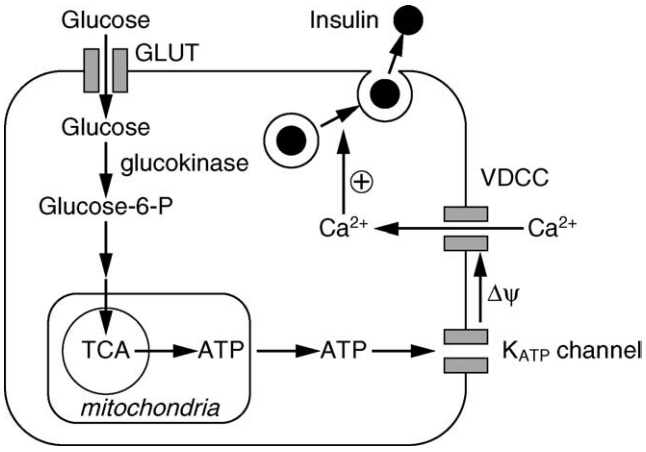

Fig. 1. Insulin secretion by glucose and sulfonylurea. See text for details.

treatment of type 2 (non-insulin dependent) diabetes mellitus (NIDDM), which stimulate insulin secretion by closing the K_{ATP} channels [22–24]. The potassium channel opener (KCO) diazoxide inhibits insulin secretion by opening the K_{ATP} channels [23–25].

On the other hand, glucose can potentiate insulin secretion in a K_{ATP} channel-independent manner [26–28]. In addition, Takasawa et al. [29] has suggested that cyclic ADP-ribose induces insulin secretion independently of the K_{ATP} channels. Thus, genetically engineered mice lacking K_{ATP} channel function is an ideal animal model to clarify the roles of K_{ATP} channels in glucose-stimulated insulin secretion.

2.1.1. K_{ATP} channels are essential for glucose responsiveness in pancreatic ß-cells

Electrophysiological analysis of the pancreatic ß-cells of *Kir6.2*$^{-/-}$ mice shows that K_{ATP} channel activity is completely absent in the pancreatic ß-cells of *Kir6.2*$^{-/-}$ mice, indicating that the Kir6.2 subunit is an essential component of the ß-cell K_{ATP} channel [10]. While *Kir6.2*$^{-/-}$ mice show transient hypoglycemia as neonates, serum insulin levels remain relatively high, indicating that regulation of insulin secretion by glucose is defective in *Kir6.2*$^{-/-}$ ß-cells. However, the hypoglycemia seen in *Kir6.2*$^{-/-}$ mice lasts only for a week, and the blood glucose levels of *Kir6.2*$^{-/-}$ mice as adults in the fed state were not significantly different from those of wild-type mice. The ß-cell membrane was hyperpolarized under the resting condition in the presence of low glucose (2.8 mM), and repetitive bursts of action potential were seen in *Kir6.2*$^{-/-}$ ß-cells. Importantly, there was no change in the membrane potential of *Kir6.2*$^{-/-}$ ß-cells in response to high glucose (16.7 mM), indicating that the Kir6.2-containing K_{ATP} channel is essential for electrical excitability of the ß-cell by glucose. Basal intracellular calcium levels ($[Ca^{2+}]_i$) in the ß-cell also were significantly elevated in *Kir6.2*$^{-/-}$ ß-cells, and neither high glucose (16.7 mM) nor tolbutamide (100 μM) elicited further change in $[Ca^{2+}]_i$ in *Kir6.2*$^{-/-}$ ß-cells. Oral glucose tolerance test revealed the insulin secretory response to glucose to be severely impaired in *Kir6.2*$^{-/-}$ mice. In addition, batch incubation and perfusion experiments using pancreatic islets has shown that neither 16.7 mM glucose nor 100 μM tolbutamide elicits significant insulin secretion in *Kir6.2*$^{-/-}$ mice. The roles of Kir6.2 in pancreatic ß-cells also were examined in transgenic mice expressing a dominant-negative Kir6.2 (Kir6.2G132S) in pancreatic ß-cells (Kir6.2G132S Tg mice) [14]. Kir6.2G132S is mutated in the first residue of the Gly-Tyr-Gly motif with Ser (residue 132) in the putative K^+ ion permeable domain (H5), which is critical for K^+ ion selectivity [30]. The pancreatic ß-cells of Kir6.2G132S Tg mice have been shown to have impaired K_{ATP} channel activity, higher membrane potentials, and elevated $[Ca^{2+}]_i$, and Kir6.2G132S Tg mice have defective insulin secretion in response to glucose [14].

Thus, the Kir6.2-pore-forming subunit of the K_{ATP} channel in pancreatic ß-cells determines both membrane potential and basal $[Ca^{2+}]_i$, and is critical in the regulation of mem-