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Focused issue on K_{ATP} channels

Mitochondrial K_{ATP} channels in cell survival and death

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Abstract

Since the discovery of the mitochondrial ATP-sensitive potassium channel (mitoK_{ATP}) more than 13 years ago, it has been implicated in the processes of ischemic preconditioning (IPC), apoptosis and mitochondrial matrix swelling. Different approaches have been employed to characterize the pharmacological profile of the channel, and these studies strongly suggest that cellular protection well correlates with the opening of mitoK_{ATP}. However, there are many questions regarding mitoK_{ATP} that remain to be answered. These include the very existence of mitoK_{ATP} itself, its degree of importance in the process of IPC, its response to different pharmacological agents, and how its activation leads to the process of IPC and protection against cell death. Recent findings suggest that mitoK_{ATP} may be a complex of multiple mitochondrial proteins, including some which have been suggested to be components of the mitochondrial permeability transition pore. However, the identity of the pore-forming unit of the channel and the details of the interactions between these proteins remain unclear. In this review, we attempt to highlight the recent advances in the physiological role of mitoK_{ATP} and discuss the controversies and unanswered questions.

Keywords: Mitochondria; Potassium; Ischemic preconditioning; Diazoxide; Glibenclamide; Succinate dehydrogenase; Apoptosis; Reactive oxygen species

1. Introduction

Ischemic heart disease remains a major health problem in the world. Most of the research in this field has focused on finding ways to prevent ischemic injury by increasing blood supply to the myocardial area at risk. However, identification of an autoprotective mechanism known as ischemic preconditioning (IPC) has raised interest that endogenous pathways can be stimulated to protect the heart from ischemic injury [1]. IPC is a mechanism by which brief periods of ischemia produce protection against subsequent longer ischemic periods [1–3]. If specific cellular pathways or proteins can be targeted to stimulate the IPC protective process, the injury from an ischemic insult can be significantly attenuated. Thus, much effort over the past couple of decades has focused on identifying the underlying molecular basis of IPC. These studies have revealed multiple intracellular pathways to mediate IPC. These include the activation of protein kinase C, G-protein receptors, nitric oxide and generation of reactive oxygen species (ROS) [4–6]. The end-effector molecule(s) targeted by these pathways remain elusive.

Early studies suggested that adenosine triphosphate sensitive potassium channels (K_{ATP} channels) may be the common effector in IPC. Since opening of the surface K_{ATP} channels results in membrane hyperpolarization and shortens phase 3 of the cardiac action potential, the cardioprotective effects were initially attributed to surface K_{ATP} channels [7]. However, Yao and Gross [8] showed that a low dose of bimakalin, which did not shorten the action potential, had a similar cardioprotective effect as higher doses that enhanced action potential shortening. Similar lack of correlation between the extent of action potential shortening and the reduction of infarct size has also been shown with cromakalim and BMS-180448 [9,10]. Furthermore, Grover et al. [11] showed that prevention of action potential shortening by concomitant treatment of dofetilide did not reverse cardioprotective effects of cromakalim. These studies suggested that the opening of the surface KATP channel may not be necessary for the cardioprotection induced in IPC. An alternative mechanism involving the mitochondrial KATP channel (mitoK_{ATP}) subsequently emerged as the possible effector of IPC [12,13].

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Since early 1990s, K^+ selective transport has been widely observed in the mitochondria. A K^+ channel activity, with characteristics similar to those of surface K_{ATP} channel, was discovered in 1991 [14]. This mitoK_{ATP} channel is modulated by a variety of K^+ channel openers and inhibitors [13]. Furthermore, these modulators significantly influence mitochondrial function and cell survival, suggesting a link between mitoK_{ATP} and protection against ischemic injury. This protective effect of mitoK_{ATP} has been demonstrated in several tissues besides the heart, including liver, brain, kidney and gut [15–18].

2. Pharmacology of mitoK_{ATP}

Table 1 lists the known activators and inhibitors of mitoK_{ATP}. Several of these chemicals are not specific for mitoK_{ATP} and can also modulate the activity of the surface K_{ATP} channel. We will detail the studies on the role of these chemicals in mitoK_{ATP} activity throughout this review.

3. Evidence for the existence of mitoK_{ATP}

3.1. Studies on intact mitochondria

3.1.1. Patch-clamp of mitochondria

In 1991, Inoue et al. [14] identified the mitoK_{ATP} channel in single channel patch-clamp recordings of rat liver mitochondrial inner membrane. Although the technique used is challenging and subject to the criticism that the mitochondrial preparation may have been contaminated with surface proteins, this study remains a compelling argument for the existence of mitoK_{ATP}. These authors identified a single K^+ selective channel, which was inhibited by ATP with a K_i of ~0.8 mM when applied to the matrix face of the channel. The channel displayed a lower unitary conductance compared with the surface K_{ATP} channel (10 pS in 100 mM matrix K^+ and 33 mM cytosolic K^+). The channel was inhibited by the K^+ channel inhibitor 4-aminopyridine and a sulfonylurea, glibenclamide at 5 μM concentrations. Since the surface K_{ATP} channel is sensitive to glibenclamide, this observation was used as additional evidence that the measured conductance was due to a K_{ATP} channel. This original report remains one of the only studies thus far directly demonstrating the presence of a mitoK_{ATP} channel on intact mitochondrial inner membrane.

3.1.2. Measurement of mitochondrial volume

K^+ influx into the mitochondria, accompanied by the movement of water, leads to mitochondrial matrix swelling. The cation flux is tightly regulated to avoid rupture of the mitochondrial membranes. This is accomplished by movement of K^+ out of the matrix through the K^+/H^+ exchanger [19,20]. However, K^+ influx by mitoK_{ATP} can transiently exceed the counterbalancing activity of the K^+/H^+ exchanger, resulting in mitochondrial matrix swelling [21]. Garlid's group has used the extent of light scattering at 520 nm to assess the steady-state matrix volume [22]. These studies have supported the results obtained in other systems as far as the effect of different pharmacological agents on mitoK_{ATP}. There are limitations associated with this technique, including the use of supraphysiological ion gradients, nucleotide concentrations or metabolic substrates, hypo-osmotic conditions of the experiments to maintain linearity of the response, and the loss of normal cytoskeletal architecture [22,23]. Nevertheless, this approach is advantageous as compared to the reconstitution studies in that the mitochondrial channels and other proteins are intact, and that the pharmacological reagents can be applied directly to the mitochondria.

Table 1
Modulators of K_{ATP} channels and their selectivity toward mitochondrial and surface channels

	mitoK_{ATP}	mitoK_{ATP} and surface K_{ATP}	Surface K_{ATP}
Openers	Diazoxide	Cromakalim	P-1075[a]
	Nicorandil	Pinacidil	MCC-134[b]
	BMS 191095	P-1060	
		Sildenafil	
		Isoflurane	
		EMD60480	
		Aprikalim	
		EMD60480	
		Minoxidil Sulfate	
		KRN2391	
		Levosimendan	
Blockers	5-Hydroxydecanoate	Glibenclamide	HMR1098 (1833)
	MCC-134	Glipizide	Glimepiride[c]

Diazoxide and nicorandil can activate surface K_{ATP} channel at high concentrations [90,91]. 5-Hydroxydecanoate can inhibit surface K_{ATP} channel at low pH [92].

[a] P-1075 is selective for surface K_{ATP} channel in rabbit myocytes [29]. In isolated rat mitochondria, it activated mitoK_{ATP} [93].

[b] MCC-134 selectively activates surface K_{ATP} and inhibits mitoK_{ATP} [32].

[c] Glimepiride inhibits surface K_{ATP} without any effect on cardioprotection [94].