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Mitochondrial KATP Channels: The Facts and the Hypotheses

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Mini Review

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Abstract

The discovery of mitochondrial KATP channel (mKATP channel) in 1991 started extensive studies of its biophysical and biochemical properties, as well as cytoprotective mechanisms afforded by mKATP channels opening. However, molecular nature of mKATP channels remained undisclosed for three decades, and several hypotheses were proposed about their molecular composition. The discovery of molecular composition of mKATP channel in 2019 was an outstanding advance in mKATP channels research; nevertheless the issue of molecular nature of mKATP channel was not answered ultimately. Novel discoveries posed still more question about physiological relevance of mKATP channels and their role in the regulation of mitochondrial functions. So, how to explain apparent multiplicity of mKATP channels found in mitochondria?. And which is physiological relevance of these channels with similar biophysical properties?. The aim of this work was a brief overview of the current knowledge on mitochondrial KATP channels and their physiological functions.

Keywords: Mitochondria; KATP Channels; Kir6.1; Kir6.2; MitoK; Cytoprotection

Abbreviations: mKATP channel: mitochondrial ATP-sensitive K channel; sKATP channel: Plasma Membrane KATP Channel; mPTP: Permeability Transition Pore; GSK-3β: Glycogen Synthase Kinase 3β; PKC: Protein Kinase C; PKG: Protein Kinase G; NF-κB: Nuclear Factor Kappa B; PKB: Protein Kinase B; mTOR: Mammalian Target of Rapamycin; HIF-1α: Hypoxia Inducible Factor 1 Alpha; FOX01: Forkhead Factor 01; SUR: sulfonylurea receptor; IPC: Ischemic Precondition; ROMK: Renal Outer Medullary Potassium Channel; PKCε: Protein Kinase C Isoform ε.

Introduction

The discovery of mitochondrial KATP channel (mKATP) channel in 1991 started extensive studies of its biophysical and biochemical properties, as well as cytoprotective mechanisms afforded by mKATP channels opening. However, molecular nature of mKATP channels remained undisclosed for about three decades, which largely prevented the progress in the design of selective pharmacological modulators of mKATP channels. Several hypotheses were proposed about molecular entity of mKATP channels, which remained elusive for a long time. The discovery of molecular composition of mKATP channel in 2019 was a great step forward in mKATP channels research. However the issue of molecular entity of ATP-sensitive K^+ transport was not answered ultimately and novel discovery did not cancel out earlier findings of the expression of different K^+ conductant and receptor subunits of mKATP channels in mitochondria. However, it appeared that earlier knowledge was too simplified, and novel discoveries answered some old problems, but posed still more questions about physiological functions of mKATP channels.

So, how to explain the apparent multiplicity of mKATP channels, which expression was found in mitochondria? And which is physiological relevance of these channels with similar biophysical properties and similar sensitivity to physiological and pharmacological modulators? There we tried to address these issues based on the brief review of the current knowledge about mKATP channels composition, and physiological functions.

The Properties of mKATP Channels

Since the first discovery of mKATP channels, a basic similarity between molecular composition of mKATP and plasma membrane KATP channels (sKATP channels) was assumed by most researchers. Both sKATP and mKATP channels are octameric multiprotein complexes composed of four pairs of K^+ conductant and receptor subunits, as it was confirmed by novel finding [1,2]. Crucial point was the nature of K^+ conductant subunit. As for sKATP channels it is known that it is composed of K^+ conductant inward-rectifier potassium channels (Kir6.1 and Kir6.2) subunits and sulfonylurea (SUR) receptor subunits (SUR1, SUR2A and SUR2B), which are the receptors for co-called sulfonylureas: glibenclamide, tolbutamide and others. But which were K^+ conductant and receptor subunits of mKATP channels remained unclear, and this issue was not answered for decades. In spite of enigmatic molecular entity of mKATP channel, it's biophysical and biochemical properties were extensively studied. Basically, the properties of mKATP channel regarding the blocking and the opening by physiological and pharmacological modulators resembled the properties of sKATP channels.

As it was known of sKATP channel, it is blocked by ATP binding to Kir subunit, whereas Mg·ADP binding (or Mg·ATP binding and hydrolysis) to SUR enhances the channel activity [1,3]. As it was shown on isolated mitochondria, mKATP channel was blocked by ATP with high affinity (IC_{50}~ 1μM), and Mg^{2+} was required for the blocking of mKATP channel by ATP [4]. Similarly to sKATP channels, it was supposed that SUR subunit of mKATP channels possessed intrinsic Mg ATPase activity, and ATP binding and hydrolysis was required for the modulation of channel activity by KATP channels openers (diazoxide, pinacidil, nicorandil, and others). MKATP channel exhibited much higher affinity to diazoxide ($K_{1/2}$~3 μM) as compared to sKATP channels [5], but unlike sKATP channels, mKATP channel activation by diazoxide was independent of ATP/ADP ratio [6]. Also, unlike sKATP channels, mKATP channel is activated by GTP [6].

Glibenclamide directly blocks sKATP channels by the binding to SUR subunit [1,3]. This blocker specifically binds to mKATP channel as well ($K_{1/2}$~ 1-6 μM). MKATP channel blocking by glibenclamide required the presence of MgATP, i.e. the channel should be opened by diazoxide (or another opener) in the presence of MgATP, and after that blocked by glibenclamide (or 5-HD) [5,7].

Worth notion that the requirement for MgATP for the modulation of mKATP channel activity is rather disputable issue. Several data including our research [8,9] showed the activation of ATP-sensitive K^+ transport by diazoxide, pinacidil, cromakalim and the blockage by glibenclamide and 5-HD without MgATP [10,11]. Recently we obtained convincing evidence that MgATP was dispensable for the activation of ATP-sensitive K^+ transport in brain and liver mitochondria by diazoxide and pinacidil [9]. These controversies regarding basic mechanisms of the regulation of mKATP channel prove once more that molecular structure of mKATP channels, even those comprising Kir6.x subunits, is different of their sarcolemmal 'homologs', and the properties of ATP-sensitive K^+ transport in mitochondria differ of the properties of K^+ currents of plasma membrane. So, the present knowledge on the regulatory mechanisms of mKATP channels activity is too incomplete, but the disclosure of these mechanisms on molecular level is impossible without the disclosure of molecular composition of mKATP channel, which task still was not resolved definitely.

Molecular Composition of mKATP Channels

Thus far, several proteins or protein complexes were proposed to play the role of "mKATP"channel. The first and most common hypothesis of mKATP channel structure was based on the findings of the expression of Kir6.1, Kir6.2, SUR1, and SUR2 (A and B isoforms) in mitochondria of different cell types: heart (SUR1, SUR2A, Kir6.1, Kir6.2), pancreatic beta cells, liver (Kir6.1 and SUR1), and brain (SUR2B) [12-15]. However, even since early studies of 90th it was doubted whether the combinations of Kir6.x and SUR subunits found in mitochondria could constitute functionally active mKATP channels, and several facts contradicted this hypothesis [16]. Later, it was shown that Kir6.x subunit was not responsible for diazoxide-induced K^+ uptake and swelling of heart mitochondria, however, it was required for cardioprotection [17].

One early alternative hypothesis proposed that channel could be a multiprotein complex formed by four mitochondrial proteins: mitochondrial ATP-binding cassette protein 1 (mABC1), phosphate carrier, adenine nucleotide translocase, and ATP synthase associated with succinate dehydrogenase, SDH [18]. Worth mention the coupling of mKATP channel activity to SDH activity [19]. However, no confirmation was ever obtained of the involvement of such multiprotein complexes either in ischemic precondition (IPC) phenomenon, or other known cytoprotective effects of mKATP channels opening.

Interestingly, this early hypothesis was partially supported by the recent discovery of K^+ conductant properties of F_0F_1 ATP synthase [20]. In a series of works, the authors showed that F_0F_1 ATP synthase possesses properties of 'K^+ uniporter', from biophysical point close to the properties of mKATP channel sensitive to diazoxide and glibenclamide [20,21]. Further progress of this research will show physiological relevance of K^+ conductant properties of F_0F_1 ATP synthase and which cytoprotective effects are afforded by this K^+ channel apparently different of mKATP channels by molecular composition.

One more alternative hypothesis of past decade proposed Kir1.1 primarily known as renal outer medullary potassium channel (ROMK) to represent a pore-forming subunit of mKATP channel [22]. This hypothesis was supported by the finding of different ROMK isoforms expressed in heart, liver and brain mitochondria [22]. At functional level, ROMK presence in mitochondria was confirmed by the sensitivity of mitochondrial potassium transport to ROMK blocker, honeybee venom tertiapin Q [22,23]. Meanwhile, pharmacological properties of ROMK differed of those known of KATP channels, and by literary data [24], in heart mitochondria none of the ROMK isoforms (Kir1.1, 3.1, or 3.4) were responsible for diazoxide-evoked swelling and/or potassium uptake (routinely used to test mKATPchannel activity). Besides, low abundance of ROMK in mitochondria reported in the literature [25] questioned its ability to produce significant bioenergetic effects. Recent study as well did not confirm the participation of ROMK channel in IPC phenomenon [26], which definitely ruled out the hypothesis of ROMK as representative of K^+ conductant subunit of mKATP channel.

Recent discovery of mKATP channel in 2019 [2] based on combined proteomic, genetic, biophysical and biochemical approaches revealed molecular nature of mKATP channel and put an end to the speculations about the existence of mKATP channel. On a whole, an octameric structure of mKATP channel comprising four pairs of K^+ conductant and receptor subunits named mitoK and mitoSUR was confirmed. The channel exhibited biophysical and biochemical properties known of mKATP channels. Expression of mitoK was critical for the maintenance of mitochondrial functions and morphology; both mitoK ablation and overexpression resulted in mitochondrial dysfunction, inability to maintain $\Delta\Psi_m$ and ATP synthesis. Also, loss of mitoK resulted in the impairment of mitochondrial morphology [2]. Molecular mechanisms of mKATP channel interaction with pharmacological and physiological modulators were not disclosed yet. Also, in the literature there was little evidence on the physiological functions of mitoK, however, in recent works, the novel role of mitoK/mKATP channels in the regulation of mitochondrial functions and dynamics was found.

It worth mention, that in spite of this recent discovery, the studies of last decade both directly and indirectly confirmed the presence of Kir6.x/mKATP channels in mitochondria [17,27,28]. The reasonable question is why there are so many ATP-sensitive K^+ channels with similar properties, but different molecular composition in mitochondria? At present it is too difficult to discriminate specific pathways triggered by structurally different mKATP channels because of scarce data in the literature, but novel researches confirmed vital role of both Kir6.x/mKATP and mitoK/mKATP channels in maintenance of mitochondrial functions and dynamics.

Physiological Roles of mKATP Channels

As it is known, cytoprotective effects of mKATP channels opening are realized *via* the involvement of mKATP channels in complex cellular signaling network, primarily ROS-dependent signaling, where mKATP channels could play a role of 'ROS sensors' capable to accept and convey ROS signals [6,29,30]. The actual role of mKATP channels in ROS-dependent signaling was dependent on the direct effects of mKATP channels opening on ROS production, which showed great diversity in different experimental settings. An elevation of ROS production by mKATP channels opening [29,30] could trigger ROS-dependent activation of mitochondrial protein kinase C isoform ε (PKCε) with eventual targeting of glycogen synthase kinase-3β (GSK-3β) and mitochondrial permeability transition pore (mPTP), the giant channel implicated in launching apoptosis and other cell death pathways [31]. However, suppression of ROS production too was capable of direct suppression of the pathways related to inflammation, apoptosis and cell death. Thus, down-regulation of proinflammatory cytokines [32,33], suppression of NF-κB pathway, down-regulation/suppression of caspase-3 activity, and reduction of Bax/Bcl ratio too resulted from mKATP opening and the inhibition of ROS formation [32-34].

Not counting MgATP, protein kinases C and G (PKC and PKG) are most proximal physiological effectors of mKATP channels [29,35]. But which are molecular mediators of cytoprotective signaling to mKATP channels, and which molecular mechanisms underlie signal transduction from plasma membrane and cytosol to mKATP channel localized in the inner mitochondrial membrane? This question was not answered yet; in the literature, there was only sporadic knowledge on the proteins directly involved in cytoprotective effects afforded by mKATP channels opening. Interestingly, not only receptor SUR subunits, but K^+ conductant subunits as well take part in cellular signaling network. Literary data gave the evidence of certain specific interactions of K^+ conductant subunits of mKATP channels with a number of thus far disclosed proteins required to produce cytoprotective effects.

However, in the light of recent discoveries, there is uncertainty now, which pathways are triggered by different mKATP channels types. In spite of the identification of mitoK as K^+ conductant subunit of mKATP channel, recent studies confirmed the requirement of mitochondrial Kir6.1 and Kir6.2/mKATP channels for cardio- and neuroprotection [27,28,36,37]. So, the activation of Kir6.1/mKATP channel by the light therapy protected against neurodegeneration in the model of Alzheimer disease [37]. In the MPTP model of Parkinson disease Kir6.1/mKATP channel functioning was protective against neurodegeneration by promoting mitophagy [27]. In rotenone model of Parkinson disease Kir6.1/mKATP channel took part in the regulation of mitochondrial dynamics; however channel activation produced adverse effects blocked by mKATP channels blocker 5-hydroxydecanoate, 5-HD [38]. In the heart, Kir6.1 knockout aggravated cardiac dysfunction in diabetic cardiomyopathy, and Kir6.1 overexpression improved cardiac function, which confirmed essential role of Kir6.1 in cardioprotection [39].

Kir6.2 too was indispensable for the maintenance of mitochondrial functions in brain, and was required for neuro- and cardioprotection. So, Kir6.2 knockout promoted morphological impairments, inhibition of ATP synthesis, and behavior impairments in mice [28]. In cardiomyocytes, protective functions of Kir6.2/SUR2A-mKATP channel against anoxia/reoxygenation damage by triggering Akt/GSK-3β and Akt/mTOR signaling pathways were shown [36]. As it was shown in earlier research, mitochondrial localized Kir6.2 was indispensable for heart protection by IPC, however it did not took part in diazoxide-induced K^+ uptake and swelling of mitochondria [17].

As it was shown in the literature, cytoprotective effects of mKATP channels openers required an interaction of Kir6.1 and Kir6.2 subunits with other proteins and transcription factors. At present there are scarce data on such interactions network, however several studies have shown that cardioprotective effects of diazoxide required an interaction of mitochondrial Kir6.1 with connexin43 [40]. The requirement of connexin43 for cardioprotective effect of diazoxide was confirmed in a recent research [41]. Protection against hypoxic injury required an interaction of Kir6.2 with heat shock protein Hsp90 [42]. diazoxide and sevoflurane post-conditioning involved the activation of mKATP channels, which positively correlated with HIF-1α and HIF-related pathways [43,44]. On transcriptional level, inverse regulation of Fox01 gene and Kir6.1 subunit of mKATP channel was shown under diabetic cardiomyopathy [39]. Fox01 activation down-regulated the expression of Kir6.1 and decreased mitochondrial membrane potential ($\Delta\Psi_m$) in cardiomyocytes and *vice versa*, Fox01 inactivation up-regulated the expression of Kir6.1 and increased the $\Delta\Psi_m$ [39].

As of mitoK, there are too scarce data on its functions yet, however it was shown that the activation of mitoK by statins improved cardiac function in ischemia/reperfusion model by targeting GSK-3β and inhibition of mPTP [45], which effect was similar to known effects of mKATP channels openers. In brain it was shown that antidepressive effect of mKATP channels opener iptakalim was afforded by the involvement of mitoK in the improvement of synaptic plasticity [46]. Also, in recent research localization of CCDC51 gene which encodes mitoK in photoreceptors was shown, and Trp82Val mutation of this gene, which resulted in the loss of mitoK functions, was found in patient with a rare disease, Rod-Cone dystrophy of retina [47].

Thus, there was convincing data showing that both mitoK- and Kir6.x/mKATP channels were indispensable for the maintenance of mitochondrial functions as well as cardio- and neuroprotection. Based on literary findings, we could hypothesize the multiplicity of mKATP channels in mitochondria. But which could be the specificity of physiological functions of mitoK and Kir6.1, Kir6.2/mKATP channels? Unfortunately, present knowledge still is insufficient to answer these questions.

To address this issue and to explain physiological sense of the actual multiplicity of mKATP channels, we hypothesize that mKATP channels role could not be necessarily restricted to their K^+ conducting functions in order to trigger cellular cytoprotective events. This assumption could be a plausible explanation of the requirement of different types of mKATP channels for different biological processes in spite of their similar bioenergetics effects in mitochondria. Worth mention that Kir6.2 was required for cardioprotection by diazoxide, however it was dispensable for diazoxide-induced K^+ transport [17]. Thus, we assume that different mKATP channels could specifically interact with different proteins and transcription factors, and variety of cellular pathways and functions could specifically require different mKATP channels types. Also, different mKATP channels types could vary in molecular mechanisms of their interactions with pharmacological and physiological modulators.

As the molecular composition of mKATP channel is disclosed now, there is a possibility that the above issues could be resolved in the near future. This will help an adequate understanding physiological relevance of mKATP channels and the development of effective therapy based on selective modulation of different mKATP channels types, their functions and properties.

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