OPEN ACCESS

GAVIN PUBLISHERS

Current Research in Biopolymers

Akopova OV. Curr Res Biopolymers: CRBP-110.

Research Article

DOI: 10.29011/CRBP-110. 000010

How Many Properties has Mitochondrial KATP Channel?

Olga V. Akopova*

Department of Circulation, Bogomoletz Institute of Physiology, NAS of Ukraine, Kiev, Ukraine

***Corresponding author:** Olga V. Akopova, Circulation department, Bogomoletz Institute of Physiology, NAS of Ukraine, Bogomoletz str. 401601, Kiev, Ukraine. Tel; +380-442562496 Email: ov_akopova@ukr.net/ olga.akopova01@mail.ru

Citation: Akopova OV (2018) How Many Properties has Mitochondrial KAPT Channel?. Curr Res Biopolymers: CRBP-110. DOI: 10.29011/CRBP-110. 000010

Received Date: 11 December, 2018; **Accepted Date:** 26 December, 2018; **Published Date:** 31 December, 2018

Abstract

KATP channels are ubiquitously present in plasma membranes and mitochondria of mammals. While sKATP channels were exhaustively described in the literature, there is still lack of the data on molecular composition, properties and functions of mKATP channel. Moreover, there is no consensus on the mechanism of mKATP channel opening by KATP channels openers (such as diazoxide and pinacidil) and blocking by mKATP channels blockers (sulfonylureas and 5-hydroxydecanoate) possibly because of multiple off-target effects of pharmacological modulators of mKATP channel activity. This paper is a brief overview of some controversial issues in the current knowledge on the properties and functions of mKATP channels.

Keywords: ATP-Sensitive K^+ Transport; Cytoprotection; Diazoxide; Glibenclamide; KATP Channel; Mitochondria

Introduction

Mitochondrial KATP Channel (mKATP channel) is well acknowledged target for cardio- and neuro-protection under several metabolic stress conditions [1,2]. Pharmacological KATP channels openers were shown to be effective in the prevention of cell death caused by ischemic and hypoxic conditions and the action of cytotoxic agents [1-5]. However, one of the main limitations in the application of these drugs in clinics is their poor selectivity towards different isoforms of KATP channels and multiple off-target effects. However, the design of more selective pharmacological modulators of mKATP channels is largely prevented by still unknown molecular composition, poor knowledge of tissue-specific isoform distribution, and the lack of knowledge on the functions of these channels.

One obvious oddity in the present knowledge on mKATP channel is the controversy regarding the subunit composition and basic mKATP channel properties related to its interaction with physiological ligands (Mg^{2+}, ATP, GTP) and pharmacological modulators of the channel activity, openers (such as diazoxide and pinacidil) and blockers (glibenclamide and 5-hydroxydecanoate, 5-HD). This largely prevents the progress in the understanding of physiological functions of mKATP channels, the mechanisms of their involvement in cytoprotection, and the mechanisms underlying cytoprotective effects of physiological mKATP Channels Openers (KCOs) under pathophysiological conditions.

Despite multiple studies since the discovery of mKATP channel in 1991 [6], there is still plenty of gaps in the knowledge on the properties of mKATP channel, and the mechanisms of cytoprotection afforded by pharmacological mKATP channel openers. The contemporary data on the structure and functions of plasmalemmal and mitochondrial KATP channels are reviewed in detail in [7-11]. The aim of this work is a brief overview of some controversial issues in the present knowledge on mKATP channels.

Molecular Composition and Spatial Organization of mKATP Channels

Molecular composition of mKATP channel thus far remains undisclosed, and the knowledge on mKATP channel structure and functions for the most part was obtained from the studies of plasmalemmal KATP channels (sKATP channels). Most recent data on the structure, properties and functions of sKATP channels was reviewed in detail by Foster and Coetzee [9].

In brief, KATP channels are octameric macromolecular protein complexes composed of four pairs of potassium conductant Kir subunits (Kir6.x), which are inward rectifier K^+ channels, bound to receptor SUR subunits, which known isoforms are SUR1, SUR2A and SUR2B [7-9,12]. An assembly of Kir and SUR subunits is required for KATP channel opening by pharmacological openers (KCOs) and blockage by pharmacological blockers [9,12]. SUR

subunits of sKATP channels comprise 17 transmembrane segments assembled in three transmembrane domains (TMD0 (segments 1-5), TMD1 (segments 6-11) and TMD2 (segments 12-17)) [8,9] schematically shown on the (Figure 1). SUR subunit, which is the receptor for sulfonylureas (glibenclamide, tolbutamide), binds pharmacological KATP channels openers (pinacidil, nicorandil, chromakalim, diazoxide) and the blockers, whereas ATP blocks both sKATP and mKATP channels directly binding to K^+ conductant Kir subunits [9,13]. In sKATP channels ATP binding site is localized on the cytosolic side of plasma membrane [9]. Convincing evidence was obtained that mKATP channel too is blocked by ATP from the cytosolic side of mitochondrial membrane [14].

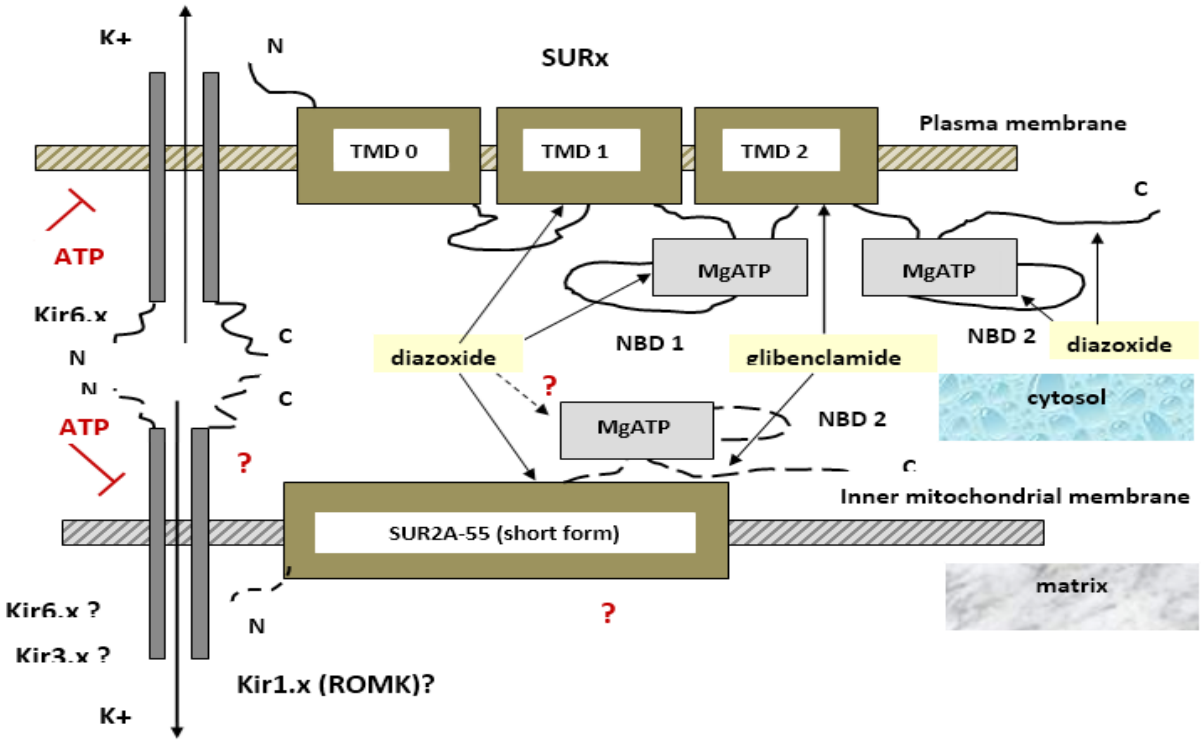

Figure 1: Schematic representation of molecular composition and the regulatory sites of KATP channels. sKATP channels are composed of four pairs of Kir6.x and SURx subumits forming an octameric multiprotein complex. SUR comprises 17 transmembrane segments assembled in 3 domains (TMD0 (segments 1-5), TMD1 (segments 6-11) and TMD2 (segments 12-17)). SUR binds KCOs and pharmacological blockers, whereas ATP blocks both sKATP and mKATP channels binding to Kir subunits [9, 13] from the cytosolic side of plasma membrane [8, 9] and mitochondria [14]. SUR1 has two sites for diazoxide binding; high affinity site is formed by TMD1 and NBD1. SUR2A binds diazoxide at the site formed by NBD2 and C-tail [16]. In mKATP channels, Kir6.x, Kir1.1 (ROMK), and Kir3.x were proposed as a pore-forming subunits, and splice variant of SUR2 (short form, SUR2A-55) was proposed as a receptor subunit. It is supposed that the regulatory sites of mKATP channel (binding ATP, KCOs and pharmacological blockers) face the cytosol [14, 19].

SUR belongs to so-called ATP-Binding Cassette (ABC) proteins and possesses intrinsic MgATPase activity. However, different of other ATP-binding proteins, MgATPase activity of SURs is not coupled to the transport properties [12]. Two Nucleotide Binding Domains (NBD) of SUR form an ATP-binding pocket comprising one lysine and one aspartate residues critical for the binding and hydrolysis of ATP. MgATPase activity was shown to be required for the binding of pharmacological ligands. While ATP blocks the channel by binding to Kir subunit, SUR subunit plays a regulatory role in ATP binding. Coexpression of Kir and SUR subunits enhances the potency of ATP block several folds [15].

KATP channels differ in their tissue-specific isoform distribution and the sensitivity to pharmacological ligands. Binding sites for diazoxide (most studied of pharmacological KCOs) are different in SUR1 and SUR2 subunits, which also differ in their affinity to this drug [9]. It was shown that high affinity site for diazoxide binding in SUR1 is formed by TMD1 domain and NBD1 fragment [7-9]. In SUR2, less sensitive to diazoxide, binding site is composed of amino acids of C-terminus and NBD2. The activation of SUR2A-containing channels required the presence of ADP, while the activation of channels formed by SUR1 and SUR2B did not [16]. The binding of pharmacological openers

of KATP channels needs a conformational change induced by ATP hydrolysis in NBD domains, and C-terminus of SUR affects KCOs affinity [15,17]. Requirement for ATP was shown for KCOs binding to SUR1, SUR2A and SUR2B. Diazoxide, similar to other KCOs, requires intrinsic MgATPase activity to elicit full stimulatory response [15,17].

Sulfonylureas binding pocket comprises multiple sites, and for glibenclamide binding high affinity sites within TMD2 domain and cytosolic loop between TMD0 and TMD1 regions were identified. However, full channel blockage by glibenclamide requires the interaction of four binding sites of the octameric protein complex of sKATP channel [9].

Much less is known on spatial organization and subunit composition of mKATP channel. Kir6.x, Kir1.1 (ROMK), and Kir3.x were proposed as a candidate for a pore-forming K^+ conductant subunit of mKATP channel [8,9], and splice variant of SUR2 (short form, SUR2A-55) was proposed to compose a receptor subunit of mKATP channel [18]. SUR2A-55 lacks first transmembrane domain and has only second NBD fragment (NBD2). It exhibited biophysical properties of full KATP channel when coexpressed with Kir6.1 and Kir6.2, however showed less sensitivity to ATP, diazoxide and glibenclamide [18].

It is supposed that the regulatory sites of mKATP channel face the cytosol, and convincing evidence was obtained that ATP and other nucleotides binding sites in mKATP channel are localized on the cytosolic side of mitochondrial membrane [14]. mKATP channel activity is regulated by Mg^{2+}, which blocks the channel with IC50 ~1mM from the matrix side [19]. Considering opposite direction of potassium transport via sKATP and mKATP channels, it is tempting to speculate that spatial organization of mKATP channel, accordingly, should "mirror" that of sKATP channel (Figure 1). However, thus far no reliable information on the topology of binding sites for pharmacological KCOs and the blockers of mKATP channels was obtained, and molecular composition of mKATP channel too remains unknown. Nevertheless, while the above notions on molecular organization of KATP channels were obtained for sKATP channels, this information was helpful for an understanding of the basic properties of mKATP channels. Molecular composition and the regulatory sites of KATP channels are schematically represented on the (Figure 1).

KATP channels are composed of four pairs of Kir6.x and SURx subumits forming an octameric multiprotein complex. SUR comprise 17 transmembrane segments assembled in 3 domains (TMD0 (segments 1-5), TMD1 (segments 6-11) and TMD2 (segments 12-17)). SUR binds KCOs and pharmacological blockers, whereas ATP blocks both sKATP and mKATP channels directly binding to Kir [9,13]. ATP binds from the cytosolic side of plasma membrane [8, 9] and mitochondria [14]. SUR1 has two sites for diazoxide binding; high affinity site is formed by TMD1 and NBD1. SUR2A binds diazoxide at the site formed by NBD2 and amino acids of C-tail; the activation of SUR2A-channels requires ADP [16]. In mKATP channels, Kir6.x, Kir1.1 (ROMK), and Kir3.x were proposed as a pore-forming subunit, and splice variant of SUR2 (short form, SUR2A-55) was proposed as a receptor subunit. It is supposed that the regulatory sites of mKATP channel (binding ATP, KCOs and pharmacological blockers) face the cytosol [14,19]. Thus far no reliable information on the topology of the regulatory sites of mKATP channels was obtained, and molecular composition of mKATP channel still remains unknown.

The Properties of mKATP Channels

This issue possibly is most controversial of what is known of mKATP channels. This regards mKATP channel interactions with physiological (Mg^{2+}, ATP, other nucleotides) and pharmacological ligands: the openers (diazoxide, pinacidil, nicorandil, cromacalim) and the blockers: glibenclamide (which is non-selective KATP channels blocker) and 5-hydroxydecanoate (specific blocker of mitochondrial KATP channel).

Inoue who discovered mKATP channel by patch-clamping giant mitoplasts obtained from liver mitochondria was first to describe mKATP channel properties [6]. Later data obtained by Garlid's and Szewczyk's groups who studied channel in native mitochondria, reconstituted in planar lipid bilayers and liposomes greatly contributed to this knowledge by studying the interactions of mKATP channels with physiological ligands (Mg^{2+}, ATP, GTP) and pharmacological agents. However, in most studies, including our own research, mKATP channel's activity was assessed using indirect methods aimed at the evaluation of K^+ uptake in isolated mitochondria. These indirect methods included light scattering and the study of K^+ uptake using fluorescent probes (PBFI) [20,21] and fluorescent Tl complex [22].

As it was shown, in isolated energized intact mitochondria mKATP channel is in its open state and exhibits K^+ conductant properties [20,23]. Channel conductance can vary from ~10 pS [6] to ~30-100 pS, which was explained by channel multimerization [13]. It is generally accepted that, similar to sKATP channels, the presence of Mg^{2+} and ATP which block an intact channel in native mitochondria is required for the opening and the blocking of mKATP channel by pharmacological agents. Also**,** it was stated that pharmacological ligands had no effect on mKATP channel activity in the absence of MgATP. The channel can be opened by KCOs only after the blocking of intact channel by MgATP, and pharmacological blockers are capable of blocking the channel only after its opening by KCOs in the presence of MgATP [20,23]. However, this issue still remains controversial. Worth notion that the properties of mKATP channel greatly differ, dependent on the preparations used to study mKATP channel activity.

mKATP Channel Blocking by ATP

From the work of Inoue, et al. [6] who was first to describe mKATP channel in liver mitoplasts, it became known that mKATP channel is reversibly blocked by ATP (IC50 ~ 0.8 mM) from the matrix side. Mg^{2+} was not required for the blocking of the channel by ATP. After half-inhibition by 1 mM ATP, the channel was inhibited by 5 mM of 4-aminopyridine (the non-selective blocker of Kv channels) and 5 μM glibenclamide [6].

Later in the works of Garlid's group, who studied mKATP channel reconstituted in planar lipid bilayers, liposomes and in isolated mitochondria, it was shown that channel properties were largely dependent on the channel preparations. Isolated Kir subunit (which was a 55-kDa protein obtained by ethanol extraction) showed biophysical characteristics similar to mKATP channel [13]. However, the channel properties in relation to ATP inhibition, activation and blockage by pharmacological agents greatly differed between the preparations studied. Thus, isolated Kir subunit was inhibited by ATP with low affinity ($K_{1/2}$ ~600 μM), and the inhibition did not require the presence of Mg^{2+} similar to mKATP channel from the work of Inoue [13]. Meanwhile, in proteoliposomes obtained from liver mitochondria, ATP inhibited mKATP channel in the presence of Mg^{2+} ($K_{1/2}$ ~22μM), and still much higher affinity for ATP inhibition was observed in intact mitochondria ($K_{1/2}$ ~1μM). An evidence was obtained that ATP- and nucleotides binding sites are localized on the cytosolic side of mitochondrial membrane, i.e. face the intermembrane space [14], Mg^{2+} was indispensable for the ATP inhibition of mKATP channel, independent of the preparation used [13]. Also, an absolute requirement for Mg^{2+} and ATP was shown for mKATP channel modulation by pharmacological ligands.

The Effects of Pharmacological Ligands on mKATP Channel Activity

As it was first shown in the works of Garlid's group, similar to the studies on ATP inhibition, mKATP channels in the intact mitochondria and the channels reconstituted in liposomes, greatly differed in their sensitivity to diazoxide and glibenclamide (most studied pharmacological ligands of KATP channels). In proteoliposomes [23] diazoxide opened mKATP channel in the presence of Mg^{2+} and ATP on sub-micromolar concentration level ($K_{1/2}$ ~0.37 μM). Meanwhile, in the intact mitochondria much higher diazoxide concentrations were required for mKATP channel opening ($K_{1/2}$ ~2.3 μM). As it was stressed in Garlid's works, independent on the preparations, there was an absolute requirement of Mg^{2+} and ATP for the opening of mKATP channel by diazoxide.

In proteoliposomes [20], glibenclamide was capable of blocking mKATP channel in the absence of ATP with high affinity ($K_{1/2}$ ~ 0.25 μM). The presence of ATP still increased the affinity of reconstituted channel to glibenclamide blockage ($K_{1/2}$ ~0.09 μM). However, similar to the opener diazoxide, neither glibenclamide, nor selective mKATP channel blocker 5-HD were capable of blocking mKATP channel in the intact mitochondria when its open state was induced by the absence of Mg^{2+} and ATP. The presence of MgATP was an absolute requirement for the blocking of mKATP channel in mitochondria, after its opening by pharmacological (diazoxide) or physiological (GTP) openers in the presence of MgATP [20]. In mitochondrial preparations, the channel affinity to glibenclamide blocking was by the order lower than in proteoliposomes ($K_{1/2}$~ 1-6 μM). This is compatible with the data on glibenclamide binding obtained by Szewczyk, et al. [19], which showed low affinity sites with K_d ~ 4 μM. Thus, Mg^{2+} and ATP were supposed to be indispensable for the blocking of mKATP channel in the intact mitochondria that was explained by the conformational changes making pharmacologically opened mKATP channel susceptible to the blocking by pharmacological blockers.

The data obtained in the works of Garlid's group [13,20,23] clearly demonstrated that in a measure of the channel "purification" starting from the preparations of intact isolated mitochondria, and ending with isolated K^+ conductant Kir subunit (mitoKir), the channels' properties were changed significantly: sensitivity of the channel to ATP inhibition dramatically decreased from ~ 1 μM (intact mitochondria) to ~600-800 μM (isolated mitoKir and, interestingly, the mitoplasts [6]), whereas "purified" channel was by the order more sensitive to pharmacological regulation by diazoxide and glibenclamide than intact one [23].

The experiments referred to clearly demonstrate the role for the membrane environment possibly decisive for the sensitivity of mKATP to ATP and pharmacological modulators. In the preparations used to study mKATP channels properties (isolated mitochondria, mitoplasts, proteoliposomes, isolated K^+ conductant subunit) the channel was more or less devoid of its native cellular membrane environment by purification procedures. Meanwhile, the interaction of native channel with other neighboring proteins in the mitochondrial membrane or the neighboring microenvironment in the cell possibly is needed for the functional activity of the channel and its involvement in the mechanisms of cytoprotection in a living organism. The data on such interactions at present are too scarce. Thus far, it was found that KATP-channels mediated hypoxic preconditioning was mediated by heat shock protein HSP90 shown to be associated with Kir6.2 [24]. HSP90 activity was linked to mitochondrial targeting of Kir6.2. Down-regulation or inhibition of HSP90 abolished the preconditioning effect similar to mKATP channel blocker 5-HD [24]. The number of such proteins possibly is much greater, and their impact on the channel conformation in the membrane and the ability to interact with physiological and pharmacological ligands needs future evaluation.

Direct and Off-Target Effects of Pharmacological Ligands of mKATP Channel

One questionable issue in the knowledge of mKATP channels properties remains the requirement for Mg^{2+} and ATP for mKATP channel interactions with pharmacological agents. Apart from the effect on mKATP channel activity, since the early works of Garlid's group, it was stated that the presence of MgATP complex was an absolute requirement for any effect of KCOs (diazoxide, pinacidil), or the blockers (glibenclamide, 5-HD) on mitochondrial K^+ transport and mitochondrial functions (respiration, matrix swelling, and Ca^{2+} uptake). However, literary data don't show consensus regarding this issue. The matter is highly complicated by the off-target effects of pharmacological modulators of mKATP channel activity.

Pharmacological modulators of mKATP channels (most studied are diazoxide, pinacidil, and glibenclamide) are known to produce several off-target effects [11]. Of the side effects of diazoxide most known are protonophoric properties of this drug [25] and the ability to inhibit succinate dehydrogenase [26]. Also, ability of diazoxide to inhibit oxidative phosphorylation by the binding to F_0F_1 ATP synthase was shown [27]. The ability of this drug to activate other than K_{ATP} potassium channels, BK_{Ca} and Kv channels, of plasma membrane of smooth muscle cells too was reported [28]. Pinacidil too possesses protonophoric properties at high micromolar concentrations (above ~50 μM), and is known to inhibit complex I [29]. Glibenclamide is known to inhibit succinate-driven respiration, thereby inhibiting K^+ and Na^+ fluxes in mitochondria respiring on succinate in the absence of MgATP, but this was observed only at high concentrations ($K_{1/2}$ ~20 μM) and ascribed to mitochondrial depolarization [19]. Also, glibenclamide was shown to interact with ATP/ADP antiporter [30], and, as we observed recently, inhibited oxidative phosphorylation in a way independent of mKATP channel blockage [31]. Other blocker of mKATP channel 5-HD was shown to be metabolized by acyl-CoA synthetase forming 5-hydroxydecanoyl-CoA, which in turn can inhibit β oxidation [29]. These off-target effects add uncertainty to the present knowledge on the mechanism of mKATP channel interactions with pharmacological ligands.

To avoid off-target effects of pharmacological modulators, it was proposed that relatively low concentrations (up to ~30 μM for diazoxide and pinacidil and ~5-10 μM of glibenclamide) can be considered as "safe" for mitochondria [20,23]. However, "safe" concentrations of the drugs did not prevent their effects on mitochondrial potassium transport observed in the absenceof MgATP.

Ability of KCOs (diazoxide, pinacidil, cromacalim) to increase, and of mKATP blockers (glibenclamide, 5-HD) to block potassium transport in the intact isolated mitochondria without MgATP was shown in several works including our own research [32,33]. Susceptibility of mitochondrial ATP-sensitive K^+ transport to the activation by KCOs without MgATP was observed in different tissues: heart [34,35], skeletal muscle [36], and liver [32]. Similarly, in the absence of MgATP glibenclamide and 5-HD partially blocked K^+ transport in skeletal muscle [36], liver [32], and brain, in a measure comparable with mKATP channel activity [33]. While in most works referred to above high micromolar concentrations of the drugs were used, in our works, on the contrary, effects of diazoxide were observed on nanomolar scale [32]. Glibenclamide in our works too was effective at concentrations assumed to be safe for mitochondria (~5-10 μM). As we have shown [33], blocking effect of glibenclamide and 5-HD in native brain mitochondria was comparable to the estimates of mKATP channel activity in mitochondrial preparations [21,33]. Ubiquity of these phenomena is too obvious to consider it as an artifact, coincidence, or merely off-target effects. As we have shown earlier [37], diazoxide too was capable of activation of ATP-sensitive K^+ transport without MgATP. However, it is still unclear, whether described phenomena reflect the effects of the drugs on mKATP channel activity, and, if so, what molecular entity in mitochondrial membrane represents ATP-sensitive K^+ transport susceptible to the activation by KCOs and the blockage by mKATP channels blockers in the absence of MgATP?

While there is still lack of reliable data to resolve this problem, as a plausible explanation for such controversy in the basic properties of mKATP channel reported in the literature, we can propose that 1) either mKATP channel possesses certain not yet disclosed properties, which could explain its sensitivity to KCOs and the blockers in the absence of MgATP; or 2) mitochondrial membrane possesses certain not yet disclosed type or the population of ATP-sensitive K^+ channels exhibiting a sensitivity to pharmacological ligands of mKATP channel without MgATP. Several proteins or protein complexes were proposed to play the role of "mKATP" channel. These hypotheses are worth to be considered in brief.

How Many ATP-Sensitive K^+ Channels are Present in Mitochondria?

Thus far, different hypotheses were proposed on the molecular nature of mKATP channel and different proteins were proposed to play this role. 1) As a receptor SUR subunit, it was proposed that a splice variant of SUR2 (SUR2A-55) identified in heart and brain mitochondria can represent a regulatory subunit of mKATP channel [18]. SUR2A-55 lacks the first, but retains second nucleotide binding domain. Its multimerization is needed to exhibit biophysical properties of "full" KATP channel [18]. However, by pharmacological properties this channel was markedly different of mKATP channel, and was reported to be 70-fold less sensitive to ATP and relatively insensitive to diazoxide, pinacidil and glibenclamide [18].

2) As an alternative to K^+ conductant Kir6.x, K^+ conductant Kir1.1 (renal outer medullary potassium channel, ROMK) was proposed to represent pore-forming subunit of mKATP channel [38]. The expression of different ROMK isoforms was found in heart, liver and brain mitochondria [38]. Identity of ROMK with mKATP channel at functional level was argued by the sensitivity of mKATP channel to ROMK blocker honeybee venom tertiapin Q. Meanwhile, pharmacological properties of ROMK too differ of the properties of KATP channels.

Recent studies [22,39] raised still more doubts regarding molecular composition of mKATP channel and the mechanism of its response to diazoxide. As it was shown by Wojtowich, et al. [22], cardioprotection afforded by diazoxide required K^+ conductant Kir6.2 subunit, while it was dispensable for K^+ conductance stimulated by the same drug in mitochondria. In other study [39], it was shown that mitochondrial swelling induced by diazoxide involved none of Kir subunits belonging to ROMK channel (Kir1.1, Kir3.1, and Kir3.4,), which was proposed as putative K^+ conductant subunit of mKATP channel [38]. Thus, it remains uncertain, which Kir subunits compose mKATP channels, which interact with diazoxide and glibenclamide, and whether mKATP channel is composed of the assembly of SUR/Kir subunits. We suppose that data showing the ability of KCOs to elicit K^+ uptake in the absence of MgATP are compatible with the above findings that K^+ current elicited by these drugs does not require any of Kir subunits.

Thus, molecular entity of either Kir, or SUR subunits of mKATP channels, even in the best studied heart mitochondria, largely remains unknown. The studies are still more complicated because of the possible expression of several splice variants of KATP channel with different biophysical or pharmacological properties [40]. Of the properties of mKATP channel that distinguish it from sKATP channel the coupling of channel activity to the complex II (succinate dehydrogenase, SDH) should be mentioned [41]. In this context, it worth mention that one of the hypotheses on the molecular composition of mKATP channel proposed that channel is 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 SDH [42].

Conclusion

The summary of the present knowledge on ATP-sensitive K^+ transport allow us hypothesize the presence of different types of ATP-sensitive K^+ conductance and, possibly, different types (or populations) of ATP-sensitive K^+ channels simultaneously present in mitochondria. These different types of ATP-sensitive K^+ conductance can play a role of "mKATP channel" and respond to different pharmacological and physiological stimuli, in a way dependent on tissue type and pathophysiological conditions.

The presence of different types of ATP-sensitive K^+ channels is one of the plausible explanations for the controversy of the data on basic mKATP channels properties. If so, physiological relevance of what is supposed to be "mKATP channel" needs to be reevaluated. However, we suppose that "basic" protection afforded by bioenergetic effects of potassium transport (mild uncoupling, modulation of ROS production, Ca^{2+} transport and ATP synthesis) is not much dependent on the type of K^+ conductance present in mitochondria, and there is no doubt in physiological relevance of ATP-sensitive K^+ transport. Disclosure of the molecular composition of these channel(s), their properties and cell-specific distribution will help bring new insight in the understanding of physiological functions of ATP-sensitive K^+ channels in a living organism.

References

1. Garlid KD, Costa AD, Quinlan CL, Pierre SV, Dos Santos P (2009) Cardioprotective Signaling to mitochondria. J Mol Cell Cardiol 46: 858-866.

2. Correia SC, Cardoso S, Santos RX, Carvalho C, Santos MS, et al. (2011) New insights into the mechanisms of mitochondrial preconditioning-triggered neuroprotection. Curr Pharm Des 17: 3381-3389.

3. Daiber A (2010) Redox signaling (cross-talk) from and to mitochondria involves mitochondrial pores and reactive oxygen species. Biochimica et Biophysica Acta 1797: 897-906.

4. Liang W, Chen M, Zheng D, Li J, Song M, et al. (2017) The opening of ATP-sensitive K^+ channels protect H9c2 cardiac cells against the high glucose-induced injury and inflammation by inhibiting the ROS-TLR4-necroptosis pathway. Cell Physiol Biochem 41: 1020-1034.

5. Shukry M, Kamal T, Ali R, Farrag F, Almadaly E, et al. (2015) Pinacidil and levamisole prevent glutamate-induced death of hippocampal neuronal cells through reducing ROS production. Neurol Res 37: 916-923.

6. Inoue I, Nagase H, Kishi K, Higuti T (1991) ATP-sensitive K^+ channel in the mitochondrial inner membrane. Nature 352: 244-247.

7. Flagg TP, Enkvetchakul D, Koster JC, Nichols CG (2010) Muscle KATP channels: recent insights to energy sensing and myoprotection. Physiol Rev 90: 799-829.

8. Tinker A, Quadeer A, Thomas A (2014) The role of ATP-sensitive potassium channels in cellular function and protection in the cardiovascular system. Br J Pharmacol 171: 12-23.

9. Foster MN, Coetzee WA (2016) KATP Channels in the Cardiovascular System. Physiol Rev 96:177-252.

10. Laskowski M, Augustynek B, Kulawiak B, Koprowski P, Bednarczyk P, Jarmuszkiewicz W, et al. (2016) What do we know about mitochondrial potassium channels? Biochim Biophys Acta 1857: 1247-1257.

11. Szewczyk A, Kajma A, Malinska D, Wrzosek A, Bednarczyk P, et al. (2010) Pharmacology of mitochondrial potassium channels: dark side of the field. FEBS Lett 584: 2063-2069.

12. Moreau C, Prost AL, Derand R, Vivaudou M (2005) SUR, ABC proteins targeted by KATP channel openers. J Mol Cell Cardiol 38: 951-963.

13. Mironova GD, Negoda AE, Marinov BS, Paucek P, Costa ADT, et al. (2004) Functional distinctions between the mitochondrial ATP-dependent K^+ Channel ($mitoK_{ATP}$) and its inward rectifier subunit (mitoKIR). J. Biol. Chem 279: 32562-32568.

14. Yarov-Yarovoy V, Paucek P, Jaburek M, Garlid KD (1997) The nucleotide regulatory sites on the mitochondrial KATP channel face the cytosol. Biochim Biophys Acta 1321: 128-136.

15. Schwanstecher M, Sieverding C, Dorschener H, Gross I, Aguilar-Bryan L, et al. (1998) Potassium channel openers require ATP to bind to and act through sulfonylurea receptors. EMBO J 17: 5529-5535.

16. D'hahan N, Moreau C, Prost AL, Jacquet H, Alekseev AE, et al. (1999) Pharmacological plasticity of cardiac ATP-sensitive potassium channels toward diazoxide revealed by ADP. Proc Natl Acad Sci USA 96: 12162-12167.

17. Matsuoka T, Matsushita K, Katayama Y, Fuhita A, Inageda K, et al. (2000) C-terminal tails of sulfonylurea receptors control ADP-induced activation and diazoxide modulation of ATP-sensitive K (+) channels. Circ Res 87: 873-880.

18. Aggarwal NT, Shi NQ, Makielski JC (2013) ATP-sensitive potassium currents from channels formed by Kir6 and a modified cardiac mitochondrial SUR2 variant. CChannels (Austin) 7: 493-502.

19. Szewczyk A, Pikula S, Wójcik G, Nałecz MJ (1996) Glibenclamide inhibits mitochondrial K^+ and Na+ uniports induced by magnesium depletion. Int J Biochem Cell Biol 28: 863-871.

20. Jaburek M, Yarov-Yarovoy V, Paucek P, Garlid KD (1998) State-dependent inhibition of the mitochondrial K_{ATP} channel by glyburide and 5-hydroxydecanoate. J Biol Chem 273: 13578-13582

21. Bajgar R, Seetharaman S, Kowaltowski AJ, Garlid KD, Paucek P (2001) Identification and properties of a novel intracellular (mitochondrial) ATP-sensitive potassium channel in brain. J Biol Chem 276: 33369-33374.

22. Wojtovich AP, Urciuoli WR, Chatterjee S, Fisher AB, Nehrke K, et al, (2013) Kir6.2 is not the mitochondrial KATP channel but is required for cardioprotection by ischemic preconditioning. Am J Physiol 304: 1439-1445.

23. Garlid KD, Paucek P, Yarov-Yarovoy V, Sun X, Schindler PA (1996) The mitochondrial KATP channel as a receptor for potassium channel openers. J Biol Chem 271: 8796-8799.

24. Jiao JD, Garg V, Yang B, Hu K (2008) Novel functional role of heat shock protein 90 in ATP-sensitive K^+ channel-mediated hypoxic preconditioning. Cardiovasc Res 77: 126-33.

25. Kowaltowski AJ, Seetharaman S, Paucek P, Garlid KD (2001) Bioenergetic consequences of opening ATP-sensitive K^+-channel of heart mitochondria. Am J Physiol 280: H649-H657.

26. Dröse S, Brandt U, Hanley PJ (2006) K^+-independent actions of diazoxide question the role of inner membrane KATP channels in mitochondrial cytoprotective signaling. J Biol Chem 281: 23733-23739.

27. Comelli M, Metelli G, Mavelli I (2007) Downmodulation of mitochondrial F_0F_1 ATP synthase by diazoxide in cardiac myoblasts: a dual effect of the drug. Am J Physiol 292: H820-H829.

28. Adebiyi A, McNally EM, Jaggar JH (2008) Sulfonylurea receptor-dependent and -independent pathways mediate vasodilation induced by ATP-sensitive K^+ channel openers. Mol Pharmacol 74: 736-743.

29. Hanley PJ, Mickel M, Löffler M, Brandt U, Daut J (2002) K(ATP) channel-independent targets of diazoxide and 5-hydroxydecanoate in the heart. J Physiol 542: 735-41.

30. Ziemys A, Toleikis A, Kopustinskiene DM (2006) Molecular modelling of K(ATP) channel blockers-ADP/ATP carrier interactions. Syst Biol (Stevenage) 53: 390-393.

31. Akopova OV. (2018) On the adverse effects of glibenclamide administration. Open Acc J of Toxicol 3: 555-618.

32. Akopova OV, Nosar VI, Bouryi VA, Mankovska IN, Sagach VF (2010) Influence of ATP-dependent K^+-channel opener on K^+-cycle and oxygen consumption in rat liver mitochondria. Biochemistry (Moscow) 75: 1139-1147

33. Akopova OV, Kolchinskaya LI, Nosar VI, Bouryi VA, Mankovska IN, et al. (2014) Effect of potential-dependent potassium uptake on production of reactive oxygen species in rat brain mitochondria. Biochemistry (Mosc) 79: 44-53.

34. Holmuhamedov EL, Jovanović S, Dzeja PP, Jovanović A, Terzic A (1998) Mitochondrial ATP-sensitive K^+ channels modulate cardiac mitochondrial function. Am J Physiol 275: H1567-H1576.

35. Riess ML, Camara AK, Heinen A, Eells JT, Henry MM, Stowe DF (2008) KATP channel openers have opposite effects on mitochondrial respiration under different energetic conditions. J Cardiovasc Pharmacol 51: 483-491.

36. Kopustinskiene DM, Liobikas J, Skemiene K, Malinauskas F, Toleikis J (2010) Direct effects of KATP channel openers pinacidil and diazoxide on oxidative phosphorylation of mitochondria in situ. Cell Physiol Biochem 25: 181-186

37. Akopova OV, Nosar VI, Bouryi VA, Kolchinskaya LI, Mankovska IN, et al. (2013) The effect of ATP-dependent $K^{(+)}$-channel opener on the functional state and the opening of cyclosporine-sensitive pore in rat liver mitochondria]. Ukr Biochem J 85: 38-51.

38. Foster DB, Ho AS, Rucker J, Garlid AO, Chen L et al. (2012) Mitochondrial ROMK channel is a molecular component of mitoK(ATP). Circ Res 111: 446-54.

39. Henn MC, Janjua MB, Kanter EM, Makepeace CM, Schuessler RB, et al. (2015) Adenosine triphosphate-sensitive potassium channel Kir subunits implicated in cardioprotection by diazoxide. J Am Heart Assoc 4: e002016.

40. Chan KW, Wheeler A, Csanády L (2008) Sulfonylurea receptors type 1 and 2A randomly assemble to form heteromeric KATP channels of mixed subunit composition. J Gen Physiol 131: 43-58.

41. Wojtovich AP, Brookes PS (2008) The endogenous mitochondrial complex II inhibitor malonate regulates mitochondrial ATP-sensitive potassium channels: implications for ischemic preconditioning. Biochim Biophys Acta 1777: 882-889.

42. Ardehali H, Chen Z, Ko Y, Mejía-Alvarez R, Marbán E (2004) Multiprotein complex containing succinate dehydrogenase confers mitochondrial atp-sensitive K^+ channel activity. Proc Natl Acad Sci 101: 11880-11885.