Mitochondrial potassium channels – an overview

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Abbreviation: ChTx – charybdotoxin; IbTx – iberiotoxin; IMM – inner mitochondrial membrane; Kv – voltage-gated potassium channels; MgTx – margatoxin; mitoBK$_{Ca}$ – mitochondrial large-conductance K$_{Ca}$ channel; mitoIK$_{Ca}$ – mitochondrial intermediate-conductance K$_{Ca}$ channel; mitoK$_{ATP}$ – mitochondrial ATP dependent potassium channels; mitoSK$_{Ca}$ – mitochondrial small-conductance K$_{Ca}$ channel; OMM – outer mitochondrial membrane, PAX – paxilline; ROMK2 – renal outer medullary K$^+$ channel (Kir1.1b); TASK-3 – TWIK-related acid-sensitive K$^+$ channel 3; TPNQ – tertiapin Q

ABSTRACT

Mitochondria play a fundamental role in ATP synthesis within the majority of mammalian cells. Potassium channels present in the inner mitochondrial membrane are fine regulators of mitochondrial function, based on inner membrane K$^+$ permeability. These channels are regulated by a plethora of factors and conditions in a way similar to plasma membrane potassium channels. Regulators of mitochondrial potassium channels include the membrane potential, calcium ions, free fatty acids and ATP levels within the cells. Recently, it was shown that these channels are regulated by the respiratory chain, stretching of the membrane and phosphorylation. The essential interest that has driven studies of mitochondrial potassium channels for nearly 25 years is their role in cytoprotection and in cell death. Mitochondrial potassium channels have been described in neurons, astrocytoma, cardiac and skeletal muscles, fibroblasts, keratinocytes and endothelial cells. In this overview, we summarize the current knowledge of mitochondrial potassium channels. This summary will be done with a special focus on studies performed over the last 20 years in the Laboratory of Intracellular Ion Channels at the Nencki Institute. These include studies on the electrophysiological and pharmacological properties of mitochondrial potassium channels and on their regulation by endogenous intracellular substances. Additionally, the regulation of mitochondrial potassium channels by the respiratory chain and by stretching of the inner mitochondrial membrane will be reviewed. Properties of mitochondrial potassium channels in various organisms will also be summarized.

INTRODUCTION

Mitochondria play a fundamental role in ATP synthesis within the majority of mammalian cells, particularly where there is a high density of these organelles in a tissue, such as cardiac muscle or brain. This canonical function of mitochondria is accompanied by their high metabolic activity and signaling role, for example by reactive oxygen species (ROS). Mitochondria are the only cellular organelles with a very high membrane potential difference (~ 200 mV). This is due to respiratory chain activity and results in the negative polarization of the mitochondrial interior (matrix). This property has a fundamental impact on the role of ion permeability through the inner mitochondrial membrane on mitochondrial function. In other words, the function of mitochondria within the cells is very often based on ion permeability through the mitochondrial membranes. Hence, transport of ions, especially through the inner mitochondrial membrane, is strictly controlled.

Potassium channels present in the inner mitochondrial membrane are good candidates for fine regulators of mitochondrial function based on inner membrane permeability [1]. First, the density of these channels is relatively low in the inner mitochondrial membrane. We roughly estimate only a few copies of the channel protein per "idealized" mitochondrion. Hence, even full opening of the channels should not cause a dramatic influx of K$^+$ into the mitochondrial matrix causing harmful mitochondrial swelling and membrane depolarization.

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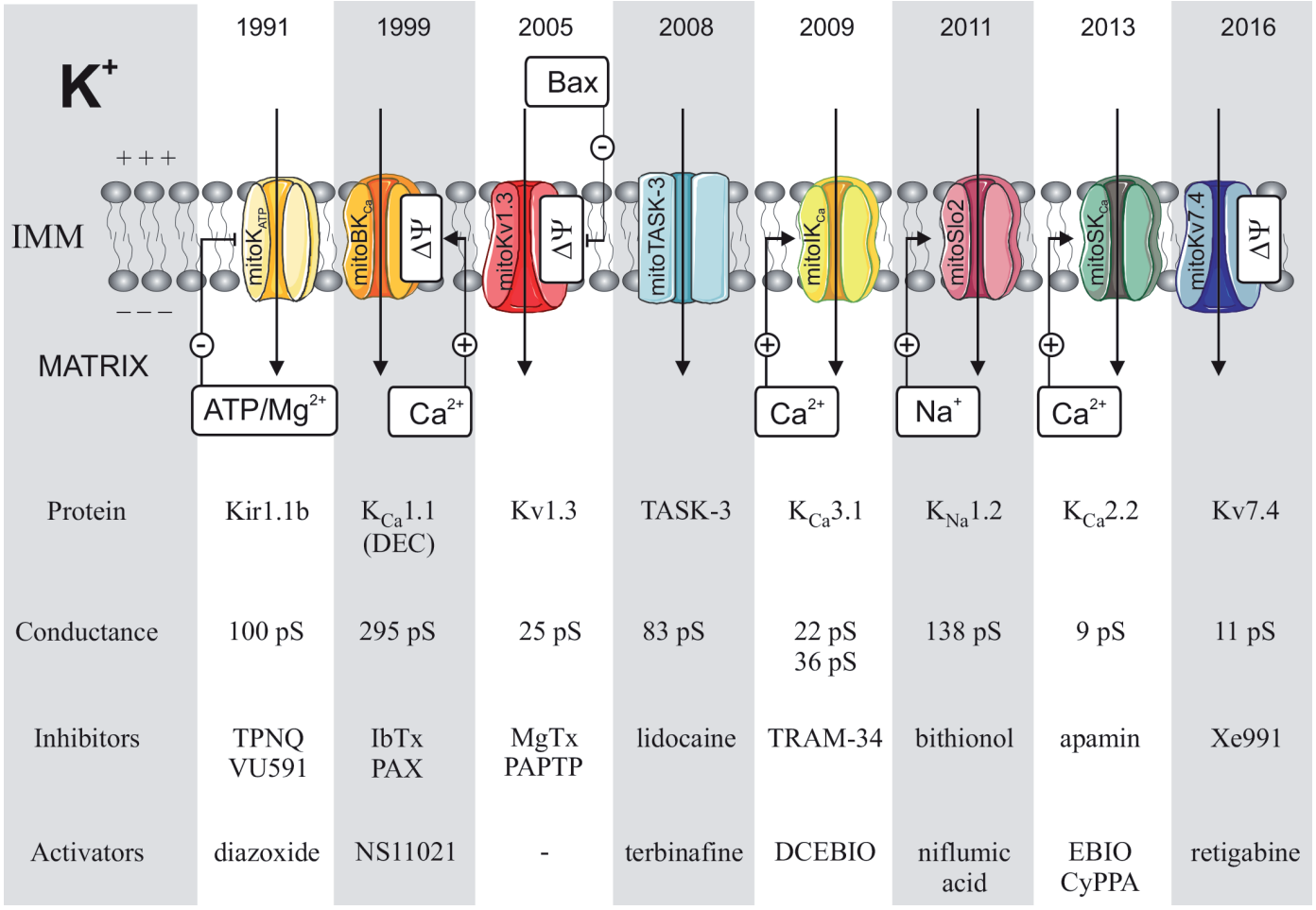


Figure 1. Timeline of discovery and basic properties of mitochondrial potassium channels. Single channel conductance data were derived from patch-clamp experiments on mitoplast for: mitoKv1.3 [1]; mitoTASK-3 [2]; mitoIK$_{Ca}$ [3]; mitoSlo2 [4] or for plasmalemmal channels for K$_{Ca}$2.2 [5] and Kv7.4 [6]; the single channel activity of mitoK$_{ATP}$ was recorded (modified from [98]).

Second, mitochondrial potassium channels are regulated by a plethora of factors and conditions in a way similar to plasma membrane potassium channels. Regulators of mitochondrial potassium channels include the membrane potential, calcium ions, free fatty acids and ATP levels within the cells. Recently, it was shown that channel protein phosphorylation also may regulate mitochondrial potassium channel activity. All these properties are crucial for the strict regulation of K^+ fluxes via the inner mitochondrial membrane.

The essential interest that has been driven studies on mitochondrial potassium channels for nearly 25 years is their role in cytoprotection and cell death. The ubiquitous presence of mitochondria (and hence mitochondrial potassium channels) offers a unique possibility to use them as therapeutic targets in various tissues. Mitochondrial potassium channels have been described in neurons, astrocytoma, cardiac and skeletal muscles, fibroblasts, keratinocytes and endothelial cells.

In this overview, we summarize the current knowledge of mitochondrial potassium channels (Fig. 1). This will be done with a special focus on studies performed over the last 20 years in the Laboratory of Intracellular Ion Channels at the Nencki Institute. These include studies on the electrophysiological and pharmacological properties of mitochondrial potassium channels and on their regulation by endogenous intracellular substances. Additionally, regulation of mitochondrial potassium channels by the respiratory chain and stretching of the inner mitochondrial membrane will be reviewed. Properties of mitochondrial potassium channels in various organisms will also be summarized.

DIVERSITY OF POTASSIUM CHANNELS IN INNER MITOCHONDRIAL MEMBRANES

CLASSIFICATION OF MITOCHONDRIAL POTASSIUM CHANNELS

It is believed that the ancestry of K^+ channels might be traced back to the prokaryotes [2,3] and the complex K^+ channels in animals and plants evolved from a simple bacterial channel [4]. This channel looked similar to the pore module of modern K^+ channels, which is composed of two transmembrane (2-TM) domains connected by a pore helix containing the canonical filter sequence of K^+ channels, TVGYG, and assembles into a functional tetramer with a central pore, which is the conduction pathway for the potassium ions [5]. This 2-TM pore module exists in all K^+ channels, and more complex K^+ channels also contain it as a core structure [4]. The abundance of K^+ channels that exists in

organisms today results from major genetic events, such as gene fusions and duplications.

The 2-TM pore module, as the only transmembrane unit, can be found today in the bacterial channel KcsA [6] and in eukaryotic inward rectifying channels (Kir). Duplication and fusion of the 2-TM pore module led to the two-pore-domain potassium channels (K2P) (4-TM topology), which form functional dimers [7].

In the largest group of potassium channels, voltage-gated potassium channels or Kv channels, the 2-TM pore module is fused to a voltage-sensing domain (VSD). The VSD was shown to exist as a voltage sensor in proteins not related to potassium channels, voltage-gated phosphatases [8] and voltage-gated proton channels [9]. The VSD has four TMs (called S1 to S4), and the S4 sequence is highly unusual, with lysine or arginine present in every third or fourth position in an otherwise hydrophobic stretch [10]. As a consequence, the voltage-gated potassium channels have a 6-TM topology, with the first four TMs belonging to the VSD. 6-TM channels form functional tetramers.

In the subfamily of Ca^{2+}- or Na^{+}-regulated K^{+} channels, which are topologically similar to Kv channels, there is an extra transmembrane segment near the amino terminus (7-TM topology), but functionally more important is the presence of two "regulator of K^{+} conductance" (RCK) domains at the C-terminus, which regulate channel activity by binding Ca^{2+} or Na^{+} ions [11,12].

In summary, potassium channels can be subdivided into families (in accordance with the NC-IUPHAR subcommittees on potassium channels [13]), based on their structure into: i) inwardly rectifying potassium channels (Kir channels, 2-TM); ii) two P-domain potassium channels (K2P channels, 4-TM); iii) voltage-gated potassium channels (Kv channels, 6-TM); and iv) calcium- and sodium-activated potassium channels (K_{Ca}/K_{Na} channels, 7-TM).

Surprisingly, mitochondria from various organisms and tissues seem to be equipped with channels from all these families.

Kir channels, which underlie mitoK_{ATP} activity, were the first channels postulated to be present in the inner mitochondrial membrane, but only a few years ago it was convincingly shown that the renal outer medullary K^{+} channel ROMK2 (Kir1.1b) could be the channel-forming subunit of mitochondrial ATP-dependent potassium channels (mitoK_{ATP}) [14].

K2P channels produce so-called background conductance and are responsible for the maintenance of the interior negative membrane potential of all cells. They are regulated by a variety of stimuli, including changes in membrane voltage, tension, temperature, extracellular and intracellular pH, phospholipids, and other signaling molecules. Up to now, only one member of this family, TWIK-Related Acid-Sensitive K^{+} Channel 3 (TASK-3), has been shown to reside in mitochondria [15-19].

The presence of Kv channels in mitochondria is well documented for Kv1.3 [20-24], but the presence of Kv7.4 was recently reported [25].

All known types of K_{Ca} channels have been found in the inner mitochondrial membrane, including K_{Ca}1.1 or large-conductance K_{Ca} channel (BK_{Ca}), the activity of which was observed in mitoplasts from a number of organisms and tissues [26-31]; K_{Ca}3.1 or intermediate-conductance K_{Ca} channel (IK_{Ca}) [32-34]; and the small-conductance K_{Ca} channel (SK_{Ca}) [35,36].

K_{Na} channels activated by sodium ions [37] were also recently reported to be present in mitochondria [38].

TISSUE SUBTYPE SPECIFICITY OF POTASSIUM CHANNELS IN MITOCHONDRIAL MEMBRANES

The knowledge about the tissue distribution of particular mitochondrial ion channels is very fragmentary, as it requires not only data on the expression of the gene encoding for the particular channel but also the investigation of the subcellular distribution of the gene product and the correlation of this information with channel activities observed in patch-clamp experiments. All this is difficult, especially taking into account the low level of expression and existence of different splice variants, which mechanism of import into mitochondria is not understood. Basically, all mitochondrial potassium channels identified thus far are counterparts of well-known plasma membrane channels, and many of them display multiple subcellular localizations. The vital question is whether the same channel isoform is sorted into different compartments within the cells or specific sequences are responsible for its localizations.

The activity the mitoK_{ATP} channel is widely distributed among tissues. It has been described in the mitochondria of liver [39], fibroblasts [40], lymphocytes [41], heart [42], brain [43,44], skeletal muscle [45], smooth muscle [46], and kidney [47]. However, the molecular identity of mitoK_{ATP} is still unclear. One of the proteins proposed for this function was Kir6.1 or 6.2, which interact with Sur2A or 2B to form octamer complexes. However, there is a controversy over the presence of these proteins in mitochondria (see [48] for review). Alternatively, as mentioned above, a splice variant of Kir1.1, the renal outer medullary K^{+} channel ROMK2 (Kir1.1b), could be the channel-forming subunit of mitoK_{ATP} [14]. The ROMK channel initially was reported to be expressed in kidney [49,50]; however, it was found in other tissues including glial-like cells in mouse taste buds [51], parietal cells [52], liver [53], epithelia, and muscles (cardiac, striated, and smooth) [54], indicating a wider distribution and importance than previously thought. However, nothing is known about the presence and activity of ROMK2 in mitochondria from these tissues.

The activity of the mitoKv1.3 channel has been reported in mitochondria from lymphocytes [23] and brain [55]. In addition, Kv1.3 was also reported in the plasma membrane of cells in the kidney [56], adipocytes [57] and epithelia [58].

The presence of mitoKv7.4 protein was discovered in cardiac mitochondria [59], and the activity of this channel was observed by the enhanced thallium flux in isolated mitochondria in response to the Kv7.4 opener retigabine [59].

The activity of the mitoBK$_{Ca}$ channel was reported in several mammalian cell types, including heart [60], brain [61], skeletal muscle [30], fibroblasts [62] and endothelium [63]. All isoforms of the BK$_{Ca}$ channel are products of alternative splicing of a single *KCNMA1* gene [64]. Unfortunately, the molecular identity of the mitoBK$_{Ca}$ isoform is not yet fully understood. It is believed that the mitochondrial splice variant of the BK$_{Ca}$ channel has an extended C-terminal domain, ending with the amino acid residues DEC [65] (see paragraph 4.3 for additional discussion).

The activity of mitoIK$_{Ca}$ (mitoK$_{Ca}$3.1) channel was described in mouse embryonic fibroblasts, HeLa cells [34], cells derived from human colon cancer [32], and in pancreatic carcinoma [66].

Mitochondrial isoforms of SK$_{Ca}$ channels have been described thus far in cardiac muscle [67,68] and brain [35].

The activity and mitochondrial localization were observed for the TASK-3 channel in mitochondria of aldosterone-producing zona glomerulosa cells [19], keratinocytes of HaCaT cells [18] and in melanoma cells [17].

Curiously, many of those channel activities have been recorded in mitochondria derived from immortalized or cancerous cell lines, indicating that channel mitochondrial localization might be related to oncogenic transformation.

The prime example here is the Kv1.3 channel, which could be a target for multiple conditions [69]. Kv1.3 is overexpressed in some cancer cell lines, and expression of Kv1.3 in the plasma membrane is correlated with that of mitoKv1.3 [70]. MitoKv1.3 was identified as a novel protein partner of the pro-apoptotic protein BAX, and physical interaction between the two proteins resulted in inhibition of channel activity and cell apoptosis [22]. Distinct membrane-permeant but not membrane-impermeant inhibitors of Kv1.3 induced death in human and mouse cancer cells, strongly supporting a crucial role of mitoKv1.3. Astonishingly, modulation of mitoKv1.3 by pharmacological means significantly reduced melanoma tumor size, with no adverse effects in a preclinical mouse model [71] and selectively induced death of primary tumor cells from leukemia patients [72]. Thus, inhibition of mitoKv1.3 represents a novel strategy to selectively eliminate cancer cells.

The K$_{Ca}$3.1 channel is expressed in glioblastoma cells and in tumor-infiltrating cells and could serve as a marker for the mesenchymal subgroup of cancer stem cells [73]. It is important to sustain cell invasion and proliferation, and this constitutes a potential novel therapeutic approach to reduce tumor spreading into the surrounding tissue [74]. The K$_{Ca}$3.1 channel is overexpressed in 32% of glioma patients, and its expression correlates with poor patient survival [75]. It was also suggested that high expression of K$_{Ca}$3.1 in patients with clear cell renal carcinoma predicts a high risk of metastasis and poor patient survival [76]. K$_{Ca}$3.1 is also abundantly expressed in pancreatic cancer cell lines and is important in cell invasion [77]. With the exception of one study in which the inhibition of mitoIK$_{Ca}$ appeared to contribute to melanoma cell apoptosis [78], it is unclear what is the relative contribution of the plasma membrane and mitochondrial isoforms of K$_{Ca}$3.1 to the cancer phenotype.

The role of BK$_{Ca}$ in cell migration, proliferation, and apoptosis, as well as its overexpression in brain cancers and a number of glioma cell lines, is well established (see [79] for review). However, due to the localization of the BK$_{Ca}$ protein to multiple compartments, there is no clear evidence for the role of mitoBK$_{Ca}$ in tumorigenesis.

The mitoTASK-3 channels contribute to the regulation of cell survival; their silencing compromises the mitochondrial membrane potential and induces apoptotic cell death in melanoma cells [16]. Therefore, the mitoTASK-3 channel may be a target for future melanoma therapies.

MITOCHONDRIAL POTASSIUM CHANNELS IN THE ENDOTHELIUM

Endothelium can be treated as an organ spread throughout the whole body. The endothelium lines all of our blood vessels, such as arteries, arterioles, venules, veins, capillaries and lymphatic vessels. The endothelium is not homogenous tissue. It has an average weight of approximately 1 kg in the human body [80] and differs in phenotype depending on its location in the cardiovascular system [81-83]. Endothelial cells play critical roles in controlling vascular function. The primary function of endothelial cells is to maintain a selectively permeable barrier between vessel lumen and vascular smooth muscle and regulates blood flow. Thus, endothelium affects the regulation of arterial pressure and blood supply to tissues. Endothelial cells have an effect on blood clotting and angiogenesis. Pathogenesis of the endothelium can lead to atherosclerosis, which also occurs in untreated diabetes or hypertension. The endothelium participates in the regulation of inflammatory processes and edema formation [84]. Importantly, at least 1 capillary is adjacent to every cardiomyocyte, and cardiomyocytes are outnumbered on average 3:1 by endothelial cells, which line the microvasculature and small vessels of the heart [85]. One of the main disturbances in the course of endothelial dysfunction is a reduction in the production of nitrogen oxide (NO). NO is the most important substance produced by the endothelial cells. The key role of this small gas molecule in vasodilation, inflammation and oxidative stress is due to the production of reactive oxygen species (ROS). NO has a short half-life of approximately 6–30 s, and it is continuously synthesized from L-arginine by nitric oxide synthase enzyme (NOS) [86,87]. Some of the gaseous molecules can regulate not only the activity of oxidative phosphorylation but also the activity of the BK$_{Ca}$ channel (see the gaseous section of this article). The endothelial cells are highly glycolytic, but they can still produce significant amounts of ATP in oxidative phosphorylation processes [88]. At least 75% of ATP synthesized by cultured pig aortic endothelial cells is provided by glycolysis [89]. However, compared with other cell lines in culture, the amount of mitochondria in endothelial cells

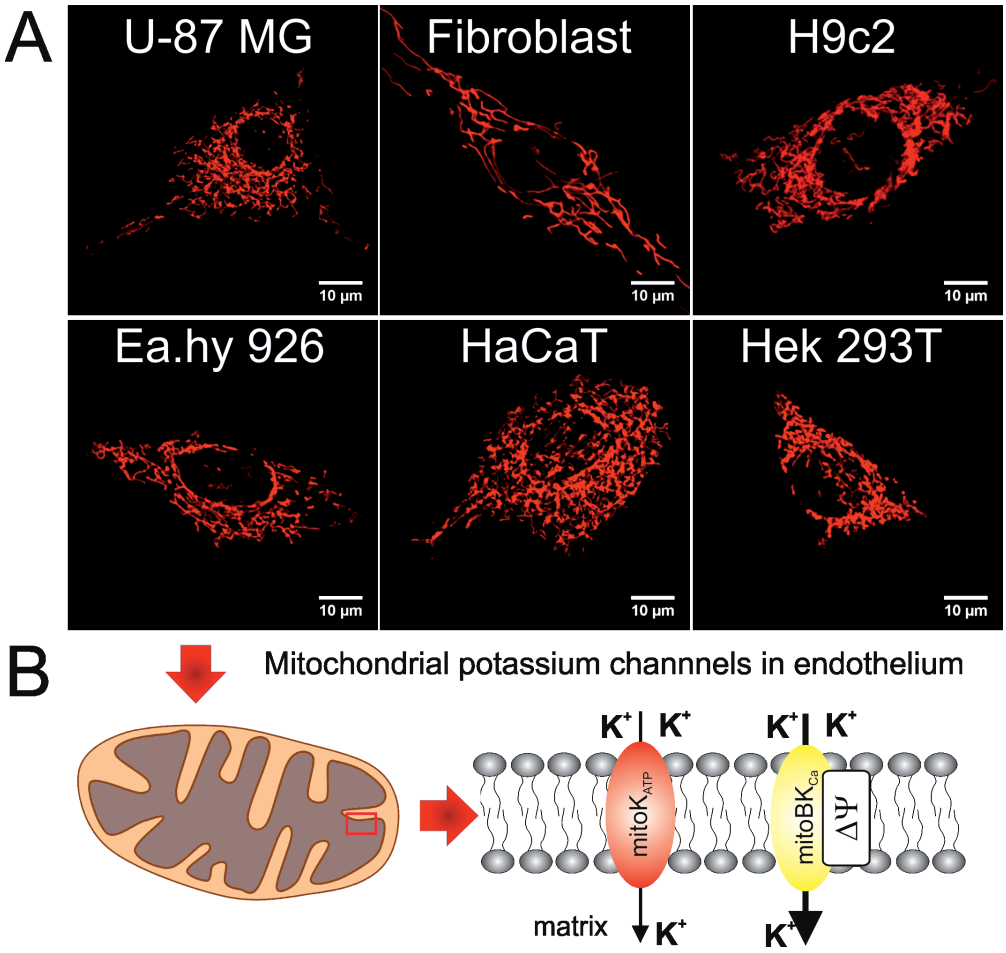


Figure 2. **A**. The confocal images of mitochondria for various cell lines. MitoTracker™ Red CM-H_2XRos was used as a fluorescence probe to visualize mitochondria. Cell lines visible on the confocal images: U-87 MG – human astrocytoma, fibroblast – human dermal fibroblast, H9c2 – rat heart myoblast, Ea.hy 926 – human endothelial cell line, HaCaT – human keratinocyte, Hek 293T – human embryonic kidney cell. **B**. The location scheme of mitochondrial potassium channel in endothelial inner mitochondrial membrane.

is quite substantial (Fig. 2A). It was revealed that, as in other cells, mitochondria in endothelial cells play a role as signaling organelles rather than source of intracellular ATP in physiological conditions [90].

Recently, potassium channels in endothelial cell mitochondria were discovered [63,91,92]. Among the potassium channels in the endothelial mitochondria, two channels have been identified: mitoBK$_{Ca}$ and mito$_{ATP}$ [91-93] (Fig. 2B). Mitochondrial potassium channels are located in the inner mitochondrial membrane. It has been suggested that potassium channels are responsible for cytoprotection against necrosis and apoptosis [93]. It was also suggested that they control mitochondrial metabolism by regulating matrix volume and mitochondrial homeostasis [94,95]. The table 1 summarizes the previously described mitochondrial potassium channels in the endothelial cells, their role, and studied activators (openers) and inhibitors of these channels.

MITOCHONDRIAL INNER MEMBRANE POTASSIUM CHANNELS AS FORMS OF CHANNELS LOCATED IN THE PLASMA MEMBRANE

The molecular identity of mitochondrial potassium channels remains one of the most intriguing questions regarding these molecules. Considering biophysical and pharmacological properties, mitochondrial potassium channels are very similar to their plasma membrane counterparts. Therefore, the concept of a plasma membrane potassium channel "mirror image" was developed regarding the composition of the channels from mitochondria [98]. Historically, the composition of the mitoK$_{ATP}$ channel, which was the first discovered mitochondrial potassium channel, was a matter of intense debate. A typical K$_{ATP}$ channel from plasma membrane consists of four potassium-selective pore-forming subunits from the Kir6.x family and auxiliary SUR components [99]; therefore, most attention was paid to these proteins as structural components of mitoK$_{ATP}$. However, dominant negative suppression [100] of Kir6.x proteins, as well as a genetic knockout, did not result in the suppression of mitoK$_{ATP}$ activity [101-103]. Additionally, potential mitoK$_{ATP}$ subunit analysis based on the application of antibodies failed due to nonspecific interactions [104].

Recently, it has been proposed that mitoK$_{ATP}$ channels consist of isoform 2 of the Kir1.1 (ROMK) channel. Originally, ROMK channels were described in kidneys; however, the expression of these channels was shown in heart, brain, and liver [14]. Knockdown of ROMK in H9c2 cardiac myoblasts resulted in a decreased uptake of thallium ions

Table 1. Mitochondrial potassium channels in endothelial cells.

Channel	Cell type or location	Main subject	Method	Reference
mitoK$_{ATP}$	Aortic endothelial cells	Angiotensin II increases the H_2O_2 and it has an effect on: mitochondrial ROS, mitochondrial respiration, membrane potential, glutathione, endothelial NO. Inhibitors of Angiotensin II action: – apocynin (inhibitor of NADPH oxidase) – uric acid (peroxynitrite scavenger) – chelerythrine (inhibitor of protein kinase C) – NG-nitro-L-arginine methyl ester (inhibitor of NO synthase) – 5-hydroxydecanoate (inhibitor of mtK$_{ATP}$) – Glibenclamide (inhibitor of mtK$_{ATP}$; antidiabetic medication)	Electron spin resonance spectroscopy Dihydroethidium high-performance liquid chromatography Fluorescent imaging	[91]
	Rat cerebral arteries	The influence of mitochondrial depolarization on vasodilation by mitoK$_{ATP}$ activators: – BMS-191095 – Diazoxide Compounds influencing vasodilation: – inhibitor of mtK$_{ATP}$ – inhibitor of phosphoinositide-3 kinase – inhibitor of NO synthase	Electron spin resonance spectroscopy Western blot Fluorescence imaging	[92]
mitoBK$_{Ca}$	Guinea pig heart, rat aortic rings, human endothelial EA.hy926 cells	CGS7184 (BK$_{Ca}$ opener) affects calcium homeostasis, mitochondrial membrane potential, NO production and mitochondrial respiration. Compound reducing vasodilation: – NG-nitro-L-arginine methyl ester (inhibitor of NO synthase)	Fluorescence Respiration measurements	[96]
	Human endothelial EA.hy926 cells	Open probability of BK$_{Ca}$ increased with calcium ions and NS1619, NS11021 (potassium channel opener). Blockers of the channel activity: – paxilline – iberiotoxin	Patch-clamp Western blot Fluorescence imaging	[63]
	Human endothelial EA.hy926 cells	The effect of anandamide as a direct BK$_{Ca}$ opener.	Patch-clamp	[97]

by mitochondria, which suggested that this protein might be responsible for the mitoK$_{ATP}$ activity. The N-terminus of the ROMK2 isoform is 19 amino acids shorter than the canonical ROMK1 isoform [99]. It has been proposed that this truncation results in unveiling a mitochondrial targeting sequence. Interestingly, the overexpression of ROMK2 resulted in increased resistance of H9c2 cells against oxidative stress. The same protein was identified in human skin fibroblasts [40]. Tertiapin-Q-sensitive activity was detected by mitoplast patch-clamping corresponding to the typical mitoK$_{ATP}$ channel, corroborating the presence of the active ROMK channel. Additionally, Western blot analysis and fluorescence microscopy images confirmed the presence of ROMK protein in the mitochondrial fraction. Finally, the transcript of the mitochondrial ROMK2 isoform was present in these cells [40]. These data confirm that ROMK2 is the protein responsible for mitoK$_{ATP}$ channel formation. The ROMK2 protein can also form an active channel in the plasma membrane, suggesting that the targeting of this protein to mitochondrial membranes might be regulated by a more sophisticated mechanism. Additionally, the possibility that other pore-forming proteins could be components of the mitoK$_{ATP}$ channel in various tissues cannot be excluded.

Basic electrophysiological and pharmacological properties of mitoBK$_{Ca}$ clearly suggest that its pore-forming α subunit is encoded by the KCNMA (Slo1) gene, which is also responsible for the BK$_{Ca}$ channel activity identified in the plasma membrane [1,29,98]. Indeed, proteins forming the α subunit and regulatory β subunits were identified in mitochondria from various tissues, including heart, brain and skeletal muscle [30,31,105,106]. However, a large number of reported and potential transcripts of this gene made the identification of the mitochondrial isoform difficult. A study based on the identification of splice variants in mouse cochlea suggested that the BK$_{Ca}$-DEC isoform of the α subunit can be targeted to mitochondrial membranes [64,65,107]. A major feature of this splice variant is a specific sequence of approximately 50 amino acids in the C-terminal part of the protein [65]. Expression of this isoform in cardiomyocytes showed exclusive targeting to mitochondria, in contrast to alternative BK$_{Ca}$ isoforms such as BK$_{Ca}$-VYR [65]. However, the BK$_{Ca}$-DEC splice variant might not be the only pore-forming isoform of mitoBK$_{Ca}$. A recent study describing mechanosensitivity of mitoBK$_{Ca}$ from astrocytoma cells showed a lack of BK$_{Ca}$-DEC isoform expressed in these cells [108]. Interestingly, the same study revealed the presence

of a STREX variant, which was shown to be responsible for the mechanosensitivity of BK_{Ca} channels [108]. Thus, it is possible that alternative splicing variants of BK_{Ca} form the channel in the inner mitochondrial membrane.

Identification of the molecular identity of mitochondrial potassium channels definitely opens new doors in the field; however, there are still plenty of questions to be answered, for example regarding the sorting and targeting mechanisms of these proteins to mitochondrial membranes.

ELECTROPHYSIOLOGICAL CHARACTERISTICS OF POTASSIUM CHANNELS IN THE INNER MITOCHONDRIAL MEMBRANE

ELECTROPHYSIOLOGICAL DIVERSITY OF INNER MITOCHONDRIAL MEMBRANE POTASSIUM CHANNELS

The functional diversity and regulatory mechanisms of potassium channels are surely dependent on the cell type [109]. These channels are present in non-excitable and excitable cells and control a wide variety of cell functions. Finding the physiological significance for the spectrum of single-channel conductance's in K^+ channels is also challenging because there is not a clear connection. Electrophysiological techniques have been successfully applied to study single channel properties of the plasma membrane and intracellular ion channels. In the inside-out patches, the K_{ATP} channel from liver mitochondria had a conductance of approximately 10 pS in 100/33 mM KCl [39]. By patching the mitoplasts obtained from human lymphocytes, an outwardly rectifying K_{ATP} channel with a conductance equal to 15 pS at negative potentials and 82 pS at positive potentials in 150 mM KCl was observed [41]. Additionally, it was shown that the unitary conductance of approximately 100 pS of $mitoK_{ATP}$ from dermal fibroblasts was similar to that described in other mammalian tissues [1,110]. These values probably differ due to differences in the molecular components of K_{ATP} channels and experimental conditions. Recently, it has been proposed that a certain splice variant of the renal outer medullary potassium channel (ROMK) may be the long-sought molecular constituent of the $mitoK_{ATP}$ channel [14]. These proteins usually form potassium channels of 35 pS conductance [111]. However, the ROMK protein is also a part of the thick ascending limb potassium secretory channel, exhibiting a conductance of 70 pS [112]. The conductance of mitochondrial K_{ATP} channel may be considered to be in line with expectations based on studies on plasma membrane K_{ATP} channels, although the pharmacology is slightly different.

Similar differences in conductance are also observed in the case of the BK_{Ca}-type channels. These channels have been identified in the mitochondria of astrocytes, ventricular cells, skeletal muscle, and brain and endothelial fibroblast cells, with unitary conductance values ranging from 145 to 307 pS [1,60].

Differences of conductance between the plasma membrane and mitochondrial channels can be a result of various factors: posttranslational modifications of the pore forming units, the presence of protein partners, or the composition of membrane lipids. Additionally, temperature and ion concentrations applied in experimental models could affect apparent conductance.

REGULATION OF MITOCHONDRIAL POTASSIUM CHANNELS BY GASEOUS MOLECULES

For many years, gases such as nitric oxide (NO), hydrogen sulfide (H_2S) and carbon monoxide (CO) were recognized as toxic molecules. However, in recent years these gases have been termed gasotransmitters, which in low concentrations cause beneficial effects in many physiological processes. One of the numerous targets of NO, H_2S and CO are mitochondrial potassium channels, in particular, the $mitoBK_{Ca}$ channel and $mitoK_{ATP}$ channel, and these types of interactions can play an important role in cytoprotection. Below, we briefly summarize the current state of knowledge about the interactions of CO, NO, and H_2S with mitochondrial potassium channels.

NO is produced by nitric oxide synthase (NOS) during the oxidation of L-arginine to citrulline, both in the cytosol and in mitochondria, and is a key signaling molecule in ischemic preconditioning [113]. Nitric oxide cytoprotective properties suggest that NO-mitochondrial potassium channel interactions are possible, and these assumptions were confirmed by experimental studies from various groups. Sasaki *et a*l., 2000 showed that NO may selectively activate the $mitoK_{ATP}$ channels from rabbit ventricular myocytes. The measurement of mitochondrial redox potential corresponded to $mitoK_{ATP}$ channel opening. The application of S-nitroso-N-acetyl-*DL*-penicillamine (SNAP) as an NO donor resulted in the dose-dependent oxidation of the mitochondrial matrix, which was blocked by the selective $mitoK_{ATP}$ channel blocker 5-hydroxydecanate (5-HD) and by NO scavengers. In addition, the activation of $mitoK_{ATP}$ channels by NO was a direct effect of NO [114]. Similar effects were observed for rat cardiac $mitoK_{ATP}$ channels that were reconstituted into lipid bilayers. It was shown that exogenous NO donors directly activated $mitoK_{ATP}$ channels, and this activation was inhibited by 5-HD and glibenclamide. The above results indicate a possible NO contribution to myocardial preconditioning [115]. On the other hand, Dahlem et al. showed that NO directly and irreversibly inhibits the activity of $mitoK_{ATP}$ channels from human T-lymphocytes (Jurkat cell line) [41]. Unfortunately, nothing is yet known about NO interactions with other mitochondrial potassium channels.

H_2S is synthesized from L-cysteine by several enzymes [116] and plays an important role in many processes, such as apoptosis [117], inflammation [118] and the preservation of mitochondrial functions [119]. Unfortunately, little is known about the effects of H_2S on the activity of mitochondrial potassium channels. In 2016, Testai *et al*. found that 4-carboxyphenyl isothiocyanate (4CPI), used as an H_2S donor in Langendorff-perfused rat hearts subjected to ischemia/reperfusion, enhanced the recovery of myocardial functional parameters and reduced tissue injury that was antagonized by 5-HD [25]. 4-CPI was also added to the isolated rat heart mitochondria, resulting in the depolarization of the mitochondrial membrane potential that was abrogated by the addition of ATP, which is a physiological blocker

of mitoK$_{ATP}$ [25]. Similar results were obtained by Sivarajah *et al.* [120]. They showed that NaHS, a different H_2S donor, exerts cardioprotective effects on rat cardiomyocytes that were impaired by 5-HD application . The above results indicate that mitoK$_{ATP}$ is a possible target for H_2S action and that H_2S is likely a mitoK$_{ATP}$ channel opener. Unfortunately, there are no electrophysiological data on the regulation of mitochondrial potassium channels by H_2S.

Carbon monoxide, the third gasotransmitter, is produced endogenously from heme during oxidative breakdown by heme oxygenases (HOs) [121]. CO is an important molecule in the control of numerous physiological processes because of its vasoactive properties, anti-inflammatory effects, and therapeutic potential [122]. One of the most important properties of CO is its ability to interact and regulate several classes of ion channels such as BK$_{Ca}$, K$_V$, Ca^{2+} channel (L-type) families, and tandem P-domain potassium channels (TREK1) [123]. Unfortunately, at this time no studies have investigated the regulation of mitochondrial potassium channels by CO.

POTASSIUM CHANNELS AS A PART OF RESPIRATORY COMPLEXES

The properties and roles of potassium channels are strictly related to location and interactions with partner proteins. Mitochondrial potassium channels function in a different environment than their plasma membrane counterparts. Interactions of potassium channels with other proteins seem to be crucial for their regulation. For example, it was previously shown that the BK$_{Ca}$ channel from plasma membrane interacts with hemoxygenase-2 [124]. The same study showed that the activity of the plasma membrane channel is reduced during hypoxia, and hemoxygenase-2 is crucial for such channel behavior. This observation is in contrast to studies showing that mitoBK$_{Ca}$ channel activity increases when oxygen availability is low [125,126]. These contrary data clearly show that the properties of the channel strongly depend on partner proteins. Interestingly, studies describing the interactions of BK$_{Ca}$ channels showed that at least 20% of potential interacting proteins are localized in mitochondria [107].

The basic mitochondrial function consists in the activity of electron transport chain complexes localized in the inner mitochondrial membrane. The electrochemical gradient generated by these complexes is later utilized to generate ATP. Mitochondrial potassium channels dissipate the electrochemical potential across the inner membrane, thus their activity directly influences respiratory chain function. Recent observations have suggested physical interactions between mitochondrial potassium channels and respiratory chain complexes. Electrophysiological studies revealed that the activity of mitoBK$_{Ca}$ channels is regulated by the mitochondrial respiratory chain [127]. The activity of the channel from astrocytoma U-87 MG cells changed upon application of respiratory substrates, suggesting a direct interaction between cytochrome *c* oxidase and the subunits of mitoBK$_{Ca}$. Indeed, analysis of complexes formed by regulatory subunit β4 suggested a physical interaction between respiratory complexes and mitoBK$_{Ca}$ [127]. The interaction between complex IV of the respiratory chain and β1 of mitoBK$_{Ca}$ was also observed in HEK293 cells after transient expression [128]. Later, studies of mitoBK$_{Ca}$ channels of brain and heart muscle revealed a high number of potential interacting partners, including complexes of the respiratory chain and other mitochondrial proteins such as enzymes involved in the Krebs Cycle [129,130].

The potential coupling between respiratory chain complex II and mitoK$_{ATP}$ has also been suggested [131,132]. The activity of mitoK$_{ATP}$ was enhanced by malonate, which is an inhibitor of succinate dehydrogenase. Therefore, it is possible that the channel may be indirectly regulated by complex II through changes of the mitochondrial redox status. Alternatively, the channel might possess a binding site for malonate, because the observed effect was also present in mitochondria respiring with complex I substrates [131].

Apart from the mitoK$_{ATP}$ and the mitoBK$_{Ca}$ channels, interactions between mitoTASK-3 and mitochondrial proteome have recently been described [19]. Analysis with the use of a yeast two-hybrid system and co-immunoprecipitation followed by mass-spectroscopy revealed the potential interaction of mitoTASK-3 channels with the respiratory chain in adrenal cells [19].

What could be the functional consequences of coupling between mitochondrial potassium channels and the respiratory chain? The role of these interactions might be specifically visible during ischemia/reperfusion-induced injury. The opening of the mitochondrial potassium channels results in cytoprotection, thus changes in respiratory chain activity can directly regulate potassium fluxes across the inner membrane. On the other hand, changing mitochondrial potassium channel activity, for example during the hypoxic period, could regulate mitochondrial function by triggering cytoprotective signaling. A more detailed analysis and a better understanding of signal transfer mechanism between the respiratory chain and the mitochondrial potassium channels are surely required.

PHYSIOLOGICAL SIGNIFICANCE

INVOLVEMENT OF MITOCHONDRIAL POTASSIUM CHANNELS IN CYTOPROTECTION

Mitochondrial potassium channels gained attention because of their possible role in cytoprotection. It has been shown that activation of these channels promotes the survival of cells and tissues after various injuries [98,133]. This phenomenon is not fully understood; however, it has been observed that the application of potassium channel openers can mimic ischemic preconditioning, which decreases cell death after ischemia/reperfusion injury [133]. Although potassium channels are present both in plasma membranes and in the membranes of cellular organelles, accumulating evidence suggests that the activation of potassium channels from the inner mitochondrial membrane is a key event that induces the cytoprotection cascade [98]. For example, it has been observed that the application of diazoxide could induce the cytoprotection of cardiac cells, and this effect was reversed by 5-HD, which inhibits the activity of the mitoK$_{ATP}$ channel [134,135]. On the other hand, the diazoxide

effect was not abolished by HMR1883, a known inhibitor of the K_{ATP} channels from the plasma membrane [134]. This observation clearly suggested the involvement of mitochondrial channels in cytoprotection. Further studies revealed that mitoK_{ATP} induces cytoprotection in neuronal tissue. For example, in a model of global ischemia in newborn pigs, diazoxide reduced neuronal cell death in a 5-HD-dependent manner [136]. Later, studies confirmed the role of this channel in neuroprotection [137]. The involvement of mitoK_{ATP} in the cytoprotection of blood vessels and the significant role of this channel in endothelial cells has also been described [1].

Similarly, the activation of mitoBK_{Ca} leads to cytoprotection. The application of a BK_{Ca} channel opener, NS1619, prevented heart tissue damage of guinea pig cardiomyocytes in a model of ischemia/reperfusion. The observed cardioprotection was reversed by paxilline, an inhibitor of mitoBK_{Ca} channels [31]. The role of mitoBK_{Ca} in cardioprotection was also reported in various toxicity models in cardiac cells from mouse, rat, and rabbit [1,31]. The beneficial role of mitoBK_{Ca} activation has also been described in neuronal tissue. For instance, pre-incubation of hippocampal slice cultures exposed to glutamate with NS1619 resulted in decreased neuronal cell death [138]. Apart from mitoBK_{Ca}, cytoprotective properties of other calcium-regulated potassium channels have been described [139]. The activation and overexpression of mitoSK_{Ca} channels increased the survival of HT22 cells in a model of glutamate-induced oxidative stress [35]. Similarly, activation of the mitochondrial Slo2 channel contributes to protection against hypoxic injury [140]. Finally, a cytoprotective role of mitoTASK-3 has been proposed. In skin keratinocytes, silencing of the channel resulted in increased cell death after UV treatment [18].

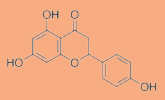
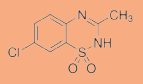
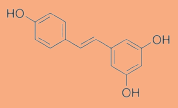
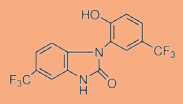
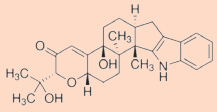
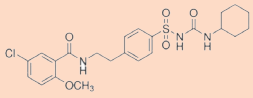
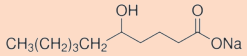
Several hypotheses explaining the mechanism of cytoprotection induced by the opening of the mitochondrial potassium channels have been proposed. Activation of the channels regulates the synthesis of mitochondrial ROS, which appears to be a critical step in the protection mechanism. This is in line with observations showing that ROS signaling is crucial for ischemic preconditioning [141]. Several studies have shown that the application of potassium channel openers (KCOs) increased ROS synthesis by mitochondria; therefore, it has been proposed that the opening of the mitochondrial potassium channels stimulates ROS generation in various tissues [142,143]. Increased ROS was proposed to play a signaling role triggering a pro-survival pathway. On the other hand, some studies suggest that activation of the channels decreases mitochondrial ROS. This was observed in various tissues including heart, skeletal muscle, brain, liver, and spleen cells [1, 144-147]. Decreased ROS synthesis by mild depolarization of the inner mitochondrial membrane might be important during the reperfusion phase. It was observed that hypoxic conditions resulted in an increased succinate accumulation in the mitochondrial matrix, and subsequent reperfusion of tissue stimulates ROS synthesis by means of reverse electron flow (RET) [148]. RET-stimulated ROS synthesis is dependent on the mitochondrial membrane potential; therefore, increased potassium ion influx after channel opening results in the reduction of mitochondrial ROS generation [145,146]. Activation of the mitochondrial potassium channels has also been connected with a reduced influx of calcium ions into the mitochondrial matrix. Increased Ca^{2+} influx accompanies the reperfusion phase, which might be dangerous for cell survival. Uncontrolled accumulation of Ca^{2+} in the mitochondrial matrix results in mitochondrial permeability transition pore opening, which subsequently leads to the release of cytochrome *c*, translocation of Bax protein and, consequently, cell death [98]. Therefore, the opening of the potassium channels followed by K^+ influx and mitochondria depolarization might inhibit calcium ion accumulation and promote cell survival [149,150]. Additionally, the regulation of mitochondrial volume and changes in ATP synthesis after the opening of mitochondrial potassium channels might also be a part of the cytoprotection mechanism [151,152].

The application of pharmaceutical agents modulating the activity of mitochondrial potassium channels is always connected with the risk of unspecific interactions of these compounds. Thus far, a vast number of cellular targets have been described for KCOs [93, 153-155]. Therefore, the involvement of mitochondrial potassium channels in cytoprotection induced by KCOs has been questioned by some studies [154,156,157]. Nevertheless, strong evidence supports the participation of mitochondrial potassium channels in a cytoprotection mechanism. However, data obtained with the application of potassium channel modulators must be carefully interpreted.

STRETCH-ACTIVATED POTASSIUM CHANNELS

Mitochondrial dynamics, *via* the balance between fusion and fission, serves as a central mechanism for bioenergetic adaptation to metabolic requirements of the cell [158]. Some known regulators of mitochondrial dynamics have been linked to mitochondrial biogenesis and respiratory functions, impacting cell fate and organism homeostasis (for a recent review see [159]). At the molecular level, mitochondrial fusion is a two-step process requiring the coordinated fusion of both the outer mitochondrial membrane (OMM) and the inner mitochondrial membrane (IMM) by separable sequential events. In mammals, this process depends on three fusogenic proteins: the OMM-located mitofusins 1 and 2 (MFN1 and MFN2) and the IMM-located (OPA1) [160]. Both OPA1-dependent and MFN-dependent bioenergetic functions affect cellular physiology and organism energy homeostasis. Mitochondrial fission proteins include dynamin-related peptide 1 (DRP1) and fission protein 1 (FIS1). The fusion and fission processes must influence the tension within mitochondrial membranes. Stretching and bending of the membranes causes changes in the lipid packing within the lipid bilayer [161]. Stress changes in the membrane are sensed directly by the mechanosensors located in the lipid membranes. This special class of proteins consists of mechanosensitive channels that react to changes in membrane tension by opening and allowing the flow of ions [162]. The main ion of the cytoplasm and the mitochondrial matrix is potassium. Changes in K^+ conductivity across the inner mitochondrial membrane cause not only the change in proton motive force but also result in the osmotic flow of water and volume regulation of the mitochondrial matrix. Even though volume changes of mitochondria have been

Table 2. Selected mitochondrial potassium channels modulators.

Modulators	Natural origin	Synthetic
Activators	 naringenin	 diazoxide
	 resveratrol	 NS1619
Blockers	 paxilline	 glibenclamide
	 iberiotoxin	 5-hydroxydecanoic acid sodium salt

known for a long time, little data exists regarding the mechanosensitivity of these organelles [163]. It is known that in chloroplasts, where fission takes place with the help of filamentous temperature sensitive Z (FtsZ) ring, and the Min system, mechanosensitive channels MSL2 and MSL3 have been described to colocalize with the plastid division protein MinE and to profoundly alter chloroplast size and division [164]. In the case of plant mitochondria, MSL1, another mechanosensitive channel, seems to play a role. Increased fluctuations in the potential of single mitochondria isolated from MSL1-deficient cells have been observed, which is indicative of stabilization of the potential by this mitochondria-specific mechanosensitive channel [165].

The existence of a more widely present mechanosensitive channel within mitochondria is apparent after the recent discovery of the mechanosensitivity of mitoBK$_{Ca}$ in U-87 MG glioma cells [108]. The pore-forming α-subunits of BK$_{Ca}$ channels are encoded by a single gene, *KCNMA1*, which undergoes extensive alternative pre-mRNA splicing. It has been suggested that the mechanosensitivity of the plasma membrane BK$_{Ca}$ channel is due to the presence of a STREX exon in specific BK$_{Ca}$ splice variants [166,167]. However, mitochondria-specific splice variant BK$_{Ca}$-DEC was identified [65]. This raises the question as to why mitoBK$_{Ca}$ is mechanosensitive. STREX and DEC exons are located in different positions; therefore, it is eventually possible that a tandem STREX-DEC transcript of BK$_{Ca}$ is present, but as yet it has not been detected [108]. Alternatively, other splice variants may be imported in the mitochondria of U-87 MG cells. For instance, the BK$_{Ca}$ channel specific for glioblastoma (gBK$_{Ca}$) is expressed in U-87 MG cells and partially colocalizes with mitochondria [168]. An interesting prospect is the formation of α subunit heteromers between STREX and other splice variants. This might result in channels that are mechanosensitive to various degrees, which is consistent with the observed heterogeneity of the response of mitoBK$_{Ca}$ to mechanical stimulation [108]. Heteromerisation of α subunit splice variants of BK$_{Ca}$ was observed in previous studies [169-171], including those of the DEC variant [172,173]. Another explanation for the variable mechanosensitivity of mitoBK$_{Ca}$ might be the formation of heterogeneous complexes of the channel pore-forming α subunit with auxiliary β (1-4) subunits. The presence of the β4 subunit in the inner mitochondrial membrane of human cells was previously shown [106]. This subunit interacts with cytochrome *c* oxidase, indicating the localization of the mitoBK$_{Ca}$ channel within cristae [127]. In addition, the β1 subunit is expressed in U-87 MG cells and appears to also interact with cytochrome *c* oxidase (subunit I) [128]. Recent exciting results suggest that the extracellular loop of the β1 subunit is involved in the regulation of BK$_{Ca}$ channel mechanosensitivity independently of the presence of the STREX sequence [174], which supports earlier observations that STREX-lacking BK$_{Ca}$ channels in colonic smooth muscle cells of mice are mechanosensitive [175].

Irrespectively of the molecular mechanism by which mitoBK$_{Ca}$ channels are activated by mechanical stimuli, an unanswered question remains—what is the physiological significance of mechanogating of mitoBK$_{Ca}$? In the context of the importance of OPA1 in mitochondria fusion and fission, it is interesting to note that this protein could interact with mitoBK$_{Ca}$ [129]. We hypothesize that this interaction might reflect the role of mitoBK$_{Ca}$ in mitochondrial dynamics (fusion/fission, cristae remodeling). Mechanically activated mitoBK$_{Ca}$ may locally and directly affect the cristae volume (regulation of respiration) and the opening of cristae junctions (regulation of apoptosis associated with cytochrome *c* release) [176]. However, data to support these assumptions is still needed.

MITOCHONDRIAL POTASSIUM CHANNELS AS PHARMACOLOGICAL TARGETS

The mitochondrial potassium channels are involved in the regulation of cell physiology. Regulation of mitochondrial potassium channels by natural origin or synthetic compounds may induce protective cellular mechanisms. Additionally, it has been observed that mitochondrial channel inhibition may cause cell death [1]. It is widely accepted that preconditioning with KCOs results in cytoprotection through the activation of mitochondrial channels [177]. Hence, the pharmacological modulation of mitochondrial potassium channels has become a promising new approach for the treatment of cardiovascular and neurodegenerative diseases. However, defining the biophysical and pharmacological characteristics of mitochondrial potassium channels remains incomplete.

SYNTHETIC MODULATORS OF POTASSIUM CHANNELS

For many years, laboratories investigating the channels found in the mitochondrial membrane have tested various substances of synthetic or natural origin that can activate

or block the activity of single channels. This is important because these compounds could be used to design different therapies. In some therapies, it is necessary to activate the mitochondria, while in other therapies the mitochondria should be inhibited (e.g., the mitochondria of cancer cells). Below are described some synthetic activators and inhibitors of the mitochondrial potassium channels [178].

Diazoxide is a well-known activator of potassium channels that causes local relaxation of smooth muscle by increasing the permeability of the cell membrane to K^+ ions. The outflow of potassium ions from the cell causes the closure of voltage-dependent calcium channels, which reduces their functional potential. Diazoxide is generally considered to be a specific activator of the mitochondrial isoform of the ATP-regulated potassium channel (mitoK_{ATP} channel) (Table 2). It has been shown that this synthetic substance acts on mitoK_{ATP} channels located in various types of tissue, such as skin, liver, brain and skeletal muscle [178]. The activation of the mitoK_{ATP} channel is primarily associated with the cytoprotective role of diazoxide [179]. Other valuable tools for studying the physiological role of mitochondrial potassium channels are 5-HD and glibenclamide (Table 2). Glibenclamide, known as an antidiabetic drug, is a derivative of second-generation sulfonylurea and was described as a blocker of K_{ATP} channels. It strongly stimulates the secretion of insulin from pancreatic cells and increases the sensitivity of tissues to insulin. It also exhibits a confirmed inhibitory effect on the ATP-dependent mitochondrial potassium channel, which classifies it into the group of mitochondrial potassium channel inhibitors, on a par with 5-HD. Glibenclamide affects the regulation of the physiological properties of mitochondria, e.g., by affecting the polarization of the mitochondrial membrane, as observed in the mitochondria of many cell types, including fibroblasts and rat uterine smooth muscle cells [40,180]. In contrast to glibenclamide, which acts on both mitochondrial and plasma membrane channels, 5-HD is considered to be selective for mitoK_{ATP} channels [181]. The relatively simple structure of this compound compared with other modulators of potassium channels makes it unique (Tab. 2). However, all of the aforementioned drugs have off-target effects, which should be kept in mind while interpreting the experimental results [93]. Another group of exogenous and synthetic modulators are highly specific to the large-conductance Ca^{2+}-regulated potassium channels (BK_{Ca} channels). These substances are also frequently used in experiments focused on mitochondrial BK_{Ca} channels [29,127]. By far, the most extensively used modulator is a compound called NS1619 (Tab. 2). It belongs to the group of synthetic benzoimidazolone derivatives, and it has been shown that NS1619 significantly increases the probability of mitoBK_{Ca} channel opening, which makes it cytoprotective.

NATURAL COMPOUNDS AS EXOGENOUS MODULATORS OF POTASSIUM CHANNELS

Potassium channels are regulated by endogenous factors such as depolarization or an increase in the concentration of calcium ions. There are also known substances of natural origin belonging to different structural classes that can modulate the activity of potassium channels. One class of these is the flavonoids [182]. Most flavonoids are pigments that accumulate in the surface layers of plant tissues, giving an intense color and reducing the harmful effects of ultraviolet radiation. Some flavonoids have beneficial effects on cardiovascular function, mainly due to their antioxidant activity, and can be cardioprotective [183,184]. They can also interact with ion channels and modulate redox processes in mitochondria. One of the flavonoids, naringenin (Tab. 2), which occurs in grapefruit, has cytoprotective properties and activates potassium channels [185]. Our findings indicate that adding naringenin to mitoplasts isolated from primary human dermal fibroblasts cells causes an increase of the mitoBK_{Ca} channel activity. Moreover, other compounds with similar properties, e.g., apigenin, luteolin, and 5-hydroxyflavone, are also described as modulators of the potassium channels [186].

Another interesting organic compound is resveratrol. This polyphenol is present in the skin of grapes. Resveratrol might be incorporated into the smooth muscle membrane to interact with membrane ion channels [187]. Recently, it has been demonstrated that resveratrol can activate BK_{Ca} channels in smooth muscle and vascular endothelial cells [187]. Resveratrol has cardioprotective properties, as do other polyphenols, and it has been suggested that this substance activates rat cardiac sarcolemma K_{ATP} channels [188].

One of the most well-known natural blockers selective for BK_{Ca} channels is paxilline (Tab. 2). This substance is an indole alkaloid and is the major toxin produced by *Penicillium paxilli* [186]. Our studies with mitoplasts isolated from different types of cells confirmed that after adding the selective BK_{Ca} activator, the channel activity is irreversibly inhibited by paxilline. Paxilline is probably the most well-known and highly used substance in electrophysiological experiments, which blocks the BK_{Ca} channel by binding its α subunit.

The first high-affinity peptide to be discovered that inhibited large- and small-conductance Ca^{2+}-regulated potassium channels was charybdotoxin. This toxin was isolated from the venom of the scorpion *Leiurus quinquestriatus hebraeus*. Unfortunately, charybdotoxin is not selective against BK_{Ca} channels because it can also block other voltage-gated potassium channels [186]. Another toxin isolated from the venom of the scorpion *Buthus tamulus*, with 68% sequence identity with charybdotoxin, is iberiotoxin. This toxin is more specific, binds to the extracellular side of the BK_{Ca} channels and blocks the conduction pathway. Our research indicates that iberiotoxin inhibits mitoBK_{Ca} in various cell lines in a dose-dependent manner [98].

SUMMARY

Despite nearly 25 years of studies on mitochondrial potassium channels, there are plenty of outstanding questions concerning the properties and function of these proteins. These unresolved issues could be grouped, based on our experience in this field, into three themes.

The first concerns the physiological role of mitochondrial potassium channels. How do they contribute to cell protection or cell death? Is there any contribution of these proteins to another complex process, such as cell aging? Understand-

ing the functional role of mitochondrial potassium channels will help the possible usage of these proteins as therapeutic targets, for example during ischemia-reperfusion injury.

The second theme concerns the regulatory mechanisms of mitochondrial potassium channels unique to mitochondria. Mitochondrial channels are regulated similarly to those found in the plasma membrane. For instance, we have recently shown that potassium channels in mitochondria are regulated by membrane stretching. Are there any regulatory mechanisms exclusive to mitochondrial channels?

The third theme concerns the pharmacology specific to mitochondrial potassium channels present in various cell types. Potassium channels are present in all cell types. Can substances acting specifically on mitochondrial potassium channels be identified?

The answers to these questions should not only improve our understanding of the role of mitochondrial potassium channels but should allow for the use of this knowledge in biomedical applications.

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Mitochondrialne kanały potasowe: podsumowanie

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STRESZCZENIE

Podstawową rolą, jaką odgrywają mitochondria komórek ssaków w większości jest synteza ATP. Kanały potasowe występujące w wewnętrznej błonie mitochondrialnej są jednym z regulatorów funkcji mitochondriów. Ich mechanizm działania oparty jest na umożliwieniu przemieszczania się K+ przez nieprzepuszczalną dla tych jonów wewnętrzną błonę mitochondrialną. Kanały te są regulowane przez wiele czynników i warunków w sposób podobny do kanałów potasowych występujących błonie komórkowej. Modulatory mitochondrialnych kanałów potasowych wpływają min. na potencjał błonowy wewnętrznej błony mitochondrialnej, stężenie jonów wapnia, ilość wolnych kwasów tłuszczowych i poziom ATP w komórkach. Ponadto, ostatnio wykazano, że kanały te są regulowane przez łańcuch oddechowy, naprężenia wewnętrznej błony mitochondrialnej oraz fosforylację. Szczególne zainteresowanie mitochondrialnymi kanałami potasowymi, nad którymi od blisko 25 lat prowadzone są ich badania, wynika z roli jaką odgrywają w procesach cytoprotekcji i śmierci komórkowej. Występowanie mitochondrialnych kanałów potasowych opisano w neuronach, astrocytomie, mięśniach serca, mięśniach szkieletowych, fibroblastach, keratynocytach i komórkach śródbłonka. W niniejszej pracy przeglądowej podsumowano aktualną wiedzę na temat mitochondrialnych kanałów potasowych. Przeglądu literatury dokonano ze szczególnym naciskiem na badania przeprowadzone w Laboratorium Wewnątrzkomórkowych Kanałów Jonowych w Instytucie Biologii Doświadczalnej im. M. Nenckiego w ciągu ostatnich 20 lat. Obejmuje on badania właściwości elektrofizjologicznych i farmakologicznych mitochondrialnych kanałów potasowych oraz ich regulację przez egzogenne i endogenne substancje wewnątrzkomórkowe. Dodatkowo opisany został przegląd mechanizmów regulacji mitochondrialnych kanałów potasowych przez łańcuch oddechowy i naprężenia wewnętrznej błony mitochondrialnej. W niniejszej pracy zostały również podsumowane właściwości mitochondrialnych kanałów potasowych występujące w różnych organizmach.