Chapter 2

Mitochondrial KATP Channel Function under Hypoxia

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Additional information is available at the end of the chapter

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Abstract

Hypoxic states and conditions result in complex alterations of the energetics and metabolism at the level of the whole cell and mitochondria, including the modulation of metabolic pathways and activation of transcription factors and signaling events. Common feature of the alterations of mitochondrial functions under hypoxia is the activation of mitochondrial potassium channels. Most studied of mitochondrial potassium channels, ATP-sensitive K^+ channel (mKATP channel), is supposed to play important role in the adaptation to hypoxia. However, the main obstacles in the understanding of mKATP channel functions under hypoxic conditions are contradictory data on the direct bioenergetic effects of mKATP channels opening and the lack of knowledge on cell specificity of mKATP channel functioning and of cell signaling pathways triggered by mKATP channels opening. So, the aim of this review was to outline the present knowledge on mKATP channel functions under hypoxia and to discuss how alterations to mitochondrial energetics and metabolism caused by mKATP channels opening (primarily at the level of ROS production and ATP synthesis) could be involved in multiple adaptive responses of a living organism to oxygen deprivation conditions.

Keywords: hypoxia, mitochondria, mKATP channel, potassium transport, ROS production, ATP synthesis

1. Introduction

Hypoxia produces deep alterations in a living organism at systemic and cellular level. Cells respond to hypoxia by complex metabolic reprogramming and molecular mechanisms aimed to minimize detrimental consequences of the oxygen deprivation. Moderate hypoxia exposure (such as intermittent hypoxia) is supposed to possess a great therapeutic potential, while severe and prolonged hypoxia has pronounced pathophysiological consequences [1, 2]. Adaptive responses to hypoxia primarily involve metabolic and functional alterations in

mitochondria. Being the main consumers of cellular oxygen (up to ~90%) and highly sensitive to oxygen shortage [3–5], mitochondria are first to respond to oxygen deficiency. Hypoxia evokes complex network of the mechanisms aimed to adapt mitochondria, their morphology, functions and metabolism to oxygen deprivation. In agreement with the present knowledge, the first step in the adaptation to hypoxia is the expression, stabilization and activation of hypoxia-inducible factor HIF, which is the transcription factor that triggers metabolic reprogramming resulting in the shift from oxidative to glycolytic metabolism [6–8]. Multilevel mitochondrial response to oxygen shortage includes modulations at the transcription level [6, 8], morphological changes [2, 9, 10], alterations in the functioning of ETC at the level of respiratory complexes [11, 12], shift of ATP synthesis from oxidative to glycolytic pathway [7, 11, 13], alterations in the mechanisms of ROS production by the respiratory chain [3, 4, 14], triggering of signaling pathways specific for hypoxic conditions [6, 15, 16] and the modulation of ROS control by matrix antioxidants [17–19]. These mechanisms working separately or together could explain high effectiveness of the moderate exposures to hypoxia in the adaptation of a living organism to severe oxygen deprivation, such as ischemia and anoxia [1, 12].

One common feature of the metabolic alterations in mitochondria under hypoxia is the activation of mitochondrial potassium transport, which is thought to be a part of the adaptive responses of a living organism to oxygen deficiency [20–22]. Mitochondrial system of potassium transport is represented by several types of potassium channels, which are the pathways for potassium uptake (ATP-sensitive K^+ channel (KATP channel), large conductance Ca^{2+}-activated K^+ channel (BK_{Ca} channel), voltage-gated K^+ channels and others, reviewed in [23]), and K^+/H^+ exchanger, which is the pathway of potassium efflux (reviewed in [24]). In the literature, hypoxia was shown to increase the activity of both mKATP and BK_{Ca} channels [20, 25–27] and the overall potassium uptake in mitochondria [21, 28]. Potassium transport is an all-round modulator of mitochondrial functions: oxygen consumption, Ca^{2+} transport, ATP synthesis, ROS production and mitochondrial morphology [10, 24]. But which are the functions of potassium transport and what benefits could be gained by the activation of potassium channels under hypoxia?

Mitochondrial ATP-sensitive potassium channel (mKATP channel) is the most abundant of the K^+ channels present in the inner mitochondrial membrane, and the functional effects of ATP-sensitive potassium transport are best studied as compared to other types of K^+ transport in mitochondria [23, 24]. For this reason, primarily the functions of ATP-sensitive potassium transport under hypoxia and physiological relevance of mKATP channel functioning will be discussed below based on the published data and the results of the author's research.

2. The impact of hypoxia on mitochondrial functions and metabolism

2.1. The impact of hypoxia on mitochondrial morphology and the functions of the respiratory chain

2.1.1. The impact of hypoxia on mitochondrial morphology and subcellular distribution

"Mitochondrial response" to hypoxia, starting from the modulation of mitochondrial morphology and metabolism, is directed at the adaptation of the organelles to the conditions of

oxygen shortage. Morphological changes are highly dependent on the duration and severity of oxygen deprivation. Generally, it was reported that short-term and intermittent hypoxia resulted in the increase of the total number of mitochondria and the enrichment of their subsarcolemmal fraction [9, 10], while severe prolonged hypoxia, on the contrary, suppressed mitochondrial biogenesis and dramatically reduced the number of subsarcolemmal organelles [2, 11]. Apparently, "primary" response to oxygen deficiency is to improve oxygen supply to mitochondria, whereas response to severe prolonged hypoxia fits with the decrease of respiratory capacity and metabolic shift from oxidative mitochondrial to glycolytic metabolism [7, 8].

Thus, it was observed [10] that even short-term exposure to hypoxia (a 30-min hypobaric hypoxia) resulted in obvious changes in mitochondrial morphology and their subcellular distribution. As it was shown in cardiac and muscle tissues [9, 10], oxygen deficiency increases localization of mitochondria near the plasma membrane, in the close proximity to capillaries, and the enrichment of subsarcolemmal fraction of mitochondria, while not affecting interfibrillar one. Also, hypoxia exposure resulted in moderate swelling of cardiomyocyte mitochondria (by 25% from the initial diameter) and the formation of vesicular cristae [10]. Adaptive changes after exposure to 10–14% O_2 were also observed in cerebral cortex mitochondria [29]. More dense cristae package was found in the animals showing higher adaptive capacities to hypoxia [29]. It was observed too that short-term hypoxia exposure promoted mitochondrial division, thereby greatly increasing the number of mitochondria due to the formation of new microorganelles [10]. These changes were supposed to improve oxygen supply to mitochondria and the effectiveness of the oxygen consumption because of greatly increasing the total surface of mitochondria [10]. Interestingly, the effects similar to short-term hypoxia on mitochondrial morphology were produced by mKATP channel opener diazoxide. Thus, diazoxide administration *in vivo* enhanced division of mitochondria and increased the number of newly formed organelles while channel blocker 5-HD abolished this effect [10]. It is worth mentioning that higher adaptive capacities of the animals to hypoxia coincided with higher mKATP channel activity [28, 29], which implies the role of mKATP channel in the modulation of mitochondrial dynamics and agrees with supposed role of the channel in the adaptation to hypoxia.

In contrast, prolonged exposure to severe hypoxia has pathogenic consequences for the organism [1] and detrimental consequences for mitochondria and results in the loss of mitochondrial density, depletion of subsarcolemmal mitochondria, suppression of their biogenesis, decrease in the expression of the respiratory complexes, lowered pyruvate oxidation (complex I substrate), decreased respiratory capacity and de-energization [2, 11]. Thus, chronic exposure to hypobaric hypoxia (5000–6000 m) resulted in ~21% loss of total mitochondrial density and 73% loss of subsarcolemmal mitochondria accompanied by decreased expression of the complexes I and IV [2], which corresponds to the shift of metabolism from oxidative to glycolytic pathway. Thus, it seems reasonable to agree with Ref. [1] that therapeutic effect of hypoxia is a matter of dose and assumes that increase in oxygen-sensing properties of mitochondria is a first step in the adaptation of a living organism to hypoxia.

Hypoxia alters mitochondrial functions and metabolism primarily at the level of the respiratory chain. Thus, hypoxia affects sensitivity of mitochondria to oxygen and the functions of the respiratory complexes, the sources of electron supply to the respiratory chain, pathways

of ATP synthesis and the mechanisms of ROS formation and signaling. There we consider the changes in mitochondrial functions, which are supposed to be a part of non-pathophysiological adaptive responses of a living organism to moderate hypoxia exposures.

2.1.2. The functioning of the respiratory chain and ATP synthesis under hypoxia

Respiratory chain is the subject of complex modulation under oxygen deficiency. At the level of ETC, mitochondrial response to hypoxia is manifested by elevated ROS production and HIF stabilization [3–6], downregulation of the respiratory complexes [2] and ATP synthase, switch from the oxidative to glycolytic ATP production [7, 11–13] and triggering of the mechanisms aimed to suppress the respiration, e.g. by S-nitrosation of the respiratory complexes, which is supposed to save oxygen from excess consumption and prevent excess HIF activity [30]. Nitric oxide is supposed to be active player in hypoxia sensing by mitochondria [30, 31]. Thus, it was proposed that under low P_{O_2} electrons from the respiratory chain could reduce nitrite (NO_2^-) to $^{\bullet}NO$, which then reacts with oxygen producing superoxide ($^{\bullet}O_2^-$). The excess NO production in the presence of $^{\bullet}O_2^-$ results in S-nitrosation of mitochondrial proteins [31], particularly, complexes (I and IV) thereby suppressing respiration. The elevated production of hydrogen sulfide capable to directly donate electrons to the respiratory chain [32] opens the pathways of electron supply substituting for oxygen shortage. Also, the impact of hypoxia on the oxygen-sensing properties of mitochondria appears in the modified sensitivity of the electron transport chain to oxygen *via* the modified kinetic properties and increased oxygen affinity of cytochrome oxidase (complex IV) [9]. All these alterations are supposed to be directed at the adaptation of mitochondria to oxygen deprivation.

The primary step in sensing oxygen deficiency and complex reprogramming of mitochondrial functions under hypoxia is the activation of hypoxia-inducible factor HIF, a transcription factor that takes control over a multiplicity of genes [6]. HIF family counts three known at present members, HIF 1α, HIF 2α and HIF 3α. Most studied are the functions and the regulation of HIF 1, which is composed of constitutively expressed HIF 1β and three HIF α subunits (HIF 1α, HIF 2α, HIF 3α) that are highly sensitive to the changes in oxygen concentration. HIF α subunits are unstable under normoxic conditions (21% oxygen) but are stabilized under oxygen deficiency (10–14% oxygen) and assembled with HIF 1β forming functionally active heterodimers [6]. HIF life span is controlled by prolyl hydroxylases, which require oxygen for their activity and are inactivated when oxygen supply is insufficient. Oxygen-dependent hydroxylation of proline residues (402 and 564 in HIF 1α) by hydroxylase PHD2 and asparagine residue by factor inhibiting HIF (FIH) promotes binding of the von Hippel-Lindau tumor-suppressor protein (VHL), which in turn triggers pathway of HIF degradation by proteasome [6]. ROS formation by mitochondrial respiratory chain contributes to inactivation of prolyl hydroxylases and HIF stabilization, thus HIF stability is critically dependent on both oxygen concentration and ROS formation [4]. Silencing or pharmacological inhibition of prolyl hydroxylases enhanced HIF stability [4, 33], whereas ROS scavenging by antioxidants (N-acyl cysteine, and mitochondrial ROS scavenger mitotracker red) abolished HIF stabilization and HIF-dependent signaling even under oxygen shortage [4].

ROS-dependent stabilization and activation of HIF [3–5] triggers complex metabolic rearrangement resulting in a switch from oxidative to glycolytic metabolism, which is a hallmark of all

hypoxic states, including embryonic and tumor cells known to function in highly hypoxic environment. At transcriptional level, adaptive responses of a living organism to hypoxia involve upregulation of proteins and the enzymes along glycolytic pathway: glucose transporter (GLUT), hexokinase 2 (HK2) and lactate dehydrogenase (LDH). HIF-dependent upregulation of genes encoding glucose transporters [8] results in the enhanced uptake of glucose and the activation of glucose metabolism with eventual formation of the end product lactate.

As shown in literary data, under normoxic conditions about 25% of cellular ATP is supplied by glycolysis, which, for example, in dorsal root ganglion neurons constituted ~3.5 nmol/mg protein [13]. Hypoxia sharply changes relative contribution of the oxidative phosphorylation (OxPhos) and glycolysis to ATP production dramatically suppressing OxPhos pathway while simultaneously upregulating glycolysis. Thus, dependent on the conditions, hypoxia was capable of reducing ATP content by ~50% (which in the above example constituted from ~11 to as low as ~6 nmol/mg [13]), of which about ~5 nmol/mg (i.e. ~80%) was produced by glycolytic pathway. This pattern shows upregulation of glycolysis by ~1.5 times accompanied by nearly complete inhibition of the OxPhos.

ATP obtained by glycolysis, as well as ATP of mitochondrial origin, is consumed by several energy-consuming processes, such as maintenance of transmembrane ion gradients and membrane potential by the work of Na^+, K^+-ATPase, metabolic processes and protein synthesis. Literary data showed not only inhibition of ATP synthase caused by impaired mitochondrial bioenergetics but also its down-regulation along with down-regulation of the respiratory complexes.

As it was established in several studies (in embryonic cardiomyocytes [34], dorsal root ganglion neurons [13], malignant cell lines [35]), there was a reciprocal dependence between impaired mitochondrial bioenergetics, compromised ATP synthesis and upregulation of all steps of glycolytic pathway. Especially in tumors, which metabolic phenotype has much in common with that of normal tissues functioning under hypoxia, elevated expression of glycolytic proteins, starting from glucose transporter and ending with lactate dehydrogenase, and simultaneous downregulation of respiratory complexes and ATP synthase were observed in different cell lines [35].

Under oxygen deficiency, glycolysis was shown to be upregulated not only at transcriptional level but also at the level of metabolism. Thus, as it was shown in the early work of Hohachka et al. [7], insufficient production of ATP and lowering of cellular ATP content result in the elevation of cellular level of ADP that reaches the range of K_m (~100 μM) required for ADP-dependent kinases of glycolysis (phosphoglycerate kinase, pyruvate kinase), which is much higher than it is required for mitochondrial oxidative metabolism (~30 μM). Reduced level of ATP is reflected in lowered phosphocreatine/ATP ratio, which is one of the multiple hallmarks of oxygen deficiency [7, 11].

Another aspect of downregulation of the OxPhos is the conversion of ADP to AMP, the increase of the level of AMP and the activation of AMP-dependent protein kinase (AMPK), which was shown to afford several cytoprotective effects first established under the conditions of ischemia/reperfusion [36]. Thus, AMPK activation, which takes place when ATP demand exceeds the supply, i.e. under oxygen deprivation and compromised mitochondrial ATP production (ischemia, hypoxia [37]), was shown to protect tissues of oxidative stress, opening

of mitochondrial permeability transition pore (mPTP) and apoptosis induction. Also, it was shown to be indispensable for the activation of glycolysis as a part of adaptive responses to the lack of oxygen aimed to compensate for ATP deficiency [35, 36, 38].

At present, it still remains elusive, which is the "molecular link" between metabolic alterations and elevated expression of KATP channels observed under hypoxia in several works. Recently, it was shown [37] that AMPK activation under exposure to moderate hypoxia increased the level of the receptor SUR2A subunit of cardiac KATP channels, which was supposed to be a part of adaptive response to oxygen deprivation. Increased expression of SUR2A in cardiomyocytes was also observed after application of AMPK activator AICAR [37]. Thus, AMPK activation under hypoxia appears to be one of the mechanisms connecting metabolic rearrangements with KATP channels opening.

Thus, oxidative ATP synthesis under hypoxia gives way to glycolysis, and as it was shown in the literature, glycolysis becomes the prevailing source of ATP production, at dramatic diminution of ATP production by OxPhos. Upregulation of glycolytic metabolism primarily occurs because of ROS-dependent stabilization and activation of transcription factor HIF, triggering of HIF-dependent signaling and upregulation of glycolytic enzymes. Increased level of ADP and AMP because of compromised OxPhos and activation of AMP kinase [36] largely contribute to upregulation of glycolysis and glycolytic ATP production.

While metabolic alterations and redistribution of ATP production between OxPhos and glycolysis is one aspect of hypoxia's impact on mitochondrial and cellular functions, another as well important aspect of the functional rearrangements under hypoxia is triggering of redox signaling specific to the states of oxygen deficiency [5, 6, 14]. Elevated ROS production under hypoxia, resulting in HIF activation, is accompanied by the activation of redox signaling that in the literature was shown to be largely mediated by plasmalemmal and mitochondrial potassium channels and cytosolic Ca^{2+}.

2.2. The impact of hypoxia on mitochondrial ROS production and signaling

2.2.1. The sources of ROS under hypoxia

Even short-term exposure to hypoxia triggers complex network of cell-specific signaling pathways involving the induction of early genes [6, 15, 39] and activation of signaling pathways: PKC (phosphatydil-inositol-3-kinase (PI3K)/protein kinase B (Akt), mitogen-activated protein kinase (p38MAPK), AMP-activated protein kinase (AMPK) [15, 16, 40, 41]). Under hypoxia, signaling is known to be tightly coupled to mitochondrial ROS production. The major sources of ROS are NADPH oxidase (NOX), which activation was shown under the states of oxygen deficiency [16, 42, 43], and the respiratory chain [4, 14, 44]. Respiratory chain was shown to be a trigger of redox signaling in response to hypoxia [4, 5, 14]. Literary data show critical role of complexes I and III in HIF stabilization and redox signaling under hypoxia [4, 14, 43]. Mitochondrial complexes I, II and III are known to be the main sites of ROS formation in the respiratory chain [45]. Complex I releases ROS to the matrix space, while complex III releases ROS on both sides of mitochondrial membrane—to the matrix and the intermembrane space

[45]. Mitochondrial complex III is supposed to play a pivotal role in triggering ROS signaling [3, 4, 14]. Suppression of mitochondrial respiration by the respiratory inhibitors such as rotenone (complex I), myxothiazol and stigmatellin (complex III) [4]; genetic deletions within the complexes I [43] and III [4], and ROS scavenging by mitochondria targeting antioxidants (mitotracker red) have shown that under hypoxia ROS signaling and HIF stability were primarily dependent on the ROS production by the respiratory chain. As it was shown by many authors, under hypoxia, the primary site of ROS formation within the respiratory chain shifts to the complex III, and therein Q-cycle [3, 4] and Rieske protein (FeS cluster) [44] were shown to be the major sources of ROS responsible for HIF activation. It is worth notion that HIF stabilization by mitochondria-derived ROS exhibited site specificity. Thus, using approaches based on genetic ablation and pharmacological inhibition, it was shown that Q_o site facing cytosol and Rieske protein of complex III were critical for HIF stabilization under hypoxia, while ROS formation at Q_i site facing matrix space did not contribute to HIF stability [4]. Critical role of Q_o site for HIF stabilization allows an assumption that not so "bulk" ROS production or the lack of oxygen is most important for HIF stability and activation, as ROS signaling from outer boundary of mitochondrial membrane [4]. In line with this observation is the interplay between NOX- and mitochondria-derived ROS, which in the recent decades became a subject of keen interest [16, 42–44, 46, 47]. Voltage-gated K^+ channels of plasma membrane (Kv channels) and mKATP channels were shown to be important link mediating interplay between NOX and mitochondrial ROS formation, which triggers redox signaling specific to the states of oxygen deficiency [16, 42–44, 47–49].

Under hypoxia, the elevation of ROS production in the cell and mitochondria is accompanied by the increase in the level of cytosolic calcium, $[Ca^{2+}]_c$, which was shown to be ROS-dependent [44, 48, 49] and results either from Ca^{2+} entry *via* plasma membrane [49] explained by suppression of Kv channels by mitochondria-derived ROS and sarcolemmal depolarization [43, 46] or, alternatively, Ca^{2+} release from sarcoplasmic reticulum *via* ryanodine receptors [42, 44]. The role of ROS in the elevation of $[Ca^{2+}]_c$ was shown by its abolition by antioxidants (pyrrolidine dithiocarbamate, N-acetyl cysteine) as well as overexpression of glutathione peroxidase (GPx), catalase (CAT) and matrix Mn-SOD [48, 49], which showed its dependence on ROS formation by mitochondria. The elevation of ROS, activation of PKCε and the rise in $[Ca^{2+}]_c$, could contribute to the inhibition of Kv channels, extracellular Ca^{2+} influx [49] or Ca^{2+} release from intracellular stores [42, 44].

As it was shown in several studies, mKATP channels opening was capable to increase mitochondrial ROS production and trigger redox signaling mediated by PKCε [16, 47, 50, 51]. An interplay between NOX and mitochondrial ROS, dependent on mKATP channel opening; the rise in intracellular $[Ca^{2+}]_c$ and the activation of PKCε and other signaling pathways under hypoxia (Akt, MAPK, ERK [40, 41, 52, 53]) were shown in several works. Thus, hypoxia-induced NOX activation was shown to be dependent on mitochondrial ROS, and the suppression of ROS production by respiratory inhibitors (rotenone, myxothiazol) abolished NOX activation [42, 47]. As it was found, the role of mKATP channel in mediating NOX-mitochondria interplay was the direct activation of PKCε, resulting from the increase of mitochondrial ROS production following ATP-sensitive K^+ uptake [16, 50].

Alternatively, mKATP channel activation was supposed to be a part of a feedback loop mechanism, started by NOX activation [42, 47], ROS release and the increase in mKATP channel activity, which in turn triggered PKCε activation both in mitochondria and cytosol by increasing mitochondrial ROS production [16, 51]. The activation of mKATP channel shown under hypoxia by many authors as well could contribute to the increase in $[Ca^{2+}]_c$, because mKATP channel opening and uncoupling of the respiratory chain by potassium transport favors the elevation of $[Ca^{2+}]_c$, by reducing Ca^{2+} uptake in mitochondria [54–57]. Thus, an impact of mKATP channel activity on mitochondrial ROS formation and Ca^{2+} uptake becomes an important modulator of Ca^{2+}/ROS-dependent signaling under hypoxia.

2.2.2. The control of ROS production under hypoxia

Hypoxia evokes specific mechanisms to control ROS overproduction by the upregulation of antioxidant enzymes: SOD, catalase (CAT) and glutathione peroxidase (GPx). Exposure to different hypoxia regimens resulted in the increased expression and activity of SOD, CAT and GPx. Thus, chronic intermittent hypoxia was shown to upregulate the system of matrix antioxidants: SOD and (CAT), which exhibited elevated expression and activity after hypoxia exposure. Higher expression of SOD, CAT and GPx found in myocardium after the exposure to intermittent hypobaric hypoxia afforded preconditioning-like effect explained by the induction of antioxidant defense [19].The effect was similar to the pretreatment of the hearts with antioxidant mixture containing SOD and CAT, which helped to restore cardiac contractile function after ischemia/reperfusion [18]. Thus, while mitochondrial ROS generated by the respiratory chain are supposed to trigger the response to hypoxia shown by the increase in $[Ca^{2+}]_c$, HIF stabilization and triggering of redox signaling [3, 4, 42–44], elevated expression and activation of Mn-SOD, CAT and GPx are capable to abolish or attenuate this response [48, 49] and prevent excess lipid peroxidation and depletion of reduced glutathione [17].

Overexpression of the antioxidant enzymes in pulmonary artery smooth muscle cells showed selectivity towards the inhibition of hypoxic increase in ROS and $[Ca^{2+}]_c$ [48]. Common to other cell types, in smooth muscle cells hypoxia exposure increased both ROS production and $[Ca^{2+}]_c$. Overexpression of GPx and CAT, both cytosolic and mitochondrial, attenuated the response to hypoxia. Overexpression of cytosolic Cu, Zn-SOD had no effect on both ROS and $[Ca^{2+}]_c$, whereas overexpression of matrix Mn-SOD augmented $[Ca^{2+}]_c$ but had no effect on ROS signaling [48]. These data indicated H_2O_2 to be signaling molecule to trigger the response to hypoxia in smooth muscle cells. The absence of the effects of SOD on ROS signaling could be explained by increased H_2O_2 production and signaling explained by the increased SOD activity.

ROS-dependent stabilization and activation of HIF, downregulation of the OxPhos, lack in cellular ATP, activation of AMPK and other signaling pathways, elevation of ROS production and triggering of ROS-dependent signaling result in the opening and activation of mKATP channels, which is supposed to be a part of the adaptive response to hypoxia. As it will be shown below, multiple mKATP channel functions under hypoxia are aimed at controlling mitochondrial respiration, ATP synthesis and ROS production relevant to the conditions of oxygen deficiency.

3. Mitochondrial potassium transport under oxygen deficiency

Cells maintain high transmembrane gradients of sodium and potassium, which support cellular membrane potential built up by the work of Na^+, K^+-ATPase, plasmalemmal K^+ and Na^+ channels and transporters (Na^+/H^+, Na^+/Ca^{2+} and others), in order to maintain cellular functions and metabolism. Potassium is a prevalent cation of cytosol and mitochondrial matrix, where its concentration reaches 120–150 mM, and virtually there is no transmembrane gradient of this cation between the matrix and the cytosol [50]. Possibly, for this reason, K^+ transport for decades was not paid attention needed, till the discovery of mKATP channel (1991), and its importance for tissue protection first observed in experimental models of ischemia/reperfusion [58]. Shortly after it appeared that mKATP channel plays an equally important role in the adaptation of a living organism to oxygen deprivation [20], and later similar effects of the opening of large conductance calcium activated K^+ channel (BK_{Ca} channel) were observed [27]. These findings served as a powerful stimulus for extensive studies of the properties and functions of mitochondrial K^+ channels and cytoprotective mechanisms triggered by K^+ channels opening.

The system of mitochondrial potassium transport is represented by several types of potassium channels: ATP-sensitive K^+ channel (mKATP channel) large conductance Ca^{2+}-activated K^+ channel (BK_{Ca} channel), intermediate conductance Ca^{2+}-activated K^+ channel (IK_{Ca} channel), voltage-gated K^+ channel (Kv 1.3), twin pore potassium channel and other types of K^+ conductance (reviewed in more detail in [23]). Potassium uptake via K^+ channels is opposed by K^+/H^+ exchanger, which acting coordinately constitute potassium cycle [24].

As it was reported, different regimens of hypoxia exposure (such as intermittent hypobaric hypoxia [10, 21, 41], brief hypoxia exposure (hypoxic preconditioning) [25], chronic hypoxia [20, 27, 59]) resulted in the activation of potassium transport: mKATP channel [10, 20, 21, 41], BK_{Ca} channel [27] and K^+/H^+ exchange [21]. According to these data, mitochondrial K^+ channel opening and activation are ubiquitous consequence of oxygen shortage, indicating that K^+ channel opening is involved in the response of mitochondria to the lack of oxygen. So, in the light of the above metabolic and functional rearrangements caused by the oxygen deficiency, it is reasonable to ask which advantages are gained by the activation of mitochondrial potassium transport under hypoxia. Potassium uptake and potassium cycling are energy-dissipating processes affecting mitochondrial bioenergetics. So, with regard to the purpose of this review, most important is to consider how the modulation of mitochondrial functions by mKATP channels opening might affect oxygen-sensing properties of mitochondria and "mitochondrial response" to oxygen deficiency.

KATP channel is an octameric multiprotein complex ubiquitously present in plasma membranes and mitochondria. KATP channels comprise conducting subunit (Kir6.1 and Kir6.2) highly selective towards K^+ and receptor subunit SUR (SUR1A, SUR2A and SUR2B) differently distributed in tissues. The channel is specifically blocked by ATP in the presence of Mg^{2+}. Receptor subunit of the channel binds nucleotides and pharmacological modulators: sulfonylureas (glibenclamide, tolbutamide), which are channel blockers, and the openers (pinacidil, chromakalim, nicorandil, diazoxide). The properties and molecular composition of KATP channels are reviewed in detail in [60, 61].

In the literature, it was supposed that protection of tissues against the impairments caused by hypoxia afforded by mitochondrial K^+ transport is largely based on bioenergetic effects of K^+ transport and signaling triggered by K^+ channels opening [16, 41, 50, 53]. The impact of ATP-sensitive K^+ transport on the oxygen consumption, membrane potential, ATP synthesis, Ca^{2+} transport and ROS production is largely dependent on the abundance of the channel in mitochondrial membrane. Oxygen deficiency affects functional consequences of mKATP channels opening by modulating channels expression and activity [20, 53, 59]. As it was shown in cardiomyocytes, the activation of cardiac mKATP channels under hypoxia was mediated by the interactions of conducting subunit Kir6.2 with heat shock protein 90, HSP90 [25] and Kir6.1 with gap junction protein connexin 43 and PKCε [26]. Silencing or pharmacological inhibition of HSP90 and connexin 43 abolished protective effects afforded by mKATP channels opening [25, 26]. At present, there are scarce data on such interactions, which could contribute to cell specificity of molecular mechanisms regulating mKATP channels opening and its functional consequences under hypoxia. To assess how mKATP channels can be involved in mitochondrial response to oxygen deprivation, direct bioenergetic and functional effects of mKATP channels opening need to be considered.

3.1. Direct bioenergetic consequences of mKATP channels opening

In energized mitochondria, potential-dependent potassium transport directed to the matrix space takes place at the cost of proton-motive force ($\Delta\mu_H$), a free energy generated by the electron transport chain. As $\Delta\Psi_m$ is the main part of $\Delta\mu_H$, K^+ uptake, accompanied by the obligatory electroneutral water uptake [24], occurs at the cost of $\Delta\Psi_m$ and thus results in depolarization. Because of its dramatic effect on $\Delta\Psi_m$ and matrix swelling, K^+ uptake would be detrimental for mitochondria, if there was not the work of respiratory chain and K^+/H^+ exchange. Thus, the loss of $\Delta\Psi_m$ is opposed by the "compensatory" work of respiratory chain [62], which increases oxygen consumption proportional to the rate of K^+ transport in order to restore $\Delta\Psi_m$; on the other hand, matrix swelling is opposed by potassium extrusion *via* K^+/H^+-exchanger, which is accompanied by the matrix contraction [24]. Concurrent work of K^+ channels and K^+/H^+ exchanger constitutes mitochondrial K^+ cycle [24], of which potential-dependent component (K^+ uptake) dissipates $\Delta\mu_H$ and in this way uncouples mitochondria and affects potential-dependent mitochondrial functions: ATP synthesis, Ca^{2+} transport and ROS production.

The impact of mKATP channels opening on mitochondrial bioenergetics greatly depends on the channels' activity and their abundance in mitochondrial membrane, which is responsible for the effects of mKATP channels opening on mitochondrial energy state and decides for cell specificity of mKATP channel functions [63]. Thus, higher density of mKATP channel distribution in brain results in slight depolarization, which was observed in the literature and in our studies [63, 64], while lower amount of the channels in the heart and liver was of no effect on $\Delta\Psi_m$ even at full activation [24, 65, 66]. Elevated expression of mKATP channel and the channel activation that were observed under hypoxia [20, 21, 41, 59] increase the "weight" of ATP-sensitive K^+ transport in the regulation of mitochondrial functions and metabolism. This is still more visible in malignant cells functioning in hypoxic environment, in which overexpression of mKATP channel was shown [53].

Unlike protonophoric uncoupling that reduces transmembrane pH (ΔpH), uncoupling of the respiratory chain by mKATP channel opening is accompanied by the elevated ΔpH because of K^+ uptake into matrix occurring in exchange for protons. However, the activation of K^+/H^+-exchanger reduces this minor gain in ΔpH, and besides, simultaneous increase in the rate of oxygen consumption due to K^+ uptake dissipates $\Delta\mu_H$, largely at the cost of $\Delta\Psi_m$. Thus, the regulation of ROS production and other potential-dependent functions of mitochondria, dependent on cell type, are largely affected by the effects of ATP-sensitive K^+ transport on $\Delta\Psi_m$ and the rate of respiration.

3.1.1. The impact of mKATP channels opening on ROS production in mitochondria

Generally, it is supposed that cytoprotective effects of mKATP channels opening are primarily based on the modulation of Ca^{2+} transport and mitochondrial ROS production, which prevent Ca^{2+} overload [54, 56, 57] and trigger ROS-dependent signaling, thereby preventing the opening of cyclosporine-sensitive pore (mPTP) [50]. However, of all functional effects produced by mKATP channels opening (the modulation of mitochondrial morphology [9, 10], respiration [63, 65], Ca^{2+} transport [54–56], potassium cycle [24, 66], ATP synthesis [20, 67, 68] and ROS production [21, 50, 64]), the effects of ATP-sensitive K^+ transport on ROS production appear to be the most controversial. This diversity needs to consider the direct effects of mKATP channels opening on ROS production in mitochondria.

ROS production in mitochondria is regulated by a number of thermodynamic and kinetic factors [45]. The diverse, and even contrary, effects of mKATP channels opening on ROS production in mitochondria are difficult to evaluate because mitochondrial ROS production depends on a wide variety of conditions, which include mitochondrial energy state (quantitatively represented by $\Delta\mu_H$), redox potential of the main sites of ROS formation in the respiratory chain [69–71], the source of the electron supply to the respiratory chain, the rate of respiration [70] and, at last, the concentration of oxygen [3, 4], which is the end electron acceptor in the redox reactions in the respiratory chain.

Standard redox potential of one-electron oxygen reduction to superoxide constitutes −160 mV, and on this basis, the respiratory chain in highly energized mitochondria comprises multiple putative sites of ROS formation [45, 69]. At complex I, ROS formation largely occurs in the course of thermodynamically unfavorable reverse electron transport, which requires high $\Delta\mu_H$ and critically depends on both $\Delta\Psi_m$ and ΔpH [72, 73]. This mechanism of ROS formation is one best studied "classical" example of thermodynamically regulated ROS production in mitochondria. Unlike this, ROS production at complex III is dependent on both thermodynamic (such as the redox state of the ubiquinone pool) and kinetic factors [45, 69–71], such as the quantity and the life span of free radical intermediates of the redox reactions, which are regulated by the rate of respiration and the relations between the rates of ROS formation and the removal of these species. Q-cycle is supposed to be the main source of ROS in complex III [45], and ROS formation at this site exhibits a bell-shaped dependence on the redox state of Q-cycle [69]. Partially oxidized Q-cycle was shown to be most favorable for ROS production at complex III [74], which implies its dependence both on mitochondrial energy state and the rate of respiration.

The share of ATP-sensitive K^+ transport in the total K^+ transport in brain and liver mitochondria by our estimations, which agreed with literary data [24], was about ~30–35% [64, 66]. However, in spite of the well-defined characteristics of ATP-sensitive K^+ transport obtained in mitochondria of different cell types, the effects of mKATP channels opening on ROS production are difficult to quantify because of their dependence on several mutually dependent parameters. Overlay of the moderate alterations in mitochondrial functions caused by ATP-sensitive K^+ transport with closely interrelated thermodynamic and kinetic factors regulating ROS formation in mitochondria could explain apparently contradictory effects of mKATP channel opening on ROS production reported in the literature. Interestingly, both the elevation [16, 41] and suppression [21, 40] of ROS production were reported to improve cardiac and cardiomyocyte functions after the exposure to hypoxia in a way dependent on mKATP channel opening. Based on the published data, it is tempting to hypothesize that bidirectional regulation of ROS production by potassium transport observed in the literature could represent a flexible mechanism of the fast response to the elevation of ROS levels generally observed under hypoxia and that, dependent on conditions, could prevent ROS overproduction [57, 75] or trigger ROS-dependent signaling [16, 41, 50, 53], which makes this function of mKATP channel of especial importance under limited oxygen availability.

3.1.2. Direct effects of mKATP channel opening on F_0F_1 ATP synthase activity

In several works, including our own studies, an inhibition of both ATP synthesis and hydrolysis, ensuing from mKATP channels opening, was reported [67, 68, 76, 77]. Biochemical mechanism of this effect is not well understood, but, based on the published data, its physiological relevance can be considered.

As we have observed in our work on liver mitochondria, even full activation of mKATP channel by diazoxide moderately increased the rate of state 4 respiration and resulted in slight mitochondrial uncoupling not accompanied by depolarization [64]. However, these moderate changes in mitochondrial functions apparently suppressed phosphorylation, which could not be explained by the mild uncoupling effect. This was reflected in the decreased rates of state 3 respiration and phosphorylation, which were proved by measuring respective rates of proton transport after ADP addition [68]. It is worth mentioning that mKATP channel opening essentially reduced oxygen consumption in the course of phosphorylation and increased apparent P/O ratio [68]. These effects were coincident with concurrent activation of K^+ cycling, which was the cause of stimulation of state 4 respiration [66]. Based on the literature [78], we assumed that activation of K^+ cycling could be the plausible cause for inhibition of F_0F_1 ATP synthase functioning, not explained by respiratory uncoupling caused by ATP-sensitive K^+ transport.

Considering that ATP synthesis and hydrolysis are coupled to proton translocation across mitochondrial membrane, we supposed that concurrent K^+ cycling could disturb the molecular mechanism of F_0F_1 ATP synthase both at the stage of ATP synthesis and hydrolysis. Possibly, close mechanism of such molecular uncoupling called "decoupling" was observed in the literature under the action of K^+/H^+-ionophore gramicidin, which occurred without apparent changes in $\Delta\mu_H$ [78]. While the biochemical mechanism of such decoupling is not quite clear,

its physiological meaning appears to be more evident and needs to be considered. In agreement with the literature, we suppose that it is the regulation of cellular levels of ATP [67, 77], but what is still more important, the regulation of the oxygen consumption by mitochondria.

3.2. Functional consequences and molecular targets of mKATP channel opening under hypoxia

The functional effects of mKATP channels opening under hypoxia are similar to those observed in normoxic cells. Thus, under oxygen deprivation, mKATP channel activation reduced mitochondrial Ca^{2+} loading [57, 79], preserved ATP levels [67, 77] and increased cell survival [16, 40, 41, 80] by suppression of apoptosis *via* targeting glycogen synthase kinase 3β (GSK3β), an enzyme involved in triggering cell death by promotion of the opening of mitochondrial permeability transition pore, mPTP [81]. Suppression of cell death pathways resulted in stabilization of membrane potential [16, 59, 80] and the restoration of ATP synthesis [82]. Increased expression of both Kir6.2 [59] and SUR2A [37], similar to pharmacological mKATP channels opening, too was shown to improve the viability and the resistance of cardiomyocytes to hypoxia.

As one can see from the above examples, cell response to hypoxia was essentially dependent on the bioenergetic effects of mKATP channels opening. This allows assume that cytoprotection afforded by mKATP channels opening is largely based on a synergistic action of bioenergetic effects of mKATP channel functioning (primarily ROS production and ATP synthesis [20, 40, 41, 67, 79]), and the redox signaling critically dependent on ROS formation caused by mKATP channels opening [16, 50].

In the literature, it was obtained rather unambiguous evidence of the suppression of the OxPhos by mKATP channels opening [67, 76, 77]. However, it seems to be surprising that under hypoxia, similar to other metabolic stress conditions, cytoprotection was afforded by contrary effects of mKATP channels opening on free radical formation, and both the reduction [40, 80] and the elevation [16, 41, 50] of ROS production were shown to afford cytoprotective effects. To smooth this apparent contradiction, we recently proposed [83] that, dependent on the direct impact of ATP-sensitive K^+ transport on mitochondrial bioenergetics, mKATP channels opening could afford protection at least in two ways: either directly, by the direct reduction of ROS formation under certain conditions [40, 75, 80, 84] or indirectly, by the elevation of ROS production and triggering of ROS-dependent signaling shown to be cytoprotective under oxygen deprivation (ischemia and hypoxia) [16, 41, 50]. To shed more light on physiological role(s) of mKATP channels under hypoxia, functional consequences of mKATP channels opening on ROS production and ATP synthesis should be considered in more detail.

3.2.1. Triggering of ROS-dependent signaling and controlling of ROS production in mitochondria

With reference to hypoxia, it is generally supposed that mitochondria respond to oxygen deprivation by the generation of ROS and activation of ROS-dependent signaling pathways [3–5, 14]. mKATP channel was shown to be involved in ROS signaling triggered both upstream (by the activation of kinases PI3K/Akt, PKCε [16, 80]) and downstream (p38MAPK

[52], PKCε, Akt [16, 41]) of mKATP channels opening. This implies the ability of mKATP channel to sense and convey ROS signals, which agrees with the function of the channel as a "ROS sensor" proposed in the literature [75, 84]. The ability of mKATP channel to accept and convey ROS signals is well illustrated by the fast response to hypoxia exposure by NOX/ROS-dependent activation of PKCε *via* mKATP channel opening and feedback ROS/PKCε-dependent activation of NOX [16, 42, 47], PI3K/Akt and PKC activation upstream and feedback PKCε activation downstream of mKATP channel opening *via* increase in ROS formation [51] and ROS-dependent Akt and PKCε activation downstream of mKATP channel opening [41], which exerted anti-apoptotic effect by the inhibition of GSK3β and mPTP opening. The ability of ATP-sensitive K^+ transport to trigger cytoprotective signaling based on the modulation of ROS production has adverse effects in tumors functioning under limited oxygen supply and known to exhibit high mKATP channel activity. Thus, radioresistance of malignant glioma cells overexpressing mKATP channel was shown to be dependent on mKATP channel opening, increasing mitochondrial ROS emission and triggering of MAPK/ERK signaling, which also resulted in suppression of mPTP opening and prevention of tumor cell death [53].

As shown in the above examples, a hypothesis of mKATP channels acting as ROS sensors [75, 84] could be useful in the appraisal of physiological functions of mKATP channel under hypoxia. It is well known that mKATP channel can be activated by ROS [85], and elevated channel activity in response to excess ROS formation could serve to regulate mitochondrial metabolism and prevent ROS overproduction [57, 79]. This enables us to consider mKATP channel as the trigger of both ROS-dependent signaling and "ROS sensor" involved in the regulation of mitochondrial ROS production *via* modulation of mitochondrial bioenergetics. Oxidative modification of mKATP channel can represent a feedback mechanism for the regulation of mKATP channel activity. Being at one time a subject of an oxidative modification and a regulator of ROS formation, mKATP channel could be an effective tool in controlling of mitochondrial ROS production under hypoxia.

The impact of mKATP channel opening on mitochondrial energy state, dependent on the channel activity, could serve as a regulatory mechanism directed either on triggering of redox signaling or prevention of ROS overproduction. Apparently, controversial data on the regulation of ROS production by mKATP channel opening possibly reflect one integrated mechanism regulating fast response of mitochondria to the changes of ROS levels in the mitochondrial environment.

3.2.2. ATP-sensitive K^+ transport in the regulation of oxidative phosphorylation

Physiological role of mKATP channel functioning under hypoxia is not limited to the regulation of ROS production and antiapoptotic effects. In our recent work [68], we proposed that F_0F_1 ATP synthase can be one of the principal targets of mKATP channels opening. The modulation of ATP synthesis by ATP-sensitive K^+ transport can play particularly important role under hypoxia, which is the regulation of cellular ATP and controlling of oxygen consumption:

Generally, it is supposed that suppression of ATP hydrolysis by mKATP channels opening is a plausible explanation for the preservation of cellular ATP of excess depletion observed

after application of pharmacological mKATP channel openers under pathophysiological conditions [67, 77]. This assumption was supported by the data showing that inhibition of hydrolytic activity of F_0F_1 ATP synthase by mKATP channel openers helped to preserve cellular ATP levels under ischemic conditions [67]. Possibly, under hypoxia, suppression of ATP hydrolysis would be helpful in saving ATP available from the glycolytic pathway. Besides, the dramatic fall of the total level of ATP under hypoxia and suppression of ATP synthesis by ATP-sensitive K^+ transport should keep mKATP channel in functionally active state in order to maintain other physiological functions of the channel. However, we suppose that inhibition of ATP synthesis could be of particular significance under oxygen deprivation.

Under hypoxia, controlling of cellular oxygen level becomes important for cell survival [3–5, 46]. Mitochondria consume most part (up to 90%) of cellular oxygen. With reference to hypoxia, it needs to be considered that ATP synthesis, which continually occurs in a living cell, is a highly oxygen-consuming process. Thus, it is reasonable to suppose that controlling of oxygen consumption by controlling the rate of ATP synthesis and the reduction of oxygen expenses for oxidative phosphorylation is one vitally important function of mKATP channel under hypoxia. This is in line with other mechanisms suppressing mitochondrial respiration and OxPhos reported in the literature: the activation of AMPK and glycolysis, S-nitrosation of the respiratory complexes and downregulation of F_0F_1 ATP synthase. Possibly, this function of ATP-sensitive K^+ transport (and K^+ transport on the whole) to reduce oxygen consumption and save oxygen for oxygen-dependent processes by suppression of the oxidative ATP synthesis could move into first place under hypoxia. Concomitant suppression of ATP hydrolysis should prevent excess ATP consumption, which was confirmed by the data showing a preservation of cellular ATP ensuing from the mKATP channel opening.

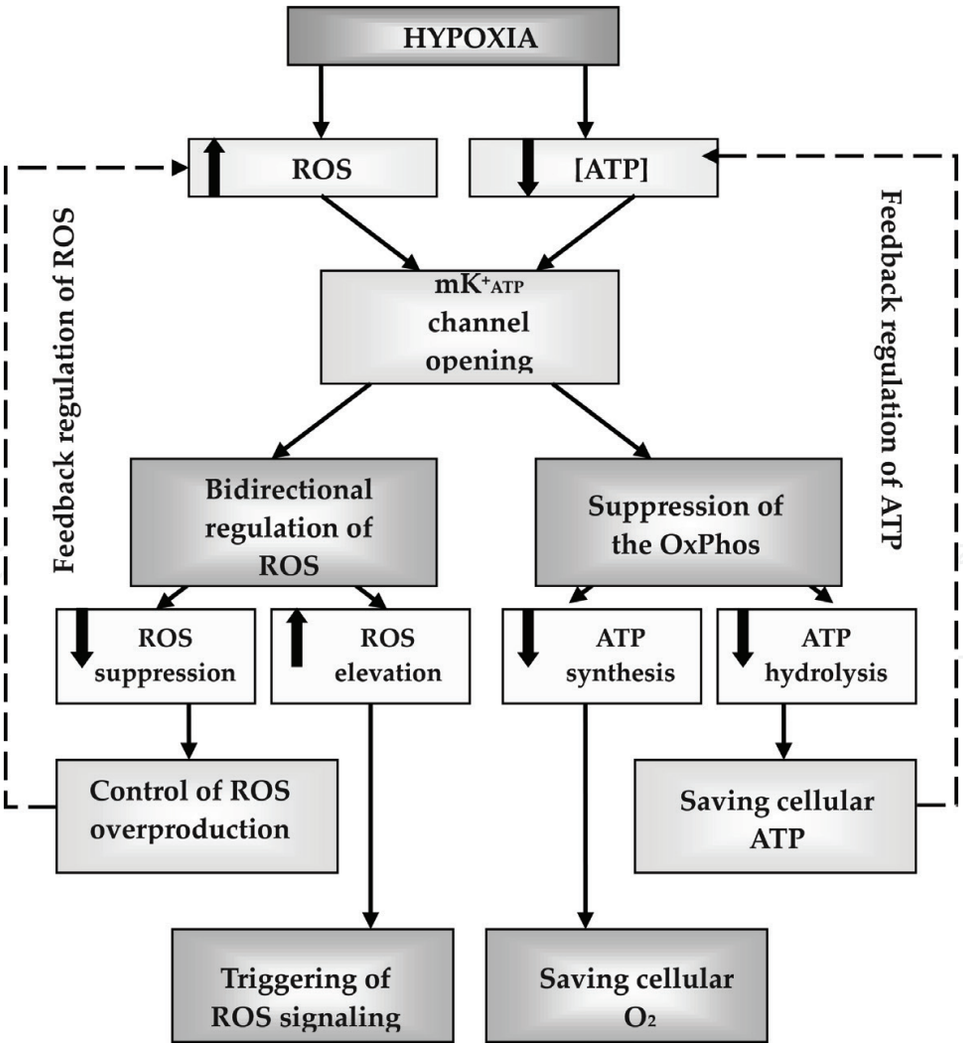
4. Conclusions: physiological relevance of mKATP channel functions under hypoxia

Mitochondria respond to hypoxia by triggering ROS signaling, HIFs activation, controlling of oxygen consumption, ROS production and the level of cellular ATP. Potassium channels of mitochondria and plasma membrane were shown to be both oxygen sensors and ROS sensors and thus are first to respond to the changes of ROS and oxygen levels in the cell. Several published data discussed in this review allow us suppose that activation of potassium transport in mitochondria and controlling the above processes *via* mKATP channel opening could be one of the key events in the adaptive responses of the organelles to hypoxia.

As it was supposed by many authors, mitochondria, being the main oxygen consumers, deprive the rest of the cell of oxygen. Under these conditions, ATP synthesis *via* OxPhos becomes too oxygen expensive function of mitochondria. So, phosphorylation should be down-regulated in order to rescue the whole cell from severe oxygen deficiency. Thus, under hypoxia, several mechanisms are brought into action in order to reduce oxygen consumption by mitochondria, i.e. by downregulation and nitrosylation of respiratory complexes, by

producing H_2S as electron donor to the respiratory chain, by downregulation of the OxPhos and by the activation of mitochondrial ATP-sensitive K^+ transport to reduce ATP synthesis and oxygen expenses for one of the most oxygen-consuming mitochondrial functions. Thus, hypoxia upregulates glycolysis in order to save oxygen and preserve cellular ATP needed for energy-consuming processes, such as maintenance of membrane potentials, metabolism, protein synthesis and other cell functions. Inhibition of ATP hydrolysis by potassium transport helps to save ATP obtained by glycolytic pathway.

The activation of mitochondrial potassium transport is a ubiquitous phenomenon under the limited oxygen availability. The above brief survey of the literature enables us to propose the following important functions of mKATP channels relevant to hypoxia: (1) ability to accept and convey ROS signals, triggering of ROS signaling specific for hypoxia; (2) controlling of mitochondrial ROS production and preventing overproduction; (3) controlling the level of cellular oxygen by oxygen-saving control of OxPhos and ATP production and (4) saving cellular ATP (obtained from both oxidation and glycolysis) by suppression of ATP hydrolysis. Multiple mKATP channel functions under hypoxia discussed in this work can be summarized in the following scheme.



Scheme. mKATP channels functions under hypoxia.

Being important for the understanding of physiological role of mKATP channel, these aspects of mKATP channel functions, largely based on bioenergetic effects of ATP-sensitive K^+ transport, cannot yet help in appraisal of the specificity of mKATP channel, as compared to other potassium channels present in mitochondria. Possibly, novel concepts of physiological role(s) of mKATP channels based on the molecular and cellular mechanisms regulating mKATP channel functioning are required to extend our understanding of physiological relevance and the mechanisms regulating mKATP channel functions under hypoxia.

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