Some Aspects of the Mitochondrial KATP Channel Functioning under Hypoxia

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Abstract

Oxygen deficit is known to produce profound alterations to mitochondrial functions and metabolism. Primarily, it concerns the complexes of the respiratory chain, the functions of antioxidant and pro-oxidant enzyme systems in the cell and mitochondria, pathways of ATP synthesis, ROS production and signaling. But one common feature of the metabolic alterations in mitochondria under hypoxia is the activation of mitochondrial potassium transport. The system of mitochondrial potassium transport is represented by several types of potassium channels and K^+/H^+ exchanger, which acting coordinately constitute potassium cycle. Potassium transport is an all-round modulator of mitochondrial functions: oxygen consumption, Ca^{2+} transport, ATP synthesis, ROS production and matrix volume. But what are the functions of potassium transport and which are the benefits of the activation of potassium channels under hypoxia? The purpose of this mini-review is an attempt to find answers to these questions based on the published data and the results of the author's research.

Keywords: Hypoxia; Mitochondria; Potassium transport; Oxygen consumption; ATP synthesis; ROS production

Introduction

Oxygen deficit caused by several hypoxic states and conditions produces deep alterations in a living organism at systemic and cellular level. Cells respond to hypoxia by multiple metabolic alterations and molecular mechanisms aimed to minimize detrimental consequences of the oxygen deprivation. Primarily, adaptive responses to hypoxia involve metabolic alterations in mitochondria. Changes in mitochondria functions and metabolism appear at the level of the respiratory chain, the functions of antioxidant and pro-oxidant enzyme systems, ATP synthesis, ROS production and signaling. Even short-term exposure to hypoxia triggers complex network of cell-specific signaling pathways involving the activation of kinases (phosphatydil-inositol-3-kinase (PI3K))/protein kinase B (Akt) pathway, mitogen activated protein kinase (p38MAPK), AMP activated protein kinase (AMPK), and the induction of early genes [1-5]. 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 family counts three known members, HIF1α, HIF2α, and HIF3α), the transcription factor, which triggers metabolic reprogramming resulting in the shift from oxidative to glycolytic metabolism [6-8]. Hypoxia is characterized by the elevated ROS production [2,9]. At cellular level, primary source of ROS is NADPH oxidase [2], whereas at the level of mitochondria, electron supply shifts from the NADH-dependent substrates (complex I) to succinate (complex II) [8,9], and the major site of the ROS formation moves to the complex III of the respiratory chain [10,11].

ROS, which are the products of the incomplete reduction of oxygen (superoxide, hydroperoxide, •OH radical, and others), for a long time were considered to be dangerous to the cells and a whole living organism because of their well-known detrimental action on lipids, proteins and nucleic acids. However, past decades of extensive studies resulted in a completely new look on physiological functions of oxygen-derived free radicals. Now it became evident that virtually all cellular processes, including signal transduction and metabolism, could trigger, or involve, or are subject to ROS action. Mitochondria are supposed to be one of the main sources of cellular ROS, thus modulation of mitochondrial ROS production has important physiological consequences. Thus, ROS production at complex III, and ROS-dependent HIF stabilization was shown to be critical for complex metabolic reprogramming of the cells under oxygen deficiency [10,11]. Notable is that a common feature of the metabolic and functional alterations occurring 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 deprivation [12,13].

Potassium is a prevalent cation of cytosol and mitochondrial matrix, where its concentration reaches 120-150 mM. Cells maintain high transmembrane gradients of sodium and potassium, which support cellular membrane potential and are supported by the work of plasmalemmal K^+ and Na^+ channels, transporters (Na^+/H^+, Na^+/Ca^{2+}, and others), and Na^+, K^+-ATPase, in order to maintain cellular functions and metabolism. Practically there is no transmembrane gradient of this cation between the matrix and the cytosol [14]. Possibly, for this reason K^+ transport for decades was not paid an attention needed, till the discovery of mKATP channel (1991) and its importance for tissue protection first observed in experimental models of ischemia/reperfusion [15]. Shortly after it appeared that mKATP channel plays an equally important role in the adaptation of a living organism to oxygen deprivation [16], and later similar functions of large conductance calcium activated K^+ channel (BKCa channel) too were shown [17]. These findings served a powerful stimulus for extensive studies of the properties and functions of mitochondrial K^+ channels, and cytoprotective mechanisms triggered by K^+ channels opening. So, in the light of the above metabolic rearrangements, it is reasonable to ask which advantages could be gained under the

conditions of reduced oxygen availability by the activation of potassium transport in mitochondria.

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, however multiple issues regarding molecular composition, tissue distribution and physiological functions of mKATP channel still remain to be clarified [14, 18]. For the above reasons, primarily the functions of ATP-sensitive potassium transport will be discussed below and some aspects of the regulation of ROS production and ATP synthesis by mKATP channels opening relevant to hypoxia will be considered.

Functional consequences of mKATP channel opening under hypoxia

Short-term or moderate hypoxia exposures (such as hypoxic preconditioning or intermittent hypoxia) put into action adaptive mechanisms capable to protect an organism against severe oxygen deprivation. mKATP channels opening, which is the part of adaptive response, was shown to be cytoprotective under exposure to hypoxia, anoxia and several metabolic stress conditions [1-3,13]. Thus, mKATP channels activation reduced mitochondrial Ca^{2+} loading [19,20] preserved ATP levels [21,22], and increased cell survival [2,3,23-25] by suppression of apoptosis *via* targeting glycogen synthase kinase 3β (GSK3β), an enzyme involved in triggering apoptosis and promotion of the opening of mitochondrial permeability transition pore, mPTP [26]. Suppression of cell death pathways, in turn, resulted in stabilization of membrane potential [2,3,27], and the restoration of ATP synthesis [28]. Increased expression of both Kir 6.2 [27] and SUR2A [5], similar to pharmacological mKATP channels opening, too was shown to improve the viability and the resistance of cardiomyocytes to hypoxia. Interestingly, both the elevation [2,24] and suppression [3,13,23] of ROS production was reported to improve cardiac and cardiomyocyte functions after the exposure to hypoxia in a way dependent on mKATP channel opening.

As one can see from the above examples, cell response to hypoxia was essentially dependent on the bioenergetic effects of mKATP channels opening. This allow us to assume that cytoprotection afforded by mKATP channels opening largely is based on a synergistic action of bioenergetic effects of mKATP channels functioning (primarily directed at the modulation of ROS production and ATP synthesis [16,20,21,23-25]), and the redox signaling critically dependent on ROS formation caused by mKATP channels opening [2,29]. However, in the light of the above data, it is rather surprising that under hypoxia, similar to other metabolic stress conditions, cytoprotection was afforded by contrary effects of mKATP channels opening on free radical formation: both the reduction [3,23] and the elevation [2,28-30] of ROS production was shown to afford cytoprotective effects. To smooth this apparent contradiction (which up to date is not yet well understood) we recently proposed [31] 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 [3,23,32,33], or indirectly, by the elevation of ROS production and triggering ROS-dependent signaling shown to be cytoprotective under ischemia and hypoxia [2,24,30]. Thus to shed light on physiological role(s) of mKATP channels under hypoxia, bioenergetic consequences of mKATP channels opening should be considered in more details.

Bioenergetic consequences of mKATP channel functioning

The impact of mKATP channels opening on ROS production in mitochondria

Of all functional effects produced by mKATP channels opening (the modulation of mitochondrial morphology [34], respiration [35,36], Ca^{2+} transport [19,20], potassium cycle [14,37], ATP synthesis [21,38,39] and ROS production [29,30]) the effects of ATP-sensitive K^+ transport on ROS production appears to be the most controversial. This diversity needs to consider the direct effects of mKATP channels opening on ROS production in mitochondria.

Direct functional consequences of mKATP channels opening: In energized mitochondria potential-dependent potassium transport directed to the matrix space takes place at the cost of electrochemical proton potential (protonmotive 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, which is accompanied by the obligatory electroneutral water uptake [14], 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, loss of $\Delta\Psi_m$ is opposed by the "compensatory" work of respiratory chain [40], 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 [14]. Concurrent work of K^+ channels and K^+/H^+-exchanger constitutes mitochondrial K^+ cycle [14], 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.

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 effects of K^+ transport on $\Delta\Psi_m$ and the rate of respiration, dependent on cell type, become important determinants in the regulation of ROS production.

The impact of mKATP channels opening on mitochondrial bioenergetics greatly depends on the channels activity and their abundance in mitochondrial membrane [36]. Elevated expression of mKATP channel, as well as the channel activation, that both was observed under hypoxia [5,13] increase the weight of ATP-sensitive K^+ transport in the regulation of mitochondrial functions and metabolism. This is evident not only in normal cells under oxygen deficiency, but also in malignant cells known to function in hypoxic environmemt, in which overexpression of mKATP channel was shown [41].

The effects of mKATP channels opening on free radical formation: ROS production in mitochondria is regulated by a number of thermodynamic and kinetic factors [42]. 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 [42-45], the source of the electron supply to the respiratory chain, the rate of respiration [38], and at last, the concentration of oxygen [45, 46], 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 sites of ROS formation [42,43]. At complex I ROS formation largely occurs in the course of reverse electron transport, which process is thermodynamically unfavorable, requires high $\Delta\mu_H$, and critically depends on both $\Delta\Psi m$ and ΔpH [47,48]. 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 [42-45], such as the quantity and the life span of free radical intermediates of 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 [42], and ROS formation at this site exhibits a bell-shaped dependence on the redox state of Q-cycle [43]. Partially oxidized Q-cycle was shown to be most favorable for ROS production at complex III [49], 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 [14], was about ~30-35% [37,50]. Full channel activation, that in both cases was accompanied by the moderate increase in state 4 oxygen consumption, which fits with the term of "mild uncoupling", was of no effect on $\Delta\Psi m$ in liver mitochondria [37] and capable only of minor depolarization (by ~20% in brain mitochondria [50]). However, in spite of the well-defined characteristics of the 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. However, based on the direct effects of ATP-sensitive K^+ transport considered above, it is tempting to hypothesize that this 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, which makes this function of mKATP channel of especial importance under limited oxygen availability.

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, which are supposed to be a part of the adaptation to hypoxic conditions [10,11]. mKATP channel was shown to be involved in ROS signaling triggered both upstream (by the activation of kinases PI3K/Akt, PKCε [2,3]) and downstream (p38MAPK [4], PKCε, Akt [2,24]) of mKATP channels opening. This implies the ability of mKATP

channel to sense and convey ROS signals, which agrees with the function of mKATP channel as a "ROS sensor" system proposed in the literature [32,33]. Ability of mKATP channel to accept and convey ROS signals is well illustrated by the example of fast response to hypoxia exposure by NADPH oxidase/ROS-dependent activation of PKCε *via* mKATP channel opening and feedback ROS/PKCε-dependent activation of NADPH oxidase [2], PI3K/Akt and PKC activation upstream and feedback PKCε activation downstream of mKATP channel opening *via* increase in ROS formation [51], ROS-dependent Akt and PKCε activation downstream of mKATP channel opening [24], which exerted anti-apoptotic effect by the inhibition of GSK3β and mPTP opening. However, ability of ATP-sensitive K^+ transport to trigger cytoprotective signaling based on the modulation of ROS production has adverse effects in tumors, known to function under limited oxygen access and 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 [41].

As show the above examples, a hypothesis of mKATP channels acting as ROS sensors [32,33] 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 [52], and elevated channel activity in response to excess ROS formation could serve to regulate mitochondrial metabolism and prevent ROS overproduction [19,20]. In the light of literary data, mKATP channel can be considered as: 1) trigger of ROS-dependent signaling; 2) "ROS sensor" involved in the regulation of mitochondrial ROS production *via* modulation of mitochondrial bioenergetics; 3) the subject of oxidative modification, which may 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 feedback mechanism limiting ROS overproduction by mKATP channel activation.

With reference to hypoxia, it is tempting to propose one more putative function of mKATP channel based on the controlling of ROS production. Thus, stabilization of HIF was shown to be critically dependent on ROS production at complex III [10,11]. Considering that primary site of ROS production under hypoxia shifts to complex III, the controlling of ROS production at this site of the respiratory chain by potassium transport implies a promising role of mKATP channel in the regulation of HIF activity and HIF-dependent signaling as a part of adaptation to oxygen deficiency.

Thus, based on the published data, we propose that mKATP channel, dependent on the conditions, takes part either in triggering of ROS-dependent signaling, or controlling of ROS production (by preventing overproduction) in mitochondria. 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.

ATP-sensitive K^+ transport in the regulation of oxidative phosphorylation: mPTP is one acknowledged molecular target of cytoprotective ROS signaling triggered by mKATP channels opening [30]. However, physiological role of mKATP channels functioning

under hypoxia is not limited to the regulation of ROS production. In our recent work [39] we proposed that F_0F_1 ATP synthase can be another principal target of mKATP chanels opening, and the modulation of ATP synthesis by ATP-sensitive K^+ transport can play an especial role under hypoxia. In several works, including our own research, an inhibition of both ATP synthesis and hydrolysis was reported [21,38,39,53]. Biochemical mechanism of this effect is not well understood, but, based on the published data, its physiological relevance can be considered.

Direct effects of mKATP channel opening on F_0F_1 ATP synthase activity: 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 [39]. However, these moderate changes in mitochondrial functions apparently suppressed phosphorylation, which was not explained by the mild uncoupling effect. This was reflected in the decreased rates of state 3 respiration and phosphorylation, which was proved by measuring respective rates of proton transport after ADP addition [39]. Worth mention that mKATP channel opening essentially reduced oxygen consumption in the course of phosphorylation and increased apparent P/O ratio [39]. These effects were coincident with concurrent activation of K^+ cycling, which was the cause of stimulation of state 4 respiration [37]. Based on the literature [54], we assumed that activation of K^+ cycling could be the plausible cause for inhibition of F_0F_1 ATP synthase functioning, not explained by bioenergetic effects of ATP-sensitive K^+ transport.

Considering that ATP synthesis and hydrolysis is 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, one example 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 $\Delta\mu_H$ [54]. While the biochemical mechanism of such decoupling is not quite clear, its physiological meaning seems to be more apparent. In agreement with the literature, we suppose that it is the regulation of cellular levels of ATP [21, 53], but what is as well important, the regulation of the oxygen consumption by mitochondria.

The regulation of cellular ATP: Generally, it is supposed that suppression of ATP hydrolysis by mKATP channels opening is a plausible cause for the preservation of cellular ATP of excess depletion under pathophysiological conditions [21,53]. This assumption was supported by the data showing that inhibition of hydrolytic activity of F_0F_1 ATP synthase by mKATP channels openers helped to preserve cellular ATP levels under ischemic conditions [21]. Possibly, under hypoxia suppression of ATP hydrolysis would be helpful in saving ATP available both from the oxidative and glycolytic pathway. On the other hand, 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 F_0F_1 ATP synthase could be of special significance under oxygen deprivation.

As it is known, under hypoxia controlling of cellular oxygen level becomes important for cell survival [10,11,46]. 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. As we suppose, this implies one more important function of mKATP channel, i.e. controlling oxygen consumption by controlling the rate of ATP synthesis and reducing oxygen expenses for

phosphorylation. Possibly, this function of ATP-sensitive K^+ transport (and K^+ transport on the whole) to reduce oxygen consumption and save the 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 [21,22].

Conclusion

Physiological relevance of mKATP channels functions under hypoxia: Mitochondria respond to hypoxia by triggering ROS signaling, HIFs activation, controlling of oxygen consumption and the level of cellular ATP. Several published data allow us suppose that mKATP channel opening and controlling the above processes could be one of the key events in the adaptive responses of mitochondria to hypoxia. The above brief survey of the literature enables us to propose following important functions of mKATP channels relevant under hypoxia: 1) ability to accept and convey ROS signals; 2) controlling ROS production at complex III, which implies indirect regulation of HIF activity; 3) controlling the level of cellular oxygen by oxygen-saving control of ATP production; 4) saving cellular ATP (obtained from both oxidative and glycolytic pathways) by suppression of ATP hydrolysis. To be quite correct, the above aspects of mKATP functioning rather describe the functions of ATP-sensitive K^+ transport, but not functions of mKATP channel *per se*. Being important for the understanding of physiological role of mKATP channel, these aspects of mKATP channel functions cannot help in appraisal of the specificity of mKATP channel, as compared to other potassium channels present in mitochondria.

Further research and novel concepts of physiological role(s) of mKATP channels (based not so on the properties of ATP-sensitive K^+ transport, as on the molecular and cellular mechanisms regulating mKATP channels functioning) are required to extend our understanding of physiological relevance and the mechanisms regulating mKATP channels functions under hypoxia.

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