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On the impact of K(ATP) channel opening on mitochondrial reactive oxygen species production

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Abstract

Mitochondrial reactive oxygen species (ROS) production was shown to be regulated by cell-specific mechanisms. Cytoprotective role of mKATP channels functioning appeared to be important in the regulation of ROS production in different cell types under different pathophysiological conditions. But how to explain contradictory data respective to the impact of mKATP channels opening on ROS formation and what is physiological relevance thereof? The main complexities arising when addressing these issues are discussed below.

Cytoprotective potential of mitochondrial KATP channels (mKATP channels) functioning are thought to be based largely on bioenergetic effects of mKATP channel opening, primarily the regulation of ATP synthesis and ROS production [1,2]. mKATP channels are thought to be "ROS" sensors capable of controlling ROS production in different cell types in response to different stimuli what means their important role in cellular ROS signaling [2-4]. From the contemporary point of view, mKATP channels are: 1) subject of ROS-dependent modification, which may represent a feedback mechanism for the regulation of mKATP channel activity; 2) "ROS sensors" involved in the regulation of mitochondrial ROS production *via* modulation of mitochondrial bioenergetics; 3) "triggers of ROS signaling" involved in certain ROS signaling pathways (well-known example of such regulation is mitochondrial PKC activation *via* hydroperoxide formation ensuing from mKATP channel opening [3-5].

Being at one time a subject of an oxidative modification and a regulator of ROS formation, mKATP channel could be a promising tool in controlling of mitochondrial ROS production. Besides theoretical interest, this issue likewise is of interest for health care practice. So, hypothesis of mKATP channels as "ROS sensors" seems to be very attractive but for one oddity. It is that there is actually no means to predict an effect of mKATP channel opening on ROS production because of very contradictory results regarding this issue obtained in different tissues. Meanwhile, this question needs to be answered for the more extensive clinical application of pharmacological mKATP channel openers.

The one complexity in predicting the effect of mKATP channel opening on ROS production is a cell-specificity of the impact of mKATP channel opening on mitochondrial bioenergetics. Generally, inward potassium transport *via* mKATP channel dissipates $\Delta\mu_H$, a free energy generated by electron transport chain. Being energy consuming process, K^+ uptake always enhances state 4 oxygen consumption and the respiration rate. Unlike protonophoric uncoupling that diminishes or even abolishes ΔpH, uncoupling of the respiratory chain by mKATP channel opening results in elevated ΔpH because of K^+ uptake into matrix. So, the main "bioenergetic target" of mKATP channel opening is $\Delta\Psi_m$, and the effect of K^+ transport on $\Delta\Psi_m$ becomes important determinant of ROS production.

As it is known, isoform distribution and the impact of mKATP channel opening on mitochondrial bioenergetics, particularly ΔΨm, largely varies between cell types. mKATP channels are known to comprise four subunits, two pore-forming Kir 6.x (Kir 6.1 and 6.2) and two sulphonylurea receptor SUR (SUR1 and SUR2, SUR2A and SUR2B) subunits heterogeneously distributed between tissues [6]. The effect of mKATP channels opening on $\Delta\Psi_m$ is directly dependent on the rate of ATP-sensitive K^+ transport and its share in state 4 respiration. The latter in turn depends on the abundance of the channels in mitochondrial membrane, which too is cell-specific. One early attempt to address this question was that of Garlid's group who conducted semi-quantitative estimation of the distribution of mKATP channel in mitochondria of different tissues. They found that in brain density of the mKATP channels in mitochondrial membrane largely prevailed over one found in heart and liver tissues, which implies a special importance of potential-dependent regulation of ROS production by ATP-sensitive K^+ transport in neuronal mitochondria [7]. This was confirmed in our own studies where we found a suppression of ROS production well explained by ~20% depolarization ensuing from mKATP channel opening. In turn, this agreed with the share of mKATP channel in state 4 respiration and the dependence of ROS formation on $\Delta\Psi_m$ in our mitochondrial preparations [8]. Literary data obtained on neuronal mitochondria too agreed with the observation that mKATP channel opening was accompanied by depolarization and suppression of ROS production [9].

Meanwhile, in liver and heart mitochondria mKATP channel opening did not result in depolarization, and ROS production in these organelles was governed by other, "potential-independent" mechanisms. The one regularity observed in our works studying Ca^{2+}

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transport at constant membrane potentials was the increase in the rate of ROS formation, directly dependent on the steady state rate of respiration, so that quasi-linear dependence of the rate of ROS formation on the rate of respiration was found [10]. Thus, if ΔΨm is unaffected by mKATP channel opening there is a great probability that mKATP channel opening would enhance ROS production.

However, this issue is much more complicated considering a cell-specific regulation of mitochondrial ROS production and usually impaired energy state of mitochondria under several pathophysiological conditions. It is reasonable to suppose that primary sites for ROS formation, shown to differentiate between different cell types can be differently affected by mKATP channel opening, especially, in damaged mitochondria [11]. All these variables make the prognosis of the impact of mKATP channel opening on ROS production a highly complicated task. As it is known, published data demonstrated quite opposite effects regarding this issue. Indeed, when considering cardiac mitochondria only, literature showed just so many examples of the elevation of ROS production, as the cases of its suppression [4, 12-14]. It is rather strange that these controversies never were discussed in the literature. Possibly, discrepancies could arise from different experimental conditions used to study the effect of mKATP channel opening on ROS formation, but this is not the answer to the question under consideration.

The one more strangeness considering published data is that both the elevation and suppression of ROS production ensuing from mKATP channel opening were shown to result in cell salvation under different pathophysiologicsl conditions. What else, as it was shown, cardioprotection afforded by mKATP channel opening was not necessarily mediated by ROS formation [15,16]. Possibly this means the presence of a "third part" decisive for triggering pathways of cell survival. This "third part" is a complex network of cell signaling triggered by mKATP opening [4,17,18]. However, multiple issues still need to be solved. Thus, was not it rather intriguing that both the elevation and suppression of ROS production ensuing of ATP-sensitive potassium transport were shown to be equally helpful for cell survival? What is cell specificity of signaling pathways triggered by mKATP channel opening? And what is more, whether indeed there was no cell death pathways triggered with the aid of mKATP channel opening? These questions need to be answered for proper understanding of physiological relevance of mKATP channel opening. So, a gap remains between the notions of biophysical properties of mKATP channel, bioenergetic effects of its functioning, and the knowledge of cell-specific pathways involved in cytoprotective effects of mKATP channel opening. At present, it seems that we are only at the very beginning in the understanding of physiological functions of mKATP channel. Efforts need to be made for the disclosure of cell-specific ROS signaling pathways triggered by mKATP channel opening.

Conclusions

mKATP channel plays a cell-specific role in the regulation of mitochondrial ROS production. This is largely dependent on the abundance of the channel in mitochondrial membrane which is decisive for the role of the channel in the regulation of mitochondrial energy state (primarily, ΔΨm). The impact of mKATP channel opening on ΔΨm (extent of depolarization) could be a link of a feedback mechanism limiting ROS overproduction in case of excess mKATP channel activation. Different effects of mKATP channel on ROS production too might depend on cell-specific regulation of ROS formation in the respiratory chain. Cytoprotective effects of ATP-sensitive K^+ transport based on the modulation of ROS production should involve cell-specific signaling events which could explain high specificity of protective pathways of mKATP channel opening in different cell types.

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