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 coordina-M

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

production depends on a wide variety of conditions, which include: mitochondrial energy state (quantitatively represented by ΔμH), 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 ΔΨm and ΔpH [47,48]. T is 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.

T e

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 efect is not well understood, but, based on the published data, its physiological relevance can be considered.

Direct efects 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

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