Modulation of the activity of the mitochondrial BK-channel and of the permeability transition pore by hypoxia and apoptotic factors

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Abstract

Hypoxia causes severe damage to the cell by initiating signaling cascades that lead to cell death including necrosis and apoptosis. The apoptotic factors Bax and Bcl-$_{XL}$ can determine the destiny of the cell by their ability to influence the intrinsic pathway of apoptosis, which involves the mitochondria. Recently, there appeared evidence that mitochondrial ion channels are sensitive to low levels of oxygen and apoptotic factors. As our laboratory is interested in proving the interaction of the mtBK-channel and the PTP and their relation to apoptosis we assumed that studying hypoxia and cell death modulating substances would lead us to a better understanding of these mechanisms.

The effects of hypoxia induced by N_2 and DTN on the mtBK-channel from mitoplasts of rat astrocytes and at the PTP from mitoplasts of rat liver were studied by means of patch-clamp techniques. It is demonstrated here that hypoxia reversibly activated the mtBK-channel while the PTP was irreversibly inhibited. Experiments measuring $\Delta\Psi$ of intact rat brain mitochondria (using the fluorescence dye safranine O) exhibited an increased Ca^{2+}-retention capacity during hypoxia implying impaired opening of the PTP. Ca^{2+}-retention capacity was also reduced by 100 nM iberiotoxin, a selective BK-channel inhibitor. Thus, I show that an open mtBK-channel keeps the PTP closed. Moreover, I found that GST-Bax inhibited the mtBK-channel from both, intra- and extracellular side already at the very low concentration of 1 nM. This inhibition is progressively enhanced with time. The antiapoptotic factor GST-Bcl-$_{XL}$ activated the mtBK-channel at hyperpolarizing potentials, inhibited the PTP, and abolished the effect of GST-Bax on the mtBK-channel.

The responses of the mtBK-channel and of the PTP to hypoxia could be considered as antiapoptotic and cytoprotective, because activation of the mtBK-channel contributes to cell survival and inhibition of the PTP disrupts the intrinsic apoptotic pathway. These effects might be mediated by the mitochondrial Ca^{2+} uptake and the oxygen sensitivity of the mitochondrial respiratory chain. Bax decreased the activity of the mtBK-channel so that opening of the PTP by Ca^{2+} is eased. This would result in activation of the downstream cascade of the intrinsic apoptotic pathway. Thus, Bcl-$_{XL}$ exerts its antiapoptotic activity not only through inhibition of Bax and the PTP, but also through activation of the cytoprotective mtBK-channel.