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Meeting abstract

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In brain mitochondria, calcium and cell death-associated permeability transition are controlled by possibly associated proteins, 2',3'-CNPase, Centaurin-alpha1 and peripheral benzodiazepine receptor, and their substrates/ligands

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Mitochondria play a central role in calcium homeostasis and cellular calcium signaling. During cellular calcium overload, mitochondria take up cytosolic calcium, which, in turn, induces opening of the permeability transition pore (PTP), disruption of mitochondrial membrane potential and cell death. PTP is a protein complex changing according to the needs of the cell and responding to different external and internal stimuli. The identity of the PTP is still unresolved. 2',3'-cyclic nucleotide 3'-phosphodiesterase (CNP) and p42(IP4) (centaurin-alpha1) have been shown to be associated with rat brain mitochondria (RBM), but the exact role of these proteins in mitochondria is still obscure. Localization of p42(IP4) and CNP within the inner membrane and contact sites indicates further functions for these proteins. We found interaction of p42(IP4) with CNP by pull-down binding assay and by immunoprecipitation.

Since PTP opening is important in mitochondrial events leading to programmed cell death, we studied whether p42(IP4) and CNP are involved in calcium-induced calcium release and consequently PTP. Simultaneous measurements of the respiratory rate, trans-membrane potential and calcium transport in the mitochondrial suspension were performed. We also developed the method of isolation of functionally active mitochondria from several cell types. We determined the calciumcapacity and lag-phase for PTP opening in mitochondria isolated from p42(IP4)-transfected and from control neuroblastoma cells. Overexpression of p42(IP4) led to promotion of calcium-induced PTP opening. The enzymatic activity of CNP was reduced under PTP opening, whereas the level of CNP detected in RBM before and after PTP opening were unchanged. Involvement of CNP in PTP operation was confirmed in further experiments using mitochondria isolated from CNP-knock-down oligodendrocytes (OLN93 cells). In mitochondria isolated from OLN93 cells transfected with CNP-targeting siRNA, CNP reduction was correlated with facilitation of calcium-induced PTP opening. The CNP substrates, 2',3'-cAMP and 2',3'-cNADP, induced PTP opening in RBM. The peripheral-type benzodiazepine receptor (PBR) is an 18 kDa mitochondrial membrane protein with still elusive functions. A release of pro-apoptotic factors, AIF and cytochrome c, from RBM was shown at threshold calcium load. Anti-PBR antibody blocked the release of AIF but did not affect the cytochrome c release. The endogenous PBR ligand, protoporphyrin IX, facilitated PTP opening and phosphorylation of the mitochondrial proteins, thus, inducing effects opposite to anti-PBR antibody. This study provides evidence for PBR involvement in PTP opening, controlling the calcium-induced calcium efflux, and AIF release from mitochondria.

In summary, our results provide evidence that PBR, CNP and p42(IP4) are involved in regulation of calcium-induced PTP opening, important stage of initiation of programmed cell death.