Mitochondria and neurodegeneration/neuroprotection – a focus on the permeability transition and interacting proteins/ligands as a targets for novel protection mechanisms

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In most neurodegenerative diseases, sudden increase of the permeability of the inner mitochondrial membrane in response to threshold calcium concentration or oxidative stress causes formation of an unselective permeability transition pore (PTP) complex. Intense studies of the PTP did not yet allow unraveling the biochemical mystery and the structure of this pore complex. Gene knockout experiments ruled out the earlier accepted involvement of voltage-dependent anion channel and adenine nucleotide translocase as structural elements of PTP. We analyzed how the peripheral benzodiazepine receptor (PBR), now designated the 18-kDa translocator protein (TSPO) of the outer membrane, takes part in PTP regulation. We present data showing how ligands of TSPO or PBR (PK11195, Ro5-4864, protoporphyrin and diazepam binding inhibitor) modulate the induction of Calcium-induced PTP in rat brain mitochondria. Furthermore, we summarize the contribution of two novel proteins, 2',3'-cyclic nucleotide 3'-phosphodiesterase and $p42^{IP4}$ (centaurin α1; ADAP 1), to Ca^{2+} efflux from rat brain mitochondria loaded by threshold [Ca^{2+}] and thus to induction of PTP. Finally, most recent data on the possible role of calcium-induced permeability transition control by carbenoxolone through targeting the gap junction protein connexin43 are presented. In conclusion, the mitochondria permeability transition pore complex in brain with its interacting proteins presents a promising target for protection in many neurodegenerative diseases