

Mitochondrial Permeability Transition Pore-as a Promising Target for Novel Neuroprotective Agents

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Editorial

Despite the differences in symptomatic pictures among Neurodegenerative Diseases (ND) all of them result in selective or generalized neuronal loss. The cascade of events leading to the neuronal death is multifactorial. The factors involved include metabolic disturbance, acidosis, excitotoxicity, oxidative stress, neuroinflammation, pathological aggregation of some proteins, and dysregulation of mitochondrial functions.

Mitochondrial dysfunction has been implicated in number of neurodegenerative diseases such as Alzheimer's Disease (AD), Parkinson disease, Huntington disease, Amyotrophic Lateral Sclerosis (ALS), multiple sclerosis and others [1]. Mitoprotective strategy for prevention of a series of neurodegenerative diseases, in particular, AD, being now one of the most promising approach in the development of neuroprotective drugs [2,3]. Aside from being an important source of cellular energy (ATP), mitochondria maintain the intracellular Ca^{2+} levels within closely defined ranges for the mediation of signaling, control of neuronal excitability, and the synaptic function. The neurons within the brain are highly vulnerable to metabolic disturbances; therefore, impairment of mitochondrial ATP generation clearly threatens the viability of both neurons and glial cells, the function of neuronal networks, and, consequently, normal brain function. Dysregulation of cytosolic Ca^{2+} levels by failure of mitochondrial Ca^{2+} buffering, and/or release of the sequestered Ca^{2+} ions present within mitochondria contribute to the severe damage of brain tissue in response to glutamate excitotoxicity, metabolic insults, and neurotoxins [4]. Similarly, abnormally amplified levels of Reactive Oxygen Species (ROS) generated by mitochondria also threaten neuronal viability, since the multiple ROS buffering mechanisms can be overwhelmed [5]. The phenomenon of Mitochondrial Permeability Transition (MPT) is tightly connected with these abnormalities. MPT is defined as a sudden increase of inner mitochondrial membrane permeability to solutes of up to 1,500 Da that is elicited in response to exposure to abnormally high levels of Ca^{2+} ions. The main reason for this transition is the opening of a non-selective mega-channel, the Mitochondrial Permeability Transition Pore (MPTP) [6,7]. It leads to the release of the mitochondria-accumulated calcium and different proapoptotic factors from the intermembrane space and loss of the proton gradient and cell respiration, resulting in ATP deficit and overproduction of ROS. However, this phenomenon is not well characterized at the molecular level to date.

Different agents and conditions can modulate MPT. The most common are inorganic phosphate increase (indicating the redox status of pyridine nucleotides), increase of the intracellular calcium, and oxidative stress. All these conditions happen in the case of neurodegenerative pathology and, in particular, as a result of β -

amyloid ($A\beta$) toxic effect. The intracellular oligomeric forms of $A\beta$ and other misfolded proteins (tau-protein, α -synuclein, SOD1, Huntington) may also trigger the MPT [8,9]. It is important that the vulnerability to MPT-inducing factors increases with aging and it may be a consequence or delayed effect from the different stress factors, including the environmental factors, stroke, hypoxia and trauma [10]. Some neurotoxins with the specific neuronal selectivity are widely used to model ND. Among these are the dopaminergic neurotoxin 1-methyl-4-phenylpyridinium (MPP⁺) iodide, which can induce symptoms of Parkinson's disease, cholinergic neurotoxin ethylcholine mustard aziridinium (Af64a) and the endogenous β -amyloid peptide- $A\beta$ (25-35), which can reproduce the AD symptoms. Earlier it was shown that these neurotoxins can induce or potentiate the MPT [11].

The development of drugs with the capacity to delay the neurological deficits associated with ND is an urgent and important goal. One potential approach to achieve it is to use small molecules that interfere with cell death signaling mechanisms, which may contribute to the neuronal loss in ND. From this standpoint the approach to restore mitochondrial functions and stop the neuronal progressive death by stabilizing mitochondria looks very attractive. It was reported that coenzyme Q10 (3) acts as an effective therapeutic agent for increasing oxygen consumption and ATP production in brain mitochondria [12]. Another promising agent that may target mitochondria is an agent Dimebon originally invented as antihistamine drug. Last years in numerous research it was shown that neuroprotective effect of Dimebon and some structurally close agents related to it to the stabilization of the mitochondrial functions, in particular, by modulating the MPTP [13,14]. Further search for selective mitoprotectors can open new window for the development novel generation of efficient neuroprotectors for broad spectrum of neurodegenerative disorders.

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