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Editorial

Mitochondria-Targeted Plastoquinone Antioxidant Skq1 Rescues Amyloid-Beta-Induced Impairment in Hippocampal Synaptic Plasticity

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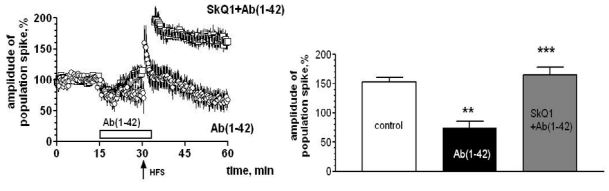
Mitochondria-targeted antioxidants SkQ1 and MitoQ are known to improve a number of pathologic disorders mediated by the reactive oxygen species (ROS) such as heart ischemia, stroke and Alzheimer's disease [1]. Evidence emerging from studies on aging and Alzheimer's disease models shows that the harmful trio "aging, amyloid- β peptide (Aβ), and tau protein" triggers mitochondrial dysfunction. This is realized through a number of destructive pathways including excessive production of ROS, resulting in oxidative modification of mitochondrial proteins, which in turn causes impairment of oxidative phosphorylation, apparently contributing to the onset and progression of the disease [3].

In this study we intended to learn whether SkQ1 injections in vitro and in vivo can rescue Aβ- induced impairment of long-term potentiation (LTP) in hippocampal slices - a model of synaptic plasticity underlying learning and memory.

The study was carried out on transverse hippocampal slices prepared from the brain of 4-6 week-old male Wistar rats. Field responses to Schaffer collateral stimulation were recorded in the CA1 pyramidal layer, and the amplitude of its peak component (PS) was measured to evaluate changes in hippocampal pyramidal cell responsiveness after drug or tetanus delivery. Concentrated aqueous solutions of β- amyloid peptide 1-42 (Aβ, 200nM) (Sigma Aldrich, USA) were stored as frozen aliquots. The stored Aβ solution was diluted with the perfusion medium immediately before use and injected into bathing medium15 min before the high frequency stimulation of Schaffer collaterals (HFS). Slices were incubated in SkQ1 (250 nM, 1 hour.) (In vitro experiments) or drug was injected intraperitoneally (1nmol/kg) into rats 24 hours before the slices preparation (ex vivo experiments). Fluorescent derivate of Skq1 (SkqR1) was also used in some cases to visualize staining of mitochondria. Statistical analysis of mean values and mean errors (M±m) was done using the nonparametric Mann–Whitney test and Student's test. The standard HFS (100Hz, 1sec) induced LTP in all slices under investigation (n=6). Mean amplitude of the PS was 145.9±7.8%. Injection of Aβ into the bathing medium completely blocked the LTP induction: the amplitude of PS 30 min after HFS was 57.1±10.8% compared to control level (n=5). Pretreatment of slices by their incubation in SkQ1 (250 nM, 1 hour,) led to rescue of LTP from its block by Aβ. Mean amplitude of PS after HFS was even higher than in control (164±13%) (n=5) (Figure 1). When SkQ1was injected intraperitoneally 24 hours before the slice preparation (6 rats) in blind experiments LTP impaired by Aβ was rescued in all slices (n=6). The mean value of the PS amplitude after HFS was 135.7±16.2% [4]. To check whether the rescue of LTP was determined by plastoquinone (and not by lipophilic cation- triphenilphosphonium-C12TPP-which drags plastoqinone through mitochondrial membrane) action of this compound was studied (n=5). It was found that C12TPP alone does not rescue LTP (60 min after HFS amplitude of PS was the same as in control. It is also worth noting that in slices from SkQ1 and C12TPP treated animals (without Aβ, n=6) the LTP amplitude does not differ significantly from the control level.

Fig.1 Suppression of induction of LTP in hippocampal slices by Aβ and rescue of LTP by pretreatment of slices by SkQ1 (n=5)



It was found that soluble form of Aβ injected into the bathing medium impairs the LTP induction in the area CA1 of rat's hippocampal slices. Mitochondria-targeted plastoquinone antioxidant SkQ1 introduced in bathing medium (in vitro) or being injected intraperitoneally to rats 24 hours before

slice preparation (ex vivo) rescues of LTP impairment. This effect could be mediated by the ability of mitochondria-targeted antioxidants to decrease the level of ROS in mitochondria and as a result influence synaptic plasticity. The data demonstrate that the SkQ1 therapy is capable to compensate the Aβ- induced impairment of LTP in hippocampus, which is the main cause of memory loss and other cognitive disfunctions associated with the Alzheimer's disease.

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