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Commentary

Mitochondria-Targeted Antioxidants as Promising Drugs for Treatment of Age-Related Brain Diseases

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Abstract. Much experimental evidence suggests that age-related brain pathologies are most often mediated by reactive oxygen species primarily originating from mitochondria (mROS). Two papers with such evidence have been recently published in the *Journal of Alzheimer's Disease* (Stefanova et al., *J Alzheimers Dis* 21, 476–491, 2010; Lloret et al., *J Alzheimers Dis*, doi: 10.3233/JAD-2011-110890). In the first paper, it was shown that appearance of a typical behavioral trait of aging in rats (that old animals do not enter an open arm in a maze) was completely reversed by ten weeks treatment of the old rats with the mitochondria-targeted antioxidant SkQ1. In the second article, the authors identified molecular mechanisms by which amyloid-β-induced mROS can mediate hyperphosphorylation of the tau protein, a key event in Alzheimer's disease. Conventional antioxidants prevented such hyperphosphorylation. In this article, I will summarize the present state of the art in this field. I conclude that mitochondria-targeted rechargeable antioxidants are promising as tools to treat brain pathologies developing in elderly humans.

Keywords: Alzheimer's disease, behavior, hippocampus, mitochondria-targeted antioxidant, plastoquinone, stroke

There is general agreement among gerontologists that oxidative stress gradually increases as organisms age. This can be a consequence of (i) stimulation with age of production of reaction oxygen species (ROS); (ii) decrease in quenching of ROS; (iii) both of these factors; or (iv) simply duration of life-long exposure of an aging organism to endogenous ROS. Any of these effects can, in turn, be a result of occasional damage to organismal regulatory systems or require activation of a special aging program (or inactivation of a "youth" program) representing the final step of ontogenesis (for details, see [1–3]). ROS generated on the outer surface of the cell membrane are mainly produced by a special superoxide ($O_2^{-\bullet}$)-forming enzyme (NADPH oxidase). Of those generated inside the cell, they are assumed to be often a result of a leakage of electrons transported by the mitochondrial respiratory chain when $O_2^{-\bullet}$ is formed by initial or middle spans of the chain instead of H_2O formation by its terminal enzyme, cytochrome oxidase [2, 3]. If this is the case, aging might be slowed by treatment with antioxidants quenching $O_2^{-\bullet}$ and other ROS. Unfortunately, ROS normally perform several physiological functions

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of vital importance, and their total elimination entails death of the organism. For example, mice and rats kept in a chamber with $O_2^{-\bullet}$-free air die within three weeks [5]. Thus, the goal is to specifically lower only those ROS that are involved in aging processes. If it really is mitochondrial ROS (mROS) that promote the aging process, there is a chance to decelerate aging by moderate doses of mitochondria-targeted antioxidants that would not dramatically affect extra-mitochondrial ROS operating in the cytosol as secondary messengers of some physiological signals, or outside the cell as killers of microorganisms invading damaged tissues. In our group, mitochondria-targeted antioxidants [plastoquinonyl decyltriphenylphosphonium (SkQ1) and plastoquinonyl decylrhodamine 19 (SkQR1)] have been synthesized [6]. We found that these membrane-penetrating cations are specifically accumulated in the inner mitochondrial membrane [6] due to the fact that the mitochondrial interior is the only negatively charged compartment in the cell [7]. Further studies revealed that the SkQs prevent peroxidation of cardiolipin in isolated mitochondria and H_2O_2-induced apoptosis of human fibroblasts and HeLa cells [8]. It was found that SkQs not only interrupt chain reaction of cardiolipin peroxidation by already formed ROS but, at higher concentrations, they also lower the rate of ROS formation in respiratory chain due to mild uncoupling. Both SkQ1 and SkQR1 proved to be carriers of fatty acid anions, catalyzing in this way H^+ transport through mitochondrial membrane, mediated by fatty acid cycling [9]. Besides this effect, SkQR1 *per se* was shown to be cationic protonophorous uncoupler [10]. The SkQ-induced partial uncoupling decreases mitochondrial transmembrane electric potential ($\Delta\Psi$) and, as a consequence, prevents ROS formation which is very sensitive to a $\Delta\Psi$ lowering [11].

It was shown that SkQ1 treatment prolongs the lifespan of the fungus *Podospora anserina*, the crustacean *Ceriodaphnia*, the fly *Drosophila*, the short-lived fish *Nothobranchius furzeri,* mice [8, 12], hamsters, and mole-voles (Anisimov VN et al., unpublished). Numerous traits of aging were shown to be delayed, prevented, and in some cases even reversed by SkQs [8–12].

Several effects of SkQs were observed when brain functions were studied. In particular, a single intraperitoneal injection of SkQR1 (0.5–2 μmol/kg body weight) to rats strongly decreased the infarct volume in brain and related behavioral defect (performance in the limb placement test) caused by transient occlusion of the middle cerebral artery (Fig. 1). These data were obtained by Zorov and coworkers in our group in Moscow [13, 14]. A demonstrative effect of

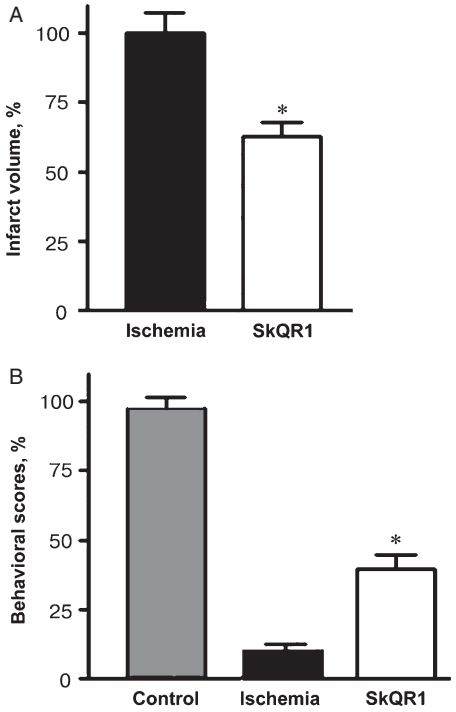

Fig. 1. SkQR1 lowers brain infarct volume as well as damage to the performance of the limb placement test in rats after transient middle cerebral artery occlusion. Where indicated, 1 μmol SkQR1 per kg of body weight was injected intraperitoneally 24 h before the 60 min occlusion of the artery. The ischemia effect was studied 24 h after the occlusion. *, here and below, $p < 0.05$ for SkQ effect. Reprinted from Plotnikov et al. [13], with permission.

in vivo treatment with SkQ1 was observed in Kolosova's group in Novosibirsk, where age-dependent behavioral effects were studied in Wistar rats [15]. Rats of 3- and 14-month age were investigated. An elevated plus maze with two open and two closed arms was used. Young animals placed in the maze center entered both types of arms with equal probability. However, the 14-month-old rats preferred to enter the closed arms only, the probability of entering the open arms being extremely low. If, nevertheless, a 14-month-old rat entered an open arm, the animal immediately left this arm. Addition of very small amount of SkQ1 to the food (250 nmol/kg body weight daily) for 10 weeks completely reversed the age effect. With SkQ1, the probability of entering an open arm for the 14-month-old rats was as high as for young rats and, when entering an open arm, the SkQ1-treated old rats spent in it a time which was almost as long as for the young rodents (Fig. 2). Number of squares crossed by the animals in the open field test proved to be slightly (by 25%) smaller in the 14-month-old rats than for the 3-month-old animals. This difference was also

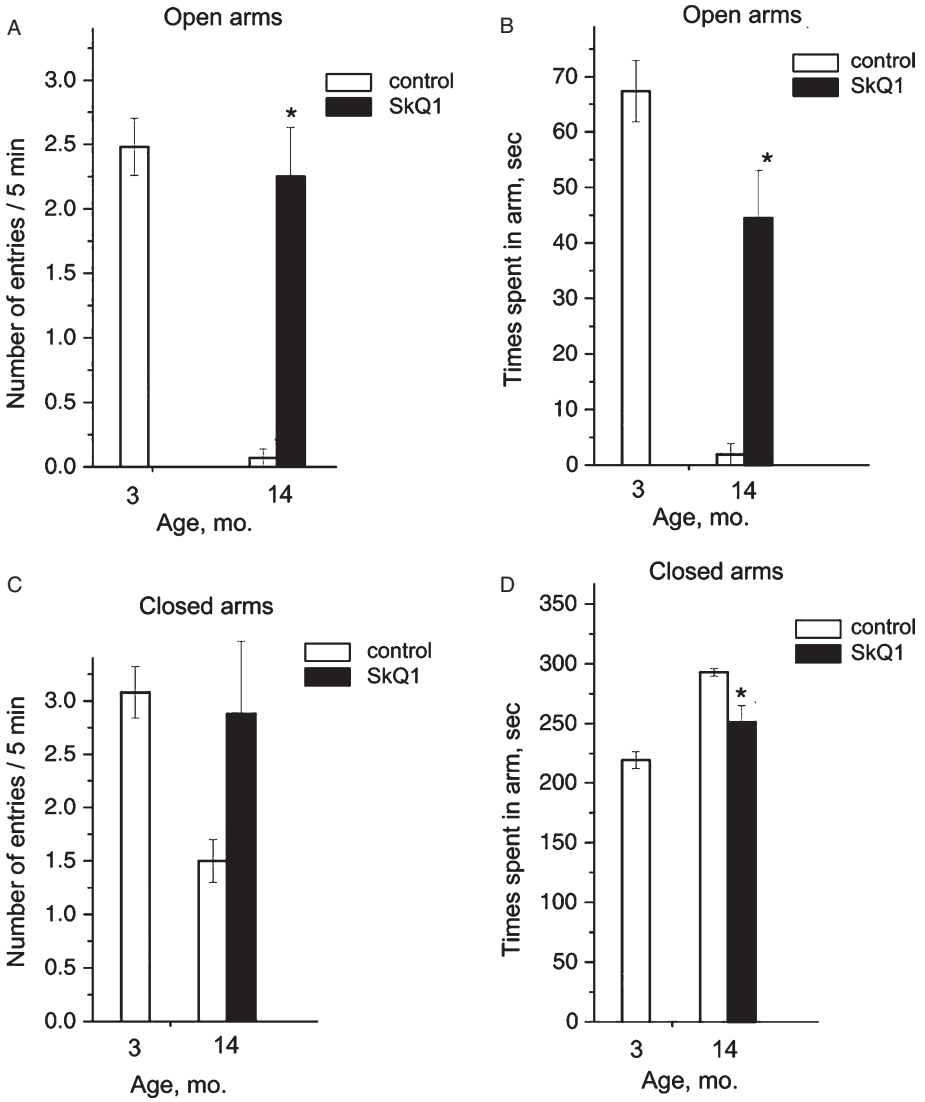

Fig. 2. SkQ1 reverses age-dependent behavioral defects in Wistar rats. The elevated plus maze was used. Where indicated, SkQ1 (250 nmol /kg body weight daily) was added to the food of old rats during the final 10 weeks. Reprinted from Stefanova et al. [15], with permission from IOS Press.

abolished by SkQ1. Rearings in the maze or the open field and head dips in the maze were age-independent and SkQ1-insensitive [15].

There is only one treatment which prolongs life of many species and delays development of numerous traits of aging as does SkQs. This is calorie restriction. Our explanation for this similarity is that both SkQs and calorie restriction interrupt execution of the aging program. Among the traits in question, there is behavior of an animal during the final week(s) of life. As mentioned by Dr. Arlan A. Richardson of San Antonio, "calorie restriction minimizes the period in which an animal is morbid, sitting around its cage, waiting to meet its maker" (cited after [16]). As shown by Shabalina et al. in Stockholm and Anisimov et al. in St. Petersburg (unpublished), this effect is not observed when mice receive SkQ1 with drinking water throughout their lives. The animals are mobile and active as long as they are alive. Notably, SkQ1 did not affect the food consumption by the animals (Anisimov VN et al. and Shabalina IG et al., unpublished).

It is well established that one of the key events in the development of Alzheimer's disease (AD) is the release of amyloid-β peptide (Aβ) from its protein

precursor (AβPP) (for review, see [4]). It is also clear that impairment of synaptic plasticity occurs before apoptotic and neurodegenerative events typical for the terminal stage of AD. It correlates with accumulation of Aβ, causing the synaptic dysfunction and loss of memory accompanying AD [17–19]. As a model of cell memory, an electric response of a hippocampal slice (long-term potentiation, LTP) is used [20]. Quite recently, Kapay and coworkers from our and Dr. V.G. Skrebitsky's groups in Moscow performed a direct experiment on prevention of Aβ toxicity in hippocampus by *in vivo* treatment of rats with 1 μmol SkQR1 per kg of body weight. The compound was injected intraperitoneally into the animal 24 h before hippocampal slices were obtained to measure long-term potentiation (LTP). Some slices were pretreated with Aβ for 15 min. As is seen in Fig. 3, Aβ impaired LTP. Treatment of the animal with SkQR1 prevented such impairment [21]. When this paper was in preparation, a publication by Ma et al. [22] appeared where another penetrating mitochondria-targeted cationic antioxidant, MitoQ, was used to prevent the effect of Aβ on LTP. To this end, however, the antioxidant was added *in vitro*, i.e., directly on the hippocampal slice. Consistent with our observation with the *in vivo* antioxidant treatment, the *in vitro* addition of 0.5 μM MitoQ prevented the Aβ-induced impairment of LTP. A similar effect was produced by adding a superoxide dismutase and the catalase mimetic EUK134 as well as by hyperproduction of mitochondrial superoxide dismutase. LTP damage could also be observed in AβPP/PS1 AD mutant mice. In this case, LTP could also be normalized by *in vitro* MitoQ [22][1]. The authors did not try MitoQ *in vivo*, where a narrow concentration window between anti- and prooxidant effects, inherent to this quinone derivate, may create problems. Just this property of MitoQ introduced by Murphy and Smith before SkQs were tested [24] might be the reason why clinical trials of MitoQ were without positive results in the case of Parkinson's disease [24, 25] and Friedrich's ataxia [26]. For SkQs, the beneficial concentration window is as wide as about 1,000, a fact which should strongly increase the likelihood of success of *in vivo* treatments [6, 8].

Another important observation was reported by Ma and colleagues [22]. They showed that addition of Aβ to hippocampal slices greatly increased the mROS level, and MitoQ *in vitro* or hyperproduction of mitochondrial superoxide dismutase *in vivo* abolished this

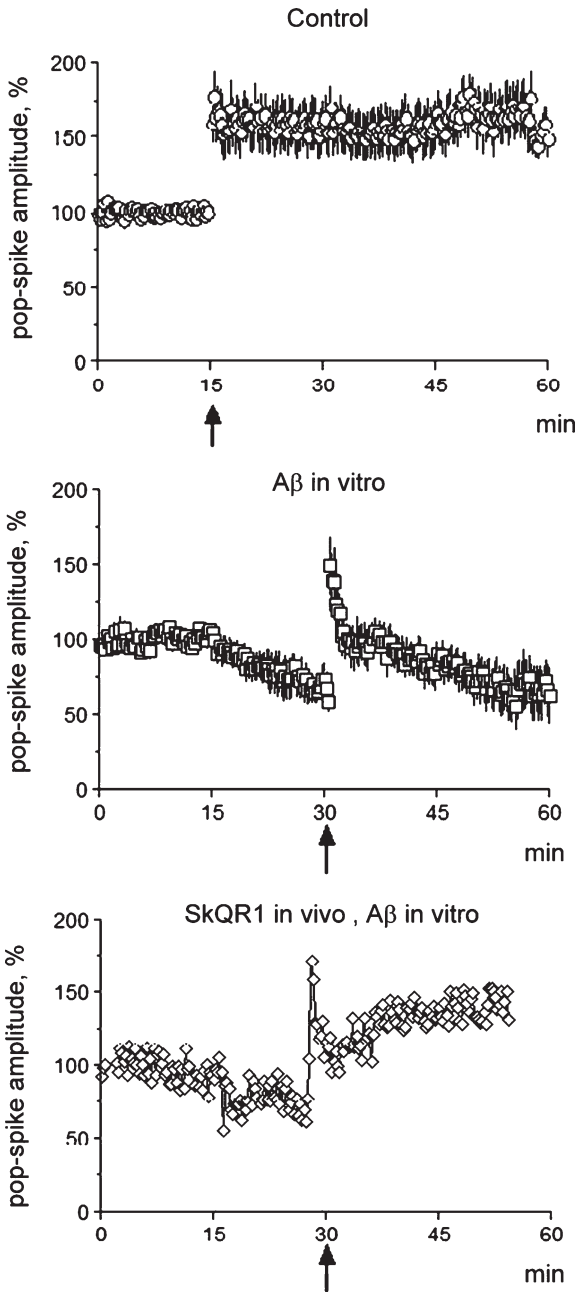

Fig. 3. SkQR1 treatment *in vivo* prevents decay of the long-term potentiation (LTP) caused by *in vitro* addition of Aβ to a hippocampal slice. For the SkQR1 treatment, see Fig. 2. Aβ was added 15 min before the LTP induction with high-frequency electric stimulation (arrow). Reprinted from Kapay et al. [21], with permission.

increase. There are numerous facts indicating that Aβ initiates ROS production *in vitro* and *in vivo* [4, 22, 27–35], and these ROS primarily originate from mitochondria [4, 26, 39–42]. It was also found that Aβ accumulates in the mitochondrial matrix, being

[1] For prevention by added MitoQ of inhibiting *in vitro* action of Aβ, see ref. [23].

transported through the outer and the inner mitochondrial membrane by the TOM and TIM complexes, respectively [4, 35, 39–43]. Inside mitochondria, Aβ inhibits cytochrome oxidase, pyruvate and α-ketoglutarate dehydrogenases, ATP/ADP antiporter, presequence peptidase and some other enzyme complexes, entailing a decrease in respiration, mitochondrial membrane potential and respiratory ATP synthesis [4, 35]. As a result, respiratory chain-linked mROS production strongly increases, causing synaptic failure and, later, apoptosis of brain cells [4, 35, 36].

Toxicity of Aβ added to brain mitochondria isolated from young males was much higher than from young females, the latter being rather resistant to Aβ. The resistance disappeared with age. This interesting observation was made by Viña and his colleagues from Valencia [44]. Quite recently, his group identified a chain of AD-inherent events occurring downstream from mROS. They showed that ROS somehow upregulate expression of the regulator of Calcineurin gene, RCAN1. RCAN1 protein inhibits the ability of calcineurin to operate as a phosphatase of tau-protein. As a result, tau-protein is hyperphosphorylated by glycogen synthase kinase-3β (GSK3β), a tau-kinase. This effect is stimulated by an RCAN1-induced increase in tau-kinase activity of GSK3β. Hyperphosphorylation of tau protein leads to formation of neurofibrillary tangles, thus causing synaptic failure and apoptosis (Fig. 4; for reviews, see [4, 35]). Viña and his

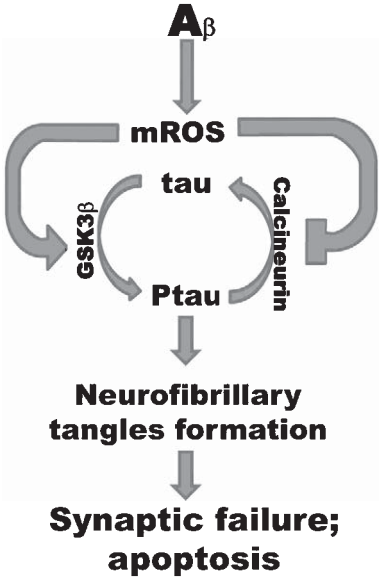

Fig. 4. Tentative scheme illustrating how mitochondrial reactive oxygen species (mROS) mediate the Aβ-induced damage to AD neurons. For details, see the text and ref. [45].

colleagues studied fetal rat cortical neurons and succeeded in interrupting the Aβ-induced damage by *in vitro* addition of high (1 mM) concentrations of water-soluble antioxidants, i.e., Trolox and GSH-mono ethyl ester [45]. In experiments of Ma et al. on hippocampal slices, 0.5 μM MitoQ, a mitochondria-targeted antioxidant, was used for this purpose. In our experiments on the same system, we employed *in vivo* treatment of rats with 1 μmol SkQR1/kg body weight, a more potent antioxidant addressed to mitochondria. Its effective concentration should be much lower than that of the *in vitro* added MitoQ. As shown by direct measurement of pharmacokinetics of SkQ1 in rats, its level in brain was lower than in some other tissues [12]. Such high efficiency of SkQs can be explained by a combination of the following factors:

(1) SkQs are rechargeable antioxidants which are reduced in center *i* of respiratory chain complex III, localized in the inner leaflet of the inner mitochondrial membrane [12, 46].

(2) SkQs are very effectively concentrated in this mitochondrial membrane leaflet. In cytosol, [SkQ] must be about 10-fold higher than in the solution outside the cell due to electrophoretic movement of SkQ supported by $\Delta\Psi$ across the outer cell membrane (about 60 mV). The $\Delta\Psi$ across the inner mitochondrial membrane is about 180 mV, which means that [SkQ] in the mitochondrial matrix should be 10^3 higher than in the cytosol. The distribution of SkQ1 in the membrane/water system is about 10^4:1. Altogether, this should result in SkQ concentration in the inner leaflet of the inner mitochondrial membrane 10^8 times higher than in the extracellular solution [12].

(3) In mitochondria, SkQ combines which cardiolipin, the mitochondria-specific phospholipid which is first of all attacked by mROS initiating a chain reaction of lipid peroxidation in the inner membrane of mitochondria [12, 46].

These unique properties of mitochondria-targeted rechargeable antioxidants make them promising in treatment of AD and other mROS-mediated brain pathologies. Notably, non-targeted antioxidants (α-tocopherol, ascorbate, and α-lipoate) proved to be safe but ineffective in treating AD patients [47]. This is hardly surprising since these antioxidants are not only non-specific to the intracellular compartments but also are not rechargeable and, hence, much less efficient than SkQ. The latter is also true for mitochondria-targeted α-tocopherol. As to mitochondria-targeted antioxidant enzymes, they cannot be applied for *in vivo* treatment of humans. Elucidation of details of molecular mechanisms of antioxidant SkQ effects and clinical

trials of these new compounds is now in progress in our and some other groups [48].

DISCLOSURE STATEMENT

The author's disclosure is available online (http://www.j-alz.com/disclosures/view.php?id=998).

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