Chapter 32

SAMP8: A model to understand the role of oxidative stress in age-related diseases including Alzheimer•s disease

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Abstract

The senescence-accelerated mouse (SAM) is an accelerated aging model that was established through phenotypic selection from a common genetic pool of AKR/J mouse strain. Among the SAM mice, SAMP8 mice are considered as a good model for gerontological research as they exhibit learning and memory de“cits with age. SAMP8 mice also show age-related increased oxidative

exhibit learning and memory de“cits with increasing age. SAMP8 mice show age-related impairment in learning and memory [3] that occurs as early as at 2 months compared to SAMR1 mice of the same age. In addition SAMP8 mice also showed neuropathological changes such as reduction in spine density, astrogliosis, spheroidal axonal dystrophy etc. Further, SAMP8 mice also demonstrated increased deposition of beta-amyloid (A

in mitochondrial energetics have been reported for these mice, which suggests that certain anti-oxidant and energy-protective strategies may prove therapeutic.

Lipoic acid (LA) has been shown to act as a powerful micronutrient with diverse pharmacologic and antioxidant properties [44]. In biological systems LA exists in proteins linked covalently to lysyl residues as a lipoamide. Lipoic acid exists in reduced and non-reduced forms, and the mitochondrial E3 enzyme, dihydrolipoyl dehydrogenase, reduces lipoate to dihydrolipoate at the expense of NADH. The antioxidant property of LA is associated with the reduced form of LA, dihydrolipoic acid that reacts with oxidants such as superoxide radicals, hydroxyl radicals, hypochlorous acid, peroxyl radicals, singlet oxygen, and HNE. Further, the antioxidant property of the LA could be associated with the recycling of cellular antioxidants, including coenzyme Q (CoQ), vitamins C and E, and glutathione (GSH). Recent studies suggested that the LA antioxidant function occurs via its ability to function as a pro-oxidant and by activation of transcription factor Nrf2, which can lead to transcriptional activation of phase II detoxi“cation enzymes as well as antioxidant proteins such as glutathione-S-transferases, gamma-glutamylcysteine synthetase, ferritin, NAD (P) H: quinone oxidoreductase-1, and heme oxygenase-1, etc. Hence, LA potentially could be useful as a treatment for a number of diseases that are associated with oxidative stress. Moreover, LA has been reported to readily cross the blood…brain barrier, and this would be helpful in diseases involving brain.

As mentioned above, SAMP8 mice overexpress APP and have elevated levels of Aβ in the brain and consequently have increased levels of beta-amyloid and free-radical associated damage to proteins and lipids [5,19]. Mitochondrial dysfunction has been reported in SAMP8 mice, which could be associated with the increased production of free radicals in these mice [45,46]. Further, SAMP8 mice also exhibit age-related impairment in memory and learning at age of 12-months [47]. LA treatment improves learning and memory in old-SAMP8 mice treated with LA as assessed by the T-maze footshock avoidance paradigm and lever press appetitive task. Further, LA treatment reduced age-associated increase in the markers of oxidative stress such as protein oxidation, lipid peroxidation, Electron Paramagnetic Resonance (EPR)-determined W/S ratio of a cysteine-selective spin label in brain membranes from old SAMP8 mice compared to young SAMP8 mice [26,48].

Proteomics studies from our laboratory showed that LA treatment signi“cantly increased the expressions of three brain proteins, i.e., neuro“lament triplet L protein, alpha-enolase, and ubiquitous mitochondrial creatine kinase, augmenting the expression of these proteins in LA treatment, suggesting that the administration of LA may improve cellular energetics and also improve the structure of neurons. Such changes could thereby play an important role in neuronal plasticity and consequently in improving the learning and memory process in old SAMP8 mice. LA treatment has also been shown to signi“cantly decrease speci“c carbonyl levels of lactate dehydrogenase B, dihydropyrimidinase-like protein 2 (CRMP2), and alpha-enolase in the aged SAMP8 mice, and these proteins are important for cellular energetics and axonal growth [49]. The antioxidant effect of LA can also be related to its presence as a cofactor for a number of mitochondrial associated proteins such as alpha-ketoglutate dehydrogenase etc. [50].

Glutathione (GSH) is present in millimolar concentrations and is the most abundant antioxidant in the brain. In a reaction involving oxidative stressors, GSH is converted to oxidized glutathione (GSSG), and the ratio of GSH/GSSG is used as a measure to check the redox and oxidative stress status of the cell. The levels of GSH are maintained by GSH peroxidase and glutathione reductase activity. The reduced form of the GSH scavenges reactive oxygen species (ROS) and other toxic and highly reactive products of lipid peroxidation such as HNE and acrolein, in addition to its ability to protect the thiols groups in proteins. The nucleophilic adducts of HNE and acrolein by GSH are normally formed by the reaction of the enzyme glutathione-S-transferase (GST) and are ef"uxed out from the cell by the multidrug resistance protein-1 (MRP-1) [51,52]. Glutathionylation of proteins is a reversible process where the GSH is removed by the action of glutaredoxin, a thiol transferase [53], and this process might help to protect the proteins that are redox sensitive proteins. Previous studies from our laboratory have identi"ed a number of proteins that showed glutathionylation in AD brain and this modi"cation is further associated with decreased activity of the glutathionylated proteins [54,55]. Hence, one approach for potential therapy of age-related neurodegenerative disorders is to increase the levels of GSH in the cell to reduce the levels of oxidative stress and thereby prevent or delay the diseases associated with oxidative stress. The rate limiting amino acid for the synthesis of glutathione is cysteine. Since free cysteine is highly reactive, this amino acid is mostly present as a component in the non-protein form as GSH. Hence, to increase the levels of GSH a number of previous studies have used N-acetylcysteine, which has been shown to lead to increased levels of GSH in the brain and also peripheral cells [26,56]. Further, in vitro and ex vivo studies showed that intraperitoneal (i.p.) injection of NAC protected brain against peroxynitrite, hydroxyl radicals, and acrolein induced toxic effects [57Š59]. Moreover, mice treated with NAC prior to intracerebroventricular (i.c.v.) injections of Aβ showed decreased oxidative stress markers and also had improved learning and memory [60]. The protective effect mediated by NAC has been reported to involve not just the elevation of GSH levels; rather, the NAC mediated protection also is via its effect on other signaling pathways including activation of the Ras/ERK pathway, stimulating p35/Cdk5 activity, and reduced phosphorylation/deactivation of MLK3-MKK7-JNK3 signaling cascade [61Š63]. In SAMP8 mice NAC has been shown to partially restore memory de"cits in SAMP8 aged mice as well as reducing levels of lipid peroxidation and protein carbonyls [26]. This reduced level of oxidative stress markers and improvement observed in learning and memory could be related to the antioxidant property associated with NAC via up-regulation of reduced glutathione levels or could be associated with the down-regulation of APP gene transcription [64].

As mentioned above, SAMP8 mice showed increased production of Aβ_{42} and consequently the decrease in learning and memory in SAMP8 mice could be associated with Aβ-induced oxidative stress. To explore the role of Aβ_{42} in the SAMP8 induced learning and memory problem we have injected antisense in 12-month-old SAMP8 mice (antisense oligonucleotide targeted at the Aβ_{42} region of the APP gene), and showed that AO treatment improved learning and memory and also reduced oxidative stress [65]. Further using redox proteomics we found that the levels of the speci"c protein carbonyl levels of aldoase 3 (Aldo3), coronin 1a (Coro 1a) and peroxiredoxin 2 (Prdx2) were signi"cantly

decreased in the brains of 12-month-old SAMP8 mice treated with AO compared to age-matched SAMP8 mice treated with random AO [66]. Oxidations of these proteins explain the increased observation of the markers of oxidative stress in these mice at 12-month of age and also loss of cellular energetics, all of which are important for learning and memory. Further, using expression proteomics we also showed that the protein level of a-ATP synthase was signi“cantly decreased, whereas the expression of pro“lin (Pro-2) was signi“cantly increased in the brains of SAMP8 mice treated with AO.

6. Future studies

This review summarizes the current “ndings of increased oxidative stress in SAMP8 mice and therapeutics approaches that were employed to protect against age-dependent increase in oxidative stress. Further studies are required to unravel the mechanisms of aging using this model. SAMP8 mice also show an abnormal APP and Aβ metabolism; hence, these mice could serve as a potential model for studying the role of APP in Alzheimer•s disease pathogenesis. From this review, it is clear that oxidative stress is critically important for impairment of learning and memory and Aβ may play a signi“cant role in age-related cognitive decline in SAMP8. SAMP8 mice could serve as a model to test the therapeutic ef“cacy of drugs used to treat age-associated diseases in which cognitive effects are clinically present.

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