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Editorial

Importance of Improving Mitochondrial Function in Alzheimer's Disease

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Dementia can be considered as the most prevalent age associated human ailments. Elder people over the age of 65 years are under the risk for dementia due to vascular and Alzheimer's diseases (AD). Familial occurrence of AD due to mutations of presenilins-1 and-2 (catalytic units of *gamma*-secretase which process the amyloid precursor protein to amyloid beta 42 peptide) is rare. Several etiological factors were suggested for their increased incidence during aging. Polidori., *et al.* demonstrated that in age-related deterioration in cellular homeostatic mechanisms the oxidative stress can be used as a marker [1]. The role of reactive oxygen species (ROS) on neurodegenerative diseases has been described as well [2].

The post mitotic cells like neurons have a diminished capacity to withstand the redox imbalance, hence even a minor stress can lead to irreversible injury [1]. Polyunsaturated fatty acids (PUFA) rich status in brain will aggravate the self-perpetuating lipid peroxidation chain reaction. AD patients have increased level of lipid peroxidation products such as malonedialdehyde, 4-hydroxynonenal which are highly toxic and mutagenic to brain [3]. Their level is also elevated in cerebrospinal fluid and plasma. Furthermore, in post-mortem brain samples of AD patients declined level of PUFA has been evidenced [4]. Epidemiological studies have found inconclusive evidences on the antioxidant intake and reduced incidence of AD. Among the natural substances, vitamins E, vitamin C, curcumin, gossypin, *Ginko biloba, alpha*-lipoic acid, selenium, coenzyme Q and melatonin showed protective effect against Aβ-mediated neurotoxicity in experimental studies [5]. Combination of antioxidants also showed increased effectiveness. Recent clinical trials suggested the beneficial effect of omega-3 fatty acids on the cortical functions in children and ageing, whereas supplementation is not beneficial in AD [6]. Furthermore, several studies using micronutrients and antioxidants did not raise a clear conclusion on their beneficial effect in AD patients [7].

Despite the etiological factors suggested, mitochondrial impairment and associated oxidative stress has been demonstrated as the early mechanism in the pathophysiology of dementia. As the age advances, mitochondrial impairment has gradually increased. Mitochondria has central role not only in the production of energy but involved in cellular apoptosis and activating hypoxia-inducible factors (HIFs) during decreased oxygen tension (< 5%) [8]. The generated ROS, from the complex III of electron transport chain (ETC) can modulate the HIFs expression as well as its stabilization in the cytosol [9]. This sub cellular organelle also has a peculiar DNA content and, thereby, regulates its own multiplication. The activity of complexes of ETC was declined during aging which will eventually result in the generation of oxygen radiacls [10]. The generation of ROS was evidenced when the electron flow through the ETC is blocked. Mitochondrial DNA is more prone to ROS mediated damage due to its close vicinity to the ETC. During ageing, the mitochondrial DNA subjected to ROS mediated damages mainly deletions or point mutations which can affect the genes for the synthesis of proteins for the ETC. Since the damaged and wild type DNA coexists (heteroplasmic nature) in a cell, the clinical manifestations could explain with the degree of damages. The mitochondrial impairment and the altered membrane potential is the initial signal for the release of cytochrome C to trigger the apoptosis.

In Alzheimer's disease, a close association with the mitochondrial impairment was evidenced from the increased amyloid beta-42 (Aβ42) production. This is formed form the processing of translocase of inner mitochondrial membrane clogged APP. This will aggravate the generation of ROS, alter the membrane permeability and, thereby, induces the apoptosis. A visual cycle has been demonstrated for the ROS and Aβ formation as well. ROS can also favour the Aβ fibrillization in AD. Therefore, preserving the mitochondrial function in the CNS may remain the primary target for maintaining the neuronal function and thereby for the early treatment of dementia. The main limitations of their delivery into mitochondria of cells in CNS were due to the negative membrane potential as well as the blood brain barrier. Recent review discusses about the advanced research during the last decades on organic cation triphenylphosphonium ligated coenzyme Q and vitamin E; salen manganese complexes and Szeto-Scheller peptides as mitochondria targeted agent [11]. Though the experimental studies in animal and *in vitro* models proved their efficiency against inflammation and oxidative stress, no concluded clinical trials in AD patients or elder subjects are available so far to suggest their wide clinical use. Hence, the new therapeutic strategy 'mitochondrial medicine' needs to be developed for the prevention of irreversible neurodegerative diseases.

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