

Euro Neuropharmacology 2018: The oxidative stress initiated mitochondrial DNA over proliferation and deletion in the context of the cancer and neurodegeneration: Recent challenge in Neuropharmacology - Gjumrakch Aliev - University of Atlanta.

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Abstract:

Oxidative Stress describes an imbalance between the systemic manifestation of reactive oxygen species and a biological system's ability to readily detoxify the reactive intermediates. Nitric Oxide dependent Oxidative stress results in abnormal changes of mitochondria & DNA damages in case of Alzheimer disease. A progressive dementia (Alzheimer disease) affecting a large proportion of the aging population. The histopathological changes in Alzheimer disease includes neuronal cell death, formation of amyloid plaques and neurofibrillary tangles. The major component of the amyloid plaques is amyloid β -peptide ($A\beta$) which is toxic to neurons in cell culture, $A\beta$ deposits formed by overexpression of the amyloid precursor protein (APP) in transgenic mice does not cause sufficient neuronal death, suggesting other factors are necessary to promote the progression of the disease. Tangle formation initiates in brain such as the entorhinal cortex precede the clinical diagnosis of Alzheimer disease. The major component of NFTs is hyperphosphorylated microtubule-associated protein tau (MAP-tau). The abnormal MAP-tau is resistant to proteolytic enzymes suggesting glycation, disulphide bond formation, phosphorylation and formation of core fragments contribute to extensive cross-linking between MAP-tau monomers. There is an evidence that brain tissue in patients with AD is exposed to oxidative stress (e.g., protein oxidation, lipid oxidation, DNA oxidation and glycooxidation) during the course of the disease. Advanced glycation end products (AGEs) contains in amyloid plaques in AD, and its extracellular accumulation causes accelerated oxidation of glycated proteins. AGEs participate in neuronal death causing direct (chemical) and indirect (cellular) free radical production and consequently increase oxidative stress. The development of drugs for treating AD that breaks the vicious cycles of oxidative stress and neurodegeneration offer new opportunities. These include AGE-inhibitors, antioxidants and anti-inflammatory substances, which prevent free radical production. An important aspect of the antioxidant defense system is the low molecular weight reducing equivalent glutathione, which is responsible for the endogenous redox potential in the cell. The most important function of glutathione is to donate electrons to ROS and by doing so to protect them. Intracellular glutathione (GSH) concentration decreases with age in different animal models, and it also decreases in aged mammalian brain regions including hippocampus. Introduction of hydroxyl groups in the generation of protein based carbonyls. Carbonyl groups are introduced in proteins by oxidizing amino acid residue side-chain hydroxyls into ketone or aldehyde derivatives. Measurement of protein carbonylation is such a good estimation for the extent of oxidative damage of proteins associated with various conditions of oxidative stress, aging, physiological

disorders and AD. Lipids are modified by ROS and where there is a strong correlation between lipid peroxides, antioxidant enzymes, amyloid plaques and NFTs in AD brains. Several breakdown products of oxidative stress, including 4-hydroxy-2,3-nonenal (HNE), acrolein, malondialdehyde and F2-isoprostanes have been observed in AD brains compared to age-matched controls. Evidence continues to mount that bifunctional HNE are the major cytotoxic products of lipid peroxidation. Following lipid peroxidation, a 2-pentylpyrrole modification of lysine is the only presently known "advanced" (stable end-product) adduct that forms from the modification of proteins by HNE in AD cases. In AD, brain ROS induces calcium influx, via glutamate receptors and triggers an excitotoxic response leading to cell death. Increased levels of DNA strand breaks have been found in AD. They were considered to be a part of apoptosis, but now widely accepted that oxidative damage is responsible for DNA strand breaks and this is consistent with the increased free carbonyls in the nuclei of neurons and glia in AD. Apoptosis considered to be the major type of cell death in AD and there are many other mechanistic links between oxidative stress and apoptosis reported in AD models. A study on fibroblasts from AD patients and control subjects found that two antiapoptotic proteins (HSP 60 and Vimentin) were oxidized in response to treatment with $A\beta$ peptide. A sequence of reactions results thereafter in the formation of AGEs, which are composed of irreversibly cross-linked heterogeneous protein aggregates. There is increasing evidence that the insolubility of $A\beta$ plaques is caused by extensive covalent protein cross-linking. Glucose metabolism in the brain limits the synthesis of acetylcholine, glutamate, aspartate, γ -aminobutyric acid, glycine and ATP production. Whereas the cerebral energy pool is only slightly diminished during the normal aging process, glucose metabolism and cellular energy production are severely reduced in AD. Higher GSH levels were also associated with poorer performance in cognitive tests. This could be a compensatory mechanism, where more GSH are produced in response to the increased oxidation. In line with these data, the levels, but not activities, of GR were elevated in hippocampus from patients with amnesic MCI compared to controls. Conjugation of HNE, produced by lipid peroxidation, to the neuronal glucose transport protein GLUT3 causes $A\beta$ impairs glucose transport, which is followed by a decrease in cellular ATP levels. Oxidative stress and energy depletion simulated by addition of chemical uncoupling agents to neuroblastoma cells leads to the appearance of NFTs; feeding a thiamine-deficient diet to mice leads to the formation of dystrophic neurites similar to those in Alzheimer Diseases. NO has both genotoxic and angiogenic properties and reported to inhibit the release of mitogen from platelets. Another strategy for tumor treatment has focused on

the inhibition of tumor angiogenesis. It has been well established that angiogenesis is a critical event in tumor growth and metastasis. Increased NO production may selectively support mutant p53 cells and may also contribute to tumor angiogenesis by up regulation of vascular endothelial growth factor. There is a growing scientific agreement that antioxidants, particularly the polyphenolic forms, may help lower the incidence of disease, such as certain cancers, cardiovascular, and neurodegenerative diseases, DNA damage, or even have antiaging properties. The absence of neuronal control in tumor vessels suggests that endothelial-derived vasoactive substance, namely NO and ET-1, may be key factors in controlling tumor blood flow during tumor growth and metastasis. An imbalance between endothelial-derived vasoconstrictors and vasodilators, along with deficiency of antioxidant systems may result in mitochondria lesions in tumors. NO-induced mitochondrial failure is a causative factor in the diseased tumors, especially tumor angiogenesis. This research hypothesize that mitochondrial involvement in this cascade may be a major factor that controls tumor growth and metastasis.