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Role of oxidative stress in Alzheimer's disease

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Abstract
Alzheimer's disease is the leading cause of disability in people over 65. Amyloid (Aβ) peptide deposition, neurofibrillary tangles of hyperphosphorylated protein, and dementia are hallmarks of AD [1]. The neurotoxic oligomer Aβ peptide and tau protein [2] mediate neurodegeneration, one of the main causes of the disease. Oxidative stress [3], an imbalance between antioxidants and oxidants, causes and exacerbates these symptoms. Free radicals, which have one or more unpaired electrons in their outer shell, can augment or reduce antioxidant defence, causing this imbalance. The reduction of molecular oxygen in water produces superoxide, which produces hydrogen peroxide by adding an electron. Reactive oxygen species (ROS) [4]—hydroxyl radicals produced by hydrogen peroxide reduction—can react with lipids, proteins, nucleic acids, and other molecules and change their structures and activities. Due to its makeup, ROS affects tissues and organs, particularly the sensitive brain. High oxygen usage and highly oxidizable lipids make up the brain.

Keywords: Subclinical hypothyroidism (SCH), thyroid-stimulating hormone, neck swelling, nat. MUR, individualisation, homoeopathy

Introduction
Alzheimer's disease (AD) is the most common dementia in in individuals age 65 and older. The pathological substrate of dementia is altered metabolism of amyloid precursor protein (APP), which forms amyloid (neuritic or senile) plaques in the cortex and limbic system, and altered microtubule-associated protein tau, which forms neurofibrillary tangles (NFT). Cognitive and behavioural symptoms are caused by synaptic loss, cholinergic, serotonergic, and noradrenergic dysfunction, and glutamatergic. Early amyloid deposition occurs in heteromodal association areas. Memory deterioration suggests that soluble amyloid and its oligomers directly affect the pathogenic cascade and cognitive function.

NFT pathology begins in the mesial temporal areas and progresses to the allocortex and neocortex). AD begins with short-term memory, word-finding, and language problems and develops to general cognitive impairment. As the disease advances, aberrant neurological and psychiatric symptoms increase in frequency and intensity and have been linked to faster cognitive and functional loss.

According to investigations, oxidative stress signs can be seen even before AD symptoms appear. As a result of altered bioenergetics caused by mitochondrial depletion, pre-symptomatic AD has also been linked to this. In addition to decreasing the production of ATP, mitochondrial insufficiency causes an excessive amount of reactive oxygen species to be produced (ROS). These ROS have also been linked to cell death, cytoskeletal changes, and membrane damage. Although several molecular explanations have been proposed, the precise nature of the relationship between oxidative stress and other hallmarks of AD pathogenesis is unknown.

Risk factors for AD [5]
Traumatic brain injury, stroke, hypertension, diabetes, hypercholesterolemia, and hyperhomocystinemia increase AD risk. Aluminum exposure, smoking, high calorie intake, lack of exercise, and intellectual inactivity are lifestyle and environmental AD risk factors. All these risk factors increase reactive oxygen species production and/or decrease endogenous antioxidant capacity. Nutrients and free radical-inhibiting agents also reduce AD. Vitamins C and E, oestrogen, nonsteroidal anti-inflammatory drugs, statins, omega-3 polyunsaturated fatty acids, and red wine are antioxidants.

In experimental animals, calorie restriction, exercise, and intellectual activity boost endogenous antioxidant defences, promoting neuronal survival.

Free radicals, active oxygen species, and oxidative stress [4]

An atom typically consists of an orbiting pair of electrons and a central nucleus. Free radicals, on the other hand, are atoms and molecules that have unpaired electrons. Due to the unpaired electrons' propensity to form pairs with other electrons, free radicals are typically unstable and extremely reactive. As an oxygen molecule (O_2) is metabolised in vivo, it goes through a four-electron reduction. Reactive oxygen metabolites are produced during this process by the secondary excitation of electrons caused by the addition of energy or by interaction with transition elements. The metabolites of reactive oxygen created in this way are active oxygen species because they are more reactive than the parent oxygen molecule. Active oxygen species in the strict sense include singlet oxygen, superoxide, hydrogen peroxide, hydroxyl radicals, and hydrogen peroxide.

Aerobic organisms must remove highly reactive active oxygen species to survive. Hence, antioxidant defence mechanisms have evolved. These oxygen metabolites' strong reactivity controls biological events.

Under healthy settings, the body's complex mechanisms to eliminate active oxygen species and free radicals make these by-products of oxygen metabolism harmless. If active oxygen species or free radicals are created abundantly or at atypical places, the balance between generation and elimination is lost, causing oxidative stress. Hence, active oxygen species and free radicals can damage biological membranes and tissues, causing illnesses. Oxidative stress is a "state damaging to the organism, which emerges when oxidative reactions outweigh antioxidant reactions because the equilibrium between them has been lost".

Oxidative stress and Alzheimer's disease [6]

Alzheimer's disease (AD) causes neuronal death and protein accumulation, including extracellular amyloid plaques (Aβ) and intracellular tau tangles (neurofibrillary tangles).

Oxidative imbalance and neuronal damage may cause and progress AD. In AD patients, high ROS generation may cause mitochondrial dysfunction, but the cause and mechanism of redox imbalance are unknown.

Aβ build up increases oxidative stress and mitochondrial dysfunction and energy failure even in early AD. Earlier research have suggested that Aβ-induced oxidative imbalance may increase the amounts of by products of lipid peroxidation (4 hydroxynonal, malonidialdehyde), protein oxidation (carbonyl), and DNA/RNA oxidation (8-hydroxyldeoxyguanosine and 8-hydroxylguanosine). Patients have lower amounts of antioxidants like uric acid, vitamin C and E, and antioxidant enzymes like superoxide dismutase and catalase.

Aβ may increase oxidative stress in AD because mutant amyloid precursor protein (APP) and presenilin-1 (PS-1) transgenic mice models exhibit higher H2O2 and protein and lipid peroxidation.

Oxidative stress can also increase the synthesis and aggregation of Aβ and tau protein phosphorylation, creating a vicious cycle of AD development. Oxidative stress increases Aβ synthesis, according to numerous studies. In transgenic mice with APP mutation, antioxidant defence deficits increased oxidative stress and Aβ accumulation. Oxidative stress may decrease α-secretase activity, increase β and γ-secretases [7], and increase Aβ formation.

Oxidative stress appears to cause tau pathology. Overexpressed tau protein may deplete peroxisomes, making cells more susceptible to oxidative stress. Transgenic mice expressing mutant (P301S and P301L) tau proteins [8] had reduced NADH-ubiquinone oxidoreductase activity and mitochondrial malfunction, which enhanced ROS generation.

AD has various signs of mitochondrial dysfunction. AD often reduces brain energy metabolism. In AD, neuronal expression of mitochondrial electron transport chain component genes are reduced. Also, AD patients have decreased pyruvate dehydrogenase complex, α-ketoglutarate dehydrogenase complex and cytochrome oxidase activity. Clinical severity and senile plaque were substantially associated. AD patients have reduced Complex IV activity in hippocampus [9] and platelet mitochondria. Aβ-induced mitochondrial dysfunction impairs calcium homeostasis. Calcium excess and reduced reuptake follow. ROS generation and PTP opening (10)may increase mitochondrial calcium. It may cause apoptosis by translocating pro-apoptotic substances from mitochondria to cytosol. Calmodulin-dependent kinase and calpain activity indicate intracellular calcium increase. Early AD has enhanced calmodulin-dependent kinase and calpain activity. Finally, AD patients have higher mitochondrial DNA mutations due to increased oxidative damage.

Impact of exercise and diet on mitochondrial function and oxidative stress

One of the finest strategies to maintain the health of our body and brain is exercise. Many mitochondrial activities are increased by physical activity and a healthy diet. Exercise and calorie restriction slow down the ageing process in both people and animals. Exercise boosts mitochondrial activity in peripheral organs and completely halts brain atrophy in mice models. People are becoming more aware of how exercise boosts health and combats degenerative diseases like Alzheimer's. Several research show that exercise benefits AD patients' cerebral blood flow, hippocampus thickness, neurogenesis, cognitive performance, neuropsychiatric symptoms, and disease progression.

ROS and neuroinflammation are exacerbated by sedentary lifestyles in neurodegenerative disorders. Exercise lowers oxidative stress and inflammation. Clinical traits including insulin sensitivity and cellular ageing may be improved by its attenuation. Without exercise, mitochondrial ETC activity falls in healthy individuals.

The greatest strategy to maintain antioxidant status may be through vitamin, mineral, and antioxidant-rich fruits and vegetables. Foods high in vitamin C minimise ROS. Vitamin C is used either persistently or briefly in clinical and laboratory research, either alone or in conjunction with other antioxidants. Vitamin C protects mitochondria in both cells and animals and lowers ROS.

In healthy adults, a constant calorie decrease of 15-25% over the course of 24 months improved quality of life and markedly lowered ROS levels. Through modulating cell stress, ageing, and death through Sirt1 and AMPK-dependent regulation of mTOR signalling, calorie restriction promotes autophagy/mitophagy [11]. Calorie restriction

promotes mitochondrial production and turnover, which reduces the accumulation of defective organelles, enhances the dynamics, shape, and Ca2+ retention of the mitochondria, and protects against excitotoxicity, a major AD pathogen. In MCI and AD patients, calorie restriction and the ketogenic diet slow cognitive deterioration. The ketogenic diet is neuroprotective [12] in Alzheimer's disease because ketones power mitochondria more effectively than glucose. To protect mitochondrial and brain function, ketone bodies boost mitochondrial respiration, lower ROS generation, strengthen antioxidant defence, and restrict mPTP opening. A healthy lifestyle can help prevent AD since it encourages the health of the mitochondria, redox balance, and mental function.

Conclusion

Oxidative stress accelerates brain ageing and Alzheimer's disease. Mitochondria create free radicals during respiration and malfunction in ageing and AD. Damaged mitochondria produce hazardous oxidative stressor amyloid beta, according to the mitochondrial cascade hypothesis. Free radicals damage mitochondrial DNA, mostly unprotected and histone-free. AD brains have substantially more double strand breaks than older brains, and defective DNA repair accelerates disease development. Oxidative stress leads to brain aging's faulty circuits.

Oxidative stress therapies can improve cognition and reduce ROS levels. Antioxidants have variable effects on cognition in elderly and AD patients, therefore dosage, timing, antioxidant combinations, and diet must be carefully studied to generate consistent benefits.

Based on recently identified modifiable risk factors for AD, it is suggested that a low-calorie diet and engaging in both mental and physical activity constitute an essential antioxidative strategy for AD prevention.

Conflict of Interest

Not available

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