

Review Article

ROLE OF OXIDATIVE STRESS IN THE PATHOGENESIS OF NEURODEGENERATIVE DISEASES

Mansi Rastogi

Moradabad Educational Trust Group of Institutions Faculty of Pharmacy Moradabad 244001, Uttar Pradesh India.

* **Corresponding Author:** Tel. No. : +91 7351773390, Email: rastogimansi60@gmail.com

ARTICLE INFO

Received 18 September 2021

Revised 26 December 2021

Accepted 4 January 2022

Keywords:

- Alzheimer's disease
- Amyotrophic lateral sclerosis
- Mitochondrial dysfunction
- Antioxidant.

ABSTRACT

Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS) are all neurodegenerative conditions that affect an increasing number of senior people. A gradual loss of neurons, impaired motor or cognitive functions, and aberrant protein buildup are hallmarks of many disease disorders. In organs that require a high level of energy, such as the heart, muscles, brain, or liver, mitochondrial dysfunction is a common characteristic of the ageing process. Synaptic plasticity and neurotransmitter synthesis all rely on the mitochondria, which supply the energy needed for most cellular functions. Due to the brain's high oxygen consumption, inadequate antioxidant defences, and high polyunsaturated fat content, it is particularly vulnerable to oxidative stress and damage. To sustain neuronal integrity and survival, the necessity of protective mechanisms, such as antioxidant defences, cannot be overstated. This comprehensive perspective will help to better understand the connection between mitochondrial oxidative stress and neurodegenerative disorders.

1. INTRODUCTION

Oxidative stress is simply the elevation of free radicals (reactive oxygen species/reactive nitrogen species) found in cells that accumulate to higher-than-normal levels. Excessive or inappropriate oxidative stress damages cell and tissues, specifically, mitochondria, cell membranes, DNA, proteins and lipids which leads to irreversible damage to the neurons. Biochemical integrity of the brain is vital for normal functioning of the central nervous system (CNS). One of the factors contributing to cerebral biochemical impairment is a chemical process is called oxidative stress. Oxidative stress occurs upon excessive free radical production resulting from an insufficiency of the counteracting antioxidant response system. The brain with its high oxygen consumption & lipid rich content is highly, susceptible to oxidative stress. Oxidative stress induced damage to brain has a strong potential to negatively impact normal CNS functions [1-3]. Oxidative stress has historically been considered to be involved mainly in neurodegenerative disorders such as

Alzheimer diseases, Parkinson diseases and its involvement in neuropsychiatric disorders including anxiety, depression.

1.1 Role of different reactive oxygen species

Reactive oxygen species (ROS) have long been known to be a component of killing response of immune cells to microbial invasion. Reactive oxygen species (ROS) is a phrase used to describe a number of reactive molecules and free radicals derived from molecular oxygen. The production of oxygen based on radicals is the bane to all the aerobic species. These molecules, produced as by product during the mitochondrial electron transport of aerobic respiration or by oxidoreductase enzymes & metal catalyzed oxidation have the potential to causes a number of deleterious events [4]. ROS have a role in cell signaling, including apoptosis, gene expression & activation of cell signaling cascades. It should be noted that ROS can serve as both intra & intercellular messengers.

1.2 Reactive Oxygen Species

Most reactive oxygen species are generated as by product during mitochondrial electron transport. ROS are formed as necessary in term of metal catalyzed oxidative reaction. The sequential reduction of oxygen through the addition of electron leads to the formation of a number of ROS including; superoxide, Hydrogen peroxide, Hydroxyl radical, Hydroxyl ion & nitric oxide [5, 6]

1.3 Role of different reactive nitrogen species

RNS are a family of antimicrobial molecules derived from nitric oxide (NO) and superoxide (O₂) produced via the enzymatic activity of inducible nitric oxide synthase (NOS₂) and NADPH Oxidase respectively NOS₂ is expressed primarily in macrophages after induction by cytokines and microbial products, notably interferon- γ (IFN- γ) and lipopolysaccharides (LPS). Reactive nitrogen species act together with reactive oxygen species (ROS) to damage cells, causing nitrosative stress [7-10]

1.4 Pathogenesis of oxidative stress.

Chronic inflammatory diseases place a burden on the majority of health systems all around the world, essentially due to the lack of safe, effective & affordable therapies. Diabetes, allergies & chronic obstructive pulmonary diseases are classified by the world health organization as specific chronic inflammation – mediated diseases. Oxidative stress is caused by an overproduction of reactive oxygen species, resulting in deleterious effects such as oxidative damage of DNA lipids & proteins. It can also lead to the activation of various proinflammatory signaling pathways that result in production of series of cytokines & chemokines, growth factor, cell cycle regulatory molecules etc [11]. The role oxidative stress in the pathophysiology of chronic inflammation mediated diseases. We (biochemical or cellular) & or (in vivo studies on inflammation; allergies, diabetes, arthritis & joint diseases, cardiovascular, renal, neurodegenerative, chronic obstructive, pulmonary & gastrointestinal diseases.

Some points include but not limited to follow:

- General role of oxidative stress in the inflammatory process.
- Cellular production of reactive species in inflammatory diseases.
- Detection of reactive species in inflammatory diseases.
- Expression/Production/Modulation of inflammation mediators triggered by reactive prooxidative species.
- Strategies to prevent/treat oxidative stress – related inflammatory diseases.

1.5 Role of oxidative stress in apoptosis

Apoptosis or programmed cell death, is essential for the normal functioning and survival of most multi –cellular organism. The morphological and biochemical characteristics of apoptosis, however are highly conserved during the evolution. It is

currently believed that apoptosis can be divided into at least three functionally distinct phases, i.e., induction, effectors and execution phase. Antioxidants and thiol reductants, such as N-acetylcysteine, and overexpression of manganese superoxide (MnSOD) can block or delay apoptosis. Bcl-2 an endogenously produced proteins, has been shown to prevents cells from dying of apoptosis apparently by an antioxidative mechanisms. Taken together ROS and the resulting cellular redox change, can be part of signal transduction pathways during apoptosis. During mitochondrial dysfunction, several essential players of apoptosis, including pro caspases, cytochrome C, apoptosis-inducing factors (AIF), and apoptotic protease-activating factors-1 (APAF-1) are released into the cytosol. The multimeric complex formation of cytochrome C, APAF-1 and caspase 9 activates downstream caspases leading to apoptotic cell death [12, 13]. All the three functional phases of apoptosis are under the influence of regulatory controls. Thus, increasing evidences provide support that oxidative stress and apoptosis are closely linked physiological phenomena and are implicated in pathophysiological of some of the chronic diseases including AIDS, autoimmunity, cancer, diabetes mellitus, Alzheimer's and Parkinson's and ischemia of heart and brain.

1.6 Role of oxidative stress in Inflammation

Oxidative stress occurs due to the imbalance between the production of reactive oxygen species (ROS) and the availability of antioxidants or radical scavengers. The excess ROS produced can either oxidize biomolecules or can structurally modify proteins and genes so as to triggers signaling cascade that can lead to the onset and progression of inflammatory diseases. ROS –induced activation of transcription factors and pro inflammatory genes lead to the onset of inflammation. Inflammation causes immune cells to secrete various cytokines and chemokines in order to recruit various other immune cells to the site of oxidative stress/infection. Reflexively, an enhanced ROS generation by immune causes oxidative stress and tissues injury [14].

1.7 Role of oxidative stress in mitochondrial dysfunction

Oxidative stress and mitochondrial damage have been implicated in the pathogenesis of several neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis. Oxidative stress is characterized by the overproduction of reactive oxygen species, which can induce mitochondrial respiratory chain, alter membrane permeability, and influence Ca²⁺ homeostasis and mitochondrial defense systems. All these changes are implicated in the development of these neurodegenerative disease, mediating or amplifying neuronal dysfunction and triggering neurodegeneration [15, 16].

1.8 Oxidative stress in pathogenesis of Parkinson Diseases

Current concepts of the pathogenesis of Parkinson's diseases (PD) center on the formation of reactive oxygen species & the onset of oxidative stress leading to oxidative damage to substantia nigra pars compacta. Extensive postmortem studies have

provided evidence to support the involvement of oxidative stress in the pathogenesis of PD; in particular these include alteration in brain iron content, impaired mitochondrial function, alteration in the antioxidant protective systems (most notably superoxide dismutase [SOD] and reduced glutathione [GSH]), and evidence of oxidative damage to lipids, proteins, and DNA. Iron can induce oxidative stress, and intranigral injections have been shown to induce a model of progressive parkinsonism. A loss of GSH is associated with incidental Lewy body disease and may represent the earliest biochemical marker of nigral cell loss. GSH depletion alone may not result in damage to nigral neurons but may increase susceptibility to subsequent toxic or free radical exposure. The nature of the free radicals' species responsible for cell death in PD remain unknown, but there is evidence of involvement of hydroxyl radical (OH), peroxynitrite and nitric oxide) [17, 18]. Central to many of the process involved in oxidative stress and oxidative damage in PD are the actions of monoamine oxidase –B(MAO-B). MAO –B is essential for the activation of 1-methyl-4-phenyl-1,2,3,6- tetrahydropyridine to 1- methyl-4-phenylpyridinium ion, for a component of the enzymatic conversion of dopamine to hydrogen peroxide (H₂O₂), and for the activation of other potential toxins such as isoquinolines and beta carbolines. Thus, the inhibition of MAO-B by drugs such as selegiline may protect against activation of some toxins and free radicals formed from the MAO-B oxidation of dopamine. In addition, selegiline may act through a mechanism unrelated to MAO-B to increase neurotrophic factor activity and upregulate molecules such as glutathione, SOD, catalase and BCL-2 proteins, which protect against oxidant stress and apoptosis [19]

1.9 Role of Alzheimer Disease in pathogenesis of oxidative stress

Cellular changes show that oxidative stress is an event that precedes the appearance of the hallmark pathologies of the disease, neurofibrillary tangles, and senile plaques, while it is still unclear what the initial source of the oxidative stress is in Alzheimer disease, it is likely that the process is highly dependent on redox –active transition metals such as iron and copper. High concentrations of zinc were associated with the memory and cognitive regions of the brain, including the neocortex and amygdala and hippocampus, which are mostly affected in AD pathology. This binding of zinc has a highly ordered conformational state of A beta aggregates. Consequently, the immunological / inflammatory response to non-soluble A beta plaques involves the disruption of zinc homeostatic followed by uncontrolled cerebral zinc release, which is typical for oxidative stress. Thus, the uncontrolled accumulation of zinc or A beta leads to zinc – induced and A beta –mediated oxidative stress and cytotoxicity [20] The brain membranes phospholipids are composed of polyunsaturated fatty acid, this organ is particularly vulnerable to free radical attack. Their double bonds allow the removal of hydrogen ions and increased lipid peroxidation, which is the most prominent feature in which degenerative changes is most pronounced in the AD brain.

1.10 Role of anxiety in pathogenesis of oxidative stress

High O₂ consumption, modest antioxidant defense and a lipid rich antioxidant defense and a lipid –rich constitution makes the brain highly vulnerable to redox imbalances. Oxidative damage in the brain causes nervous system impairment. Recently, oxidative stress has also been implicated in depression anxiety disorder and highly anxiety levels. The findings which established a link between oxidative stress and pathological anxiety have inspired a number of other recent studies focusing on the link between oxidative status and normal anxiety and also on a possible causal relationship between cellular oxidative stress and emotional stress [21]

1.11 Role of depression in pathogenesis of oxidative stress

Reactive oxygen species (ROS) have a vital role in cellular signaling and in defence against invasive microorganisms. Excessive ROS generation and exhaustion of antioxidative defence trigger proinflammatory signaling, damaging vital macromolecules and inducing cellular apoptosis. The failure of cells to maintain redox homeostasis and resultant generation of proinflammatory mediators leads to cell necrosis. The brain is more vulnerable to oxidative stress (OS) because of its higher oxygen consumption, higher lipid, content, and weaker antioxidative defence. OS is a main cause of neurodegeneration and its involvements in the pathogenesis of major depressive disorder (MDD) is unequivocally established. OS and proinflammatory signaling have emerged as mainstays in the pathogenesis of MDD. Targeting these changes with suitable antioxidants could be an effective strategy to treat MDD [22].

1.12 Role of Amyotrophic lateral sclerosis (ALS) in pathogenesis of oxidative stress

Amyotrophic lateral sclerosis (ALS) is characterized by progressive loss of motoneurons and degradations of neuromuscular junction (NMJ). Consistent with the dying back hypothesis of motoneuron degeneration the decline in synaptic function initiates from the presynaptic terminals in ALS. Oxidative stress is a major contributory factor to ALS pathology and affects the presynaptic transmitter releasing machinery. Indeed, in ALS mouse models nerve terminals are sensitive to reactive oxygen species (ROS) suggesting that oxidative species, along with compromised mitochondria Ca²⁺ amplifies the presynaptic decline in NMJ. This initial dysfunction is followed by a neurodegeneration induced by inflammatory agents and loss of tropic support. To develop effective therapeutic approaches against ALS, it is important to identify the mechanisms underlying the initial pathological events. Given the role of oxidative stress in ALS, targeted antioxidant treatments could be a promising therapeutic approach. However, the complex nature of ALS and failures of monotherapies suggest that an antioxidant therapy should be accompanied by anti-inflammatory intervention to enhance the restoration of the redox balance [23,24].

1.13 Role of different cellular enzymes against ROS AND RNS

There is a significant evidence that, in living systems, free radicals and other reactive oxygen and nitrogen species play a double role, because they can cause oxidative damage and tissue dysfunction and serve as molecular signals activating stress responses that are beneficial to both play a major role in tissue oxidative damage and dysfunction and provide protection against excessive tissue dysfunction through several mechanisms, including stimulation of opening of permeability transition pores. Until recently, the functional significance of ROS sources different from mitochondria has received lesser attention. However, besides confirming the mitochondrial role in tissue oxidative stress and protection, show interplay between mitochondria and other ROS cellular sources, so that activation of one can led to activation of other sources. Thus, it is currently accepted that in various conditions all cellular sources of ROS provide significant contribution to processes that oxidatively damage tissues and assure their survival, through mechanisms such as autophagy and apoptosis [25, 26].

2. CONCLUSION

During the past 30 years, the role of mitochondria and oxidative stress in ageing and neurodegenerative diseases has been intensively investigated According to the study's general conclusion, age-related changes in both systems contribute to the course of neurodegenerative diseases, if not the initiation of these diseases. While mitochondrial failure and oxidative stress may be used as early warning signs of ageing problems, it is unclear whether they may also be used as therapeutic targets. Understanding the involvement of mitochondria and oxidative stress in ageing and neurodegeneration could lead to a variety of new approaches to enhancing the quality of life for the aged.

REFERENCES

1. Blesa J, Przedborski S. Parkinson's disease: animal models and dopaminergic cell vulnerability. *Front Neuroanat* 2014; 8: 155. <http://dx.doi.org/10.3389/fnana.2014.00155> PMID: 25565980
2. Pluvinage JV, Wyss-Coray T. Systemic factors as mediators of brain homeostasis, ageing and neurodegeneration. *Nat Rev Neurosci* 2020; 8: 1-10. <http://dx.doi.org/10.1038/s41583-019-0255-9>
3. Cai Z, Zeng W, Tao K, Lu F, Gao G, Yang Q. Myricitrin alleviates MPP-induced mitochondrial dysfunction in a DJ-1-dependent manner in SN4741 cells. *Biochem Biophys Res Commun* 2015; 458(2): 227-33. <http://dx.doi.org/10.1016/j.bbrc.2015.01.060> PMID: 25623535
4. Phom L, Achumi B, Alone DP, Muralidhara, Yeniseti SC. Curcumin's neuroprotective efficacy in Drosophila model of idiopathic Parkinson's disease is phase specific: implication of its therapeutic effectiveness. *Rejuvenation Res* 2014; 17(6): 481-9. <http://dx.doi.org/10.1089/rej.2014.1591> PMID: 25238331
5. Rowinska-Zyrek M, Salerno M, Kozlowski H. Neurodegenerative diseases – understanding their molecular bases and progress in the development of potential treatments. *Coord Chem Rev* 2015; 284: 298-312. <http://dx.doi.org/10.1016/j.ccr.2014.03.026>
6. Solanki I, Parihar P, Mansuri ML, Parihar MS. Flavonoid based therapies in the early management of neurodegenerative diseases. *Adv Nutr* 2015; 6(1): 64-72 <http://dx.doi.org/10.3945/an.114.007500> PMID: 25593144
7. Rein MJ, Renouf M, Cruz-Hernandez C, Actis-Goretta L, Thakkar SK, da Silva Pinto M. Bioavailability of bioactive food compounds: a challenging journey to bioefficacy. *Br J Clin Pharmacol* 2013; 75(3): 588-602. <http://dx.doi.org/10.1111/j.1365-2125.2012.04425.x> PMID: 22897361
8. Spuch C, Saida O, Navarro C. Advances in the treatment of neurodegenerative disorders employing nanoparticles. *Recent Pat Drug Deliv Formul* 2012; 6(1): 2-18. <http://dx.doi.org/10.2174/187221112799219125> PMID: 22272933
9. Podędek A, Redzyna M, Klewicka E, Koziółkiewicz M. Matrix effects on the stability and antioxidant activity of red cabbage anthocyanins under simulated gastrointestinal digestion. *BioMed Res Int* 2014; 2014365738 <http://dx.doi.org/10.1155/2014/365738> PMID: 24575407
10. Srivastava R, Choudhury PK, Dev SK, Rathore V. Neuroprotective effect of α -pinene self-emulsifying nanoformulation against 6-OHDA induced neurotoxicity on human SH-SY5Y cells and its in vivo validation for anti-Parkinson's effect. *Journal of Biochemical and Molecular Toxicology*. 2021 Nov;35(11):e22902.
11. Pereira DM, Valentão P, Andrade PB. Nano- and micro delivery systems for marine bioactive lipids. *Mar Drugs* 2014; 12(12): 6014-27. <http://dx.doi.org/10.3390/md12126014> PMID: 25522314
12. Yao M, Xiao H, McClements DJ. Delivery of lipophilic bioactives: assembly, disassembly, and reassembly of lipid nanoparticles. *Annu Rev Food Sci Technol* 2014; 5: 53-81. <http://dx.doi.org/10.1146/annurev-food-072913-100350> PMID: 24328432
13. Mun S, Kim YR, McClements DJ. Control of β -carotene bioaccessibility using starch-based filled hydrogels. *Food Chem* 2015; 173: 454-61. <http://dx.doi.org/10.1016/j.foodchem.2014.10.053> PMID:25466045
14. McClements DJ. Utilizing food effects to overcome challenges in delivery of lipophilic bioactives: structural design of medical and functional foods. *Expert Opin Drug Deliv* 2013; 10(12): 1621-32. <http://dx.doi.org/10.1517/17425247.2013.837448> PMID: 24053714
15. Wu W, Lee SY, Wu X, et al. Neuroprotective ferulic acid (FA)-glycol chitosan (GC) nanoparticles for functional restoration of traumatically injured spinal cord. *Biomaterials* 2014; 35(7): 2355-64. <http://dx.doi.org/10.1016/j.biomaterials.2013.11.074> PMID: 24332460
16. Srivastava R, Choudhury PK, Dev SK, Rathore V. Bioactive Loaded Lipid-based Nanostructures: A Novel Insight for Age-related Neurodegeneration. *Current Molecular Medicine*. 2021 Nov 1;21(9):724-94.
17. Yin N, Yao X, Zhou Q, Faiola F, Jiang G. Vitamin E attenuates silver nanoparticle-induced effects on body weight and neurotoxicity in rats. *Biochem Biophys Res Commun* 2015; 458(2): 405-10. <http://dx.doi.org/10.1016/j.bbrc.2015.01.130> PMID: 25661000
18. Zare K, Eidi A, Roghani M, Rohani AH. The neuroprotective potential of sinapic acid in the 6-hydroxydopamine-induced hemiparkinsonian rat. *Metab Brain Dis* 2015; 30(1): 205-13. <http://dx.doi.org/10.1007/s11011-014-9604-6> PMID: 25123753
19. Amri A, Le Clanche S, Théron P, et al. Resveratrol self-emulsifying system increases the uptake by endothelial cells and improves

- protection against oxidative stress-mediated death. *Eur J Pharm Biopharm* 2014; 86(3): 418-26. <http://dx.doi.org/10.1016/j.ejpb.2013.10.015> PMID: 24184672.
20. Cheng KK, Yeung CF, Ho SW, Chow SF, Chow AH, Baum L. Highly stabilized curcumin nanoparticles tested in an in vitro blood-brain barrier model and in Alzheimer's disease Tg2576 mice. *AAPS J* 2013; 15(2): 324-36. <http://dx.doi.org/10.1208/s12248-012-9444-4> PMID: 23229335
21. Nair P, Malhotra A, Dhawan DK. Curcumin and quercetin trigger apoptosis during benzo(a)pyrene-induced lung carcinogenesis. *Mol Cell Biochem* 2015; 400(1-2): 51-6. <http://dx.doi.org/10.1007/s11010-014-2261-6> PMID: 25359171
22. Frozza RL, Bernardi A, Hoppe JB, et al. Lipid-core nanocapsules improve the effects of resveratrol against Abeta-induced neuroinflammation. *J Biomed Nanotechnol* 2013; 9(12): 2086-104. <http://dx.doi.org/10.1166/jbn.2013.1709> PMID: 24266263
23. Lu X, Xu H, Sun B, Zhu Z, Zheng D, Li X. Enhanced neuroprotective effects of resveratrol delivered by nanoparticles on hydrogen peroxide-induced oxidative stress in rat cortical cell culture. *Mol Pharm* 2013; 10(5): 2045-53. <http://dx.doi.org/10.1021/mp400056c> PMID: 23534345
24. Coradini K, Lima FO, Oliveira CM, et al. Co-encapsulation of resveratrol and curcumin in lipid-core nanocapsules improves their in vitro antioxidant effects. *Eur J Pharm Biopharm* 2014; 88(1): 178-85. <http://dx.doi.org/10.1016/j.ejpb.2014.04.009> PMID: 24780440
25. Srivastava R, Choudhury PK, Dev SK, Rathore V. Molecular Simulation Studies of Alpha Pinene, an Alkene in Search for Oxidative Stress Targeted Therapeutic Paradigms for the Treatment of Parkinson's Disease: A Computational Approach and Its In-Vitro Antioxidant Validation. *Letters in Drug Design & Discovery*. 2021 Nov 1;18(12):1117-35.
26. Nunes S, Madureira AR, Campos D, et al. Solid lipid nanoparticles as oral delivery systems of phenolic compounds: Overcoming pharmacokinetic limitations for nutraceutical applications. *Crit Rev Food Sci Nutr* 2017; 57(9): 1863-73.