Review Article

Oxidative stress, Mitochondrial dysfunction and Neuro-degenerative diseases: A Review

Shalini K. Sawhney*

ITS College of Pharmacy, Muradnagar, Ghaziabad, India

ABSTRACT: Oxidative stress is produced by the reactive oxygen/nitrogen species (ROS/RNS) which involves mitochondrial dysfunction. Mitochondria is one of the main sources of oxidative stress, as it utilizes the oxygen for the energy production. Overproduction of ROS, results in oxidative stress, which injures the cell structures, lipids, proteins, and DNA. Various oxidative events implicated in many diseases is due to oxidative stress which include alteration in mitochondrial proteins, mitochondrial lipids and mitochondrial DNA, which in turn leads to damage nerve cells as they are metabolically very active. Reactive oxygen/nitrogen species at moderate concentrations also play roles in normal physiology of many processes like signalling pathways, induction of mitogenic response and in defence against infectious pathogens. Oxidative stress has been considered to be the main cause in the etiology of neurodegenerative diseases, which includes Parkinson's disease (PD) and Alzheimer's disease (AD). Recent research on the dysfunction and function of PD associated genes has provided new fundamental insights into biochemical pathways that are linked with the disease process This review includes source of free radical generation, mitochondrial dysfunction and the mechanism involved in neurodegenerative diseases which involves both PD as well as in AD. This makes the mitochondria, the main target of PD and AD research.

⇑ Corresponding author at:
Shalini K. Sawhney, Associate Professor, ITS College of Pharmacy, Delhi – Meerut road, Muradnagar, Ghaziabad - 201206, India
E-mail: shaliniksawhney@its.edu.in

INTRODUCTION

Over the last several decades there has been great progress with respect to understand what triggers most neurodegenerative diseases. These reviews include both disease specific as well as more general reviews that focus on a pathway or a process that could lead to neurodegeneration [1]. In the human body, it is estimated that cell division and metabolism occur extensively till about 25 years of age. After this age, subsidiary products of metabolism and cell damage accumulate, and the phenotypes of ageing appear, causing disease formation. Among these age-related diseases, neurodegenerative diseases have drawn a lot of attention due to their irreversibility, lack of effective treatment, and accompanied social and economic burdens. In this review, we discuss the pathogenesis of age-related neurodegenerative diseases including Alzheimer's disease and Parkinson's disease [2].

Oxidative stress occurs due to metabolic reactions that use oxygen and represents, disturbance in the equilibrium status of pro-oxidant and antioxidant reactions in living organisms. The excess ROS damages cellular lipids, proteins, or DNA inhibiting their normal function. Because of this, oxidative stress has been implicated in a number of human diseases as well as in the ageing process [3]. The delicate balance between beneficial and harmful effects of free radicals is a very important aspect of living organisms and is achieved by mechanisms called "redox regulation". Redox regulation protects living organisms from various oxidative stresses and maintains "redox homeostasis" by controlling the redox status of the living organisms [4]. Brain is thus believed to be particularly susceptible to the damaging effects of ROS. In cases of AD and PD various levels of ROS damage have been reported within the definite brain region that undergoes selective neurodegeneration.

Like lipid peroxidation markers 4-hydroxynonenal and malondialdehyde are identified in the cortex and hippocampus of patients with AD and the substantia nigra of patients with PD [5-9]. Oxidative stress plays a major part in the development of various diseases such as arthritis, cancer, autoimmune disorders, aging, cardiovascular and neurodegenerative diseases. The human body has several mechanisms to combat oxidative stress by producing antioxidants that are either naturally produced, or externally supplied through external sources foods or supplements. Endogenous and exogenous antioxidants act as free radical scavengers by preventing and repairing damages caused by ROS and RNS, and therefore can boost the immune defence and lower the risk of cancer and various degenerative diseases [10-14]. Various evidence has shown the involvement of cellular oxidants in the maintenance of "REDOX HOMEOSTASIS" in the redox regulation of normal physiological functions as well as pathogenesis of various diseases, including cancer, ischemia/ reperfusion injury, inflammatory diseases, diabetes mellitus, neurodegenerative disorders and ageing. The mitochondrial electron transport chain is one of the important reservoirs of ATP in the mammalian cell and is thus essential for life. During energy transduction, a small number of electrons "leak" to oxygen prematurely, forming the oxygen free radical superoxide, which has been concerned to be the cause of pathophysiology of a range of diseases [15, 16].

Nitric oxide (NO) is a reactive radical that acts as an important biological signalling oxidative molecule in a large variety of diverse physiological processes like neurotransmission, defence mechanisms, smooth muscle relaxation, blood pressure regulation, and immune regulation [17]. Overproduction of reactive nitrogen species is called nitrosative stress [18, 19]. It occurs when the generation of reactive nitrogen species in a system exceeds the system's ability to eliminate and neutralize them. Nitrosative stress would lead to nitrosylation reactions which can deteriorate the structure of the proteins and as such inhibit the normal functioning of the protein.
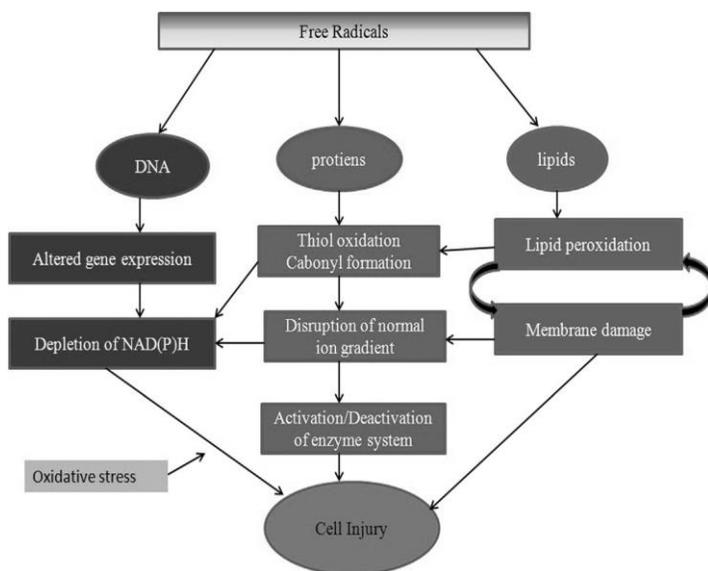

Fig. 1: This schematic representation shows the effect of free radicals on biological molecules like proteins, DNA and lipids. Free radicals react with membrane lipids, proteins and nucleic acids and as such causes cell injury

Oxidative stress and Alzheimer disease

Alzheimer's disease causes dementia and is the most common neurodegenerative disease which occurs in elderly. It has been evident from different studies that oxidative stress is an important factor that leads to the initiation and progression of AD. Mitochondrial dysfunction and aberrant accumulation of transition metals may lead to excess accumulation of reactive oxygen species and the accumulation of abnormal Abeta or tau-appear to promote redox imbalance. This leads to oxidative stress which in turn causes Abeta or tau induced neurotoxicity. Alzheimer's disease is the most common cause of dementia in elderly adults. It is estimated that 10% of the world's population aged more than 60–65 years could currently be affected by AD, and that in the next 20 years, there could be more than 30 million people affected by this disease. Vascular and metabolic dysfunctions and mitochondrial failure are now believed to be contributors to AD pathogenesis. Vascular dysfunction includes reduced cerebral blood flow (CBF), blood–brain barrier (BBB) disturbances and cerebral amyloid angiopathy (CAA).

Mitochondrial failure results in deregulation of Ca^{+2} homeostasis and elevated ROS generation, both of which are linked to neurotoxicity. Rapid accumulation of the cation by mitochondria is triggered by abnormal increase in cytosolic Ca^{+2} levels that is important in CNS given the role of Ca^{+2} in normal neurotransmission, long and short-term plasticity and regulation of gene transcription [20-26]. Moreover, deregulation in Ca^{+2} homeostasis can potentiate excitotoxicity, a phenomenon intimately associated with neurodegeneration [20, 27]. Decreased age-related Ca^{+2} buffering capacity has been shown in CNS; mitochondria being involved in this deregulated homeostasis [28]. The interaction between oxidative stress and neuroinflammation leads to amyloid-b (Ab) generation. The deposition of Ab peptide in the brain generates a cascade of pathological events.

Mitochondrial dysfunction and oxidative stress

Mitochondrial genome can be affected by diseases, ROS and RNS and mutations (some human diseases are associated with mitochondrial mutations). Mitochondrial DNA damage can lead to decreased expression of mRNA, which in turn effect the protein expression (decreased protein expression) which would affect the protein of ETC as such leads to less ATP formation and increased ROS formation. Brain requires a high consumption of oxygen to generate adenosine triphosphate (ATP). The antioxidant enzymes are superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx). The nonenzymatic antioxidants group is composed of the natural molecules glutathione (GSH) and the reduced form of nicotin-amide adenine dinucleotide phosphate (NADPH), and compounds like ascorbic and lipoic acid, polyphenols and carotenoids dietary derived [29]. AD is a disorder of the central nervous system (CNS) that results in generalized brain atrophy. Clinically, AD is characterized by the gradual and progressive loss of memory and other cognitive functions, such as the ability to solve everyday problems and emotional control [30-32]. Twin studies provide insight into the relative contributions of genetic and environmental influences on AD and other types of dementia [33-35]. Histopathologically studies have shown the presence of two specific features: neuritic plaques (NPs) and neurofibrillary tangles (NFT) in AD [36-38].

An *in vitro* study showed that Zn+2 quenched Ab-Cu+2 complexes, promoting an antioxidant function [39]. It has also been reported that B-amyloid fibrils leads to the activation of tyrosine kinase signaling pathway and as such superoxide production in microglia.

Oxidative stress and Parkinson's disease

PD is the second most common neurodegenerative disorder [40], affecting approximately 2% of the population over the age of 60 years and 4% of those over the age of 80 years [41]. The CNS is very susceptible to reactive species induced damage [42] because;

(a) it consumes a lot of oxygen,
(b) it has high content of membrane polyunsaturated fatty acids which are susceptible to free radical attack,
(c) it is relatively deficient in oxidative defenses because it has poor CAT activity and moderate SOD and GPx activities, and;
(d) high content of iron and ascorbate can be found in some regions of the CNS which enables it for the generation of more reactive species through the Fenton/Haber Weiss reactions.

Selective loss of the neurons occurs in the PD. Occupational uses of pesticides or herbicides, carbon monoxide, exposure to organic solvents, carbon disulfide, industrialization, well water, rural environment, plant-derived toxins, and viral and bacterial infection are all considered to be the causes of PD [43]. Another factor which is obviously associated with the PD is aging as it leads to the failure of normal cellular-processes as such increase's vulnerability of DAergic neurons [44]. Dopamine neurons are exposed to ROS and RNS for their whole lifespan from the metabolism of dopamine itself. Dopamine is a relatively unstable molecule in nature and undergoes auto-oxidation metabolism in the nigro striatal tract system thereby producing ROS [45] and auto-oxidation itself may increase with age [46].Oxidative deamination of primary MAO produces NH_3 and H_2O_2 with established or potential toxicity [47]. Initial evidence showed that dopamine levels decline by 50–60% during advanced normal aging [48, 49], whereas loss of dopamine neurons in patients with PD is 80–90% in the substantia nigra and 40–50% in the ventral tegmental area [50]. It has also been suggested that dopamine deficiency in normal aging by 110-115 years is sufficient to provoke PD symptoms in these individuals [49]. In familial forms of PD which are associated with mutations in a number of genes, usually leads to the degeneration of nigran neurons. Oxidative stress is said to be the main cause of both the types of cases i.e. idiopathic and genetic cases of PD. PD patients exhibit high levels of oxidized lipids, proteins and DNA and are also associated with reduced glutathione (GSH) levels [51-53]. Due to the presence of ROS-generating enzymes like tyrosine monoamine oxidase and hydroxylase, DAergic neurons are particularly prone to oxidative stress.

Mitochondrial dysfunction and Parkinson's disease

Mitochondrial dysfunction is yet another basis of oxidative stress which is associated with pathogenesis of PD. Any pathological situation which leads to mitochondrial dysfunction can cause a lot of increase in ROS.

This ROS production causes peroxidation of the mitochondrial lipids cardiolipin and as such leads to the release of cytochrome c in the cytosol which in turn causes apoptosis. As DAergic neurons are more ROS-generating intrinsically and susceptible, any event which further aggravates oxidative stress can be harmful to the cell. Leakage of electrons after the damage to the mitochondrial complex I cause ROS generation. Respiratory chain deficient DA neurons have been found to be higher in the PD patients than in age-matched controls [54]. Lots of evidences about the mitochondrial dysfunction related to oxidative stress and DAergic cell damage comes from the results that mutations in genes of mitochondrial proteins DJ-1, Parkin and PINK, are linked to familial forms of Parkinson's diseases. Cells which are derived from patients with parkin gene mutation show decreased Complex I activity [55]. Mice deficient in parkin gene has shown reduced striatal respiratory chain activity along with oxidative damage [56]. DJ-1 is a mitochondrially enriched, redox-sensitive protein and an atypical peroxiredoxin like peroxidase that scavenges H_2O_2, and DJ-1 KO mice accumulates more ROS and exhibit fragmented mitochondrial phenotype [57].

CONCLUSION

Lots of evidences have been provided in this review about the importance of mitochondria and oxidative damage it possesses, and its relation with the various diseases associated with it. Various specific mitochondrial targets that are damaged due to oxidative stress are directly responsible for deterioration of various cell constituents. This review provides considerable information about the different mitochondrial targets in toxic oxidative stress. Oxidative stress is an important factor contributing to the development of AD. Current research on the dysfunction and function of PD associated genes has provided new fundamental insights into biochemical pathways that are linked with the disease process. Also, these findings established that mitochondrial dysfunction is associated with both PD as well as in AD, which makes the mitochondria the main target of PD and AD research. Oxidative stress is inextricably linked with several major pathological processes in AD including neurotoxicity and mitochondria dysfunction. Further studies are required to exactly target these main pathways to these neurodegenerative diseases.

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