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REVIEW ARTICLE **OPEN ACCESS**

Oxidative Stress: Key Role Player in Progression of Neurodegenerative disorders

Manas Kumar Jha, Niraj Kumar Singh*
GLA University, Institute of Pharmaceutical Research,
Mathura, UP, 281406, India
Email ID: niraj.singh0@gmail.com, niraj.singh@gla.ac.in

ABSTRACT
Neurodegeneration is a heterogeneous group of disorder leads to progressive loss of neurons. The outcomes of traumatized neural cells and their degeneration are the prime consequences responsible for Alzheimer's disease (AD), Parkinsonism disease (PD), spinocerebellar ataxia (SCA) etc. Though the etiology of neurodegeneration has not been fully elucidated still but an increased oxidative stress comes up to be one of the major etiologies in various neurodegenerative disorders progressions. Oxidative stress arises as a result of an imbalance between the production of ROS and the biological system's ability to detoxify the reactive intermediates. Oxidative stress has been implicated in the progression of neurodegenerative diseases including AD, PD and many others. Oxidative stress leading to free radical attack on neural cells contributes calamitous role to neurodegeneration. Neurons in the entorhinal cortex, hippocampal, frontal cortex, and amygdala region are the populations of neurons most sensitive to the oxidative neurodegeneration associated with AD. In PD, dopaminergic neurons of the substantia nigra are the primary neurons undergoing cell death. Toxicity of ROS also contributes to protein misfolding, glia cell activation, mitochondrial dysfunction and subsequent cellular apoptosis. In addition, an accumulation of misfolded protein in the aging brain results in oxidative damage, which in turn leads to energy failure and synaptic dysfunction and contribute to the progression of neurodegenerative disorders.
Keywords: *Oxidative Stress, Neurodegenerative disorders, Alzheimer's disease, Parkinsonism disease.*

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INTRODUCTION

Affected motor or cognitive function are the outcomes of damaged neural cells and neuronal loss including diseases such as Alzheimer's disease (AD), Parkinsonism disease (PD), spinocerebellar ataxia (SCA) etc. PD is the second most affected cause in US affecting people having above 65 ages. Apart this, AD is considered as sixth major cause of death in US [1-4]. Neurodegeneration is a heterogeneous group of disorders [5,6]. Basically it causes steady loss of neurons. Though the etiology of neurodegeneration has not been fully elucidated still but an increased oxidative stress comes up to be one of the major etiologies in various neurodegenerative disorders progressions. Cellular damage, mitochondrial dysfunction and impairment in DNA repair system contribute to this disorder [7-9]. Excessive generation of reactive oxygen species (ROS) or dysfunctions of antioxidant system are also cumulative for neurodegenerative disorders. What exactly does oxidative stress means? The answer to this question is an imbalance in the biological system basically between oxidants and antioxidants. An increased level in ROS contributes to this. Molecular oxygen in biology exhibits a vital role as it ensures life of all organisms by proper cellular functioning. However, ROS are very active in brain which basically affects the neurons and glial cells leading to neuronal damage by sensitizing free radicals.

PROBLEMS ASSOCIATE WITH NEURODEGENERATION

It is basically to be noted that the neurodegenerative disorders is increasing with a rapid rate in the aged people. As per the report of WHO it is to be evident that by the year 2030 the dementia cases will elevate up to 50%. Additional to this AD will also quadruple by 2050. The current therapies for neurodegenerative disorders are totally symptomatic. Several obstacles are to be cleared for a significant

growth in the management of neurodegenerative disease. Genetic profile of patients should be taken into consideration during the treatment of such type of diseases. It has been well reported that a patient's genetic profile will alter how they respond to particular drug used for management of neurodegenerative disorders [10].

ROLE OF CERTAIN NEUROTRANSMITTERS IN NEURODEGENERATIVE DISEASE

GABA in Huntington's disease: Earlier it was thought to be a subcortical disease along with Parkinsonism but later the ideology changed. In this disorder, there is a decrease in the gabaergic markers in the striatum. But GABA agonist did not showed the same for this as when done with l-DOPA in PD [11].

Acetylcholine in AD: Decreased levels of acetylcholine were found initially in cerebral cortex and then in basal forebrain. Affected patients show the beneficial effect with the utilization of cholinestrase inhibitors [12].

Dopamine in PD: Lives of million people changed when the affected were treated with DOPA therapy [13]. Addition to this other neurochemicals such as epinephrine, norepinephrine, serotonine and GABA were also measured in this [14].

Pathophysiology of neurodegenerative disorder:

Because of increasing medical and social importance, the neurodegenerative diseases pose a major concern in the society due to the prevailing facts of capital, complex biochemistry and pathology along with inappropriate treatments. This shows certain factors such as: onset with certain age range, genetic risk, proper clinical symptoms along with particular biochemical abnormalities and addition to this dysfunction and death of particular range of neurons [15].

Aging and neurodegeneration:

The major factor for the neurodegenerative disordersof the central nervous system is the never ending increase in the age. In deep study, there are some studies and references that show relationship between the neurodegenerative disordersand the increasing age. With specific signs such as neuronal loss or specific pathological changes are also prevalent. In contradiction to this, even healthy aging also contributes to this in ways such as changes in cognitive and motor ablities of the neurons.thus, older individuals are more prone to the neurodegenerative disorder [16].

Etiology and Pathology: It is to be made clear that the proper etiology and pathology remains still unclear but with upcoming studies it has shown results in neurochemistry and synaptic transmission. Our understanding of the degenerative disorders, and development of treatment for them, is one of the fastest expanding areas in the neurosciences. In reference to glutamate excito-toxicity- Glutamate (excitatory amino acid) is the major excitatory neurotransmitter in the human nervous system with excito-toxic effects on neurons. It is accepted that glutamate over-activity caused by exogenous or endogenous factors is an etiological factor in chronic neurodegenerative disorderscharacterized by the slow progressive death of vulnerable neuronal populations. Exogenous or endogenous neurotoxic compounds might activate glutamate receptors. Enhanced glutamate activity may not necessarily be caused by neurotoxins but could also be of genetic or metabolic origin, such as in Huntington's disease or in aging. Other environmental factors individually or in combination may also facilitate a chronic, progressive, neuronal cell loss related to glutamate over-activity [17].

Protein deposition for neurodegenerative disorder:

In every disorder, one or more proteins have found to be miscoded as a result of emerging this disease. The accumulation in the affected individuals was elaborated by purification in these polypeptides of the patients. Various studies on neurodegenerative diseases, the discovery of prions has been most unexpected.

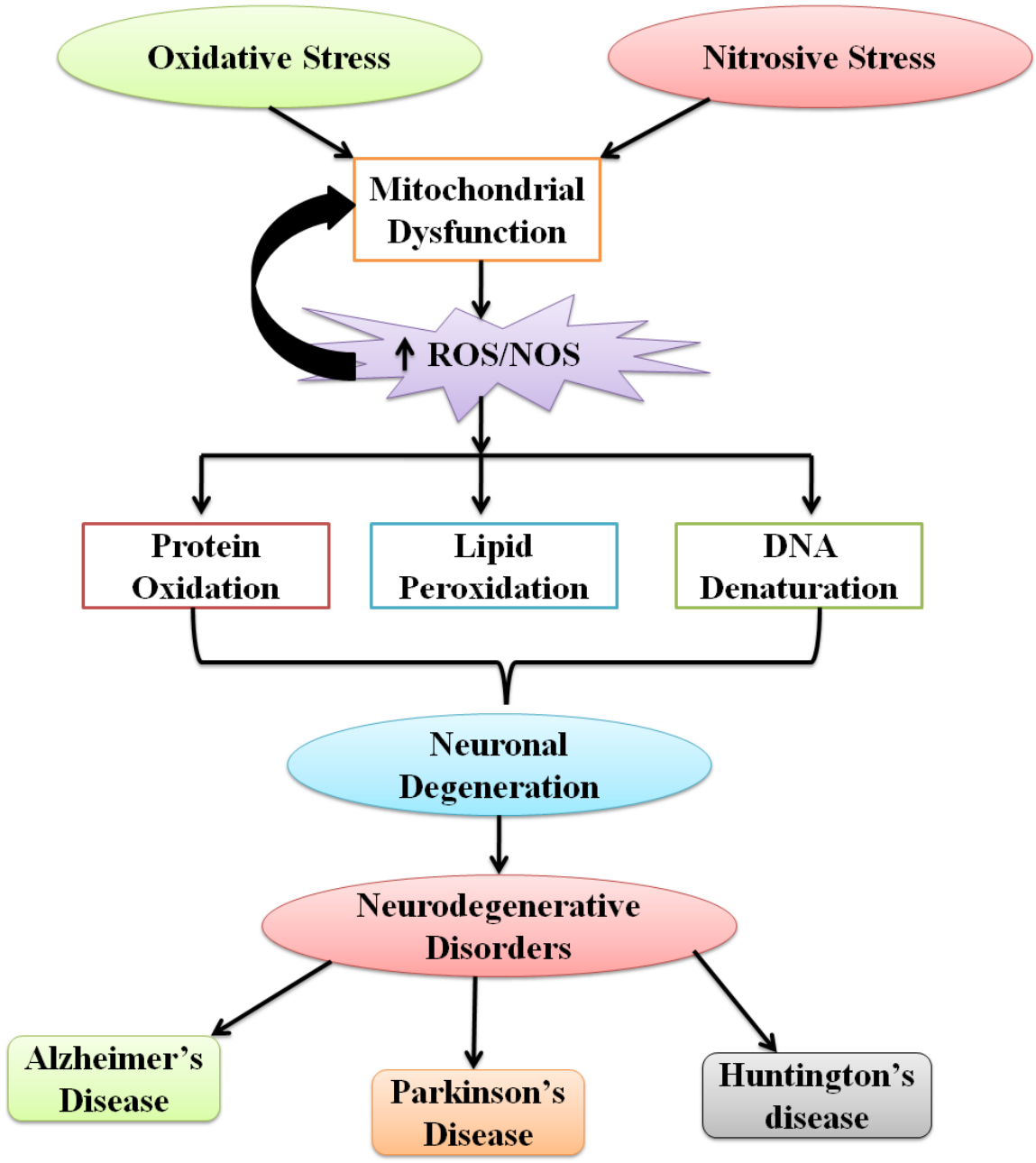

Fig. 1: Representative of consequences of oxidative stress in neurodegenerative disorders. **ROS:** Reactive Oxygen Species; **RNS:** Reactive Nitrogen Species; **PD:** Parkinson's disease; **AD:** Alzheimer's disease**; HD:** Huntington's disease.

The finding that prion can act as an infectious pathogen and cause degeneration of the CNS. The prion concept not only explained how a disease could be both infectious and genetic, but it has also created new disease paradigms and revolutionized thinking in biology [18].

Upcoming strategies: In advance to the therapeutic approach, the early diagnosis and detection should be taken into consideration. The drug should be given before any damage progression. It may be most efficacious to develop drugs that specifically block the misprocessing of a particular protein while in others; drugs that enhance the clearance of an aberrant protein of fragment may prove to be more useful.

Role of Oxidative Stress:

Free radicals are molecules with at least one unpaired electron in the outermost shell. They are highly reactive due to the presence of unpaired electron. Any free radical involving oxygen can be referred to as a reactive oxygen species (ROS) [19]. Since ROS are common outcome of normal aerobic cellular metabolism. In-built antioxidant system of body plays its decisive role in prevention of any loss due to ROS overproduction. Oxidative stress arises as a result of an imbalance between the production of ROS

and the biological system's ability to detoxify the reactive intermediates [20]. Oxidative stress has been implicated in the progression of neurodegenerative diseases including AD, PD and many others. Oxidative stress leading to free radical attack on neural cells contributes calamitous role to neurodegeneration. Toxicity of ROS contributes to protein misfolding, glia cell activation, mitochondrial dysfunction and subsequent cellular apoptosis [21].

OXIDATIVE STRESS IN NEURODEGENERATIVE DISEASES

Neurodegenerative diseases are clinically characterized by their insidious onset and chronic progression, and are pathologically characterized by progressive dysfunction and death of cells that frequently affect specific neural system. Morphologically, neuronal loss is associated with gliosis and frequently with misfolding and aggregation of proteins leading to the accumulation of abnormal extracellular and intracellular filamentous deposit in specific cell types, representing the core features/hallmarks of many neurodegenerative disorders. While many brain neurons can cope with a rise in oxidative stress, there are selected populations of neurons that are vulnerable to increase oxidative stress. This phenomenon in neurodegenerative conditions is called selective neuronal vulnerability [22]. Selective neuronal vulnerability refers to the differential sensitivity of neuronal populations in the CNS to stresses that cause cell injury or death and lead to neurodegeneration. For example, neurons in the entorhinal cortex, hippocampal CA1 region, frontal cortex, and amygdala are the populations of neurons most sensitive to the neurodegeneration associated with AD. In PD, dopaminergic neurons of the substantia nigra are the primary neurons undergoing cell death [23]. Amyotrophic lateral sclerosis is characterized by the degeneration of primarily spinal motor neurons, but also cortical and brain stem neurons [24]. The fact that specific brain regions exhibit differential vulnerabilities to oxidative stress in various neurodegenerative diseases is a reflection of the specificity in the etiology of each disease, and it is possible that the selected cells involved in the pathology of neurodegenerative diseases may share a common increased vulnerability to the detrimental effects of oxidative stress. Neuronal cells are highly sensitive to oxidative stress, because (1) their large dependency on oxidative phosphorylation for energy as compared with other cells; (2) they are exposed to high oxygen concentration, utilizing about 20% of respired oxygen, even though the brain represents only 5% of the body weight; (3) they are enriched in metal ions, which accumulated in the brain as a function of age and can be a potent catalyst for oxidative species formation; (4) they are rich in polyunsaturated fatty acids that are prone to oxidation; (5) they contain relatively poor concentrations of antioxidants and related enzymes. Under physiological condition, 1–2% of consumed O_2 is converted to ROS, leading to oxidative stress, and this percentage goes up dramatically in aged brain [25]. The brain has lower antioxidant activity in comparison with other tissues, for example, about 10% of the liver. Under normal conditions, cells are capable of counteracting the oxidant insults by regulating their homeostatic balance. However, during the progression of age-related neurodegenerative conditions, the capacity of cells to maintain the redox balance decreases, leading to the accumulation of free radicals, mitochondrial dysfunction, and neuronal injury. It is widely accepted that oxidative stress increases during aging, and it can be considered as an important age-dependent factor making the neuronal systems more susceptible to several neurodegenerative diseases such as AD and PD [26].

Oxidative stress in AD: AD is the most common neurodegenerative disordersin elderly people. It is characterized by progressive memory deficits, cognitive impairment and personality changes. Pathological features in AD are loss of neurons and synapses in the neocortex, hippocampus and other sub-cortical regions of the brain [27]. The main histological features are extracellular protein deposits called senile Aβ-amyloid plaques and intraneuronal neurofibrillary tangles [28]. Oxidative stress plays a major role in AD, believed to be stronger than in other neurodegenerative diseases [29]. In addition, an accumulation of misfolded protein in the aging brain results in oxidative and inflammatory damage, which in turn leads to energy failure and synaptic dysfunction [30]. Oxidative damage in AD exhibited through increased levels of DNA oxidation products like 8-hydroxydeoxyguanosine in mitochondria and nucleus [31]. Protein carbonyls and 4-HNE are also found to be increased in brain tissues [32]. Elevated levels of oxidized, nitrated and glycated proteins are found in plaques, helical filaments and cerebrospinal cord fluid from AD patients [33-35]. AGEs are found to accumulate in Aβ and neurofibrillary tangles and it could be shown that AGEs induce the release of various potentially neurotoxic inflammatory mediators such as IL-1 and tumor necrosis factor-a [36]. The activity of the proteasome is also impaired, as hyperphosphorylated tau that is heavily ubiquitinated forms cross-linked aggregates and inhibits the proteasome [37,38]. Transition metals are abnormally distributed in AD as well, studies revealed a marked association between redox-active iron and both Aβ-rich senile plaques and neurofibrillary tangles [39]. It is well known that AD is characterized by Aβ accumulation in senile plaques, and Aβ deposition has also been demonstrated to participate in a positive feedback loop, where oxidative stress leads to

increased Aβ generation, and, conversely, the mechanism of Aβ polymerization generates oxidative stress which in turn enhances Aβ production [40]. Additionally, Aβ has been characterized as a metalloprotein, which is able to bind transition metals (e.g., zinc, iron, copper) via three histidine (positions 6, 13, and 14) and one tyrosine (position 10) residues located in the hydrophilic N-terminal part of the peptide [41,42]. Binding of Cu^{2+} and Fe^{3+} produce toxic chemical reaction, alter oxidation state both the metals, produce H_2O_2 catalytically in presence of transition metals. The H_2O_2 can initiate a number of different events, including Fenton reactions to form toxic hydroxyl radicals and calcium dysregulation. As calcium is vital in signal transduction, it can induce further production of ROS and elicit an excitotoxicity response. On healthy person, soluble Aβ is not present in the cortical synapse. In AD, soluble oxidized Aβ accumulates within the synapse, at which the high Zn^{2+} concentrations precipitate the copper/iron-metallated Aβ, creating a reservoir of potentially toxic Aβ. Augmented metal ions concentrations and oxidative stress have been found to correlate with changes in the concentration of both soluable and deposited Aβ [43]. These Aβ interact with these metals, the peptide aggregates, form toxic oligomers and ultimately amyloid plaques. The toxicity of oligomers is elicited through interactions with the glutamatergic receptors such as the N-methyl-D-aspartate receptor. Interestingly, the metal-dependent generation of ROS by Aβ may be a good target for therapeutics. MPACs such as clioquinol (CQ, 5-chloro-7-iodo-8-hydroxyquinoline) and a copper/zinc ionophore (PBT2) seek to inhibit metal interactions with Aβ and prevent the subsequent formation of ROS and facilitate neuroprotective signaling.

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CONFLICT OF INTEREST

There is no conflict of interest.

SEARCH STRATEGY

Literature search was performed in PUBMED using different key words i.e. oxidative stress, neurodegenerative disorders, Alzheimer's disease, Parkinsonism disease, reactive oxygen species. Published reviews and/or articles in past were identified and relevant articles were selected.

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