Oxidative stress in Neurodegenerative diseases

Nasreena Sajjad[1],Rohaya Ali[1],Sumaya Hassan[1],
*Bashir Ahmed Ganai[3], Rabia Hamid[1]
[1](Department of Biochemistry, University of Kashmir, India)
[2](Centre of Research for Development, University of Kashmir, India)

ABSTRACT

Oxidative stress plays a key role in several ailments including neurodegenerative conditions. Oxidative stress occurs due to imbalance of production of free radicals and the ability of cells to defend against them. Many reports and studies elucidated the role of oxidative stress in neuronal degeneration in diseases like Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis. These diseases are characterized by progressive loss of neurons and impairment of cognitive function. Furthermore, the brain is highly vulnerable to the effects of reactive oxygen species due to its high demand for oxygen. The increase in the generation of free radicals damage the cellular biomolecules such as lipids, proteins, DNA and induce necrosis or apoptosis. Elucidating the pathways important in the production of and defense from free radicals may be important in devising new pharmacologic strategies to slow or halt neuronal degeneration.

Keywords: Oxidative stress, Neurodegenerative Diseases, Free radicals.

I. INTRODUCTION

Neurodegenerative diseases is an umbrella term used for the diseases which are characterized by progressive loss of neuronal function which in turn results in impairment of cognitive function [1]. Neurodegenerative diseases include
Alzheimer's disease (AD),Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), and spinocerebellar ataxia. These diseases generally affects the older population [2]. Reactive oxygen species (ROS) are chemically reactive molecules that have been implicated in the pathogenesis of neurodegenerative diseases. They are naturally generated within the biological system, playing important roles in mediating cellular activities such as inflammationcell survival, and stressor responses as well as many diseases including cardiovascular disorders, muscle dysfunction, allergy, and cancers [3]. Due to their reactivity, high concentrations of ROS can lead to cell death or oxidative stress (OS), which is defined as the disruption of balancebetween pro-oxidant and antioxidant levels. The complexpathogeneses of the neurodegenerative diseases remain largely unknown; however, mounting evidence suggests that ROS may play a critical role as high levels of OS are commonly observed in the brain of patients with neurodegenerative conditions. Numerous studies have been performed to investigate the roles of ROS in neurodegenerative progression [4]. Although ROS may not be the triggering factor for neurodegenerative diseases, they are likely to exacerbate disease progression through oxidative damage and interaction with mitochondria.Neuron cells are particularly vulnerable tooxidative damage because of their high polyunsaturated fatty acid content in membranes, high oxygen consumption, and weak antioxidant defense. Under physiological conditions, ROS generated from mitochondria, NADPH oxidase (Nox), and xanthine oxidase (XO), are maintained at relatively low levels by endogenous antioxidants [5]. However, the redox balance can be disturbed by neural inflammation or abnormal mitochondrial function. The pathogenesisof

several neurodegenerative disorders is associated with the accumulation of misfolded proteins. The aggregation of these modified proteins can in turn trigger inflammatory response in the brain, which induces marked ROS release and subsequent OS. Mitochondrial dysfunction, which often accompanies aberrant ROS production, is tightly linked with neurodegenerative disorders [6].

II.OXIDATIVE STRESS

Oxygen is essential for the normal function of eukaryotic organisms. Its role in survival is linked to its high redox potential, whichmakes it an excellent oxidizing agent capable of accepting electrons easily from reduced substrates. Different tissues have different oxygen demands depending on their metabolic needs. Oxidative stress refers to the cytologic consequences of a mismatch betweenthe production of free radicals and the ability of the cell to defend against them [7]. Oxidative stress can thus occur when the production of free radicalsincreases, scavenging of free radicals or repair of oxidatively modified macromolecules decreases, or both. This imbalance results in a build-up of oxidatively modified molecules that can cause cellular dysfunction and, for postmitotic cells such **as** neurons, cell death [8].

Reactive oxygen species (ROS) are by-products of aerobic metabolism. ROS include the superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals (OH·), all of which have inherent chemical properties that confer reactivity to different biological targets. ROS are often associated with the principle of oxidative stress, which suggests that ROS induce pathology by damaging lipids, proteins, and DNA [9]. The incorporation of molecularoxygen into polyunsaturated fatty acids initiates a chain reaction in which ROS-including OH-, H_2O_2, and peroxyl and alkoxy1 radicals are formed. Oxidative lipid damage, termed lipid peroxidation, produces a progressive loss of membrane fluidity, reduces membrane potential, and increases permeability to ions such as Ca^{2+}.[10]ROS can damage proteins. Oxidative damage to enzymes can increase their susceptibility to proteolysis, which is involved in the regulation of enzyme degradation and in the accumulation of altered forms of enzymes during aging [11].Oxidative stress refers to elevated intracellular levels of reactive oxygen species (ROS) that cause damage to lipids, proteins and DNA. Oxidative stress has been linked to a myriad of pathologies.[12] However, elevated ROS also act as signaling molecules in the maintenance of physiological functions — a process termed redox biology. In this review we discuss the two faces of ROS — redox biology and oxidative stress — and their contribution to both physiological and pathological conditions. Redox biology involves a small increase in ROS levels that activates signaling pathways to initiate biological processes, while oxidative stress denotes high levels of ROS that result in damage to DNA, protein or lipids. [13]

II. GENERATION OF REACTIVE OXYGEN SPECIES IN BRAIN

Free radicals are normal products of cellular aerobic metabolism. Superoxide (O_2^-)and hydroxyl (OH·)species are the predominant cellular free radicals. Hydrogen peroxide (H_2O_2) and peroxynitrite (ONOO-), although notthemselves free radicals, contribute importantly to the cellular redox state. Together, these molecules are referred to as reactive oxygen species (ROS) [14]. The major sources of ROS are mitochondrial oxidative metabolism, enzymatic reactions involving mixed-function oxidation, and autoxidation of small molecules. Neurons and astrocytes, the two major types of brain cells, are largely responsible for the brain's massive consumption of O2 and glucose; indeed, the brain represents only ~2% of the total body weight and yet accounts for more than 20% of the total consumption of oxygen [15]. Despite the essentiality of oxygen for living organisms, the state of hyperoxia produces toxicity, including neurotoxicity. The toxicity and chemical activity of oxygen depends on its electronic structure. The identical spin states of its two outer orbital electrons render

oxygen kinetically stable, except in the presence of appropriate catalysts that scramble electron spin states to produce partially reduced forms of oxygen. Partially reduced forms of oxygen are highly active because the free radical is very unstable and must either accept or be a donor of electrons. As a result, oxygen has the potential to be poisonous, and aerobic organisms survive its presence only because they contain antioxidant defences [16]. Brain cells and especially neurons require effective antioxidant protection for several reasons. They exhibit higher (about 10-fold) oxygen consumption compared to other tissues. Nondividing cells such as neurons have a long life duration. Nitric oxide has a prominent role in the brain and can form reactive nitrogen species such as peroxynitrite, in combination with some forms of oxygen such as superoxide. Nitric oxide may take part in nitrosylation of proteins; however, peroxynitrite is a highly reactive nitrogen species that can nitrate tyrosine residues of proteins and alter their function. (Fig a)

IV. OXIDATIVE STRESS IN NEURODEGENERATIVE DISEASES

It has been longrecognised that oxidative stress may be important in the etiology of a variety of late onset neurodegenerative diseases. Aging has been established as the most important risk factor for the common neurodegenerative diseases i.e., Alzheimer'sdisease (AD), and Parkinson's disease (PD). Most theories ofaging centre are on the idea that cumulative oxidative stress leads to mitochondrial mutations, mitochondrial dysfunction, and oxidative damage [17]. However, as the role of ROS becomes increasingly recognised in aging and age-related diseases, a number of controversies begin to emerge in this field. Although oxidative stress has been implicated in a range of chronic neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, Huntington's disease, and Amyotrophic Lateral Sclerosis.

Alzheimer's disease is the most common neurodegenerative disease, affecting approximately 16 million people worldwide. It is characterised by progressive neuronal loss associated with aggregation of protein as extracellular amyloid (βA) plaques, and intracellular tau tangles. AD brains also show evidence of ROS mediated-injury; there is an increase in levels of malondyaldehyde and 4-hydroxynonenal in brain and cerebrospinal fluid of AD patients compared to controls [18]. Protein carbonylmoieties are increased in the frontal and parietal cortices, and hippocampus in AD brain.There is also an increase in hydroxylated guanine in AD samples compared to age-matched controls [19]. This datafrom human brain is also supported by data from transgenic animal models of AD in which markers of protein and lipid peroxidation are increased in the cortex and hippocampus prior to the appearance of plaques or tangle pathology [20].

Parkinson's disease is the second most common neurodegenerative disease and is characterised by progressiveloss of dopaminergic neurons in the substantia nigra, and aggregation of the protein α-synuclein. In PD brain, the concentration of polyunsaturated free fatty acids in the substantia nigra is reduced, while the levels of lipid peroxidation markers (malondialdehyde and 4-hydroxynonenal) are increased. Protein oxidative damage in the form of protein carbonyls [21] is also evident in PD brain compared to controls, and there is some evidence to suggest a role for nitration and nitrosylation of certain proteins due to reactive nitrogen species in PD brain. In addition to increased levels of 8-hydroxydeoxyguanosine in PD brain, it has been reported that there is an increase in the common deletions in mitochondrial DNA in the surviving dopaminergic neurons in PD substantia nigra. Such deletions are believed to be the result of oxidative stress [22].

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder resulting in a neuronal degeneration in the striatum, followed by degeneration of the cerebral cortex and thalamus during later stages of the disease [23].The pathology of the disease has been attributed to toxic gain of functions for the mutant huntingtin protein, such as protein aggregation, transcriptional dysregulation, defective energy metabolism, oxidative stress, excitotoxicity, and inflammation.A number of

laboratories have provided evidence supporting the hypothesis that oxidative stress is a primary event in HD neuropathology. Nevertheless, trials involving classical "antioxidants" in human HD patients have largely been unsuccessful. It is important to emphasize that while molecular events, such as transcriptional dys-regulation, protein aggregation, and mitochondrial dysfunction, have been linked to HD pathogenesis, it is still not clear whether oxidative stress causes HD, or is a consequence of more primary events. This uncertainty provides a compelling reason to review the putative molecular regulatory connections between redox changes and the established early events, such as mHtt aggregate formation and transcriptional dysregulation [24].

Amyotrophic lateral sclerosis (ALS), or motor neuron disease (MND) as it is often called, is one of the more prevalent adult-onset neurodegenerative diseases, with an incidence of 1–2/100,000 in most populations. [25] The disease is characterised by progressive injury and death of lower motor neurons in the spinal cord and brainstem, and upper motor neurons in the motor cortex [26].Numerous studies have found evidence of increased oxidative stress in ALS pathogenesis. Extensive evidence shows increased oxidative damage to protein in ALS post mortem tissue compared to control samples. Protein carbonyl levels have been found to be elevated in both spinal cord and motor cortex from sporadic ALS cases, and increased 3-nitrotyrosine levels, a marker for oxidative damage mediated by peroxynitrite, was observed in both sporadic and SOD1 familial ALS patients.Whether oxidative stress is a primary cause of pathogenesis in ALS, or is merely a consequence of the disease has long been debated. The discovery that approximately one fifth of familial ALS cases showed genetic linkage to the SOD1 locus [27] was therefore exciting, given the major role that SOD1 has in anti-oxidant defense. This finding placed oxidative stress as a central mechanism in familial ALS pathogenesis

V. FIGURES

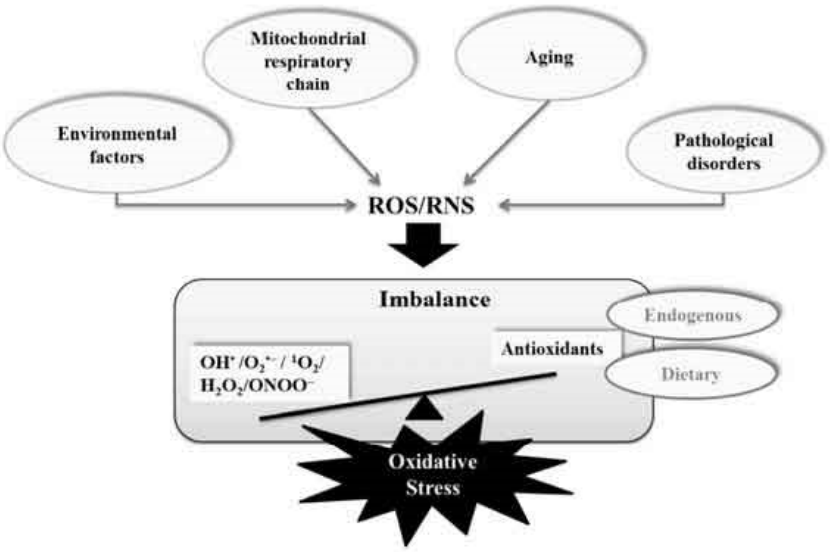

Fig a: Representation of Oxidative Stress

VI. CONCLUSION

The role of oxidative stress in the pathogenesis of neurodegenerative diseases has been well demonstrated in many preclinical and clinical studies. Since oxidative stress is involved in neurodegeneration, selecting antioxidants, metal chelators, or other compounds boosting endogenous enzymatic and nonenzymatic defense mechanism seems to be an obvious choice as a treatment to these disorders. Therefore, devising a successful regimen of antioxidants to retard the progression of these diseases remains a complicated goal. Accumulating evidence suggests that ROS may be generated via various mechanisms and have complex roles in promoting disease development. There is more than one type of ROS involved in the pathophysiology of disease progression. ROS production is subtly regulated by complex antioxidant defense systems within the biological system. High levels of OS have been implicatedin many neurodegenerative conditions. Particularly, mitochondria dysfunction is linked with sustained OS in neurodegenerative disorders. Further research is paramount in addressing the exact roles of ROS in various neurodegenerative conditions and developing antioxidant-based therapeutic interventions.

Recent evidences have greatly increased our knowledge about the AD, ALS, PD, and HD, major neurodegenerative diseases assessed above. From various studies, it has become evident that all the neurodegenerative diseases are to some extent multifactorial, and oxidative stress is inevitably intertwined with the disease mechanisms. Besides biological factors like inflammation, excitotoxicity, and to a certain extent role of genes involved in sporadic cases, environmental contributions like diet and lifestyle are also important contributing factors for the occurrence of these diseases.

REFERENCES

[1] Zhenyu Yue, Lauren Friedman , Masaaki Komatsu , Keiji Tanaka. The cellular pathways of neuronal autophagy and their implication in neurodegenerative diseases.*Biochimica et Biophysica Acta* 1793 2009, 1496–1507.

[2] Jihoon Nah, Junying Yuan, and Yong-Keun Jung. Autophagy in Neurodegenerative Diseases: From Mechanism to Therapeutic Approach *Mol. Cells* 2015; 38(5): 381-389

[3]B. Halliwell, “Free radicals, antioxidants, and human disease: curiosity, cause, or consequence?” *Lancet*, vol. 344, no. 8924, pp. 721–724, 1994

[4] G. Perry, A. Nunomura, K. Hirai et al., “Is oxidative damage the fundamental pathogenic mechanism of Alzheimer's and other neurodegenerative diseases?” *Free Radical Biology and Medicine*, vol. 33, no. 11, pp. 1475–1479, 2002

[5]B. Halliwell, J.M.C. Gutteridge, *Free Radicals in Biology and Medicine*,3rd ed., Oxford Univ. Press, Oxford, 1999.

[6] D. S. Albers and M. F. Beal, “Mitochondrial dysfunction and oxidative stress in aging and neurodegenerative disease,”*Journal of Neural Transmission Supplementum*, vol. 59, pp. 133–154, 2000.

[7]B. Halliwell, “Oxidative stress and neurodegeneration: whereare we now?” *Journal of Neurochemistry*, vol. 97, no. 6, pp.1634–1658, 2006.

[8] J.T. Coyle, P. Puttfarcken, Oxidative stress, glutamate, and neurodegenerativedisorders, *Science* 262 (1993) 689–695.

[9] W. Droge, "Free radicals in the physiological control of cellfunction," *Physiological Reviews*, vol. 82, no. 1, pp. 47–95,2002

[10]M. T. Lin and M. F. Beal,"Mitochondrial dysfunction andoxidative stress in neurodegenerative disease" *Nature*,vol. 443, pp. 787–795, 2006.

[11] Y. Gilgun-Sherki, E. Melamed, and D. Offen, "Oxidativestress induced-neurodegenerative diseases: the need for antioxidantsthat penetrate the blood brain barrier,"*Neuropharmacology*,vol. 40, pp. 959–975, 2001.

[12] N. Lev, D. Ickowicz, E. Melamed, and D. Offen, "Oxidativeinsults induce DJ-1 upregulation and redistribution: implicationsfor neuroprotection," *NeuroToxicology*, vol. 29, no. 3,pp. 397–405, 2008.

[13]Dalle-Donne I, Rossi R, Colombo R, Giustarini D, Milzani A. Biomarkers of oxidative damage in human disease. *Clin Chem.* 2006; 52(4):601–23. [PubMed: 16484333]

[14] Cross C.E, Halliwell, Borish, Pryor and Harman, D. Oxygen radicals and human disease. *Ann. Int.*
Med., 107(3), 1987, 526–545.

[15]A. C. Rego and C. R. Oliveira, "Mitochondrial dysfunctionand reactive oxygen species in excitotoxicity and apoptosis:implications for the pathogenesis of neurodegenerative diseases,"*Neurochemical Research,* vol. 28, pp. 1563–1574, 2003.

[16] Knight JA. Review: Free radicals, antioxidants and the immune system. *Ann Clin LabSci.*, 30(2), 2000, 145-158.

[17].Sonia Gandhi and Andrey Y. Abramov.Mechanism of Oxidative Stress in Neurodegeneration.*Oxidative Medicine and Cellular Longevity*Volume 2012.Article ID 428010, 11 pages, 2012. https://doi.org/10.1155/2012/428010

[18] Alzheimer's Association, "2016 Alzheimer's disease facts andfigures,"*Alzheimer's & Dementia*, vol. 12, pp. 459–509, 2016.

[19]G. Perry, A. Nunomura, K. Hirai et al., "Is oxidative damage the fundamental pathogenic mechanism of Alzheimer's and other neurodegenerative diseases?" *Free Radical Biology and Medicine*, vol. 33, no. 11, pp. 1475–1479, 2002

[20] W. J. Huang, X. Zhang, and W. W. Chen, "Role of oxidativestress in Alzheimer's disease,"*Biomedical Reports,* vol. 4,pp. 519–522, 2016.

[21] V. Dias, E. Junn, and M. M. Mouradian, "The role of oxidativestress in Parkinson's disease,"*Journal of Parkinson's Disease*, vol. 3, pp. 461–491, 2013.

[22] E. P. Dalfo, M. M. P. Portero-Otin, V. P. Ayala, A. Martinez, R.M. Pamplona, and I. M. Ferrer, "Evidence of oxidative stressin the neocortex in incidental lewy body disease," *Journal ofNeuropathology & Experimental Neurology*, vol. 64, pp. 816–830, 2005.

[23] Ross CA, Tabrizi SJ. Huntington's disease: From molecular pathogenesis to clinical treatment. *Lancet Neurol*. 2011; 10(1):83–98.

[24] Amit Kumara and Rajiv R. Ratana. Oxidative Stress and Huntington's disease: The Good, The Bad, and The Ugly.*J Huntingtons Dis*. 2016 October 01; 5(3): 217–237

[25]Lokesh C Wijesekera and P Nigel Leigh.Amyotrophic lateral sclerosis.*Orphanet J Rare Dis*. 2009; 4: 3.

[26]P.S. Fitzmaurice, I.C. Shaw, H.E. Kleiner, R.T. Miller, T.J. Monks, S.S.Lau, J.D. Mitchell, P.G. Lynch, Evidence for DNA damage in amyotrophic lateral sclerosis, *Muscle Nerve* 19 (1996) 797–798.

[27] Siân C. Barber, Richard J. Mead, Pamela J. Shaw. Oxidative stress in ALS: A mechanism of neurodegeneration and a therapeutic target. *Biochimica et Biophysica Acta* 1762 (2006) 1051–1067

.

.