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REACTIVE OXYGEN SPECIES – EFFECT ON NEURODEGENERATION

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ABSTRACT

Neurodegenerative disorders are the group of neurological disorders with diverse etiological and pathological phenomena. They are characterized by progressive damage in nerve cells neuronal loss. Common neurodegenerative disorders are Parkinsonism disease, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis. Pathogenesis of these disorders is unknown but some evidences suggest that oxidative stress, protein misfolding, neuroinflammation and apoptosis are the distinctive features of these disorders. Reactive oxygen species (ROS) are the chemically reactive molecules that are implicated in the pathogenesis of neurodegenerative diseases. A lower concentration of ROS is essential for normal cellular signaling, whereas the higher concentration and long-time exposure of ROS cause damage to cellular macromolecules such as DNA, lipids and proteins, and results in necrosis and apoptotic cell death. Oxidative stress (OS) is a condition produced by the imbalance between oxidants and antioxidants in a biological system. This review mainly focuses on the sources of ROS in brain and its involvement in pathogenesis of neurodegenerative disorders and possible ways to mitigate its effects.

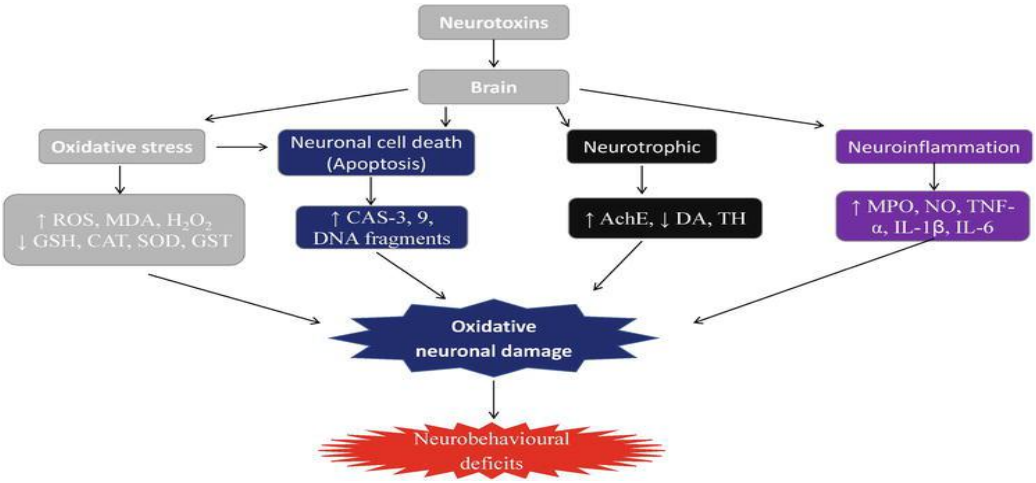
KEYWORDS: Reactive oxygen species, neurodegenerative disorders, oxidative stress, neuroinflammation.

INTRODUCTION

Oxidative stress and Neurodegeneration

Oxidative stress (OS) is produced by the imbalance between oxidants and antioxidants in a biological system. Imbalance occurs as a result of greater level of reactive oxygen species (ROS) or improper functioning of antioxidant system.[1] Molecular oxygen plays a vital role in signal transduction, gene transcription and other cellular activities, but it has also a harmful effect on biomolecules in form of free radicals and reactive oxygen species. ROS is applicable for both free radicals(super oxide O^{2-}) and non-radicals(H_2O_2) which are converted into radicals.[2-5] Due to the high reactivity of ROS, they chemically interact with biological molecules leading to changes in cell function and cell death.

Neurodegenerative disorders are Parkinsonism disease, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis in which oxidative stress, protein misfolding, neuroinflammation and apoptosis are involved in pathogenesis.



Reactive oxygen species

Experimental studies are carried out to elucidate the significance of oxidative stress in neurodegeneration.[6,7] Under unstressed physiological conditions, free radicals and ROS generated from mitochondria, NADPH oxidase, xanthine oxidase are kept at relative low levels by endogenous antioxidants.[8]

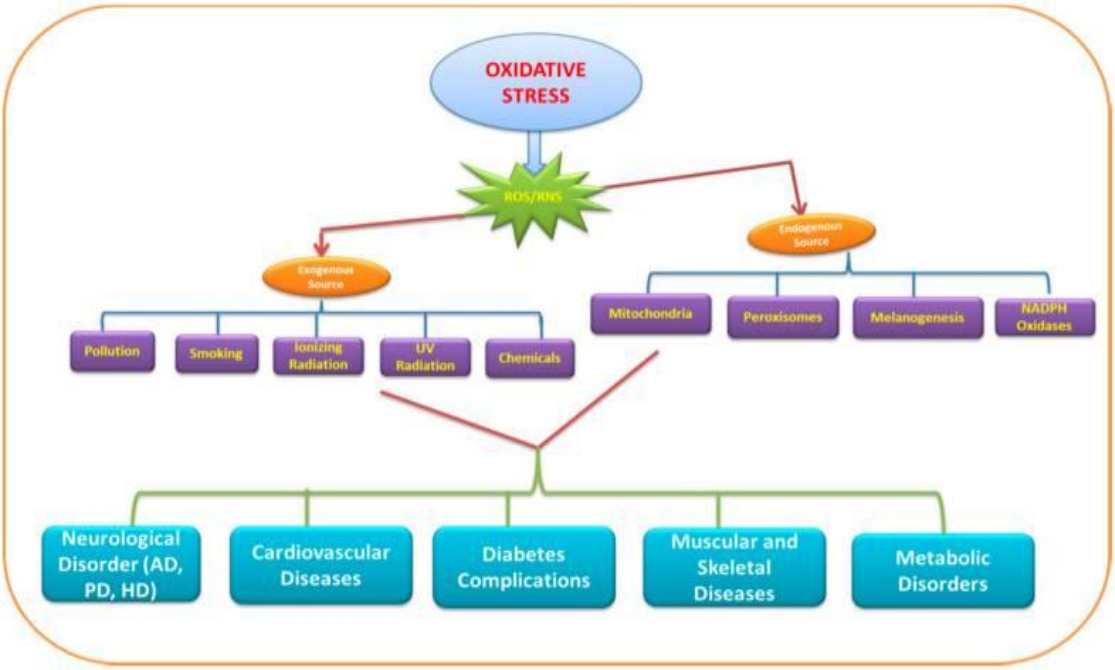


Figure: Exogenous and endogenous sources of reactive oxygen species.

Certain evidences from biochemical, genetic, cellular, molecular, neuropathological studies suggest that the protein misfolding, oligomerisation, accumulation in the brain are the main events responsible for abnormalities in neurodegenerative disorders.[9,10] The proteins that are implicated in accumulation of cerebral misfolded aggregates in neurodegenerative diseases includes : beta-amyloid in Alzheimer's disease, alpha-synuclein in parkinsonism disease, multiple system atrophy and dementia in Lewy bodies, TAR DNA-binding protein in amyotrophic lateral sclerosis.

Considering the roles of oxidative stress, neuroinflammation, protein misfolding, apoptosis in neurodegeneration, manipulation of key players in pathological mechanism represents a treatment to treat and slow down the process of neurodegeneration and decreases the severity of symptoms. This chapter mainly focuses on the Reactive oxygen species (ROS) and oxidative stress in pathogenesis and progression of neurodegenerative disorders.

Effect of oxidative stress in pathogenesis of Parkinson's disease

Parkinson's disease is the second most common disorder after Alzheimer's which is characterized by impairment or degeneration of dopaminergic neurons in substantial nigra along with the decrease in dopaminergic levels in nigrostriatal-dopaminergic pathway. This disease is characterized by insoluble inclusions known as Lewy bodies consisting mainly synuclein.

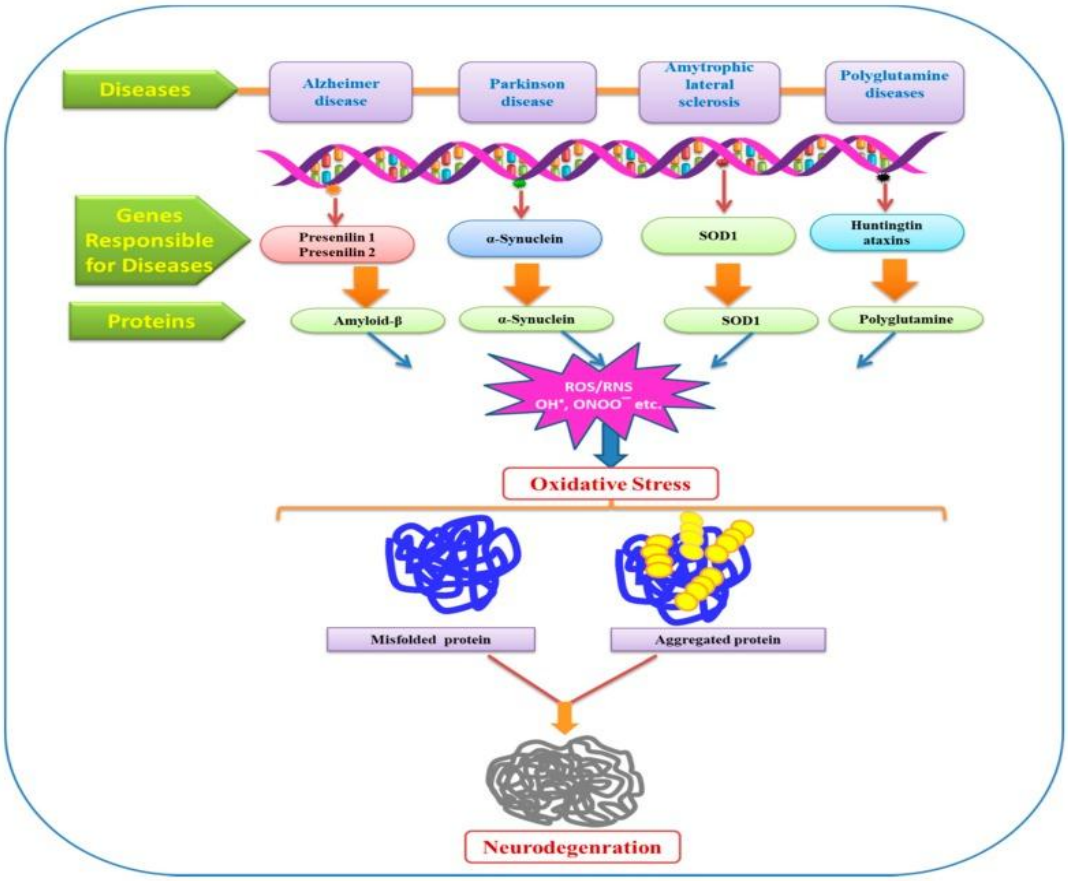
Several reports suggest that the involvement of ROS and oxidative stress are one of the factors responsible for Parkinson's disease. The exact pathway and mechanism of PD is still illusive, but it is demonstrated in many reports that in the substantia nigra of PD patients are found with elevated levels of oxidized lipids, proteins, and DNA, along with reduced levels of glutathione.[11,12,13,14]

Consequently, various proteins are found to play a major role in familial forms of PD. PTEN induced putative kinase I (PINK 1), Parkin, DJ-1, Leucine-rich repeat kinase 2 (LRRK2), and α-synuclein are the proteins that exhibits their link with Parkinson's disease.[15,16,17,18,19] Among all α-synuclein is more associated with PD. Metal mediated toxicity also enhances production of ROS, enhancing oxidative stress in cellular environment and causing damage to neurons.

PINK 1 is a protein found in all human tissues and plays a key role in mitochondrial membrane potential and prevents oxidative stress. Mutations of PTEN induced putative kinase I (PINK 1), Parkin, DJ-1, Leucine-rich repeat kinase 2 (LRRK2), and α-synuclein are all linked to the pathogenesis of PD.[20,21,22,23] These mutations results in increase in Reactive oxygen species(ROS) and oxidative stress vulnerability. DJ-1 is found to play as a marker and sensor for oxidative stress, as well as a redox-chaperone protein.[24,25]

It is also evidenced that neurons with mutations in protein LRRK2 are more vulnerable to mitochondrial toxins.[26]

Presently, there is no such effective treatment for curing Parkinson's disease. Therefore, a substantial case study is required for better understanding of PD. Many neuroprotective approaches have been identified for minimizing oxidative stress in dopaminergic neurons. Appropriate usage of antioxidants has been proved to be in reducing free radical damage.[27] Ascorbic acid and tocopherol is the antioxidant preferred. In animal study, it was discovered that treatment with lipoic acid enhanced motor coordination and ATP efficiency which resulted in neuroprotection. Treatment of lipoic acid in rotenone rats' model of Parkinsonism showed the enhanced motor performance.[28] As, no convincing evidences of neuroprotective action found in humans, Antioxidant should provide future recommendation for treating PD, aiming at limited ROS production in brain.



Effect of oxidative stress in pathogenesis of Alzheimer's disease

Alzheimer's disease is the most common neurodegenerative disorder which is characterized by progressive loss of cognitive and behavioral deterioration, leads to the impairment of daily and routine activities. It is characterized by the deposition of protein aggregates, extracellular amyloid plaques (Aβ), intracellular tau (τ) or neurofibrillary tangles, and loss of synaptic connections in specific regions of brain.[29,30] Pathophysiology is linked to formation of extracellular amyloid beta plaques and intracellular tau neurofibrillary tangles. The neuropathological diagnostic feature of AD is the accumulation of neurotoxic Aβ oligomer peptides, which, along with τ protein, mediates neurodegeneration, causing neuroinflammation.

It is evidenced that oxidative imbalance leads to the neuronal damage may play a central role in AD. ROS-induced ROS overproduction is believed to play a crucial role in the aggregation and secretion of beta amyloid in AD.[31] Accumulation of Aβ aggregates is also found to play a pivotal role in OS, which leads to mitochondrial dysfunction and energy failure. It results in overproduction of ROS, decreased ATP and altered Ca^{+2} homeostasis.[32]

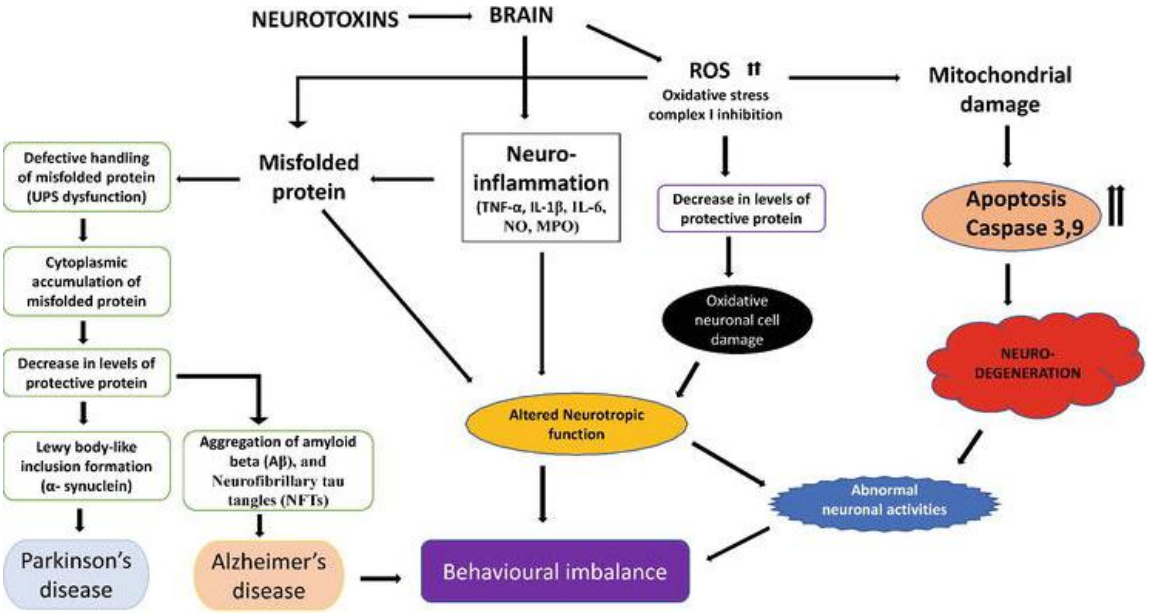


Figure: Mechanism of pathogenesis of Parkinson's and Alzheimer's disease.

Interestingly, reduced levels of antioxidants such as uric acid, vitamin C and E and antioxidant enzymes like superoxide dismutase, catalase, are also observed in AD patients. Usually, Alzheimer's disease is also called disease of ageing. Mounting evidence suggests that various metals play a crucial role in AD, such as iron, zinc, copper, which also act as an antioxidant, accumulate in brain as ageing occurs.

Over activation of N-methyl D-aspartate type of glutamate receptors also cause severe oxidative stress in Alzheimer's disease. These trigger excessive Ca+2 influx and increases cell permeability which results in neurotoxicity.[33]

JNK/stress activated protein kinase pathway is mediated by ROS.Hyperphosphorylation of tau proteins and Aβ induced cell death is linked to the activation of kinase cascades.[34] Aβ proteins can cause formation of free radicals inducing NADPH oxidase.[35] Activation of p38 mitogen activated protein kinase by Aβ – induced ROS overproduction modifies cellular signaling and initiates tau hyperphosphorylation.[36,37] Furthermore, Aβ has been shown to play a key role in cellular apoptosis and enhances the activity of calcineurin which further activates BcI-2 associated death promoter causing mitochondrial cytochrome c release.[38]

Oxidative stress can also aggravate the production and aggregation of Aβ and promote the phosphorylation of tau protein, which could induce a vicious cycle of pathogenesis in AD. There is evidence that suggest the relationship between oxidative stress and tau pathology. It has been reported that cells with over expressed tau protein showed increased vulnerability to oxidative stress, and it may be due to the depletion of peroxisomes. Aβ deposition results in microglia activation.[39] It has been suggested that activation of microglia results in release of pro- inflammatory cytokines, triggers cascade of pro-inflammation and results I neuronal loss.[40]

Aβ interact with metal ions and generate free radical. Cu+2/Zn +2 – bound Aβ has been showed to have a structure similar to superoxide dismutase. It suggest that it could have antioxidant properties.[41] Therefore, Cu+2 and Zn+2 supplementation is considered to be a novel strategy to decrease Aβ- induced ROS generation and metal catalyzed deposition of Aβ.

Drugs used for Alzheimer's disease are aimed at lowering oxidative stress, reducing Aβ oligomer and tau phosphorylation and in regulation of epigenetic changes.[42] Medications that target ROS mediated cascades like JNK (eg:Tocopherol,rutin) have demonstrated promising results in invitro and in vivo.[43] Neuroprotective therapeutic techniques like antioxidant response element (ARE) pathway regulated by nuclear factor erythroid 2 related factor (Nrf 2) have shown conditioned response against oxidative stress.[44] Binding of Nrf2 to ARE activates expression of antioxidant genes that work for oxidative detoxification. The enhancement of Nrf2-ARE cascades using adenoviral Nrf2 gene transfer has shown protective effects against Aβ deposition. Finally, transcriptional modulation of endogenous antioxidants holds the promise in treatment of symptoms of Alzheimer's disease.

Effect of oxidative stress in pathogenesis of Huntington's disease

Huntington's disease (HD) is named after George Huntington in 1872.It is a fatal and autosomal dominant inherited progressive neurodegenerative disorder. It results in neuronal degeneration in the striatum followed by deterioration of the cerebral cortex and thalamus. HD is caused by a mutation in the *huntingtin (HTT)* gene. It is characterized by an abnormal extension in the

cytosine–adenine–guanine (CAG) repeat in this gene, which in turn translates into an abnormally long repeat of polyglutathione in the mutant huntingtin protein.

Development of CAG repeats within exon 1 of huntingtin(HTT) gene results in mutation that causes polyglutamine tract to elongate and further results in HTT protein product which prone to aggregation.[45] In affected persons, the mutant huntingtin (mhtt) aggregates are accrued throughout the brain and disturbs transcription process and protein control. These alterations are responsible for impaired cognitive functions and motor aberrations in Huntington's disease.

Protein misfolding, abnormal proteolysis, protein aggregation, transcriptional dysfunction, excytotoxic and oxidative stress, and glial activation are also associated with neuronal death in HD.[46] Biomolecules play a substantial role as biomarkers for OS in HD patients. Lipid peroxidation, DNA damage, and specifically protein carbonylation were found to be more pronounced in HD.[47]

Oxidative DNA damage induces DNA repair pathways, leading to the removal of oxidized bases and restoration of the normal structure as well as function of DNA. It has been shown that repairing damaged DNA might lead to the expansion and instability of CAG trinucleotide repeats in mutant Huntingtin.[48]

According to new researches, oxidative damage is related to decreased level of glucose transporter(GLUT-3) which leads to lactate build up and glucose uptake inhibition.[49] Panov et.al demonstrated that mHTT plays a crucial role in mitochondrial dysfunction and used electron microscopy to detect that interaction between mitochondrial membranes and N- terminal of mHTT which leads to mitochondrial calcium abnormalities.[50] mHTT also inhibits respiratory complex II, this alteration of mitochondrial electron transport leads to overproduction of ROS with decrease in ATP production.

3-nitrotyrosine, thiobarbituric acid reactive substances (TBARS), and protein carbonyls are some of the other oxidative biomarkers often used in HD models.[51] Elevated levels of F2-isoprostane have been reported in the cerebrospinal fluid and brain tissue of Alzheimer's disease and HD patients. Therefore, measuring F2-isoprostane provide a useful way to assess the relevance of oxidative stress in HDpatients. Interpretation of modifications of oxidative biomarkers in HD should be done with caution due to involvement of oxidative stress in ageing, cancer.

Additionally, oxidative biomarkers alterations may not reveal adequate evidence on whether the oxidative alterations perform a significant role on the neuronal cell death or disease pathogenesis.[52] The use of more sensitive and specific indicators or biomarkers would be essential to give detailed information and elucidate the specific functions performed by free radical and oxidative stress in pathogenesis of neurodegenerative diseases, which will provide a mechanistic approach to finding a suitable drug candidate for the effective treatment of HD.

Effect of Oxidative stress in pathogenesis of amyotrophic lateral sclerosis

Also called Lou Gehrig's disease, after the famous baseball player who had this condition. Amyotrophic lateral sclerosis is a disease in which motor neurons in the anterior horn of the spinal cord gradually diminish.[53] Amyotrophic lateral sclerosis is characterized as familial or sporadic. This neurodegenerative disease is characterized by the progressive loss of upper motor neurons in the cerebral cortex and lower motor neurons in the brain stem and spinal cord, leading to muscle weakness, and progressing into muscle atrophy and paralysis, which culminates in respiratory failure and death.[54,55]

The most common form of ALS is sporadic (sALS), with no known etiology and accounts for nearly 90-95% of all the cases, and the other 5–10% of the cases are inherited (Familial ALS-fALS), which is frequently associated with an earlier age of onset.

The causes of ALS are still unknown, but the disease has been associated with different risk factors like age, smoking, body mass index, level of physical fitness, and occupational and environmental risk factors, such as exposure to chemicals, pesticides, metals, and electromagnetic fields. It is believed that some individual susceptibility factors that are coupled to external exposure of environmental factors lead to the development of ALS.[56-58]

Over 50 disease-modifying genes have been described in ALS,[59] mutations in chromosome 9 open reading frame 72 (*C9orf72*),[60,61] Cu^{2+}/Zn^{2+} superoxide dismutase type-1 (*SOD1*),[62-65] TAR DNA-Binding (*TARDBP*),[66] and fused in sarcoma (*FUS*),[67,68] are the most prevalent ones.

About 20% of familial ALS is caused by mutations in SOD 1 gene.[69] SOD1 involves in activities, includes post translational modification, energy consumption, controlling cellular respiration, and scavenging superoxide radicals (O^{-2}).[70] Despite the fact that SOD malfunction results in a loss of antioxidant capacity, research suggests that genetic ablation of SOD1 in mice does not result in neurodegenerative diseases.

SOD1 is an enzyme that converts $O2^{-}$ into hydrogen peroxide (H_2O_2) and molecular oxygen. SOD1 mutants increase Nox2-dependent ROS generation, which is assumed to be the cause of motor neuron death in amyotrophic lateral sclerosis.[71] SOD1 that has been oxidized or misfolded has been found to cause

mitochondrial dysfunction, which is been linked to the etiology of sporadic amyotrophic lateral sclerosis.

Oxidative Stress arises when the capability of the organism to maintain the balance is compromised by an excess amount of ROS or by defective antioxidant defense It can be manifested in multiple ways, which includes modifications of the redox state of critical proteins.[72,73]

The cellular antioxidant defense is composed of enzymatic and non-enzymatic antioxidants.[74] Superoxide dismutase, catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR), and thioredoxin (Trx) are the major enzymatic antioxidants which plays an important role in the catalytic removal of ROS. The non enzymatic antioxidants include low molecular weight compounds, as glutathione (GSH), vitamins A, C, and E, flavonoids, and proteins (e.g., albumin, ceruloplasmin, and metallothionein).[75]

Moreover, in erythrocytes from sALS patients, an increase in lipid peroxidation associated with a decrease in Catalase, Glutathione reductase, and glucose-6-phosphate dehydrogenase activities and a decrease in GSH.[76]

Currently, there are only two drugs approved by the US FDA for ALS treatment, Riluzole, Edaravone. Riluzole is a neuroprotective agent which only extends the ALS life expectancy period of 3months. It is a benzothiazole with antiglutaminergic properties which have shown a survival benefit in patients at a dosage of 100 mg/day without any effect in muscle strength.[77,78]

The other is Edaravone, which is an antioxidant that only delays ALS development. It eliminates lipid peroxides and hydroxyl radicals during cerebral ischemia and exerts a protective effect on the neurons of patients.[79,80] Also inhibits the opening of mitochondrial permeability transition pore (mPTP) in the brain which contributes to its neuroprotective effect.[81]

Nicotinamide adenine dinucleotide phosphate oxidase (NOX) is the enzyme that regulates ROS production in the CNS. The evidence is showing that NOX inhibition improves neurological disease conditions.[82,83] The inactivation of NOX in SOD1 transgenic mice has shown to slow disease progression and improve survival.[84,85] Pharmacological inhibition of NOX using apocynin, a natural organic compound also known as acetovanillone.[86] shows decreased O^{-2} levels and increased cell viability in human glioblastoma cells expressing mutSOD1.[87] and decreased ROS levels in primary astrocytes expressing mutSOD1, also restoring motor neuron survival.

Although several antioxidants have shown beneficial effects in ALS animal models, but they have failed to show meaningful therapeutic benefits in ALS patients. Ongoing research may provide hope and insights about the exact mechanism and pathways of the disease to develop drugs as well as a therapeutic target for the ALS.

CONCLUSION AND OUTLOOK

Mitochondria extensively generate ROS or/and are targeted by free radicals in the aetiopathology of the major neurodegenerative diseases. In most of these diseases, the overproduction of ROS or a loss of function of antioxidant pathways leads to increased oxidative stress. This Increased oxidative stress has been viewed as one of the potential common etiologies in various neurodegenerative diseases. Normally, a balance between ROS and antioxidant is essential for proper functioning of cell.

Antioxidants combat oxidative stress by neutralizing free radicals and inhibiting them from initiating the chain reactions that lead to health disorders and premature aging. Under normal conditions, the presence of a natural antioxidant system actively participates in scavenging ROS and maintains the typical cellular environment. Onset of oxidative stress produces ROS, which have a deleterious effect on the biomolecules causing lipid peroxidation, protein misfolding and aggregation, DNA damage, and mutations. ROS cause a damaging effect on neurons and accumulate in the brain, resulting in neurodegenerative diseases.

Though metals plays a crucial role for the enzyme mediated reactions in cellular metabolism and cell signaling, mutation in mitochondrial DNA and metal overload in the aged brain lead to oxidative stress. A cascade of events takes place and ultimately impairs neuronal proteins, leading to neuro-inflammation and neurological disorders manifested in loss of cognitive function (AD, PD, ALS, and HD). Mitochondrial dysfunction also plays a substantial role in the imbalance in ROS and the antioxidant system in the cellular environment.

In the current scenario, researchers are focusing on the development of antioxidant systems that efficiently scavenges free radicals and oxidative stress. Several antioxidant therapeutic targets are developed which are capable of neuroprotection prior to OS, prevents free radical production as well as modulates normal metal homeostasis. Additionally, antioxidants are developed to cure neuronal inflammation as well as free radical scavenging.[88] Interestingly, saffron has shown to act as an antioxidant, in the protection of CNS disorders. Low cytotoxicity, commercially availability, and ability to cross the blood–brain barrier makes it suitability to combat various diseases.[89] For inhibiting neurodegeneration in brain, stem-cell oriented therapy is the sole hope for regional reconstruction. Therefore, nerve damage is controlled via balancing the ROS generation and its scavenging by antioxidants. Although pre-clinical studies have shown promising results, the

benefit of antioxidant therapy for neurodegenerative diseases is still controversial in humans.[90]

Following the notion 'prevention is better than cure' help in delaying the neurodegeneration. Ageing and lifestyle are other factors play a key role in the onset of neurodegenerative diseases. However, changing one's lifestyle (continuous physical and cognitive activity), following balanced diet (along with vitamin C and E), developing efficient antioxidants and early diagnosis also assist in the treatment of neurodegenerative disorders. Ongoing research worldwide is opening new avenues and hope for future therapeutic targets to control these neurodegenerative diseases. Further studies would also deepen the translational impact of phenomenon of oxidative stress into biology and medicine.

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