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Role of Free Radical in Neurological Disorders: A Review

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Abstract

Diseases and disorders such as neurodegenerative disorders are becoming more common as the world's population grows. Reactive species damage to the mitochondria is the primary cause of the dramatically rising number of neurodegenerative disorders. Free radical are most dangerous species than we think, Free radicals are molecules that have an electron that is not coupled with another electron. These compounds are extremely reactive because they include a free electron that is not coupled with another electron. Based on their centre chemical moiety, there are two main types of free radicals i.e. Reactive oxygen species and Reactive Nitrogen species .In general, free radicals form in three stages: initiation, propagation, and termination. Oxidative stress, defined as a disturbance in the balance between the production of reactive oxygen species (free radicals) and antioxidant defence, leads to damage to cells via different pathways. In this review article we focus on free radical role in neurodegenerative disorder and approaches toward free radicals.

Keywords: Reactive Oxygen species, free radical, Neurodegenerative disorder, Parkinson Disease, Alzheimer's disease.

Introduction

In recent years, there has been a growing interest in the prevention of disease, with particular reference being made to the role that free radicals play in this process. Because free radicals are so important to health and disease, as well as to the overall quality of a Person's life, biology and medicine related to free radicals are going through a time of rapid growth. Any species of molecular entity that is capable of existing on its own and has an unpaired electron in an atomic orbital is referred to as a free radical. There is a link

between having an unpaired electron and having certain properties that most radicals have in common. There are a lot of free radicals, and many of them are unstable and highly reactive. They can either give an electron to other molecules or accept one from them, and as a result, they can behave either as oxidants or as reductants.[1] Free radicals are molecules that have an electron that is not coupled with another electron. These compounds are extremely reactive because they include a free electron that is not coupled with another electron. Studies by Denham Harman on the role of free radicals in the ageing process in 1956 sparked the first wave of interest in studies on free radicals and their impact on the biological system.[2] In the beginning, it was believed that free radicals were oxygen-centered radicals known as reactive oxygen species (ROS). However, free radicals also comprise a subset of reactive nitrogen species (RNS), and they are all a consequence of normal cellular metabolism. Based on the fact that ROS and RNS can both have positive and negative effects on biological systems, it has been determined that they serve a dual role as species that can be both beneficial and destructive. In beneficial they play a key role in the natural processes that cause cytotoxicity, change the tone of blood vessels, and send messages between nerve cells[3] and On the other hand, the body makes free radicals, which are dangerous substances, along with toxins and wastes, as part of its normal metabolic process.[4] Free radicals are made when the body burns carbohydrates, fats, and proteins to get energy. This can happen both aerobically and anaerobically. An excessive generation of free radicals may be the cause of tissue damage. In addition unsaturated lipids are used to make cell membranes, and these molecules are especially vulnerable to damage from free radicals.[5] Typically, free radicals "steal" an electron from the next stable molecule. When the "attacked" molecule loses an electron, it transforms into a free radical and initiates a chain reaction. Once initiated, the process can cascade and ultimately result in the disruption of live cells.[6] in this review article we described all types and free radicals and their role in various neurodegenerative disorders

Types of free radicals

Based on their centre chemical moiety, there are two main types of free radicals: reactive oxygen species and reactive nitrogen species. The term "reactive oxygen species" (ROS) refers to the assortment of molecules and free radicals that are formed from molecular oxygen. In addition, there is another category of free radicals that are derived from nitrogen, and this category is termed "reactive nitrogen species" (RNS).[7] These reactive species are easily transformed into reactive non-

radical species by chemical processes, either enzymatic or non-enzymatic, which can then give rise to new radicals. Which are further subdivided into different subtypes.

1. Reactive Oxygen Species (ROS)

The most significant category of radical species produced by living systems is that obtained from oxygen.[8] Prior to the publication of Gershman's free-radical theory of oxygen toxicity in 1954, the sources of the poisonous properties of oxygen were unknown. This theory proposes that the poisonous properties of oxygen are caused by partially reduced forms of oxygen, which latterly this reduced form of oxygen identifies as "reactive oxygen species." According to Michaelis et,al. Normal oxidative metabolism should also lead to the formation of free radicals. The compulsory univalent transfer of electrons is one way that molecular oxygen can be broken down. If protons are present, this process should produce OH*, HO*, and H_2O_2.[9]

Reactive oxygen species generally have negative effects on cells that resemble damage to DNA, oxidation of polydesaturated fatty acids in lipids, oxidation of amino acids in proteins, and oxidative inactivation of particular enzymes through oxidation of co-factors.

There are few subtypes of ROS discussed as below

i. Singlet Oxygen ($^1O2$)

Singlet molecular oxygen, (1 O2) is a highly reactive type of molecular oxygen that can be harmful to living systems by oxidising essential organic components.

From a biological standpoint, molecular oxygen in its diatomic (O2) ground state is a bi-radical due to the presence of two unpaired electrons, each of which resides in a distinct antibonding orbital. It is referred to as "triplet oxygen" because of the fact that the spin of these electrons can align in one of three different ways with an external field.[10] Triple-oxygen, the more prevalent form of oxygen, is the type of oxygen that our systems typically inhale. Because it has a "spin constraint," it cannot react with the vast majority of organic compounds. Due to the lowest energy arrangement of its electrons, molecular oxygen is not extremely reactive. When the two unpaired electrons in triplet oxygen move to two different orbits, they make singlet oxygen, a powerful oxidant (Stefan W. Ryter And Rex M. Tyrrell, 1998). Through the process of electron transfer, molecular oxygen can be converted into $^1O2$; the primary sources of this molecule are photosensitization and inflammatory processes. One of the other ways 1O2 is produced is when superoxide is turned into dismutase in the NADPH oxidase reaction. In addition when it comes to bacteria, singlet oxygen is the key factor that

causes photooxidative stress. Sensitized production by pigments of the photosystems is the primary source of singlet oxygen in photosynthetic bacteria, whereas in nonphotosynthetic microorganisms, cellular cofactors such as flavins, rhodopsins, quinones, and porphyrins function as photosensitizers. Singlet oxygen has fast reactions with a wide variety of biological macromolecules, including proteins, lipids, DNA, and RNA, and as a result, further reactive compounds, such as organic peroxides and sulfoxides, are generated.[12]

ii. Superoxide

Superoxide is the foremost radical that is formed when an enzyme or a non-enzyme reaction gives an oxygen molecule one electron. Superoxide is easily changed into other ROS, which makes it hard to figure out how much it contributed to a particular cause.[13] The enzymatic mechanisms that lead to the formation of superoxide can be broken down into two types. One group of enzymes uses oxygen to produce superoxide and, in some cases, hydrogen peroxide or other organic peroxides as their main products,[14] this is done in a stoichiometric way. Superoxide radicals can also change into oxygen and hydrogen peroxide by a process called dismutation, in which one superoxide radical reacts with another superoxide radical. The other class sometimes makes superoxide as a byproduct, which depends on how the environment is. In addition, superoxide does not readily traverse lipid membranes. Although evidence suggests that superoxide is relatively unreactive towards the majority of biological molecules, the minimal amounts of superoxide allowed in cells and tissues indicate that limiting cell exposure to superoxide is an important survival strategy(Fridovich, 1983).

iii. Hydrogen Peroxide (H2O2)

Because of its powerful oxidant properties that can kill germs and cells, hydrogen peroxide (H_2O_2) is frequently used as an anti-infective agent in biology and medicine, for example, to wash wounds.[16] As the key molecule of the Third Principle of the Redox Code, H_2O_2 plays a crucial function in homeostatic metabolism. In fact, H_2O_2 is regarded as one of the principal molecules involved in the sensing, regulation, and signalling of Redox metabolism, serving as one of the principal messenger molecules.[17] Enzymatic production of H_2O_2 and other second messengers (nitric oxide, NO, and hydrogen sulphide, H_2S) occurs when a receptor detects a signal. Through specific oxidations, the second messengers activate a cascade of downstream proteins, resulting in a metabolic response in the cell. This process is known as redox signalling.[18] Hydrogen peroxide can be produced

through the dismutation of $O_2^{\bullet-}$ or the direct reduction of O_2, but enzyme reactions are its primary source. The presence of oxidases (urate oxidase, glucose oxidase, and D-amino acid oxidase) in microsomes, peroxisomes, and mitochondria may result in the direct generation of hydrogen peroxide by the transfer of two electrons to molecular oxygen.[19] During physiological conditions, the primary H_2O_2 producers and consumers are peroxisomes. Hydrogen peroxide is not included in free radicals, but they have free electrons. As a result of their capacity to interact with biomolecules and damage cells, hydrogen peroxides are referred to as "reactive oxygen species." Additionally, due to their great solubility in aqueous solutions, they can quickly pass through cellular membranes, providing them with extremely harmful properties. Although H_2O_2 is generally a weak oxidizing and reducing agent and is often not very reactive at physiological levels, but it has the power to inactivate a number of enzymes and oxidise keto-acids like pyruvate and 2-oxoglutarate. It can combine with copper and iron to generate considerably more harmful species, such as $O2^{\bullet-}$. It's crucial to be aware that H_2O_2 can break down heme proteins such as cytochrome c, myoglobin, and haemoglobin.[20]

iv. Hydroxyl Radical (OH•)

The hydroxide ion exists in its neutral form, which is denoted by the symbol $^{\bullet}OH$. It has a relatively short lifetime (around 10–9 seconds),[21] but it reacts very quickly with virtually every kind of molecule that may be found in living cells, including sugars, amino acids, phospholipids, DNA, and organic acids.[22] Indeed, $^{\bullet}OH$ has a tremendously positive reduction potential of +2310 mV, making it the most reactive oxygen radical that has ever been discovered. The hydroxyl radical ($HO^{\bullet}$) is the most reactive free radical that can be produced in vivo from a chemical standpoint. It is produced through the Fenton reaction, [1] in which free iron (Fe^{2+}) combines with hydrogen peroxide (H2O2), and the Haber–Weiss process, in which superoxide reacts with ferric iron (Fe^{3+}) to produce Fe^{2+} [23]. The reaction is not restricted to iron; it may also involve several other ions (Cu^{2+}, Fe^{3+}, Ti^{4+}, and Co^{3+}), all of which are capable of being recycled through contact with the superoxide anion to create oxygen. It is estimated that every second, a cell generates approximately 50 hydroxyl radicals.

First step involve in Fenton reaction: [23]

$$Fe^{3+} + {}^{\bullet}O^{-}{}_2 \rightarrow Fe^{2+} + O_2.$$

Second step:

$$Fe^{2+} + H_2O_2 \rightarrow Fe3^{+} + OH^{-} + \bullet OH.$$

2. Reactive Nitrogen Species

RNS have been acknowledged as playing a critical role in the physiologic regulation of many, if not all, living cells, including smooth muscle cells, cardiomyocytes, platelets, and nerve and juxtaglomerular cells. Increased levels of RNS have been linked to cell harm and death via the process of inducing nitrosative stress. The term "reactive nitrogen species" (RNS) refers to free radicals that include nitrogen and exhibit a strong oxidising ability; as a result, they are engaged in the promotion of oxidative stress. Nitric oxide (NO) and nitrogen dioxide (NO2), as well as non-radicals like peroxynitrite (ONOO-), are two of the most important reactive nitrogen species (RNS).

i. Nitric Oxide

Nitric oxide (NO•) is a small molecule that has an unpaired electron on its antibonding, and as a result, it is considered to be a radical. Because of its remarkable characteristics, nitrogen monoxide (NO•) was named "molecule of the year" by a scientific magazine in 1992.[24] Because it is soluble in both aqueous and lipid solutions, it can easily diffuse through the cytoplasm and plasma membranes. This characteristic allows it to be used in biological research. NO• is produced in biological tissues by specialised nitric oxide synthases (NOSs), which metabolise arginine to citrulline via a five-electron oxidation mechanism, resulting in the production of NO•.[25] Nitric oxide (NO•) is a common reactive radical that plays a crucial role as an essential oxidative biological signalling molecule in a wide range of physiological processes. Some of these processes include neurotransmission, the regulation of blood pressure, defence mechanisms, the relaxation of smooth muscle, and the regulation of the immune system.[26] NO• is not a very reactive free radical by itself, but the overproduction of NO• is linked to ischemia reperfusion and neurodegenerative and chronic inflammatory diseases like rheumatoid arthritis and inflammatory bowel disease. NO• exposure in human blood plasma can reduce ascorbic acid and uric acid concentrations and begin lipid peroxidation.[22]

Steps involved in generation of free radical

In the science of chemistry, radical addition and radical substitution are two processes that include free radicals acting as reactive intermediates. Generally speaking, chain reactions that involve free radicals can be split up into three separate processes: [3]

a) Initiation : formation of radicals
b) Propagation: In this stage, the needed free radical is repeatedly generated via a chain reaction, allowing the reaction to proceed to completion.
c) Termination : destruction of radicals
Initiation reactions are those that lead to an overall rise in the number of free

radicals produced by the system. These processes could involve either the creation of free radicals from stable species or the interaction of free radicals with stable species in order to make more free radicals. Propagation reactions include radicals in which the overall number of radicals remains constant.[4] "Termination reactions" are any reactions that result in a net reduction in the total number of free radicals in the system. In some cases, the creation of radicals involves the homolytic breaking of covalent bonds. This is a process that requires a large amount of energy to complete. This is referred to as the homolytic bond dissociation energy, and it is typically represented by the sign DH° in abbreviated form. The structure of the molecule plays a role in determining the bond energy between two atoms that are covalently bound to one another. Homolytic bond breakage occurs most frequently between two atoms that have an electronegativity that is comparable to one another. Nevertheless, the propagation reaction is an extremely exothermic one. The oxidation or reduction of a single electron in an atom or molecule can also result in the formation of radicals. A good illustration of this would be the creation of superoxide by the electron transport chain.[27]

Sources of free radical: [28, 1, 12]

Both endogenous and exogenous chemicals are capable of contributing to the formation of free radicals. They are constantly forming in the cell and in their surrounding environment. The following is a list of different sources of free radicals:

- Radiations such as ultraviolet light, x-rays, gamma rays, and microwaves
- Reactions that are catalysed by metals
- Inflammation stimulates the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) by neutrophils and macrophages.
- Oxygen free radicals are produced as a byproduct of electron transport processes mediated by mitochondria.
- Xanthine oxidases, mitochondrial cytochrome oxidase, neutrophils, and lipid peroxidation are some of the sources that contribute to the formation of reactive oxygen species (ROS).
- oxidative stress caused by reactive oxygen species (ROS), which can be produced by the metabolism of arachidonic acid, platelets, macrophages, and smooth muscle cells.
- Interaction with chemicals, exposure to the gases produced by automotive exhaust, and the use of tobacco products such as cigarettes, cigars, and beedies.

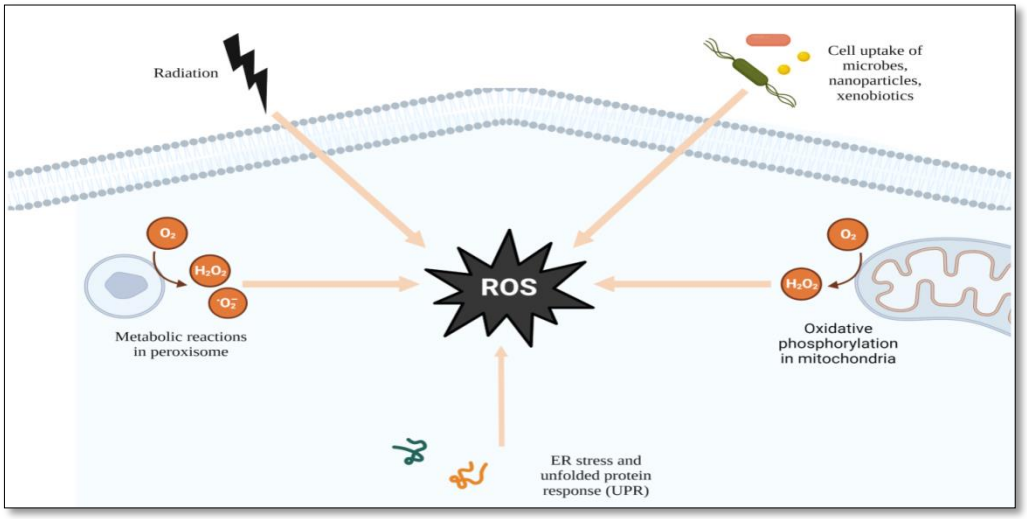

Figure No.1: Systematic Illustration Sources of ROS

Impact of Free Radical on Neurodegenerative Disorder

The brain is especially susceptible to oxidative injury due to its high oxygen consumption, high polyunsaturated fatty acid content, and presence of redoxactive metals (Cu, Fe). Oxidative stress develops with age and can therefore be viewed as a significant cause of various neurological disorders typical of elderly people. In vivo, the brain is always making free radicals and other things called "reactive species." Some are caused by "accidents of chemistry," such as the loss of electrons from the mitochondrial electron transport chain, which results in the production of the superoxide radical (O2 -). Others, such as the function of nitric oxide in neurotransmission and the synthesis of oxygen by activated microglia, are produced with the aim of providing a benefit to the body. The brain has a high ATP demand, which causes it to utilise oxygen at a quick rate. As a result, the brain is vulnerable to interference with the operation of the mitochondria, which can then lead to an increase in O2 production.[29] Despite the fact that oxygen is necessary for life, an improperly functioning metabolism and an excessive generation of reactive oxygen species (ROS) can lead to a variety of diseases, including Alzheimer's disease, Parkinson's disease, ageing, and a variety of other neural disorders. Apoptosis has been reported as the pathological cause of ageing and neurodegenerative diseases including Parkinson's disease (PD), Alzheimer's disease (AD), Multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS).[30]

Alzheimer's disease (AD)

AD is the leading cause of disability in people over 65. Amyloid (Aβ) peptide

deposition, neurofibrillary tangles of hyperphosphorylated protein, and dementia are hallmarks of AD. The neurotoxic oligomer Aβ peptide and -protein mediate neurodegeneration, one of the primarily caused which is initiated and exacerbated by oxidative stress, which is a term referring to a state in which there is an imbalance between antioxidants and oxidants, tilting the balance in favour of the oxidants. This imbalance may be caused by an increase in free radicals or a decrease in antioxidant defence. Both of these factors are possible for developing nuerological disorder. It is considered that ROS generation, activation of mitochondrial permeability transition, excitotoxicity, reduced synthesis of adenosine triphosphate, and disturbed calcium homeostasis are the mechanisms through which mitochondrial dysfunction leads to neuronal degeneration in Alzheimer's disease (AD).[31] The several hypothesis postulates that the APP-derived amyloid b-peptide enters the neuronal and Glial membrane bilayer, most likely as a tiny, soluble aggregate, and produces oxygen-dependent and possibly redox metal ion-dependent free radicals that lead to lipid peroxidation and protein oxidation.[32] Membrane damage is caused by lipid free radicals or the lipid peroxidation products HNE and acrolein, or it can be caused directly by Ab-associated free radicals, perhaps involving peptide-bound redox metal ions. Cellular dysfunction results from a loss of membrane integrity and includes ion-motive ATPase inhibition, Ca homeostasis disruption, inhibition of the Na-dependent glutamate uptake system in Glial cells, which affects neuronal excitatory NMDA receptors, loss of protein transporter function, signalling pathway disruption, activation of nuclear transcription factors, and activation of apoptotic pathways. The ultimate result of these cellular dysfunctions is neuronal death.[33]

Parkinson disease

Parkinson disease is the generally widespread neurological condition following Alzheimer's disease. Parkinson disease is characterised by bradykinesia, tremors, dyskinesia, rigidity postural instability and slow movement.[34] This are the key motor symptoms, although the clinical picture also includes a variety of non-motor symptoms (NMSs).[35] Some of these clinical symptoms can be found in a variety of illnesses, and the approach in assessing is known as "Parkinsonism “Parkinsonian disorders include Degenerative vascular, traumatic,[36] and toxic etiologies.[36] Neuronal loss in the substantia nigra promotes striatal dopamine insufficiency, and intracellular inclusions containing synuclein aggregation are Neuropathological markers of Parkinson disease.[37, 38]

Dopamine play important role for movement, when the deficiency of dopamine level in brain occurs the movement may delay and uncoordinated [39] Parkinson's disease (PD) is a neurodegenerative disorder characterised by selective neuronal loss of dopaminergic (DA) neurons in the substantia nigra pars compacta (SNc) and decreasing DA levels in the brain's nigrostriatal DA pathway[40] w. Oxidative stress has been regarded as one of the major pathophysiological factors driving Parkinson's disease (PD), despite the fact that the specific mechanism behind PD is still not fully understood. Previous research has indicated that patients with Parkinson's disease have lower activity in Complex I of the respiratory chain in their SNc. This reduced activity may contribute to the creation of excessive ROS, which in turn may promote apoptosis in the affected cells. In addition, the association between mitochondrial dysfunction[41] and PD is reinforced by the discovery that Complex I inhibitors, such as 1-methyl-4-phenyl- 1,2,3,4-tetrahydropyridine (MPTP) and its metabolite, 1-methyl- 4-phenylpyridinium (MPP+), may have lethal effects on DA neurons, resulting in a clinically parkinsonian phenotype, and promote nigral degeneration with cytoplasmic α-synuclein.[42]

There are various factor involve in mitochondrial dysfunction in PD such as age, environmental toxin, genetic factor. Environment toxin exposed with human system they cross blood brain barrier and converted into the free radical and attack on respiratory chain especially on complex 1 and produce reactive oxygen species leading to reduction in ATP synthesis.[43] ROS can operate as signalling molecules by causing lipid peroxidation or promoting excitotoxicity, all of which lead to protein alteration and cell death. ROS induce cell damage in three basic ways: oxidative DNA damage, lipid peroxidation, and oxidation of protein and nitration.[44]

Amyotrophic Lateral Sclerosis (ALS)

Amyotrophic lateral sclerosis (ALS) is an exceptionally severe disease with fatal outcomes. It typically affects middle-aged adults with increasing paralysis and results in death within five years. It is characterised by motor neuron degeneration. Included in these neural components are the anterior horn cells of the spinal cord, the motor nuclei of the brain stem, including the hypoglossal nuclei, and the upper motor neurons of the cerebral cortex.[45] The finding in 1993 that mutations in SOD1 are related with some familial types of ALS led researchers to hypothesise that a disruption in the homeostasis of free radicals might play a role in the development of the disease[31]. The two most prominent hypotheses are that the

changes might make it possible for there to be a greater contact with hydrogen peroxide (H2O2), which would result in the production of hydroxyl radicals, or with peroxynitrite, which would result in the nitrating of proteins. A recent in vitro study studied two distinct SOD1 mutations that created higher hydroxyl radicals. This increase in radical production was quantified using spin-trapping techniques, which lends support to the first theory.[46] Excessive oxidative stress has been implicated in the aetiology of amyotrophic lateral sclerosis by numerous investigations.[47] There is a lot of evidence to suggest that oxidative damage to proteins is higher in ALS postmortem tissue than in control samples. Spinal cord and motor cortex protein carbonyl levels are elevated in sporadic ALS cases, and 3-nitrotyrosine levels are elevated in sporadic and SOD1 familial ALS patients, both of which are markers for oxidative damage mediated by peroxynitrite.[48]

Huntington disease (HD)

HD is a dominantly inherited neurodegenerative ailment that affects 1–10 out of every 100,000 persons in western countries. As a result of its low incidence, HD is considered to be one of the so-called rare diseases.[49] Huntington's disease (HD) is a genetic, autosomal dominant disorder that is caused by a mutant elongated polyglutamine repeat and causes a loss of cognitive and motor skills.[50] chorea, which are sudden, uncontrolled muscle movements, problems with memory and understanding, and, in the later stages, a complete lack of muscle movement.[51] Although the toxicity of mutant HTT is the primary cause of the neurodegenerative process that is occurring in HD, several additional processes, most of which are common to other neurodegenerative disorders, such as protein misfolding, abnormal proteolysis, protein aggregation and deposition, transcriptional dysregulation, mitochondrial dysfunction, excitotoxic and oxidative events, and glial activation and local inflammatory events, have also been implicated in neuronal death in HD.[52] In addition, the oxidative damage in HD is considered a big factor in developing neurodegeneration. Multiple reports have found oxidative damage in HD model cells and patient tissue samples. Protein oxidation, lipid peroxidation, and DNA damage are just some of the damage markers that have been found to be elevated in people with HD.[8]

Oxidative Damage in HD Recent findings point to the possibility that mitochondrial energy metabolism dysfunction may be the end result of excessive oxidative damage to DNA or other neuronal macromolecules.[53] This may occur as a direct result of increased free radical and oxidant generation. Free

radicals, such as superoxide (O2 -) and hydroxyl radicals (HO-), are always produced as byproducts of aerobic metabolism.[54] However, the production of free radicals can increase when the electron transport chain is inhibited or when there are molecular defects. Elevated Ca2+ influx induced by excitotoxic processes leads to mitochondrial Ca2+ sequestration, which increases mitochondrial free radical production.[55] Free radicals can cause oxidative damage to cell macromolecules such as DNA, proteins, and lipids through a variety of different mechanisms. Some of these mechanisms include DNA strand breaks, the formation of DNA adducts such as 8-OHdG, protein carbonylation, and lipid peroxidation.[56] In addition, the cycling of free radicals and mitochondrial malfunction may explain the slow, progressive pattern of neuronal damage in chronic neurodegenerative disorders. Further evidence suggests Energy abnormalities in the HD brain are similar to those seen in cell culture when peroxynitrite inhibits complex II-III and complex IV activity in the electron transport chain.[57]

Mechanisms of Neurodegeneration

I. **Protein Aggregation & Protein (Mis)Folding**

It is becoming increasingly clear that cellular and molecular mechanisms such as protein aggregation and inclusion body formation underlie neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), and prion diseases.[58] The pathogenic characteristics of many diseases include aberrant intra- and extracellular deposition of self-aggregating, misfolded proteins and the development of high-ordered, insoluble fibrils as a result of abnormal interactions between proteins. Typically, the underlying protein's identity dictates which neurons are impacted and, consequently, the clinical presentation of each disease. The beginning of protein misfolding in a certain cell might be a random event, with the individual being at a constant risk for it throughout their entire lifetime.[59] The process known as "seeded polymerization" might be involved in the production of amyloid. Increasing the concentration of protin could potentially enhance the likelihood of aggregation.[60] Steps in the process of aggregation Protein aggregation is becoming increasingly clear to be a complex process with numerous intermediates that lead to various types of fibres or amorphous aggregates which leads to cell toxicity and cell death.[61]

II. **Oxidative Damage**

Oxidative Stress occurs when there are more free radicals or their byproducts

than antioxidants to fight them. It can damage biological molecules and set off a chain of events, such as problems with mitochondrial respiration, excitotoxicity, and a fatal rise in cytosolic calcium, which, along with nitric oxide and reactive nitrogen species, leads to cellular dysfunction.[62] The production of ROS during the early stages of protein aggregation is a basic molecular mechanism that all of these diseases express. ROS may be made in large part by electrons that escape from the respiratory chain and react with oxygen. Other factors include metal-iron-related Fenton reactions, lipid peroxidation, and protein nitrosylation caused by nitric oxide. The most dangerous free radicals made by living things are the hydroxyl radical and peroxynitrite, which can damage cells by oxidising proteins, lipids, fatty acids, and nucleic acids.[63]

III. Impaired Bioenergetics And Mitochondrial Dysfunction

Mitochondria, the "energy engine of the cell," are essential cytoplasmic organelles for the survival and function of neurons. They derive energy from aerobic metabolism; oxidative phosphorylation through the oxidative phosphorylation system (OXPHOS) is the primary source of high-energy molecules.[64] Such proteins link mitochondrial function and dynamics to the regulation of metabolism, cell-cycle control, development, and cell death, establishing mitochondria as a pivotal platform in the execution of different cellular events, including cell death. Mitochondria are key ROS targets and generators. The production of reactive oxidants, such as ROS, is enhanced in mitochondria that have been damaged, as well as in cells whose mitochondrial function has been impaired.[65] Recent studies have demonstrated that good ageing is related to lower neuronal mitochondrial metabolism and altered glial mitochondrial metabolism, which may be partially responsible for the reduction in brain function(Fei Yin et al., 2017). Oxidants can trigger the mitochondrial permeability transition, decouple oxidative phosphorylation with catastrophic effects on mitochondrial energetics, and contribute to cytotoxicity through necrosis or apoptosis. The respiratory chain enzyme and mitochondrial DNA are two key mechanisms of mitochondrial damage. During ageing, oxidative stress and damage to mtDNA impair mitochondrial energy metabolism and ion homeostasis in neurons; making them susceptible to degeneration.[67] Neuronal maintenance and axonal function are impacted by disruptions in the mitochondrial proteolytic system. Mitochondrial fusion, fission, transport, and mitophagy have a reciprocal relationship in neurodegenerative diseases. In neurodegenerative disorders, poor bioenergetics and dysfunctional

mitochondrial energy metabolism result in decreased ATP production, impaired calcium buffering, and the formation of reactive oxygen species (ROS), constituting a "deadly trio." Mitochondrial malfunction originates and perpetuates neuronal dysfunction in every age-related neuro developmental disorder.[68]

Enzymatic Antioxidants

1. Superoxide Dismutase

Superoxide dismutase (SOD), a component of the enzymatic defence system, converts the superoxide radical anion to H2O2 through oxidative decay. SOD also protects dehydratase against superoxide inactivation by reactive free radicals. In humans, there are three different versions of the enzyme SOD. SOD-1 is a copper-zinc-containing SOD (also known as CuZn-SOD), and it is found in the cytoplasm(Lee et al., 2020). It is an enzyme that specifically catalyses dismutation in a medium that does not require a pH adjustment. The SOD-1 protein is a homodimer that is made up of eight antiparallel beta strands and two metal atoms.[70] Its primary function is to catalyse the conversion of harmful O2 anions into H2O2 and O2. In particular, the catalytic action of this enzyme is dependent on copper minerals, while the structural integrity of the enzyme is dependent on zinc. By neutralising the damaging effects of superoxide radicals, SOD-1 is an essential component of the body's defence system. In addition to this, the absence of this enzyme was associated with an increased sensitivity to the harmful effects of paraquat. SOD-2, also known as manganese-containing SOD or Mn-SOD, is located in the mitochondrial matrix and is responsible for the reduction of the superoxide radical anion that is produced in the electron transport chain.[71] The SOD-1 and SOD-2 genes appear to be disturbed and/or mutated in neurodegenerative disorders. In familial ALS, SOD-1 gene mutations result in a variety of cellular alterations, including altered gene expression, atypical protein interactions, caspase activation, mitochondrial malfunction, and cytoskeletal abnormalities.[72] Overexpression of SOD-1 protects neurons against the neurotoxic effects of amyloid beta (A), whereas loss of SOD-1 increases age-related diseases and shortens the lifespan of mice.[73]

2. Catalase

This is prominent in cells that are exposed to oxygen and is usually employed to catalyse the breakdown of hydrogen peroxide (a byproduct of a variety of normal metabolic activities) into oxygen and water.[74] One molecule of catalase is capable of converting around 6 million molecules of hydrogen peroxide to water and oxygen per

minute, making it one of the enzymes with one of the greatest turnover rates. It is most prevalent in the liver, though it can be detected in other organs as well.[75] Catalase is encoded by the human CAT gene, which is located on the chromosome. In the decades that followed, a number of investigations into prokaryotic catalase as well as lower eukaryotic catalase were carried out. In particular, research on catalase extracted from Saccharomyces cerevisiae has produced data and information on the development of the enzyme at the molecular level. It has also been reported that catalase is a significant enzyme that plays a role in mutagenesis and inflammatory conditions, in addition to playing a role in the prevention of apoptosis.[2] Furthermore, increased cytotoxicity and ROS are seen when CAT activity is inhibited, pointing to CAT's critical role in preserving the proper level of oxidative stress. To be more specific, the mislocalization of CAT is linked to an increased production of reactive oxygen species (ROS) and hydrogen peroxide in the cells, [76] both of which contribute to impaired neurological function. It has been hypothesised that an absence of CAT or a dysfunction in its function may play a role in the pathogenesis of a number of age-related degenerative diseases. In neuronal culture, treatment with CAT lowers levels of reactive oxygen species (H2O2) and improves neuronal survival following Aβ-induced toxicity.[77]

Glutathione (GSH)

GSH is a key antioxidant that plays an important role in maintaining the physiological activities of all cells in vivo. It is also vital for maintaining the homeostasis of the redox states that are present in cells. Thiol residues, also known as sulfhydryl groups or SH groups, play an important role in the maintenance of redox state homeostasis within the cell.[78] GSH has multiple roles in live cells, including maintenance of the intracellular antioxidant system, redox balance, cysteine transport and storage, cell signalling, regulation of certain enzyme activities, gene expression, and differentiation and proliferation. GSH is found in relatively high concentrations in the liver and kidney, both of which utilise the transsulfuration pathway to produce cysteine from methionine via homocysteine.[79] On the other hand, GSH is found in relatively low concentrations in the brain, where the regulatory system for GSH synthesis is independent of that found in peripheral tissues. As a result, the molecular pathways that underlie GSH failure in the brain are distinct from those that underlie it in the tissues of the periphery.[80]

Antioxidants as therapeutics approaches in Neurodegenerative disorder

Neurodegenerative diseases are conditions that cause malfunctions in the brain, more specifically in the neurons. Failures in stability, breathing, movement, reflexes, motor abilities, or cardiac activity are the most prominent examples of mutually exclusive symptoms. The use of common antioxidants, such as vitamins E and C, flavonoids, and substances containing polyphenols, can help to avoid them. Antioxidants have been shown to have a significant impact on human health due to their ability to slow the ageing process by eliminating free radicals. To be more specific, vitamin C has the potential to act as a potent antioxidant, thereby lowering the risk of oxidative damage brought on by, among other things, environmental toxins, stress, and unhealthy diets. Consequently, this lowers the risk of neurodegenerative disorders over the long term. There is currently no cure for neurodegenerative diseases; nevertheless, these conditions can be controlled. The treatment of this disease lessens its symptoms, which helps to preserve the patient's quality of life. The use of naturally occurring antioxidants like polyphenols, which may be obtained through food or nutritional supplements and have a variety of positive effects, has emerged as an appealing alternative management strategy. Table 1 represent some drugs and their effect through antioxidant effect.

Table No. 1: Example of Drugs Show Antioxidant Effect in Neurodenerative Disease

Sr no	Drug	Pharmacological Effect In Neurodegenerative Disorder	References
1	Bacopa monnieri extract	Reduce oxidative stress and Ameliorates learning and memory impairments through synaptic protein, neurogranin, pro-and mature BDNF signaling, and HPA axis in PNS in the rat brain	81
2	a-Lipoic acid	Antioxidant properties in AD	82
3	Cryptotanshinone (quinoid)	Anti-apoptotic properties in PD-hiNPCs, significantly reduced cellular apoptosis through mitochondrial restoration.	83
4	Curcumin	Antioxidant, anti-inflammatory and amyloid disaggregating properties in AD	84

5	Epigallocatechin-3-gallate	Antioxidant properties in AD	85
6	Ginsenosides Rg1 and Rg3	Suppress Aβ induced neurotoxicity, Aβ associated generation of ROS and cell death In AD	86
7	Mitoquinone	Antioxidant properties in PD n by scavenging peroxyl, peroxynitrite and superoxide ROS	87

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