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Review Article

The Impact of Free Radicals on Neuronal Cells: A Biochemical Perspective

Baraa H. Ali[1*], Zinah A. Mohammed[1], Ahmed I. Saber[2], Alaa Younis Al-Hamadany[1]
[1]Department of Anesthesia Techniques, Mosul Medical Technical Institute, Northern Technical University, Mosul, Iraq
[2]Department of Pharmacy Techniques, Mosul Medical Technical Institute, Northern Technical University, Mosul, Iraq

***Corresponding Author:** Baraa H. Ali
Department of Anesthesia Techniques, Mosul Medical Technical Institute, Northern Technical University, Mosul, Iraq

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Abstract: Our bodies make molecules when they break down food and when they are stressed. These molecules are called radicals. Free radicals are important for our bodies to work properly like when we're fighting off sickness and our cells are talking to each other. When we have too many free radicals it can cause problems. Our brain cells are very sensitive to damage from radicals. This is because brain cells use a lot of oxygen they have a lot of fat they do not have things to protect them from damage and they do not fix themselves very well. Free radicals can hurt our brain cells. Cause oxidative stress. Our brain cells are very important. When free radicals hurt them it can cause big problems. Free radicals are a problem, for our brain cells. Oxidative stress causes a lot of problems like lipid peroxidation, protein oxidation, mitochondrial malfunction, DNA damage, compromised synaptic transmission and neuronal apoptosis. Oxidative stress is the reason for neurodegenerative diseases such as Alzheimers disease, Parkinsons disease, amyotrophic lateral sclerosis and Huntingtons disease. These diseases happen because of the changes that oxidative stress causes. This review talks about the production and metabolism of radicals the molecular processes that cause neuronal damage the endogenous antioxidant defense systems and the connection between oxidative stress and neurodegeneration from a thorough biochemical standpoint focusing on oxidative stress and neurodegeneration and how oxidative stress affects the body. The review covers stress and its effects on the body including neurodegeneration to understand how oxidative stress leads to neurodegenerative diseases, like Alzheimers disease, Parkinsons disease, amyotrophic lateral sclerosis and Huntingtons disease. New ways to reduce damage and keep neuronal function working are also talked about along with new ideas, for using antioxidants to treat people. If we understand the pathways that connect free radicals to neuronal deterioration better this can help us find more effective ways to prevent and treat neurological illnesses like these neurological illnesses. The more we know about the pathways that connect free radicals to neuronal deterioration the more we can do to stop neurological illnesses from happening in the first place and the more we can do to treat neurological illnesses when they do happen.

Keywords: Oxidative Stress, Neuronal Cells, Reactive Oxygen Species (ROS), Free Radicals, Neurodegeneration.

1. INTRODUCTION

The brain is very important. People think it is easily damaged by things that can hurt it like when it has a lot of fat and has to do many complicated jobs to work properly. The brain has a lot of lipids. It does many complex things to function so it is a main target for things that can cause damage. The brain is a target, for oxidative damage because of this [1]. Nitric oxide synthases and NADPH oxidases and mitochondria are really important because they make a lot of radicals. These free radicals have an effect on neuronal cells, Nitric oxide synthases and NADPH oxidases and mitochondria are necessary for things like respiration and signaling pathways. These are processes that nitric oxide synthases and NADPH oxidases and mitochondria help with [2]. Numerous reactive oxygen species and nitrogen species are produced by cells and they usually act as important signaling molecules, in many different situations that help keep the body in balance [3]. The production of Reactive Oxygen Species can be good for cells to talk to each other. It helps cells work together normally. When bad things happen to cells like neurodegeneration,

ischemia, excitotoxicity and hypoxia the production of Reactive Oxygen Species goes up a lot. This increase in Reactive Oxygen Species causes bad things to happen. The production of Reactive Oxygen Species is usually okay. When it gets too high it is not good, for the cells. The production of Reactive Oxygen Species can lead to things when it is too high [4]. The role of radicals during these sicknesses is still being studied and people are trying to learn more about them. Free radicals have a lot of effects. These effects are not fully understood yet. The way free radicals work during these sicknesses is also not completely clear. People are still doing a lot of research, on radicals to figure out what they do [5]. Oxidative stress is still a problem. It is thought to be a reason why brain cells die. This can cause a lot of brain diseases that affect millions of people all over the world. Oxidative stress is an important thing to think about when we talk about brain cells dying. Brain cells dying can lead to all sorts of diseases and disorders. Oxidative stress is something that people should know about because it can hurt people [6]. To help the brain we need to find ways to reduce the effects and make the brain cells healthier, this means we have to understand how everything in the brain is connected and how it all works together. We have to know about the balance between things that can hurt the brain and things that can help it. The brain has a lot of things going on inside it like oxidation and antioxidant activities. We have to understand how these things work together to keep the brain healthy [7].

2. Fundamentals of Free Radicals and Oxidative Stress

The high use of oxygen and the special place of mitochondria in the cells make neurons very likely to be harmed by stress. Neurons are one of the vulnerable cell types to oxidative stress. The high use of oxygen and the special place of mitochondria, in the cells make neurons very likely to be harmed by stress. Neurons are one of the vulnerable cell types to oxidative stress [8]. Therefore free radicals can be seen as both things that are made when cells use oxygen to make energy and as important parts that help decide what happens to nerve cells. Some people think they are harmful. Others think they are needed. Free radicals are part of the process in the body. They can cause damage. They also help control what happens to nerve cells. Some scientists say they are waste products. Others say they play a role, in how nerve cells grow or die. So free radicals are. A result of normal body functions and also a part of how nerve cells develop [9]. A conceptual framework anchored around redox biology enables the establishment of a coherent narrative within, This dual role creates an opportunity to elucidate processes linking their generation to damaging repercussions in a manner specific to nerves [10]. Free radicals are really important to the brain. There are some categories of free radicals and other reactive species that we should know about. These free radicals are important because they can affect the brain [11].

The aerobic metabolism of glucose has some advantages but it also does something bad to our cells. It makes something called radicals inside the neuronal cells. The aerobic metabolism of glucose is really good for us. It can also hurt the neuronal cells by making these free radicals [12]. These species can be classified into reactive oxygen and nitrogen subclasses. Reactive oxygen types include superoxide ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), hydroxyl radicals (•OH), and singlet oxygen ($^1O_2$). Sources of superoxide production include the mitochondrial electron transport chain (complexes I and III), xanthine oxidases, and NADPH oxidases [13]. Superoxide dismutation can create hydrogen peroxide and hydroxyl radicals. The role of xanthine oxidase is connected to the creation of hydroxyl radicals [14]. Singlet oxygen arises from several enzymatic pathways; its generation is unlikely to explain elevated free-radical levels in degenerative conditions. Reactive nitrogen species comprise nitric oxide (•NO) and peroxynitrite ($ONOO^-$) [15]. Nitric oxide synthetases constitute the main route of •NO synthesis, with monomeric—rather than dimeric—forms implicated in pathological generation. Peroxynitrite is formed in a reaction between •NO and superoxide [16]. Enzymatic pathways represent the primary sources of radicals; yet, intracellular or organelle-specific conditions can promote leakage through nonenzymatic routes [17]. Mitochondria are not the thing to blame when we are not healthy. Mitochondria play a role when our body is healthy but other things can cause trouble when mitochondria are not working right [18].

2.1. Generation of Reactive Oxygen and Nitrogen Species in Neurons

Reactive oxygen species (ROS), which are mostly produced by oxygen reduction, are produced by all aerobic organisms, including neurons. Superoxide ($\cdot O_2^-$), hydroxyl ($\cdot OH$), hydrogen peroxide (H_2O_2), and organic hydro peroxides (ROOH) are prevalent downstream radicals that interact with a variety of intracellular targets [19]. Reactive Oxygen Species have gained attention for their roles in signaling. They are still a big source of damage to cells because they can cause oxidation. Reactive Oxygen Species can hurt cells. This is a major problem. Reactive Oxygen Species are a deal when it comes to signaling and they can also cause a lot of damage, to cells because of oxidation [20]. Because the brain uses a disproportionate quantity of oxygen compared to its bulk, it is highly susceptible to ROS damage, especially under pathological situations. Nitric oxide ($\cdot NO$) and peroxy nitrite ($ONOO^-$) belong to a similar class of chemicals called reactive nitrogen species (RNS), which typically engages in redox dysregulation with ROS [21].

When our bodies have much of a certain kind of molecule called superoxide it can actually help our brain cells talk to each other. This is because superoxide affects things, like cyclic GMP and H_2O_2 which're like helpers that make sure our brain cells are working

properly. Sometimes when we are really sick or hurt our bodies can get too much of these molecules all at once like when our brain cells get too excited or when they do not get enough blood [22]. The delicate balance of homeostasis in neurons that no longer divide is still an important area of study. Certain parts inside the cell are linked to damage and communication. A lot of stress comes from the mitochondrial electron transport chain. It also comes from NADPH oxidases and, from nitric oxide synthase that isn't working properly. Oxidative stress can also happen when small molecules are not helped by enzymes [23]. Each source shows a pattern in space and how it becomes active. This means that different parts of the cell might have their pools of reactive oxygen species. These pools could cause effects, in specific areas of the cell [24].

2.2. Antioxidant Defense Mechanisms in the Nervous System

The body makes something called nitrogen species in the nervous system. This is especially true when it comes to oxide and the enzymes that help create it. These enzymes are important for helping the cells in our body talk to each other. The production of nitrogen species is a big deal, in the nervous system because it is connected to nitric oxide and how cells communicate with each other. It is now recognized that RNS are produced in basal conditions and that free radicals most often combined with already formed RNS are also generated under different types of stress [25]. A prominent example is peroxynitrite (ONOO−), created when NO reacts with superoxide (O2•−) under diffusion control, which can change NO's physiological signaling functions and cause cellular harm [26].

Mitochondrial respiratory chain activity generates superoxide (O2•−), the best characterized free radical produced in neurons. O2•− causes oxidative stress when it accumulates. In healthy cells, superoxide generation is essentially confined to the mitochondrial matrix, hence its role in paracrine signaling is limited; dysfunctional mitochondria may leak O2•− to the cytosol, where it can diffuse farther, and facilitate cell-to-cell propagation of redox signals [27]. Of the 19 known sources of O2•− more than half are located inside mitochondria, with the respiratory chain being the most significant under basal conditions. Other sources generating O2•− in the cytosol include NADPH oxidases, xanthine oxidase, and lipoxygenases [28].

3. Molecular Targets of Free Radicals in Neuronal Cells

Free radicals are highly reactive species that can adversely affect cellular homeostasis through oxidative modification of macromolecules, leading to cell death and tissue damage. Growing evidence reveals that radicals are important in neuronal signal transduction, synaptic plasticity, and neurotoxicity [29]. Reactive oxygen species and reactive nitrogen species are the free radicals produced most frequently in brain cells under oxidative stress. Superoxide anions, nitric oxide, peroxy nitrite, hydrogen peroxide, and hydroxyl radicals are among the many reactive species [30]. Reactive species of nitrogen and oxygen are produced by distinct metabolic pathways and specific enzymes present in different cellular compartments. Consequently, these reactive species have selective effects on neuronal cell signaling, neurodegeneration, cell toxicity and apoptosiss [31]. Neurotransmitter release requires ion channel activity as well as membrane fusion. Schoch and Südhof demonstrated the critical role of synaptic vesicle and presynaptic active zone proteins in neurotransmitter release [32]. Neurotransmitter release is a highly regulated and temporally organized process that has a significant part in the synchronization, specification, and refinement of cellular communication throughout the brain. By altering the composition and functionality of these proteins, neuronal free radicals control the release of transmitters [33]. Thus, studying the interaction of free radicals with specific target molecules not only reveals the free radical generation process but also elucidates Reactive species' play in neuronal signal transduction and neurodegeneration [34].

3.1. Lipids: Lipid Peroxidation and Membrane Integrity

Reactive oxygen species (ROS) cause oxidative damage to membrane phospholipids during lipid peroxidation, a free radical-mediated process that results in cell death [35]. Membrane integrity is compromised during oxidative stress, which significantly alters cellular capacity to store chemicals in vesicles and release them at synapses. Membranes also serve as platforms for signaling proteins that relay information encoded in existing chemical concentrations [36]. Free radicals are therefore poised to disrupt a wide range of physiological processes involving compartmentalized storage and transfer [37].

Lipid peroxidation generates active lipid-derived compounds that, depending on the specific species, can attenuate, amplify, or alter the information transduced by coexisting signaling molecules [38]. Targeted oxidative modification of phospholipids at unsaturated sites modifies the chemical composition of vesicular and cytoplasmic stores, dramatically changing the dynamics of storage and release—membrane phospholipids constitute 30–50% of the dry weight of the neuron. Sustained oxidative stress ultimately compromises membrane integrity, leading to the release of cytosolic and/or vesicular neurotransmitters, cytoplasmic acidification, ATP depletion, and elevation of cytoplasmic Na+ and Ca2+ concentrations [39].

3.2. Proteins: Oxidative Modifications and Enzymatic Dysfunction

The impact of free radicals on neuronal cells results in modifications of protein structures that alter enzymatic activity and render crucial metabolic pathways dysfunctional [40]. Numerous oxidative

changes that affect almost all 20 amino acid side chains, the polypeptide backbone, and protein–cofactor interactions can occur in proteins [41]. Numerous posttranslational modifications have been documented in proteins exposed to oxidative stress, including formation of protein carbonyls, alteration of sulfhydryl groups, thiol oxidation and formation of mixed disulfides, and nitrotyrosine formation. Such modifications are reversible or irreversible and can promote aggregation of misfolded proteins. Modification of the glutamic acid dehydrogenase protein causes a disruption in the regulation of the tricarboxylic acid cycle by reducing the ability of signaling molecules to induce enzyme activation [42]. This results in reduced metabolism of the energy substrate α-ketoglutarate and a further decrease in ATP levels, culminating in energy deficiency in neuronal cells [43].

3.3. Nucleic Acids: DNA Damage and Repair Pathways

Neurons, cells incapable of significant proliferation, are particularly vulnerable to oxidative DNA lesions, with repair failure leading to relay disruptions and potential neuropathology [44]. As a result, damage from oxidative agents is repaired by both base excision repair (BER) and apyrimidinic endonuclease 1 (APE1)-initiated nonhomologous end joining (NHEJ) [45]. Neurons, deficient in nucleotide excision repair and homologous recombination, still maintain efficient DSB repair [46].

While BER primarily corrects oxidative DNA damage, APE1 also engages the NHEJ mechanism. Colocalization between APE1 and DSB markers suggests APE1's involvement; in fact, APE1 inhibition reduces DSB formation, highlighting its role in SSB damage and NHEJ pathways following oxidative insults [47]. Despite their heightened oxidative stress, therefore, neurons retain substantial capability for repairing oxidative lesions to mitigate the risk of cell death [48].

4. Consequences of Oxidative Imbalance for Neuronal Function

Elevated levels of free radicals can adversely affect neuronal metabolic functions. Among the identified neuronal targets of free radicals, the most important components for cells in an oxidatively stressed environment are lipid membranes, proteins, and nucleic acids [49]. Neuronal cells with elevated oxidative stress experience greater damage to mitochondrial membranes, and importantly mitochondrial membranes are paramount to neuronal functionality [50]. The control of neuronal bioenergetics impacted by oxidative stress is linked to two important mechanisms. First, a number of neurodegenerative illnesses, such as Alzheimer's, Parkinson's, and Huntington's, are associated with oxidative stress. Comprehending the cellular and molecular impacts of free radicals facilitates the creation of defenses against the detrimental consequences of oxidative imbalance on neural cells [51]. The most instructive research on how oxidative damage affects neuronal function is carried out in systems where oxidative stress is specifically controlled. High levels of reactive oxygen species have a detrimental effect on synaptic transmission, according to in vitro research, which sheds important light on the connection between cellular oxidative stress and neuronal function [52]. Because of their crucial function in energy production and calcium homeostasis, changes in mitochondrial potential are one of the many cellular processes impacted by free radicals [53]. The detrimental consequences of elevated oxidative stress on neuronal network function are more difficult to assess in vitro. Nonetheless a growing body of evidence implicates neuroinflammation and the consequent activation of street signals in the disruption of network function under oxidative stress either in vivo or in brainslice preparation [54].

4.1. Synaptic Transmission and Plasticity Alterations

The aging process is inextricably linked to free radicals, particularly reactive oxygen and nitrogen species, and the evidence that is now available supports their increased generation, accumulation, and detrimental consequences as the body ages. Significant redox-active species are described, together with their spatial distribution within cell compartments, production kinetics, cellular sources, and possible pathogenic free radical propagators in the nervous system [55]. Special emphasis is given to the signaling occurring at basal and pathological situations in neurons. Synaptic transmission is a fundamental process in the nervous system that is subject to alterations via oxidative stress and inflammation [56]. Free radicals respond to varied stimuli from the environment, and the analysis of oxidative process temporal parameters provides essential information about the reactive intermediary involved, as the cellular status changes considerably with stimulus intensity and duration [57].

Synaptic transmission and, consequently, plasticity are affected by free radicals during the inflammatory processes concomitant with neurodegeneration. According to the catecholamine redox theory, alterations in dopaminergic regulation may result in the selective suppression of particular synapses. Reducing dopaminergic transmission may increase the susceptibility of some synapses to oxidative stress, potentially leading to their elimination. This hypothesis has not been extensively investigated recently, but it could significantly impact understanding of ROS effects on synaptic plasticity [58].

4.2. Mitochondrial Dysfunction and Energy Homeostasis

The brain is the primary organ that uses energy, and ATP synthesis depends on mitochondria. The primary cause of energy loss in the brain is a reduction in ATP synthesis brought on by a loss of membrane potential in the mitochondria [59]. Superoxide dismutase transforms superoxide radicals into hydrogen peroxide

when electrons from the mitochondrial electron transport chain leak out. Superoxide radicals react with significant biological molecules to produce hydroxyl, peroxynitrite, and peroxyl radicals [60]. Free radicals act on lipids, proteins and nucleic acids which lead to secondary oxidative damage and cause excitotoxicity and neuroinflammation [61].

4.3. Neuroinflammation and Cell Death Pathways

Free radicals are highly reactive substances that can oxidatively damage proteins, lipids, or DNA. Free radicals include superoxide and hydroxyl radicals. Hydrogen peroxide and lipid hydro peroxide are two more non-radical oxidants that can change nucleic acids and affect gene expression [62]. The influence of free radicals is not always deleterious, as they interact with various biomolecules and act as second messengers in intracellular signaling, thereby regulating processes such as differentiation and cell division [63]. On the other hand, excessive oxidative damage drives neurodegeneration—a leading cause of human disability. Oxidative damage frequently induces neuro inflammation, which itself is implicated in several neurodegenerative diseases and in normal aging [64]. By decreasing the nuclear concentration of transcription factors like NF-κB and the inflammation-resolving transcription factor Nrf2, oxidative damage triggers the activation of pro-inflammatory pathways. Furthermore, in some neurological disorders, oxidative stress may encourage the death of surviving neurons [65].

5. Contextual Factors Modulating Oxidative Stress in Neurons

The brain's high oxygen demand makes it particularly vulnerable to oxidative stress. Lack of proper antioxidant defense, such as low glutathione level, leads to neuronal morphological impairment, perturbation of glutamate uptake by astrocytes, and disturbance of ATP generation [66]. Age-related deficits in the glutathione (GSH) system leading to GSH depletion and oxidative stress have been observed [67].

Intracellular NADPH and other factors regulate neuronal production of superoxide and nitric oxide. Specific cell types and intracellular domains may produce one or both of these stressors, whereas nicotine may act via increases in either of these molecules in some neurons [68]. Free radical generation in neuronal cells is regulated by various physiological factors [69].

5.1. Age-Related Susceptibility and Neurodegenerative Disease Linkages

Reduced redox capability and an increased risk of neurological disorders linked to increased oxidative stress and free-radical production are associated with aging. Proteins, lipids, and nucleic acids in neuronal cells are harmed by free radicals and other reactive species, which also contribute to the development of pathogenic features typical of neurodegenerative illnesses [70]. In addition to age, wider environmental factors such as exposure to neurotoxic agents, dietary influences, metabolic conditions, and lifestyle choices can give rise to increased neuronal oxidative stress but are less well characterised than their effects on other cells [71]. Increased production of free radicals or disruption of antioxidant machinery can result from neurotoxic environmental pollutants, unbalanced dietary intake of nutrients and biogenic metals, obesity, diabetes, excessive sun exposure, sleep deprivation, anxiety, and depression. This can lead to oxidative stress in the brain and, ultimately, neuronal degeneration [72].

5.2. Environmental and Metabolic Contributors

The innate cellular processes that maintain neuronal homeostasis can alter under adverse conditions. The accumulation of redox-active transition metals, toxic environmental exogenous radical precursors, chronic illness, aging, and imbalanced intracellular redox status can perturb redox homeostasis and initiate oxidative-stress pathways in neurons [73]. Lifestyle-related, age-dependent, and environmental factors can exacerbate the generation of reactive species [74].

6. Methodological Approaches to Studying Neuronal Oxidative Damage

The mismatch between the production of reactive oxygen species (ROS) and their subsequent neutralization by antioxidants can result in cellular damage; this process is known as oxidative stress [75]. Reactive oxygen and nitrogen species (RONS) are among the many types of free radicals, function as agents of oxidative stress. These radicals can recombine to yield non-radical entities that serve significant signaling purposes critical for maintaining normal cellular operations. Usually when our body is working normally it makes something called ROS, at low levels. This mostly happens in the parts of our cells called mitochondria. Also because of some enzymes called NADPH oxidase [76]. However, an increasing amount of research indicates that reactive radicals and their aftereffects may disrupt neural processes, including bioenergetics and neurotransmission, particularly in response to a diverse array of pathological stimuli, which extends to neurotoxic agents, viral infections, age-related decline, neurodegenerative disorders, and apoptosis [77]. We need to do a lot of research to understand what happens when cells get damaged by oxidation. This research should use different methods like testing chemicals and taking pictures of cells and studying their genes. We have to do this to really understand what is going on with oxidation in brain cells and other types of cells. We can use cells in a lab and animals to study this problem. These two approaches can help us learn more about how oxidation works in cells, like where it comes from and how it moves around inside the cell [78]. The first one can use the levels of outside harmful molecules while the second one can use changes in genes that affect how the body handles these harmful molecules. Cell stress comes from things working together and one of the most important is when the balance of harmful molecules

is not right. This is when there are few or too many harmful molecules. Scientists have found this to be an important part of how cells work. This idea has been supported by a lot of studies that look at how the balance of molecules in cells relates to health results in people. Being old should not be seen as something that makes cells less likely to survive. Instead being able to keep the balance of harmful molecules inside the body is very important, for how long cells and the whole body live [79]. Consequently the levels of oxidation and reduction show a strong connection with the amount of radicals and the state of oxidation and reduction is often checked using experiments that look at changes, in free radicals. The area of research includes not just free radicals but also other substances that are closely tied to oxidative stress so it is important to clearly define what is meant by the word "free radicals" [80].

6.1. In Vitro and In Vivo Models

Free radicals have an impact, on what is going on inside the cells of our brain. They are also connected to diseases that affect the brain and nervous system, Free radicals are an important part of studying how cells make energy. By looking at radicals we can understand how cells work and what they need to function properly [81]. As a result, selecting experimental setups carefully is essential to furthering this field's study. The main components of the mammalian nervous system are neuronal cells, demonstrate an extensive array of complexities when compared to other cell types; this complexity inherently affects the study of free radicals. Consideration of appropriate spatiotemporal conditions, as well as the concept of selective vulnerability, is crucial in experimental designs. Although researchers have suggested a preference for either in vitro or in vivo models, employing both complementary approaches often yields deeper insights [82].

6.2. Biochemical, Imaging, and Genomic Techniques

Age-related and neurodegenerative diseases, such as Parkinson's disease (PD) and Alzheimer's disease (AD), are characterized by oxidative stress. Oxidative stress biomarkers are essential for comprehending the effects of free radicals on cells and assessing the effectiveness of possible neuroprotective substances [83]. Neurons, although constituting only a fraction of the body’s mass, produce the highest total quantity of free radicals due to their active energy metabolism. Atomic force microscopy (AFM) measurements indicate that diverse oxidative agents damage neuronal membranes, which is reflected in variations of membrane elasticity and topography. These physical changes corroborate biochemical findings that quercetin, a bioflavonoid, protects against oxidative injury by improving neuronal survival and modulating key signalling pathways and protein-level changes [84]. The combination of AFM with traditional biological techniques opens new avenues for probing oxidative damage and drug efficacy and indicates that AFM can serve as a useful complementary approach for studying the effects of redox-active environments on living cells [85].

By tracking minute changes in mitochondrial functions, molecular imaging using positron emission tomography (PET) enables the observation of oxidative stress in the living brain. For instance, a rise in the oxidation state of mitochondrial nicotinamide adenine dinucleotide (NADH) indicates that fluid-percussion-induced brain damage increases oxidative stress in areas with higher mitochondrial activity. PET studies show that oxidative stress is more severe in patients with neurodegenerative diseases like Parkinson's disease that are linked to mitochondrial malfunction than in healthy people [86]. When cells are under much stress from things that can damage them the systems that usually protect the cells get overwhelmed. This means they cannot stop things from happening to the cells. The things that get hurt the most are the lipids and the DNA molecules.

If we can use imaging to look at what is happening with the stress we can learn more about how different diseases start. This can also help us find diseases where the things that cause damage play a role, in the cellular antioxidant systems and oxidative stress. The study of stress will really help us understand the diseases better and how oxidative stress affects the cells. [87].

7. Therapeutic Perspectives and Protective Strategies

An imbalance in the production and removal of free radicals and other reactive species characterizes neurodegenerative illnesses, such as Alzheimer's disease (AD), Parkinson's disease, Huntington's disease, and multiple sclerosis. Oxidative stress, neural dysfunction, and cell death result from this imbalance [88]. Numerous neuroprotective drugs have been discovered and are undergoing preclinical testing, and addressing the processes linked to oxidative stress offers a potential approach for the prevention or delay of these disorders. It has been demonstrated that co-administration of antioxidants with different therapeutic modalities enhances neuroprotective effects, and controlled regulation of reactive sulfur species may offer further neuroprotective advantages [89].

Counteracting the effects of oxidative insults on neurons through exogenous antioxidant compounds is currently receiving significant attention. Endogenous neuroprotective mechanisms offer potential for therapeutic enhancement. Supplemental external antioxidants, such as vitamins, polyphenols, and carotenoids, have been found to mitigate oxidative stress-induced neuropathological damage [90]. Controlled delivery systems using biocompatible nanovehicles for site-specific release and co-administration of different classes of antioxidants for complementary and synergistic effects have been developed. Nutritional interventional strategies that

modulate redox molecules in cells and tissues contribute to delaying neurodegeneration. Diets high in antioxidants, essential nutrients, polyphenols, flavonoids, and omega-3 fatty acids support healthy aging and protect against neurodegeneration [91].

Direct regulation of neuronal redox homeostasis by targeting redox-active enzymes, transcriptional regulators, and anti-oxidative systems through small synthetic agents, drugs, molecules, or genetic manipulation has been investigated; proper spatio-temporal control during stressors optimizes protection. Specific delivery systems for synthetic agents to target redox homeostasis in neuronal populations have been developed; additional avenues, such as targeting aberrant redox-active signaling for precise redox modification under pathological conditions, provide alternatives [92].

7.1. Antioxidant Therapies and Redox Modulators

Oxidative stress disturbs the balance of reactive species and antioxidant defenses, producing reactive oxygen and nitrogen species that can damage cellular macromolecules [93]. Under physiological conditions, highly controlled metabolic processes maintain redox equilibrium, and exposure to exogenous factors or impairment of endogenous pathways causes overproduction of reactive species [94]. Neurons generate radicals mainly through mitochondrial respiration, NADPH oxidases, nitric oxide synthases, and heme oxygenases. Each source, compartment, and mechanism contributes differently to steady-state concentrations and altered states [95]. Additionally, lipoxygenases and cyclooxygenases produce lipid peroxidation derivatives. Pathological stimulation of mitochondrial complexes I and III, scavenge of local nitric oxide production, or compromised nitric oxide synthases increase the formation of superoxide [96]. Emission of reactive nitrogen species takes place mainly through nitric oxide synthases. Nitric oxide combines with superoxide to yield peroxynitrite, which exerts detrimental protein modifications. Therefore, the considerable metabolic activity of neurons heightens susceptibility to oxidative stress and broadens the range of oxidative and nitrosative macromolecular alterations [97].

7.2. Lifestyle and Dietary Interventions

The impacts of lifestyle and dietary factors on oxidative balance and free radical generation, through neuronal redox modulation, are gaining recognition in the quest to protect neurons from oxidative stress. Numerous lifestyle choices can lower oxidative stress, including diets high in vegetables and foods produced from plants have been shown to improve longevity and avoid age-related disorders [98]. At least 400 g of fruits and vegetables should be consumed each day, according to the World Health Organization. The consumption of healthy phytonutrients, vitamins, minerals, and antioxidants is increased when processed meals, refined sugars, and saturated fats are avoided in favor of nutrient-dense alternatives. Antioxidant-rich foods include walnuts, flaxseeds, seafood, olive oil, and fresh fruits and vegetables [99]. EPA and DHA, two omega-3 fatty acids, support the stability of mitochondrial membranes, and magnesium is necessary for mitochondrial oxidation-reduction processes; magnesium deficiency can increase free radical formation. Membrane lipid unsaturation levels are negatively correlated with maximum lifespan, suggesting evolutionary selection for lower unsaturation to protect tissues from oxidative damage. Nutritional oxidative stress results from an imbalance between prooxidant load and antioxidant defenses, especially after consuming lipid- and carbohydrate-rich meals, which increases susceptibility to oxidative damage in the postprandial state [100].

Antioxidants like flavonoids and polyphenols found in natural fruit and vegetable products can help prevent age-related illnesses and cognitive deterioration. Alzheimer's disease is associated with oxidative stress, which may be lessened by the combined effects of substances included in a balanced diet. Consuming antioxidants from natural sources in moderation helps neutralize free radicals while preserving essential prooxidants, which may stop the course of disease. Early-life preventive dietary interventions may be very successful in lowering the risk of oxidative stress-related degenerative illnesses [101].

7.3. Targeted Interventions for Neuronal Redox Homeostasis

Diminishing the levels of radical stress in neurons carries significant ramifications for the preservation of these cells from neurodegenerative processes. Research into the interactions between glial and neuronal cells indicates that neurons possessing suitable redox-regulatory mechanisms exhibit enhanced resilience to environmental disruptions. Two primary preventive methodologies are identified: (i) the modulation of glial and/or gut interactions that affect neuronal redox states, and (ii) the targeting of specific neuronal lipids and oxidizable pathways recognized for their role in amplifying radical-anion signaling [102]. An engineered strategy to exercise direct control over the radical-anion balance within neuronal circuits previously linked to neurodegeneration has been established. This latter approach is anticipated to be more amenable to manipulation and may provide insights for the development of safe therapeutic interventions that could advance into clinical trials [103].

8. CONCLUSION

Both cellular homeostasis and the pathophysiology of numerous neurodegenerative illnesses and brain dysfunctions depend heavily on reactive oxygen species (ROS) and reactive nitrogen species (RNS). These free radicals are very reactive and unstable atoms or molecules that have a single unpaired electron in their outermost orbital shell. Free radical

species are generally formed within the mitochondria, cytoplasm, and plasma membrane, and under the influence of multiple internal and external stimuli such as environmental toxins and metabolic overload. Excessive accumulation of free radicals leads to oxidative imbalances that can irreparably damage cellular macromolecules, leading to an aberrant neuronal network, and ultimately contribute neurodegenerative diseases.

The nervous system exhibits a unique vulnerability to oxidative stress, and neurons are particularly sensitive to free radical-induced damage. Several environmental, behavioral, and physiological factors such as age, diet, and lifestyle may significantly modulate neuronal oxidative stress levels. More specifically, neuronal sensitivity to oxidative stress is markedly increased when an imbalance occurs between free radical generation and elimination. Many life-saving therapies, including free radical scavengers and antioxidants, have demonstrated that oxidative stress plays a crucial role in the pathophysiology of numerous age-related neurodegenerative disorders. Consequently, understanding the intricate links between free radical patterning and neuronal cellular responses as well as the subsequent effects on neuronal network activity is beneficial for the development of neuroprotective strategies against head trauma, stroke, neurodegeneration, and other age-associated cognitive dysfunctions.

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