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THE ROLE OF OXIDATIVE STRESS IN NEURODEGENERATIVE DISEASES: MECHANISMS AND THERAPEUTIC IMPLICATIONS

Farheen Anjum[1], Dr. Anum Zahra[2], Tanzeela Noreen Alvi[3], Dr. Syna Pervaiz Singha[4], Dr. Amir Derick[5], Dr. Abroo Fatima Qazi[6*]

[1]Lecturer, Department of Psychology, Balochistan University of information Technology Engineering and Management Sciences (BUITEMS), Quetta, Pakistan
Email: farheen.anjum@buitms.edu.pk
[2]Senior Registrar, Department of Neurology, Rahbar Medical and Dental College, Lahore, Pakistan,
Email: aani.khalid.ak@gmail.com
[3]Research Associate, School of Biological Sciences, University of the Punjab, Pakistan,
Email: tanzeela.sbs@pu.edu.pk
[4]Associate Professor, Department of Anatomy, Isra University, Hyderabad, Pakistan,
Email: synaamir@gmail.com
[5]Assistant Professor, Department of Oral Biology, Liaquat University of Medical and Health Sciences Jamshoro, Pakistan, Email: amirdisaac@gmail.com
[6*]Associate Professor, Department of Physiology, Isra University, Hyderabad, Pakistan

***Corresponding Author:** Farheen Anjum
*Email: Abrooqazi@gmail.com

ABSTRACT

Objective: The involvement of oxidative stress in cell death mechanisms during neurodegenerative diseases, with a focus on Alzheimer's disease, idiopathic Parkinson's disease, and amyotrophic lateral sclerosis (ALS), along with the exploration of antioxidant therapeutic strategies.

Background: Oxidative stress is implicated in the pathogenesis of neurodegenerative diseases, including Alzheimer's disease, ALS, and Parkinson's disease. These diseases are characterized by selective neuronal loss and the accumulation of intracytoplasmic materials, suggesting common physiopathological mechanisms. The increase in disease frequency with age, existence of sporadic and familial forms, and possible co-occurrence of these conditions in certain populations further support the role of oxidative stress.

Methods: This review synthesizes literature on the involvement of oxidative stress in Alzheimer's disease, ALS, and Parkinson's disease, highlighting abnormal markers of oxidative stress in these conditions. The review also discusses antioxidant therapeutic strategies and their efficacy in clinical trials.

Results: In Alzheimer's disease, oxidative stress is associated with beta-amyloid protein, inflammation, and neuronal calcium metabolism disturbances. Antioxidants such as vitamin E, selegiline, vitamin C, Ginkgo Biloba extract, and non-steroidal anti-inflammatory drugs show promising effects. In ALS, hypotheses include excitotoxicity and genetic mutations affecting superoxide dismutase. Antioxidant trials have shown limited efficacy, with vitamin E in combination with riluzole being the most promising. In Parkinson's disease, oxidative stress contributes to

dopaminergic neuron death, with evidence implicating iron accumulation and respiratory chain dysfunction. Selegiline demonstrates efficacy, while vitamin E shows mixed results.
Conclusion: Oxidative stress plays a significant role in neurodegenerative diseases, contributing to cell death mechanisms. Antioxidant therapies have been explored, showing variable efficacy across different conditions. Further research is needed to elucidate the precise mechanisms of oxidative stress and optimize therapeutic interventions for neurodegenerative diseases.

INTRODUCTION

1. Alzheimer's disease

The prevalence of senile dementia is estimated at around 1% in Europe between 60 and 65 years old, reaching up to almost 35% of people over 95 years old. In more than 50% of cases, degenerative dementia is due to Alzheimer's disease, which affects 6 to 8% of people over 65, with a prevalence that is increasing rapidly. Several pathophysiological hypotheses, which involve free radicals or certain reactive compounds, have been proposed. The main ones are the hydroxyl radical ($OH\cdot^{-}$), the reactive compound peroxynitrite ($ONOO^{-}$) as well as its precursors nitric oxide and superoxide anion, and hydrogen peroxide (H_2O_2) (Akhtar, Patel, et al. 2023) (Dubey and Singh 2023)

Oxidative stress is evidenced by an increase in terminal products or certain reactive intermediates: the increase intracerebral malondialdehyde signals lipoperoxidation, the elevation of 8–OH–2–deoxyguanosine and heme oxidase signals oxidative damage to DNA; peroxynitrite and nitrotyrosine are also elevated, as well as, at the level of neurofibrillary aggregates, carbonylated proteins, and certain glycosylation products. Several mechanisms for fighting free radicals are disrupted: serum activities of Cu, Zn–SOD, and catalase are increased in patients, and elevated intracerebral concentrations of glutathione, glucose–6–phosphate dehydrogenase, catalase, and SOD are reported, compared to control subjects. These abnormalities are interpreted as an exacerbation of defense mechanisms during the disease (Dubey and Singh, 2023).

One of the main hypotheses involves the amyloid protein, which is found in the senile plaques characteristic of the disease. It has a direct toxic effect on neuronal cell cultures. Still, an alteration of neuronal glycolysis, cytoskeletal disorders, and neurotrophic factors have also been noted, with the intervention of oxidative stress in each case. The toxicity of the amyloid protein would be linked to the stimulation of lipoperoxidation of synaptic cell membranes, radical damage to proteins, nuclear DNA, or mitochondrial DNA, and stimulation of the production of free radicals in cells. Microglial but also to a pro-inflammatory type attack on vascular endothelial cells. Conversely, on the one hand, cell lines rich in catalase and glutathione peroxidase, enzymes involved in the fight against free radicals, are protected against the amyloid protein; on the other hand, vitamin E and other Antioxidants also have a protective effect (Korovesis, Rubio-Tomás, et al. 2023) (Hurst and Schnichels 2023).

An alteration of complex IV (cytochrome c oxidase) of the mitochondrial respiratory chain is also described in Alzheimer's disease, with a drop in activity of 25 to 30% in the cerebral cortex compared to normal subjects. These disorders could be due to the toxicity of the amyloid protein and result in a reduced production of ATP and an increased production of free radicals. The transfection of messenger RNA from mitochondria from subjects affected by Alzheimer's disease to controlled cell strains from which the initial mitochondrial DNA has been removed results in a reduction in cytochrome c oxidase activity in these cells and an increase in the production of free radicals (Hurst and Schnichels 2023).

There is a link between the existence of Alzheimer's disease and the presence of an E2 or E4 allele of the gene that controls the production of apolipoprotein E, located on chromosome 19: the E2 form is protective against the disease, and the E4 form is associated with more frequent development of sporadic or familial forms. Although the exact mechanism of the binding is still unclear, we know that the level of cerebral peroxidation is higher in the presence of the E4 allele (Korovesis, Rubio-Tomás et al., 2023).

Free radicals can have an action of aggregation of the amyloid protein, which constitutes a vicious circle. During the disease, there are disturbances involving metals which are involved in the generation of free radicals:

- Iron, which participates in the formation of OH radicals⁻is in high quantity in senile plaques and neurofibrillary aggregates. Alterations in iron metabolism have been suggested ;
- Copper, reduced from Cu^{++} and Cu^{+} under the action of the precursor of the amyloid protein, catalyzes the formation of free radicals, in particular $OH\cdot^{-}$. In addition, copper is necessary for the proper functioning of Cu, Zn–SOD, and cytochrome c oxidase. A decrease in copper in several brain regions has been reported.

Overall, the pathophysiology of Alzheimer's disease is complex. Inflammatory damage, multiple lesions due to amyloid protein, damage linked to gene susceptibility, disturbances in calcium metabolism, and mitochondrial functioning coexist with intervention at multiple interfaces of oxidative stress. As in several degenerative neurological pathologies, the question of whether oxidative stress is the cause or the consequence of the disease remains unanswered. Therapies with anti-radical effects seem more effective than in other conditions, such as ALS (Olufunmilayo, Gerke-Duncan, et al., 2023).

2. Amyotrophic Lateral Sclerosis (ALS)

ALS is a neurodegenerative disease, and it is also the most common neuromuscular disease. It affects around 5000 to 7000 patients in France. Its evolution is rapidly unfavorable, with a median survival of between 23 and 52 months. It manifests itself primarily in the neurological sphere. Ninety percent of patients have a sporadic form of the disease, and the others have a familial form.

Alterations in defense processes against free radicals by mutations in the gene coding for Cu, Zn–SOD1 (SOD type 1), located on chromosome 21, have been demonstrated in 10 to 20% of familial forms. This discovery is at the origin of one of the two main physiopathological hypotheses of the disease: the "oxidative" hypothesis. Given the clinical identity between familial forms and sporadic forms, as well as the existence of mutant mouse strains developing neuromuscular disorders similar to ALS, the study of SOD1 mutations has been widely studied. Developed. The second hypothesis, or excitotoxic hypothesis, associates dysregulation of *turn turnover* glutamate between glial cells and neurons with an increase in calcium entry into neurons. We will mainly describe the disorders linked to the "oxidative" hypothesis (Rehman, Sehar et al., 2023).

The Cu, Zn–SOD1 enzyme is a ubiquitous cytosolic metallo-enzyme that catalyzes the conversion of the superoxide radical to H_2O_2, which itself can be transformed into water by the action of glutathione peroxidase or catalase. There is, therefore, an anti-radical effect there. More than 60 SOD1 mutations have been described in familial ALS in various cell lines, which generally result in a 30 to 70% reduction in SOD1 activity. Compared to other types of neurons, normal human motor neurons have high expression of SOD1, perhaps related to their intense activity. Metabolic and their large size. This partly explains their sensitivity to a drop in enzyme activity and oxidative stress. The other reasons given are their low content of glutathione, with an antioxidant effect, the concentration of their cell membranes in polyunsaturated fatty acids, and finally, the high quantities of oxygen used in the normal state by neuronal metabolism, 'where a strong production of free radicals linked to mitochondrial functioning (Rehman, Sehar, et al. 2023).

Other mechanisms of toxicity may be present in the event of a drop in SOD1 activity: there may be activation of the production of OH radicals.⁻, toxic to SOD1 itself and various cytoplasmic structures; we can highlight an increase in the formation of $ONOO^{-}$, which is a non-radical toxic oxygen derivative that induces the nitration of tyrosine receptors. The increase in ONOO production⁻is identified by the dosage of 3–3-nitrotyrosine. Nitration of tyrosine radicals generates damage to neuronal growth factor receptors or neurofilaments. After SOD1 mutation, but also in the sporadic form of the disease, alterations in the neurofilament content are visible in neuronal bodies and dendrites, which can alter intracellular transport and modify cell shape. However, the reduction in SOD1 activity is not the only mechanism involved because several human mutations with reduced SOD1 activity do not lead to the development of the disease, some mutated forms have normal SOD

activity, and, in transgenic mice, certain strains that hyper express SOD1 nevertheless develop the disease (Sharma, Sharma, et al. 2023).
The consequences of the disturbances induced by the processes described above are poorly understood in detail. An increase in intraneuronal calcium, which can induce cell necrosis or apoptosis, has been demonstrated in lymphocytes from patients suffering from the sporadic form of the disease and in SOD1 mutant cultures. Mitochondria damaged by oxidative stress can also be involved in triggering apoptosis by opening the mitochondrial transition pore and transferring calcium to the cytoplasm. Abnormalities in mitochondrial membrane potential, most often in a downward direction, which can induce a reduction in energy production and promote apoptosis, have been described (Tchekalarova and Tzoneva, 2023).
During sporadic forms of the disease, the role of oxidative stress is likely; indeed, the interaction between oxygenated free radicals or $ONOO^-$and proteins can form protein-carbonyl residues, which are detected in abnormally high quantities in the motor cortex and spinal cord of patients. An increase in immunoreactivity to nitrotyrosine and NO synthase inducible is found at the level of motor neurons. An increase in 8–OH–2–deoxyguanosine, which marks DNA oxidation lesions, is demonstrated in plasma, urine, and CSF. Malon dialdehyde, which marks lipid peroxidation, is elevated in peripheral blood and spinal cord. CSF SOD activity is reduced, and abnormalities of glutathione binding sites in the dorsal and ventral horns of the spinal cord are described. Several authors have found an increase in the spinal cord of patients of other indirect markers of oxidative stress, such as glutathione peroxidase activity, selenium concentration, or the expression of metallothioneins, which are proteins*« scavengers »* free radicals. These anomalies, some also present in glial cells, are interpreted as compensatory responses to oxidative lesions. Nuclear DNA damage is observed in motor neurons, and abnormalities of various DNA repair proteins in both motor neurons and glial cells (Akhtar, Patel et al. 2023).

In relation to the physiopathological hypotheses, therapeutic trials were carried out on mutated mouse lines, on cell lines transfected with mutant SOD1 genes, and in humans. Several products were used:
• Antioxidants: vitamin E, N-acetylcysteine, selenium, coenzyme Q_{10} ;
• glutamate antagonists, such as riluzole, gabapentin, coenzyme Q_{10}. Le coenzyme Q_{10} has an in vitro protective effect against glutamate toxicity and is an acceptor of electrons from complexes I and III of the mitochondrial respiratory chain. In its reduced state, it serves as an antioxidant in the mitochondria and cell membrane;
• inhibitors of apoptosis, such as the Bcl–2 protein or penicillamine. The Bcl–2 protein inhibits the opening of the mitochondrial transition pore and the action of caspases, which are proapoptotic cytoplasmic proteases, and could have a normalizing effect on the activity of Cu, Zn–SOD. Penicillamine is a caspase inhibitor;
• Creatine, because the hypothesis of a deficiency in ATP production in mice mutated for SOD1 has been proposed. Creatine and creatine-phosphate could play a role in providing energy, as well as in limiting the opening of the mitochondrial transition pore;
• and finally, DNA repair proteins. In animals, vitamin E, selenium, and the Bcl-2 protein increase the latency period before the onset of the disease but do not modify survival, whereas the glutamate antagonists, coenzyme $Q_{10,}$ and creatine do not affect the latency period but increase survival. Supplementing the animals' diet with creatine also leads to an improvement in motor performance, a reduction in 3–3-nitrotyrosine, an increase in neuronal glutamate reuptake, and protection against the disappearance of motor neurons. These data suggest:
• That oxidative stress can occur at the start of the disease,
• that glutamate toxicity could be a secondary phenomenon,
• but also that the processes involved are probably intertwined.
• In cell lines, vitamin E, Bcl–2 protein, penicillamine, and DNA repair proteins improve cell survival.
In humans, the only effective compound is riluzole, which increases survival by several months. Gabapentin and N-acetylcysteine only showed positive results in terms of trend. Certain treatments are currently being tested (neurotrophic factors, anti-radical compounds). A recently tested

combination of riluzole and vitamin E resulted in a less severe course after one year of treatment compared to untreated patients (Akhtar, Patel, et al., 2023).

3. Parkinson's disease

The degeneration of cells in the *pars compacta* of the substantia nigra (SN), associated with the presence of Lewy bodies, characterizes the appearance of motor disorders in idiopathic Parkinson's disease (ILD). Although other cell groups are involved, the role of the SN appears essential. The hypothesis potentially implicating oxidative stress in the death of dopaminergic neurons during ILD is based on four major arguments (Dubey and Singh, 2023):

• Dopaminergic neurons are exposed to large quantities of oxygenated free radicals, the origin of which can be diverse. Part of the production of free radicals may arise from the catabolism of dopamine. This occurs along two main routes: non-enzymatic degradation, known as auto-oxidation, and degradation by oxidation. Degradation by auto-oxidation produces semiquinones, then, by polymerization, neuromelanin, which generates free radicals. Neuromelanin has a strong affinity for iron and has oxidoreductive properties (transformation of oxygen into H_2O_2) and an activity that increases the disproportionation of the superoxide anion into H_2O_2. Oxidative degradation uses mono-amine oxidase and also produces H_2O_2. Another source of free radicals is the chain mitochondrial respiration of dopaminergic neurons. Finally, the SN is one of the brain regions richest in iron, which can promote the formation of free radicals from H_2O_2 by the Fenton reaction. It is, therefore, theoretically possible that dysfunction of one of these free radical-producing systems could lead to oxidative stress and promote the destruction of dopaminergic neurons during ILD (Hurst and Schnichels, 2023);

• the neurons of the SN, which are potentially the most exposed to oxidative stress, are the dopamine neurons. Dopaminergic lesions of the midbrain are heterogeneous during ILD. In the SN, in control subjects, most dopaminergic neurons contain neuromelanin indicating significant dopamine auto-oxidation, and high concentrations of SOD, suggesting that they are exposed to high concentrations of free radicals. These neurons have weak means of defense against oxidative stress because glutathione peroxidase with antioxidant activity is mainly localized in astrocytes. And the astrocytic environment is particularly sparse in the SN. Furthermore, catalase, another enzyme capable of neutralizing hydrogen peroxide, is not very active in the central nervous system. In contrast, the neurons of the periaqueductal gray matter, a region preserved during ILD, do not contain neuromelanin and have a dense astrocytic environment. They, therefore, have effective means against oxidative stress. The situation is intermediate in terms of exposure to free radicals in regions where neuronal loss is moderate. Thus, the group of dopaminergic neurons least protected against oxidative stress is preferentially affected during MPI, explaining the distribution of lesions within the midbrain (Korovesis, Rubio-Tomás, et al., 2023);

• there are indications of oxidative stress in the SN of patients with ILD. The level of lipid peroxidation is increased in the SN, evidenced by an increase in the concentration of malondialdehyde in the CSF and at the level of the *pars compacta* from SN. The amount of reduced glutathione, a free radical detoxifying agent, is reduced, suggesting excess consumption (Olufunmilayo, Gerke-Duncan et al., 2023).

Table 1 Connection between oxidative stress and three neurodegenerative diseases: Alzheimer's disease, Amyotrophic Lateral Sclerosis (ALS), and Parkinson's disease.

Disease	Key Points	Evidence of Oxidative Stress	References
Alzheimer's Disease	- Increased free radicals and oxidative damage markers	- Elevated malondialdehyde, 8-OH-2'-deoxyguanosine, heme oxidase - Disrupted antioxidant mechanisms	Akhtar et al., 2023; Dubey & Singh, 2023

	- Amyloid protein linked to oxidative stress	- Increased lipoperoxidation, protein and DNA damage	Korovesis et al., 2023
	- Mitochondrial dysfunction	- Decreased complex IV activity	Hurst & Schnichels, 2023
	- Genetic susceptibility with apolipoprotein E allele	- Higher peroxidation with E4 allele	Korovesis et al., 2023
Amyotrophic Lateral Sclerosis (ALS)	- Mutations in Cu, Zn-SOD1 gene	- Reduced SOD1 activity, increased free radicals	Rehman et al., 2023
	- High vulnerability of motor neurons to oxidative stress	- Low glutathione, high polyunsaturated fatty acids	Rehman et al., 2023
	- Increased formation of toxic ONOO- radicals	- Elevated 3-nitrotyrosine levels	Rehman et al., 2023
	- Mitochondrial dysfunction	- Abnormalities in mitochondrial membrane potential	Tchekalarova & Tzoneva, 2023
	- Evidence of oxidative damage in sporadic ALS	- Increased protein carbonyls, nitrotyrosine, 8-OH-2'-deoxyguanosine	Akhtar et al., 2023
Parkinson's Disease	- Dopamine neurons exposed to high levels of free radicals	- From dopamine catabolism and mitochondrial respiration	Dubey & Singh, 2023; Hurst & Schnichels, 2023
	- Dopaminergic neurons in substantia nigra with weak antioxidant defenses	- High neuromelanin content, sparse astrocytic environment	Korovesis et al., 2023
	- Markers of oxidative stress in substantia nigra	- Increased malondialdehyde, decreased glutathione	Olufunmilayo et al., 2023
	- Mitochondrial complex I deficiency in substantia nigra	- Specific to Parkinson's disease	Rehman et al., 2023
	- Increased iron levels potentially contribute to free radical formation		Rehman et al., 2023

	- MPTP-induced Parkinsonism model supports role of oxidative stress	- MPP+ metabolite inhibits complex I	Sharma et al., 2023

Table 1 summarizes the connection between oxidative stress and three neurodegenerative diseases: Alzheimer's disease, Amyotrophic Lateral Sclerosis (ALS), and Parkinson's disease.

Importantly, there is a correlation between the degree of severity of the disease and the extent of the reduction in glutathione content. Furthermore, this reduction is specific to the SN of ILD because it is not observed during other Parkinsonian syndromes such as Progressive Supranuclear Palsy (PSP) and multiple system atrophies (MSA). It is, therefore, not the witness of neuronal degeneration dopaminergic but clearly reflects oxidative stress specific to the SN. Finally, a significant deficiency in complex I of the mitochondrial respiratory chain is observed in the SN of patients with ILD, compared to matched control subjects. This reduction appears significant in the SN of ILD because it is found neither within other cerebral structures (caudate nucleus, putamen, cerebellum, and cerebral cortex) nor within the SN of patients with SMA (Rehman, Sehar, et al. 2023),

In addition, the results remain significant when the activity is related to the total concentration of mitochondria, estimated by measuring citrate synthetase. These results reflect a drop in specific activity, which is not explained by the phenomenon of neuronal death nor by treatment with L–Dopa, a symptomatic treatment prescribed for Parkinsonian syndromes. Several teams have found a complex I deficiency in other cell types (muscle cells and platelets), but these results are controversial. Finally, there is an increase in the quantities of iron in the SN. Ferritin, the main iron storage protein, could be reduced in the SN, leading to a local increase in free iron, which is potentially toxic to dopaminergic neurons. Still, the results of the ferritin assay are discrepant. Another hypothesis would involve iron transport proteins, such as lactotransferrin and its receptor (Rehman, Sehar et al., 2023).

• the role of oxidative stress has been clearly demonstrated in Parkinsonian syndromes induced by 1–*methyl*– 4–*phényl*–1,2,3,6–*tetrahydropyridine*(MPTP). This Parkinsonian syndrome, initially described in drug addicts, is interesting from a physiopathological point of view because it is close to ILD. Convincingly, MPTP, the oxidation of which produces a metabolite: 1–*methyl*–4–*phényl*pyridinium ou MPP^+, is toxic to dopaminergic neurons by inhibiting complex I of the respiratory chain, which would confirm the role of this complex during MPI. The inhibition does not appear to be linked to a protein structural anomaly or a mutation in mitochondrial DNA (Sharma, Sharma, et al., 2023).

One of the MPI hypotheses involves either prolonged exposure to MPTP substances –still unidentified, or the existence of a joint deficit that could sufficiently alter mitochondrial function. A joint deficiency in alpha ketogluta rate dehydrogenase has been described during ILD but also during Alzheimer's disease. It leads to an accumulation of glutamate and, therefore, to a possible additional chronic excitotoxic phenomenon. The involvement of oxidative stress during ILD has led to the evaluation of antioxidant treatments (Tchekalarova and Tzoneva, 2023).

The results of the first therapeutic trials were disappointing. Several explanations have been put forward: the inadequate dosage of the therapies tested, initiation of treatment too late compared to the theoretical start date of the condition, and finally, lack of sensitivity of the effectiveness criteria, making it possible to discriminate between placebo and anti-inflammatory treatment. -oxidant. Subsequently, the DATATOP study demonstrated that selegiline, with its MAO-B inhibitory action, delayed the initiation of treatment with L-Dopa, although with little evidence in favor of a neuroprotective phenomenon. In the same study, however, vitamin E had no effect. It has been demonstrated that certain molecules with a structure similar to selegiline, such as CGP 3466 or TCH 346, are effective. These molecules, although lacking anti–MAO activity, can bind to a glycolytic enzyme, glycerol–3–phosphate dehydrogenase, which, among other functions, has an anti-apoptotic effect 100 times greater than selegiline. Finally, rasagiline is a selective irreversible MAO–B inhibitor

five times more potent than selegiline in the prevention of MPTP-induced parkinsonism. Other studies are underway to confirm its protective effect during ILD (Akhtar, Patel et al., 2023).

DISCUSSIONS

This paper provides a good overview of the role of oxidative stress in three major neurodegenerative diseases: Alzheimer's disease (AD), Amyotrophic Lateral Sclerosis (ALS), and Parkinson's disease (PD). Here's a breakdown of the key points and potential areas for further discussion. Oxidative Stress as a Common Denominator, all three diseases show evidence of increased oxidative stress, marked by elevated free radicals and impaired antioxidant defenses.

This suggests a potential role for oxidative stress in the disease process, although the exact cause-and-effect relationship remains unclear. The amyloid protein may trigger oxidative stress through various mechanisms. Mitochondrial dysfunction and genetic factors like ApoE4 allele might also contribute. Mutations in the Cu, Zn-SOD1 gene, responsible for clearing free radicals, are implicated in some familial ALS cases. Other mechanisms involving glutamate dysregulation and protein nitration are also discussed. Dopamine metabolism and iron accumulation in the substantia nigra create a vulnerable environment for oxidative stress. Mitochondrial complex I deficiency further exacerbates the problem in PD. Chicken or Egg? Is oxidative stress a cause or consequence of these diseases? Therapeutic Potential: Can targeting oxidative stress pathways offer new treatment options? Disease Heterogeneity: How do the specific mechanisms of oxidative stress differ between individual cases within each disease? Antioxidant Strategies: Are there effective ways to enhance the body's own antioxidant defenses or remove free radicals in these diseases? Briefly discuss the limitations of the studies mentioned. Mention any ongoing research exploring the role of oxidative stress in these diseases.

CONCLUSION

Oxidative stress assumes a primary role in all of the above neurodegenerative diseases. Specifically, AD, ALS, and PD share increased levels of free radicals and decreased scavenger activity, demonstrating the apparent involvement of OS in their development. However, the question about the importance of this role remains open . What if OS is not a primordial cause of the disease but a reaction to damage caused by other pathologies? It is easy to note that answering this question is of great value. Indeed, if OS emerges as a cause, associated pathways can be somewhat targeted as therapeutic targets. Moreover, as described above, each disease is unique in terms of OS. In AD, it is also amyloid protein . ALS is characterized by Cu, Zn-SOD1 gene mutations and glutamate dysregulation, while PD is linked to dopamine metabolism and iron accumulation in the substantia nigra. Given the substantial differences in the underlying mechanisms of oxidative stress in two conditions, this calls for separate and complex approaches to the treatment of each disease. Specifically, further research should be conducted to . At the same time, the above research must be personalized . Finally, novel antioxidant methods should be applied to strengthen human antioxidant mechanisms or eliminate free radicals. By addressing the complexity of oxidative stress in NDs, we can support improved treatment focus.

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