Chapter

Reactive Oxygen Species in Neurodegenerative Diseases: Implications in Pathogenesis and Treatment Strategies

Johnson Olaleye Oladele, Adenike T. Oladiji, Oluwaseun Titilope Oladele and Oyedotun M. Oyeleke

Abstract

Neurodegenerative diseases are debilitating disorders which compromise motor or cognitive functions and are rapidly becoming a global communal disorder with over 46.8 million people suffering dementia worldwide. Aetiological studies have showed that people who are exposed to agricultural, occupational and environmental toxic chemicals that can interfere and degenerate dopaminergic neurons are prone to developing neurodegenerative diseases such as Parkinson Disease. The complex pathogenesis of the neurodegenerative diseases remains largely unknown; however, mounting evidence suggests that oxidative stress, neuroinflammation, protein misfolding, and apoptosis are the hallmarks of the diseases. Reactive oxygen species (ROS) are chemically reactive molecules that have been implicated in the pathogenesis of neurodegenerative diseases. ROS play a critical role as high levels of oxidative stress are commonly observed in the brain of patients with neurodegenerative disorders. This chapter focus on the sources of ROS in the brain, its involvement in the pathogenesis of neurodegenerative diseases and possible ways to mitigate its damaging effects in the affected brain.

Keywords: oxidative neuronal damage, neuroinflammation, oxidative stress

1. Introduction

Neurodegenerative diseases are debilitating disorders which compromise motor or cognitive functions and are rapidly becoming a global communal disorder with over 46.8 million people suffering dementia worldwide. They are characterised by progressive damage in neural cells and neuronal loss. Common neurodegenerative diseases include amyotrophic lateral sclerosis, Parkinson's disease, Alzheimer's disease, Huntington's disease, and spinocerebellar ataxia [1]. These diseases represent major health challenges especially in the ageing population [2]. For instance, PD is the second

most prevalent neurodegenerative disease affecting 1 to 2% of the population above age of 65 while AD is ranked the top 6 leading causes of death in the United States [3, 4].

It is estimated that more than 10 million individuals with the disease will be domiciled in the top 10 most populous nation in the world by 2030. In Nigeria, the most populous nation in Africa, neurodegenerative disease related cases have a significant impact on the overall hospital frequency of neurological cases reported [5]. Some of the characterised clinical features of these diseases include bradykinesia, rigidity, postural instability, resting tremor, prolonged reaction times, and freezing of gait, which may degenerate to tightened facial expression and unconscious facial movement [6, 7]. Aetiological reports have documented that individual who are exposed to industrial, occupational and environmental toxic chemicals that can interfere with the functions of the central nervous system and degenerate dopaminergic neurons are prone to developing neurodegenerative diseases such as Alzheimer's disease, Parkinson disease [8, 9].

The complex pathogenesis of the neurodegenerative diseases remains largely unknown; however, mounting evidence suggests that oxidative stress, neuroinflammation, protein misfolding, and apoptosis are the hallmarks of the diseases (**Figure 1**). ROS may play a critical role as high levels of oxidative stress are commonly observed in the brain of patients with neurodegenerative conditions [10]. Reactive oxygen species (ROS) are chemically reactive molecules that have been implicated in the pathogenesis of neurodegenerative diseases. They are naturally generated within the biological system, playing significant functions in mediating cellular activities including stressor responses, cell survival, and inflammation. They also play pivotal role in the pathogenesis of many diseases such as cancer, allergy, muscle dysfunction, and cardiovascular disorders [11, 12]. Due to their reactivity, Presence of ROS in high quantity may lead to oxidative stress and ultimately cell death if left uncontrolled or treated. Oxidative stress is defined as the disruption of balance between pro-oxidant and antioxidant levels in biological systems [11].

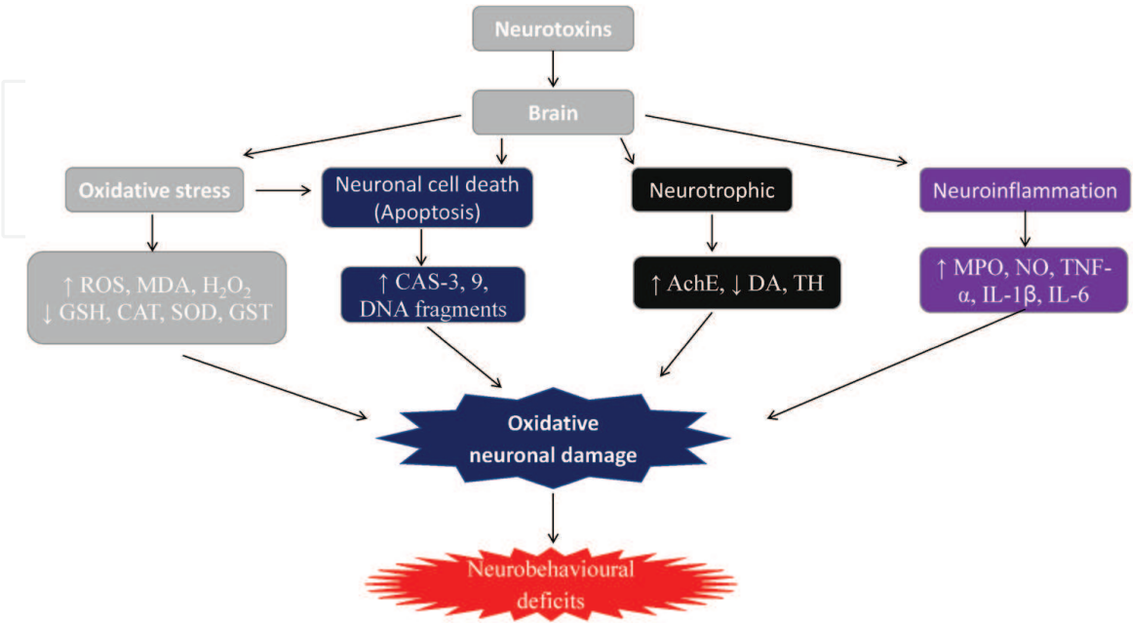

Figure 1.
Possible involvement of oxidative stress, apoptosis, and neuroinflammation in pathogenesis of neurodegenerative diseases.

A number of experimental studies have been carried out to elucidate the significances of oxidative stress in neurodegenerative diseases [13, 14]. ROS may not be sufficient itself to induce neurodegenerative diseases but they appear to exacerbate the diseases' progression through oxidative macromolecule damage and interaction with mitochondria [10]. Interestingly, neuronal cells have been identified to be vulnerable to oxidative damage due to their high oxygen consumption, high polyunsaturated fatty acid content in membranes, and weak antioxidant defence [15]. Under basal or unstressed physiological conditions, free radicals and ROS generated from mitochondria, NADPH oxidase (Nox), and xanthine oxidase are kept at relatively low levels by endogenous antioxidants [11]. Nevertheless, abnormal mitochondrial function and/or neuro-inflammation can alter the redox status and interrupt the balance [15]. Accumulation of misfolded proteins is part of the hallmark of pathogenesis of some neurodegenerative diseases such as Alzheimer disease and Parkinson disease (**Figure 2**). The aggregation of these misfolded or modified proteins can in turn triggers inflammatory response in the brain, which induces marked ROS release and subsequent oxidative stress [16]. Mitochondrial dysfunction with concomitant aberrant ROS secretion is strongly associated with neurodegenerative disorders [17]. For instance, mutant huntingtin (mHTT) in HD may directly interact with mitochondria causing compromised and alteration in energy supply and increased production of ROS [18].

Another key player in the pathogenesis of neurodegenerative diseases is neuroinflammation. The existence of neuroinflammatory processes in human brain has also been confirmed during autopsy on a molecular basis. Mogi and colleagues reported an increase in concentrations of TNFα, β2-microglobulin, epidermal growth factor (EGF), transforming growth factor α (TGFα), TGFβ1, and interleukins 1β, 6, and 2 in the striatum of patients with Parkinson's disease [19–22]. TNFα, interleukin 1β, and interferon γ were also detected in the effects indirectly. Proinflammatory cytokines, such as TNFα, interleukin 1β, and interferon γ, can induce the expression of the inducible form of nitric oxide synthase (iNOS) [23, 24] or cyclooxygenase 2 (COX2) [25]. These enzymes produce toxic reactive species. Other enzymes involved in

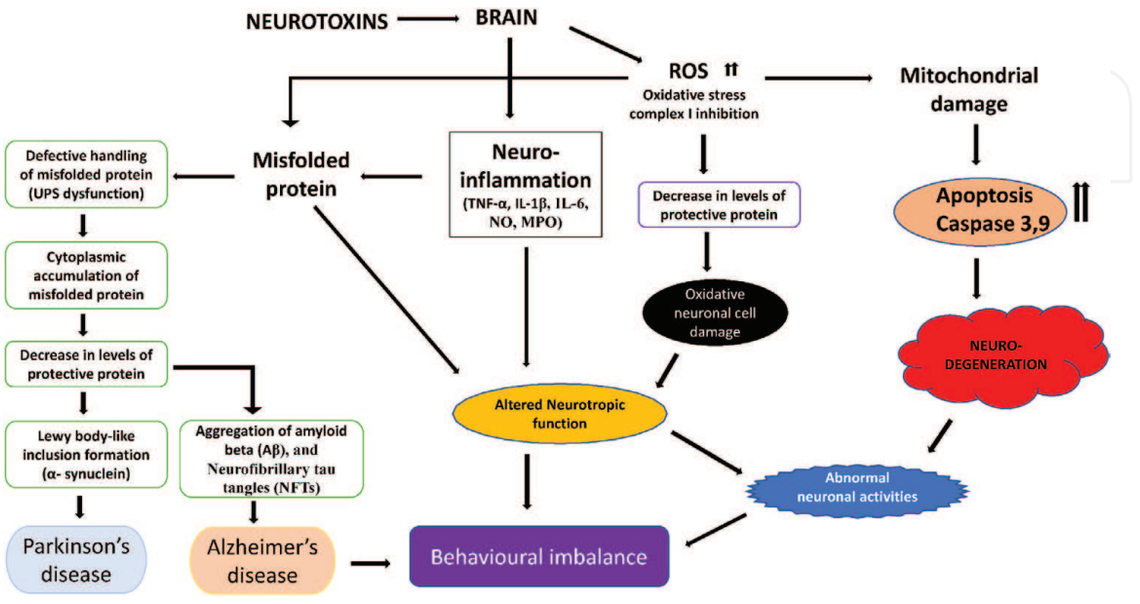

Figure 2.
Molecular mechanisms underlying pathogenesis of Parkinson's disease and Alzheimer's disease.

neuroinflammatory processes mediated by oxidative stress such as myeloperoxidase, NADPH oxidase, and COX2, also have increased concentrations in neurodegenerative diseases [26].

Apoptosis has been implicated as the major pathway involved in the progressive neuronal cell death/loss observed in neurodegenerative diseases. Degeneration of one or more nerve cell populations is a major feature in many acute and chronic neurological diseases. Many criteria for apoptotic cell death are also fulfilled during the course of chronic neurodegenerative diseases. Therefore, the development of new therapeutic strategies for the treatment of neurodegenerative diseases requires an understanding of the molecular mechanisms underlying neuronal apoptosis. Extrinsic and intrinsic apoptosis pathways and several possible avenues for crosstalk between them can be distinguished. Whereas the extrinsic pathway is initiated by cell surface activation of cytokine receptors of the tumour necrosis factor (TNF) family, the intrinsic pathway depends on the integrity and function of mitochondria within the cell [27].

Various evidences from biochemical, genetic, cellular, and neuropathological studies have shown that protein misfolding, oligomerization, and accumulation in the brain are the main events triggering pathological abnormalities responsible for neurodegenerative diseases [28, 29]. The proteins most commonly implicated in the accumulation of cerebral misfolded aggregates in neurodegenerative diseases include: amyloid-beta (Aβ) in Alzheimer disease; tau in Alzheimer disease, frontotemporal dementia, corticobasal degeneration, progressive supranuclear palsy, argyrophilic grain disease, and chronic traumatic encephalopathy; alpha-synuclein (α-Syn) in PD, multiple system atrophy, and dementia with Lewy bodies; TAR DNA-binding protein 43 (TDP-43) in amyotrophic lateral sclerosis and frontotemporal frontotemporal dementia; and prion proteins in PrDs (i.e., Creutzfeldt–Jakob disease (CJD), bovine spongiform encephalopathy, chronic wasting disease, and scrapie). Despite the fact that the protein aggregates involved in distinct neurodegenerative diseases are different, the process of protein misfolding, its intermediates, end-products, and main features are remarkably similar [30].

Considering the pivotal roles of oxidative stress, neuroinflammation, protein misfolding, and apoptosis in neurodegenerative diseases (**Figure 1**), the manipulation of major key players in each of the pathological mechanisms may represent a promising treatment option to slow down neurodegeneration and alleviate associated symptoms. This chapter examine the role of reactive oxygen species (ROS) and oxidative stress in the pathogenesis and progression of neurodegenerative diseases. This chapter focus on the sources of ROS in the brain, its involvement in the pathogenesis of neurodegenerative diseases and possible ways to mitigate its damaging effects in the brain.

2. Role of oxidative stress in pathogenesis of Parkinson's disease (PD)

PD is the second most common neurodegenerative disorder, characterised by the degeneration of dopaminergic neurons in the brain's substantia nigra pars compacta [31]. PD affects around 1–2 percent of the population over the age of 65, and the prevalence rises to 4% in people over the age of 85 [32]. Overabundance of ROS or other free radicals has been linked to the pathological mechanism underlying dopaminergic neuron degeneration. Mitochondrial dysfunction or inflammation may both cause excessive ROS production [10]. The proper role of redox-sensitive signalling proteins in neuron cells, as well as neuronal survival, is dependent on maintaining

redox homeostasis [33]. Mitochondria in neurons and glia are the main sources of ROS in the brain [10]. The production of these free radicals is exacerbated in PD due to neuroinflammation, dopamine degradation, mitochondrial dysfunction, ageing, GSH depletion, and high levels of iron or Ca^{2+} [10].

Consequently, when people with PD are exposed to environmental factors including pesticides, neurotoxins, and dopamine, ROS deposition may be exacerbated [34]. This is supported by a strong link between pesticide exposure and an increased risk of Parkinson's disease [34]. ROS have been shown to contribute significantly to dopaminergic neuronal loss [10]. Other research has indicated that the loss of dopaminergic neurons is linked to the existence of neuromelanin, since highly pigmented neurons are more vulnerable to damage [35]. The formation of neuromelanin appears to be related to dopamine auto-oxidation, a process induced by ROS overproduction [35].

Neurodegeneration produces reactive oxygen species (ROS), which can destroy key cellular proteins and disrupt lipid membranes, leading in oxidative stress. Mitochondrial dysfunction increases free radical generation in the respiratory chain [10]. Parkinson's disease has been linked to deficiencies in mitochondrial complex I in particular. Certainly, a significant portion of the unfavourable neuronal apoptosis seen in Parkinson's disease is due to a complex I deficiency [36]. A mutation in the PTEN-induced putative kinase 1 gene is associated to this impairment (PINK1). PINK1 is a protein found in all human tissues that plays a key role in keeping mitochondrial membrane potential and preventing oxidative stress [36]. The PINK1 mutation is linked to the onset of Parkinson's disease [36]. Mutations of leucine-rich repeat kinase 2 (LRRK2), parkin, alpha-synuclein, and DJ-1 have all been linked to the pathogenesis of Parkinson's disease. These mutations may impair mitochondrial function, resulting in an increase in reactive oxygen species (ROS) production and oxidative stress vulnerability. Mutant parkin may play key roles in the development of autosomal recessive PD due to its involvement in lowering ROS and limiting the production of neurotoxic proteins produced by ubiquitination [36]. Additionally, alpha synuclein aggregation has been demonstrated to disrupt mitochondrial complex I activities, causing ATP production impairment and mitochondrial malfunction [37]. Proteasomal dysfunction which is exacerbated by dopamine-derived ROS, has been linked to neurodegeneration in Parkinson's disease [37].

Currently, there is no effective cure for the treatment of Parkinson's disease, however, deeper insights into the role of ROS in the disease pathogenesis (initiation and progression) should lead to more effective treatments for PD symptoms. Many neuroprotective approaches have been discovered to minimise mitochondrial oxidative stress in dopaminergic neurons. Free radicals damage has been proven to be reduced by antioxidants [38]. GSH, ascorbic acid and tocopherol are essential antioxidants that the antioxidant lipoic acid can recycle. Secretion of GSH which enhance reduction of lipid peroxide is one of the mechanisms by which lipoic acid offered beneficial effects against oxidative damage in oxidative stress-induced mitochondrial dysfunction [39]. In an animal study, it was discovered that treatment with lipoic acid enhanced motor coordination and ATP efficiency resulting in neuroprotection [40]. Furthermore, treatment of lipoic acid in a rotenone rats' model of parkinsonian rats showed enhanced motor performance and marked reduction in neuronal lipid peroxide in the brain [40]. Neuroprotective ability of phytochemicals and antioxidant substances including polyphenols, Ginko biloba, docosahexaenoic acid (DHA), tocopherol, ascorbic acid, and coenzyme Q10, and have all been studied in animal experiments with remarkable findings [41–46]. However, no convincing evidence of their neuroprotective benefits has been found in human [47]. Failures of such

antioxidant medications should provide future recommendations for treating PD patients with combination therapies aimed at limiting ROS production in the brain and improving mitochondrial function [48].

3. Role of oxidative stress in pathogenesis of Alzheimer's disease (AD)

Alzheimer's disease (AD) is the most common neurodegenerative disease, characterised by gradual declines in memory, behaviour, and functionality that severely limit day-to-day activities [49]. The pathophysiology of Alzheimer's disease is primarily linked to the formation of extracellular amyloid beta (Aβ) plaques and intracellular tau neurofibrillary tangles (NFT) [50]. Plaques in the endoplasmic reticulum (ER) can deplete calcium ions (Ca^{2+}) storage, resulting in cytosolic Ca^{2+} overload. Endogenous GSH levels are reduced in response to an increase in cytosolic Ca^{2+}, and ROS will accumulate within the cells [51]. ROS-induced ROS overproduction is believed to play a critical role in the aggregation and secretion of Aβ in AD, and oxidative stress is emerging as a significant factor in the pathogenesis of AD [52]. Mitochondrial dysfunction can result in increased production of reactive oxygen species (ROS), decreased ATP production, altered Ca^{2+} homeostasis, and excitotoxicity. All these alterations may be implicated in the development of AD [53].

Overactivation of N-methyl-D-aspartate-type glutamate receptors (NMDARs) can cause severe oxidative stress in Alzheimer's patients. NMDAR activation has been showed to trigger excessive Ca^{2+} influx by increasing cell permeability and resulting in the production of neurotoxic levels of reactive oxygen and nitrogen species (RNS) [54, 55]. JNK/stress-activated protein kinase pathways can be mediated by reactive oxygen species (ROS). The hyperphosphorylation of tau proteins and Aβ-induced cell death have both been linked to the activation of these cascades [56]. Furthermore, Aβ proteins can directly cause formation of free radicals by inducing NADPH oxidase [57]. The activation of p38 mitogen activated protein kinase (p38 MAPK) by Aβ-induced ROS overproduction modifies cellular signalling pathways and initiates tau hyperphosphorylation. Intracellular NFT formation may be caused by an abnormal aggregation of hyperphosphorylated tau proteins [58, 59]. Consequently, Aβ has been shown to play a key role in the induction of cellular apoptosis [60]. Aβ may boost the activity of calcineurin, which then activates the Bcl-2-associated death promoter, causing mitochondrial cytochrome c release [61]. Aβ can also interact directly with caspases, resulting in neuron apoptosis [61].

Environmental stress, ageing, inflammation, and certain dietary factors (e.g., redox-active metals) may all trigger an increase in Aβ output by inducing additional oxidative stress [62]. Oxidative stress is more common in the elderly, which helps to explain why older people are more susceptible to Alzheimer's disease [62]. Increased expression of cytokines, ROS levels, and cellular toxicity are all caused by inflammation, which accelerates the development of Alzheimer's disease [63]. Aβ deposition results in microglial activation [64]. It's becoming clear that sustained activation of microglia results in the release of pro-inflammatory cytokines, triggering a pro-inflammatory cascade and leading to neuronal loss and damage [65]. Environmental factors such as toxins, chemicals, and radiation may cause oxidative stress [66]. The production of reactive oxygen species (ROS) increases, where there are excess iron deposits [66]. Aβ itself can interact with metal ions to generate free radicals, therefore methionine 35 plays an important role in these reactions [67]. Cu^{2+}/Zn^{2+}-bound Aβ has been showed to have a structure identical to superoxide dismutase (SOD),

suggesting that it could have antioxidant properties [68]. As a result, Cu^{2+} and Zn^{2+} supplementation has been considered as a novel strategy to reduce Aβ-induced ROS generation and metal catalysed Aβ deposition [68].

Drugs for Alzheimer's disease are aimed at lowering Aβ oligomers and phosphorylated tau levels, lowering oxidative stress, and regulating epigenetic changes [69]. The majority of Alzheimer's disease therapies depend on compounds with neuroprotective, anti-inflammatory, and antioxidant properties [70]. Medications that target ROS-mediated cascades like JNK and NF-B (e.g., tocopherol, resveratrol, and rutin) have demonstrated some promising results *in vitro* and *in vivo* [49]. When using antioxidants, significant factors including reaction kinetics and bioavailability (permeability, retention in the targeted region, distribution, and transport) must be taken into account [70]. Several ROS-related neuroprotective therapeutic techniques have shown great promise in the treatment of Alzheimer's disease. The antioxidant response element (ARE) pathway regulated by nuclear factor erythroid 2-related factor 2 (Nrf2) is known to be an important conditioned response against oxidative stress [71]. The binding of Nrf2 to ARE activates the expression of several antioxidant genes in a synchronised manner that can work together for oxidative detoxification. Weakened Nrf2-ARE pathways were observed in the brains of transgenic mice with AD symptoms, while the enhancement of Nrf2-ARE cascades using adenoviral Nrf2 gene transfer has shown protective effects against the toxicity of Aβ deposition [71]. As a result, transcriptional modulation of endogenous antioxidants could hold great promise in the treatment of Alzheimer's disease symptoms [71].

4. Role of oxidative stress in pathogenesis of spinocerebellar ataxia disease

Spinocerebellar ataxia is a progressive neurodegenerative illness caused by an autosomal dominant gene. Cognitive impairments, dysarthria, osculomotor abnormalities, and ataxic gait are all well-known signs of spinocerebellar ataxia, which can lead to mortality. Based on genetic descriptions, about 20 forms of spinocerebellar ataxia have been identified [72, 73]. The main pathogenic mutation in spinocerebellar ataxia has been linked to the expansion of repeated CAG trinucleotides [74]. The mutant ataxin 1 (ATXN1) protein, which has an enlarged polyglutamine, is overexpressed as a result of the mutation from expansion of repeated CAG trinucleotides. RAR-related orphan receptor alpha, which plays a key role in Purkinje cell activities, can be affected by mutant ataxin 1. Reduced RAR-related orphan receptor alpha gene expression has been linked to cerebellar hypoplasia and ataxia [75].

Majority of spinocerebellar ataxia are thought to be genetic disorders linked to ATXN mutations, however, different pathogenic pathways involving mitochondrial malfunction have been hypothesised [75]. Hakonen et al. [76] reported mitochondrial DNA depletion and respiratory complex I deficiency in the brain of infantile-onset spinocerebellar ataxia patients. Small concentration of ROS has been documented to be beneficial for cellular activities including cell signalling, nonetheless, higher concentration is dangerous to the brain being neurotoxic and have been established to cause neurodegeneration [49]. A study conducted by Stucki et al. have reported marked mitochondrial alterations and excessive accumulation of oxidative stress in the Purkinje cells of Spinocerebellar ataxia 1. It was suggested that there exists a connection between oxidative stress mediated mitochondrial impairments and the progression of spinocerebellar ataxia [75]. Similarly, the study evaluated the possible

neuroprotective roles of MitoQ (a mitochondrial antioxidant) in a spinocerebellar ataxia mouse model. The result revealed long-term treatment of MitoQ markedly improved mitochondrial morphology and enhanced its functions in Purkinje cells resulting in amelioration of spinocerebellar ataxia 1-related symptoms including motor incoordination [75]. This report demonstrated the neuroprotective potential of mitochondria-targeted antioxidants as a potential treatment for spinocerebellar ataxia 1.

Similar to previous neurodegenerative diseases discussed, pathogenesis of spinocerebellar ataxia is associated with mitochondrial dysfunction [77]. For instance, Friedreich ataxia, is characterised by the absence of frataxin, an iron transporter protein located on the mitochondrial inner membrane. Decrease in the level of frataxin, leads to increase in concentration of iron in the mitochondrial matrix, thus stimulating the Fenton reaction which convert of H_2O_2 to $^{\cdot}OH$. The highly reactive $^{\cdot}OH$ molecules can compromise the efficiency of energy production in neuron cells by causing oxidative damage to mitochondria [77]. Therefore, antioxidant supplementation, such as coenzyme Q10 and tocopherol, has been proven to increase energy production in many Friedreich ataxia patients by decreasing oxidative stress and restoring mitochondrial activity [78].

Because the brain contains so many mitochondria, mitochondrial malfunction can have a considerable deleterious impact on the nervous system. ROS are created spontaneously by the mitochondrial respiratory chain and are vital for sustaining mitochondrial function as well as brain cell resilience. However, there has been little study done to determine the potential involvement of ROS in spinocerebellar ataxia illnesses and establish optimum therapy options. More research is required to better understand the redox mechanisms driving various forms of spinocerebellar ataxias, with an emphasis on ROS-targeted therapy.

5. Role of oxidative stress in pathogenesis of Huntington's disease (HD)

Huntington's Disease, a neurological disorder is associated with unstable amplification of cytosine, adenine, and guanine (CAG) repeats in the HTT gene [79]. Development of CAG repeats within exon 1 of the huntingtin (HTT) gene results in a mutation that causes the polyglutamine tract to elongate, resulting in an HTT protein product that is prone to aggregation [79]. The mutant huntingtin (mHTT) aggregates are accrued throughout the brain of the affected persons, which can disturb transcription process and protein quality control. Those alterations are potentially responsible for the impaired cognitive functions and aberrant motor observed in HD are caused by mutant huntingtin aggregations and concomitant alterations om transcription process and protein quality control [79]. Currently available meditations for HD is palliative as it only inhibits the degree of severeness of symptoms. No meditation/remedy has effectively treated or markedly reversed or arrested the progression of the disease [79]. The mutant huntingtin has been demonstrated to suppress the expression of peroxisome proliferator-activated receptor-coactivator-1 and reduce the concentration of striatal mitochondrial [79, 80]. Similarly, mutant huntingtin has been documented as mutant of HD which has been implicated in the development of neuronal nuclear inclusion in HD as a result of excessive accumulation of cytoplasmic plaque [81]. Notwithstanding the well-proven connection between HD and OS, researches focused at providing treatment for the disease using antioxidant approach have not been successful [82].

A number of studies have documented that there exists link between irreversible neuronal damage and elevated oxidative markers [83]. The concentrations of well-established indicators of oxidative damage in HD such as neuron-specific enolase (NSE) and 8-hydroxy-2-deoxyguanosine (8-OHdG) have been monitored in one study to determine the benefits of neuro rehabilitation exercise [84]. Furthermore, Cu/Zn-SOD (SOD1) was documented as a possible peripheral indicator of neuronal oxidative damage, with levels considerably higher in HD patients compared to controls, implying a compensatory response to increasing oxidative levels in HD patients [84]. Nevertheless, consideration of SOD1 as an oxidative biomarker in HD remains undecided due to varied results obtained displaying different activity and concentration levels of SOD in HD [85]. After the end of the three weeks regimen neurorehabilitation exercise program, significant reduction in the levels of 8-OHdG and NSE were documented while SOD1 level remained high, indicating the possible neuroprotective role of SOD1 as an antioxidant enzyme mitigating against oxidative stress and scavenging free radicals [84]. Taken together, physical exercise was suggested for HD patients as it may possibly inhibit the disease progression and enhance redox homeostasis [86].

The consequence of HD on brain energy levels has stimulated researchers' interest. In HD patients, reduced glucose consumption and higher lactate levels have been observed, supporting the theory that HD reduces energy levels [81]. According to new researches, oxidative damage is connected to reduced expression of the glucose transporter (GLUT)-3, which consequences lead to lactate build-up and glucose uptake inhibition [87]. Most of ATP synthesis take place via the production of proton motive force through processes of the electron transport chain [88]. mHTT has been demonstrated to perform a crucial function in mitochondrial dysfunction. Panov et al. [89] used electron microscopy to detect that the interaction between mitochondrial membranes and the N-terminal of mHTT leads to mitochondrial calcium abnormalities. Furthermore, mHTT inhibits respiratory complex II in a direct manner [90]. This alteration of the mitochondrial electron transport could lead to over production ROS with concomitant reduction in production of ATP [90].

According to a new mechanism hypothesised in 2015 for mitochondrial damage in HD, oxidative stress could incapacitate glyceraldehyde-3-phosphate dehydrogenase catalytic activities. The incapacitated glyceraldehyde-3-phosphate dehydrogenase is linked with impaired mitochondria which serve as a signalling molecule to initiate the damaged mitochondria towards lysosome engulfment through selective degradation. However, in the existence of mHTT, incapacitate glyceraldehyde-3-phosphate dehydrogenase can react unusually with the long polyglutamine of mHTT at the mitochondrial outer membrane, which result in the inhibition of degradation pathway mediated by incapacitate glyceraldehyde-3-phosphate dehydrogenase. As a result, impaired mitochondria are unable to be engulfed by lysosomes resulting into excessive accumulation of mHTT-expressing cells, thus, facilitating cell death [91]. ROS and mitochondrial alterations can both encourage the positive feedback loops, exacerbating neuronal loss in the cortex and striatum and increases oxidative stress [79]. Excessive generation of ROS and mitochondrial alterations have been implicated in the pathogenesis of HD, however, the event that occurred first remain elusive [92].

3-nitrotyrosine, thiobarbituric acid reactive substances (TBARS), and protein carbonyls are some of the other oxidative biomarkers often used in HD models [93]. Likewise, elevated levels of F_2-isoprostane have been reported in the cerebrospinal fluid and brain tissue of Alzheimer's disease and HD patients. As a result, measuring F_2-isoprostane could be a useful way to assess the relevance of oxidative stress in HD

patients. It's worth noting that F_2-isoprostane levels between the HD and control groups may overlap in the early stages of HD development [94]. Thus, interpretation of modifications of oxidative biomarkers in HD should be done with caution due to involvement of oxidative stress in other pathological conditions such as ageing, cancer, and soon. Additionally, oxidative biomarkers alterations levels may not reveal adequate evidence on whether the oxidative alterations perform a significant role on the neuronal cell death or disease pathogenesis [94]. The use of more sensitive and specific indicators or biomarkers would be essential to give detailed information and elucidate the specific functions performed by free radical and oxidative stress in pathogenesis of neurodegenerative diseases, which will provide a mechanistic approach to finding a suitable drug candidate for the effective treatment of HD.

6. Role of oxidative stress in pathogenesis of amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis is a disease in which motor neurons in the anterior horn of the spinal cord gradually diminish [95]. Depending on whether there is a strongly outlined inherited genetic factor, amyotrophic lateral sclerosis is characterised as familial or sporadic. Sporadic amyotrophic lateral sclerosis usually appears between the ages of 50 and 60 [96]. Because the cause of sporadic amyotrophic lateral sclerosis is unknown, finding causal genes and environmental variables has been difficult. About 20% of instances of familial amyotrophic lateral sclerosis were caused by mutations in the SOD1 gene [97]. SOD1 has many activities, including posttranslational modification, energy consumption, controlling cellular respiration, and scavenging superoxide radicals ($O_2^{\bullet-}$) [98]. Despite the fact that SOD malfunction results in a loss of antioxidant capacity, research suggests that genetic ablation of SOD1 in mice does not result in neurodegenerative diseases [14]. In divergence, the gain-of-function of mutant SOD1 protein has been markedly documented in the motor neuron diseases [14]. For example, a study has exhibited that mutant SOD1 can altered the amino acid biosynthesis of cells in a yeast model and induced cellular destruction, responsible for the neural degeneration in amyotrophic lateral sclerosis [99].

Rac1 is directly regulated by SOD1 via endosome connection, which then activates Nox. Redoxosomes which as Nox-containing endosomes play an essential role in NF-kB-mediated regulation of proinflammatory signals. Nox converts molecular oxygen into $O_2^{\bullet-}$, which has vital functions in antibacterial activity, enzyme control, and cell signalling (Li et al., 2011). The ratio of reactive oxygen species to antioxidative molecules is balanced under normal physiological conditions. On the other hand, during pathological conditions, there is always rapid fluctuations in ROS levels and disturbances in antioxidant function, which result in elevated level of apoptosis, lipid peroxidation, and DNA damage during disease states [49]. SOD1 is an enzyme which convert $O_2^{\bullet-}$ into hydrogen peroxide (H_2O_2) and molecular oxygen. SOD1 mutants increase Nox2-dependent ROS generation, which is assumed to be the cause of motor neuron death in amyotrophic lateral sclerosis [100]. SOD1 that has been oxidised or misfolded has been found to cause mitochondrial dysfunction, which has been linked to the aetiology of sporadic amyotrophic lateral sclerosis [101].

Mutant SOD1 may enhance the progression of familial amyotrophic lateral sclerosis via the alterations of signal transduction pathways in motor neurons and in the activity of supportive glial cells [100]. SOD1, for instance, is regarded to be a key cell-signalling molecule with neuromodulatory functions. SOD1 is secreted via the microvesicular secretory pathway, according to studies *in vitro* and in transgenic mice

models. SOD1 secreted into the environment binds to muscanaric receptors on nearby neurons, increasing intracellular Ca^{2+} concentration and ERK/AKT signalling [102]. SOD1 preserves motor neuron integrity by activating ERK/AKT signalling, and it has been demonstrated that SOD1 secretion can be enhanced in neurons under oxidative stress conditions [103]. Propofol conditioning treatment was demonstrated to protect the spinal cord against ischemia–reperfusion injury in rats by boosting PI3K/AKT signalling, which could be mediated by enhanced SOD1 activity [104]. Furthermore, oxidative stress can cause neuron cell death by blocking the neuroprotective IGF-I/AKT pathway, implying that the role of AKT signalling in neurodegeneration should be investigated further [105].

In conclusion, over secretion of ROS in the brain leads to oxidative stress which if not suppressed or inhibited could lead to oxidative damage of essential components of the central nervous system. This can also initiate or enhance some reactions which may have detrimental effects on the physiological functions and health of the brain. These reactions such as neuroinflammation, progressive neuronal cell loss via apoptosis if not abated can exacerbate protein misfolding and formation of protein aggregates resulting into neurodegeneration and associated neurobehavioural incompetence. Considering the pivotal roles of oxidative stress, neuroinflammation, protein misfolding, and apoptosis in neurodegenerative diseases (**Figure 1**), the manipulation of these major players in each of the pathological mechanisms may represent a promising treatment option to slow down neurodegeneration and alleviate associated symptoms.

Author details

Johnson Olaleye Oladele[1,2*], Adenike T. Oladiji[1], Oluwaseun Titilope Oladele[3] and Oyedotun M. Oyeleke[2]

1 Department of Biochemistry, University of Ilorin, Ilorin, Nigeria

2 Biochemistry Unit, Department of Chemical Sciences, Kings University, Ode-Omu, Osun State, Nigeria

3 Phytomedicine and Molecular Toxicology Research Laboratories, Department of Biochemistry, Osun State University, Osogbo, Nigeria

*Address all correspondence to: oladelejohn2007@gmail.com

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