Free radicals in oxidative stress, aging, and neurodegenerative disorders

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University of Cape Coast
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Chapter 3
Free Radicals in Oxidative Stress, Aging, and Neurodegenerative Disorders

Robert Peter Biney
University of Cape Coast, Ghana

Thabisile Mpofana
University of KwaZulu-Natal, South Africa

Ella Anle Kasanga
University of North Texas Health Science Center, USA

ABSTRACT

Free radicals are intricately woven into the fabric of oxidative stress and are significant in the development of neurodegenerative disorders (NDs). This chapter examines free radicals in the context of neurodegeneration and provides overview of the multiple roles they play in the pathophysiology and clinical progression of varying NDs including Pick's disease (PiD), Parkinson's disease (PD), Alzheimer's disease (AD), prion diseases (PrD), traumatic brain injury, and aging. The molecular mechanisms of degeneration in Huntington's disease (HD) are also examined with respect to free radicals. Different antioxidant systems and their mechanisms of action are briefly reviewed in addition to the role of diet in aging. The effectiveness of selected synthetic drugs and natural products used in oxidative stress is also reviewed. Lastly, the chapter examines challenges associated with the use of antioxidants and how promising future directions like the endocannabinoid system is being pursued in the race to effectively manage NDs.

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INTRODUCTION

Since Moses Gomberg's first description of triphenylmethyl radical in literature in 1900, free radicals have remained an important subject of discussion owing to their numerous physiological effects (Gomberg, 1900). Initially they were not believed to be present in biological systems due its excessive reactivity. However, by the end of the second half of the 20th century, the scientific world had come to terms with the fact that free radicals are found in biological systems and contribute to several pathologies as well as aging (Lushchak, 2014). Today it is recognized that free radicals instigate oxidative stress and propagate neuronal injury thus playing a major role in NDs like AD, PD, amyotrophic disorders, PrD and several others (Khan et al., 2016). It is important to note that free radicals are not always deleterious such as the generation of nitric oxide in neurotransmission and the production of superoxide anion ($O_2^{\bullet}$) by activated microglia. There is a focus on free radicals in the central nervous system (CNS) and mechanisms involving free radicals in selected NDs. Free radicals are reviewed as potential targets of drug action in the management of NDs. Thus this chapter will evaluate what free radicals are and review their contribution to oxidative stress induced neurodegenerative disorders as well as aging. It is expected that at the end of this chapter further knowledge on the mechanisms of free-radical induced neurodegeneration in some NDs would have been gained in addition to an understanding of the prospects of novel therapeutic approaches. Overall, this chapter examines the interplay of free radicals and oxidative stress in the development and progression of several NDs.

BACKGROUND

Free radicals are exceptionally reactive atoms or molecules with one or more unpaired electrons and capable of independent existence (Halliwell, 1992). In some instances, free radicals have been used interchangeably with reactive oxygen species (ROS). While this may be correct sometimes, not all ROS are free radicals. Although both generate oxidative stress, ROS are chemically reactive species that contain oxygen and may or may not necessarily be a radical. For example, whereas hydrogen peroxide (H_2O_2) is a reactive oxygen species, it is not a free radical. Other examples include lipid, protein and nucleic acid peroxides. There are also reactive species that are not oxygen species such as reactive species of nitrogen (peroxynitrite ($ONOO^{\bullet}$) and nitric oxide ($^{\bullet}NO$)), carbon and sulfur.

However, the common denominator in all these terminologies is oxidative stress. Oxidative stress is a chemical process resulting from excessive free radical production due to an insufficiency of the counteracting antioxidant response system (Birben, Sahiner, Sackesen, Erzurum, & Kalayci, 2012). Free radicals and reactive species of oxygen or otherwise participate in chain reactions that culminate in oxidative stress. Normally in aerobic organisms, molecular oxygen is reduced to water via intermediate steps of oxygen reduction that forms $O_2^{\bullet}$, $H_2O_2$and the hydroxyl radical ($^{\bullet}OH$) (Halliwell & Gutteridge, 1990). Free radicals and other reactive species' production in the body is approximately balanced by antioxidant mechanisms needed to mop up these reactive species. However NDs as well as aging, the production of free radical is higher than antioxidant defense. Antioxidants are molecules which at minimal concentrations compared with that of an oxidizable substrate, appreciably slows or stops oxidation of that substrate (Halliwell & Gutteridge, 1990). These enzymatic or non-enzymatic antioxidants, reduce the potential damage of the reactive species thus only minor reactive species induced-damage occurs. Therefore, oxidative stress arises in the event of a significant disparity between the production of free

radicals and other ROS and antioxidants production (Halliwell, 2007). In other words, it is a disturbance in the oxidant–antioxidant balance in favor of oxidant mechanisms with a resulting potential tissue damage regarded as oxidative damage (Sies, 1997).

CENTRAL NERVOUS SYSTEM, FREE RADICALS AND NEURODEGENERATIVE DISORDERS

During normal physiological processes, the brain utilizes about 20% of the total oxygen in the body which leads to the generation of more free radicals than in any other tissue (Joshi & Praticò, 2014; Smith, Cappai, & Barnham, 2007). Reactive oxygen species (ROS) are important in numerous cellular and signaling pathways at physiological concentrations such as cell cycle regulation and enzyme activation (Dröge, 2002; Zorov, Juhaszova, & Sollott, 2014). When in excess, they are however scavenged by defense mechanisms which may be enzymatic and non-enzymatic antioxidants. Overproduction of ROS leads to generation of oxidative stress, which has been shown to cause several harmful effects including Deoxyribonucleic acid (DNA), lipid and protein damage (Ohta, Yashiro, Ohashi, & Imai, 2012). Oxidative stress remains a major feature contributing to cerebral biochemical impairment seen in some NDs (Huang, Zhang, & Chen, 2016).

The brain, in comparison to other body organs, has been shown to be predominantly exposed to oxidative damage. This is due to its high metabolic rate, due to a highly active mitochondria metabolism. Additionally, the brain vulnerability to oxidative damage is because a huge proportion of it is made of lipids (Birben et al., 2012. Also, another important factor is the fact that the brain contains low antioxidant defense mechanisms (Birben et al., 2012). Furthermore, neurons have a longer life span than other cells and so are exposed to accumulated oxidative damage over time (Magrassi, Leto, & Rossi, 2013). These among others make the neurodegeneration due to oxidative damage more significant in the brain and spinal cord.

Neurodegeneration is characterized by the progressive loss of specific neuronal cells with an accompanying protein aggregation leading to disorders such as AD, PD and amyotrophic lateral sclerosis (ALS). The genesis of these disorders is attributed to a myriad of factors which are yet not completely understood (Khan et al., 2016). Among these factors include: a genetic basis and familial inheritance, exposure to environmental risk factors, altered immune and inflammatory responses, idiopathic protein aggregation, ageing and of course, the ubiquitous oxidative stress, and its attendant damage (Khan et al., 2016).

Another conceivable mechanism of oxidative stress-induced pathology implicates a dysfunction of ROS-mediated cell-cell communication. Excessive $O_2^{\bullet}$, $OH^{\bullet}$ production by NADPH oxidases (NOXs) and the free radical peroxynitrite ($ONOO^-$) by nitric oxide synthase cause massive cell damage through endoplasmic reticulum (ER) stress, impaired calcium handling, and nitration of tyrosine residue of several proteins. NOX is a multi-subunit enzyme which is composed of membrane and cytosolic components including NOX (NOX1-5) and phox subunits. NADPH produces $O_2^{\bullet}$ by transporting an electron from NADPH to oxygen (Ma et al., 2017). The enzyme has been implicated in diverse roles including host defense and cellular signaling (Panday, Sahoo, Osorio, & Batra, 2015). This cell damage perturbs the structure of proteins and alters the catalytic action of enzymes thus, impairing cell signaling pathways which depends on such proteins and enzymes. Additionally, several cell signaling cascades require ROS

as messengers therefore a constant rise in concentrations of ROS can cause an over-activation of such pathways, with several damaging consequences (Freixes, Rodríguez, Dalfó, & Ferrer, 2006).

The high oxygen demands of the brain yet with limited defense strategies against oxidative stress increases its susceptibility to oxidative damage and makes oxidative damage a significant causative effect of neurodegeneration. Evidence to this is led by the several observations of markers of oxidative damage in the brain, spinal fluid and plasma of AD (Arlt, Beisiegel, & Kontush, 2002; Butterfield, Castegna, Lauderback, & Drake, 2002; Selley, Close, & Stern, 2002), PD (Dexter et al., 1989) and ALS (Pedersen et al., 1998; Sayre, Smith, & Perry, 2001) patients. Additionally, DNA damage due to oxidative stress is observed as DNA nitration and hydroxylation in AD brains and increased 8-hydroxy-2-deoxyguanosine and 8-hydroxyguanine levels in PD brains (Alam et al., 1997; Gabbita, Lovell, & Markesbery, 1998). Furthermore, the brain is rich in oxidizable catecholamines such as noradrenaline and dopamine that can undergo auto-oxidation to generate free radicals in the presence of metal ions and propagate neuronal damage (Gerlach, Ben-Shachar, Riederer, & Youdim, 1994; Halliwell & Gutteridge, 1990).

Antioxidant Response System and Biomarkers of Oxidative Stress

The antioxidant defense system is an endogenous enzymatic and non-enzymatic system in place to protect the body from oxidative damage (Ohta et al., 2012). It comprises of enzymatic (superoxide dismutase, glutathione peroxidase and catalase) and non-enzymatic low molecular weight reductants (glutathione, α-tocopherol, and ascorbic acid). The antioxidant defense system prevents free radical mediated damage of cells by converting the overproduced free radicals to non-destructive cellular molecules. Astrocytes also important in maintaining high intracellular concentrations of some antioxidants, making them resistant to oxidative damage by elevating expression of some antioxidant enzymes; increasing glucose metabolism and transport; increasing manufacturing of glutathione; and salvaging ascorbic acid (Cabezas et al., 2014). Ascorbic acid is very important for sustaining oxidative balance as it acts a cofactor for antioxidant enzymes. Studies have shown that ascorbic acid deficiency plays acute role in oxidative damage seen in AD and normal aging (Dixit et al., 2015). Glutathione (GSH) is the main brain antioxidant molecule (Johnson *et al*., 2012). A progressive diminution of GSH concentration during aging as well as age-associated diseases like has been suggested is some studies (Carvalho, Lim, Nijland, Witte, & Van Horssen, 2014; Johnson, Wilson-Delfosse, & Mieyal, 2012). GSH protects neurons from oxidative damage, primarily by serving as a redox regulator and hence crucial for the detoxification of ROS in neurons (Johnson et al., 2012).

Several markers of oxidative stress have been measured in peripheral blood; these include lipid peroxides, GSH, ascorbic acid and α-tocopherol (Sinclair et al., 1998). Lipid peroxidation is a central feature of oxidative stress (Lushchak, 2014). Oxidative stress-mediated membrane lipids peroxidation is detrimental as it results in modifications in the biological properties of the membrane i.e.the magnitude of membrane fluidity (Lushchak, 2014). This leads to inactivation of membrane-bound receptors and that may ruin cellular functioning and disrupt tissue permeability. Products of lipid peroxidation such as malondialdehyde (MDA), have been used as possible markers of oxidative stress (Sultana et al., 2013).

Measurement of the plasma antioxidants provides an indication of the level of oxidative stress and is routinely used as biomarker of oxidative stress in NDs. This was shown by previous studies that demonstrated a decrease in peripheral levels of retinol, ascorbic acid and α- tocopherol along as well as a diminished activity of SOD and glutathione peroxidase in AD patients (Sinclair et al., 1998; Ferreira

et al., 2015). Other works also correlated the increase in oxidative stress with a decreased GSH activity (Sinclair et al., 1998).

Role of Diet in Oxidative Stress and Neurodegeneration

Diet may play a huge role in providing supplementary antioxidants. A typical meal possibly contains several naturally occurring antioxidant molecules (Bayram et al., 2012). These antioxidant compounds are found in different concentrations in vegetables, legumes, fruits, cereals, olive oil, wine, cocoa, and tea (Bayram et al., 2012; Coelho, Hermsdorff, & Bressan, 2013). Studies have shown that an antioxidant-rich diet potentially averts oxidative damage and cognitive decline due to its free radical or active oxygen scavenging properties (Coelho, Hermsdorff, & Bressan, 2013). This has led to a great need to search for nontoxic active ingredients of natural resources that could reverse the biochemical imbalances that occur in NDs.

Oxidative Stress-Induced Mitochondrial Dysfunction in Neurodegeneration

In the brain, the primary sites of ROS generation include mitochondria in the neurons and glia. The production of free radicals in these areas is exacerbated in disorders like PD due to inflammation, dopamine degradation, mitochondrial dysfunction, aging, GSH depletion, and high levels of iron (Dias, Junn, & Mouradian, 2013). Mitochondrial dysfunction, increased apoptosis together with low antioxidant levels are also evident in the development of AD (Birben et al., 2012). In addition, neurodegeneration-induced ROS causes damage in key cellular proteins and disrupt lipid membranes thus promoting oxidative stress (Dias et al., 2013; Birben et al., 2012). Mitochondrial dysfunction leads to increased free radical production in the respiratory chain (Dias et al., 2013; Huang et al., 2016). Particularly, mitochondrial complex I deficiency has been identified to be strongly associated with PD. Indeed, a large amount of the unfavorable neural apoptosis observed in PD can be attributed to the complex I defect (Huang et al., 2016).

Aging and Oxidative Stress

Aging has been shown to be a major risk factor for ND (Moll, El-Ami & Cohen, 2014; Bickford, Flowers & Grimmig, 2017). Aging is a complex phenomenon that results in reduced organ functioning, decline in cognition and overall decline in the organism's homeostasis. As stated already, the brain is prone to oxidative stress however an aging brain is highly susceptible to a greater extent as a result of a loss of resilience associated with aging (Bickford et al., 2017). This leads to a decreased resistance to various forms of stress as well as an increased susceptibility to oxidative stress and thus several diseases. Even though, aging is poorly understood, one of the most widely accepted theories is the 'Free Radical Theory' which attributes aging to the deleterious effects of free radicals on cell components (Harman, 1956).

The environment of the aged brain has been associated with two main biological processes; oxidative stress and inflammation with microglia being one of the major cell types implicated in both processes (Bickford et al., 2017). In the healthy, young brain, microglia (known as the resident tissue macrophages in the CNS) perform housekeeping duties and constantly assess the microenvironment thereby effectively protecting the CNS from invading pathogens amid other attacks (Koellhoffer, McCullough & Ritzel, 2017). Thus, microglia in the CNS induce an innate immune response and once activated can perform several functions including phagocytosis (Fenn, Henry, Huang, Dugan & Godbout, 2012). It

has been shown that there is an increase in reactive microglia in aged brains with an associated increase in inflammatory markers (Fenn et al., 2012). Aged microglia is also identified in the pathophysiology of Traumatic Brain Injury, AD, and worsening outcomes in stroke (Koellhoffer et al., 2017).

Some agents with anti-oxidant activity such as polyphenols have been shown to be potent modulators of neuroinflammation. This effect may be due to the stimulation of the transcription factor, nuclear factor erythroid related factor 2 (Nrf2)-antioxidant response element (ARE) pathway thereby reducing the production of pro-inflammatory cytokines and modulating glial function (Bickford et al., 2017). The Nrf2-ARE pathway is very vital for the proper functioning of microglia. Polyphenols may therefore be very important in neuroprotection as shown by a study by Bickford et al., 2017 where NT-020, a polyphenolic rich mixture, was able to improve the aging environment as well as cognition with minimal side effects. In fact, when NT-020 was administered to aged human participants (65-85 years) for two months, it was noted that there was an increase in processing speed (according to memory tests) suggesting the important role that antioxidants play in neurodegeneration (Bickford et al., 2017).

MOLECULAR MECHANISMS OF FREE RADICAL-INDUCED DEGENERATION IN NEURODEGENERATIVE DISORDERS

Alzheimer's Disease and Other Dementias

Dementia is a syndrome caused by several disorders which negatively influence cerebral structures and functions, to cause deterioration of memory functions and behavior (Sosa-Ortiz, Acosta-Castillo, & Prince, 2012). Most common causes of dementia include AD, frontotemporal lobar degeneration (FTLD), vascular dementia, Creutzfeldt-Jakob disease (CJD), PD, and Lewy Body dementia (LBD). There is a very strong association age with the prevalence of dementia, so there is an expected increase in the number of people living with dementia as the aging population increases (Sosa-Ortiz et al., 2012).

AD is a very common ND which affect around 16 million of the elderly population worldwide and is the leading cause of dementia (Butterfield & Boyd-Kimball, 2004). It accounts for 60-80% of dementia in the elderly population (Sosa-Ortiz et al., 2012; Huang et al., 2016). AD is characterized by neurofibrillary tangles composed of hyperphosphorylated tau protein and amyloid-beta (Aβ)-containing plaques in addition to cognitive impairment and progressive neurodegeneration. The neocortex and hippocampus are the main affected brain areas. AD symptoms usually start with minor amnesic episodes and progress toward a vivid change in personality (Sosa-Ortiz et al., 2012). The etiology of AD is multifaceted including major environmental and genetic risk factors (Huang et al., 2016). Increased lipid peroxidation and inadequate antioxidants were shown in the peripheral tissues of AD patients. Similar to most NDs, the specific biochemical mechanism of the pathogenesis of AD remains unknown although evidence suggests a massive loss of acetylcholine and a possible role of oxidative stress (Butterfield et al., 2001). Oxidative damage plays an important part in Aβ deposition in AD. Lushchak (2014) reviews complex relationships between excitotoxicity and Aβ deposition, as well as production of ROS in AD.

FTLD, example PiD, are diseases which degeneration primarily affect the frontal (front) and temporal (side) regions of the brain (Diehl et al., 2004). PiD is characterized by the presence of abnormal bodies also known as Pick's bodies in affected neurons (Rademakers, Neumann, & Mackenzie, 2012). Though the symptoms appear similar to those seen in AD, PiD is unique in that it progresses very rap-

idly. Symptoms include inability to recognize people as well as deterioration of skilled movement and language abilities, (Mendez & Shapira, 2011).

Lewy Body dementia (LBD) is characterized by the deposition of abnormal proteins called Lewy bodies in affected brain regions (Diehl et al., 2004). Dementia with Lewy bodies and Parkinson's disease dementia (Lewy body dementia), are ranked second among the commonest types of degenerative dementia in patients older than 65 years (Gomperts et al., 2012). LBD patients present with symptoms similar to AD. During early stages, symptoms of LBD may be mild but ultimately result in significant impairment of cognitive function (Postuma, Gagnon, Pelletier, & Montplaisir, 2013).

Motor Neuron Disorders

Motor neuron disorders (MND) are group of progressive conditions in which lower and upper motor neurons degenerate and result in decreasing strength in limb, abdominal, thoracic and bulbar muscles without affecting oculomotor and sphincter muscles (Wijesekera & Leigh, 2009). The term generically applies to a complete spectrum of the diseases including progressive bulbar palsy, amyotrophic lateral sclerosis (ALS) and progressive muscular atrophy and of which ALS is the most common and devastating. It is characterized by progressive injury and cell death of motor neurons in the motor cortex, brain stem and spinal cord. This results in the progressive muscle weakness, wasting upper and lower motor neurons with pathologically brisk reflexes of the limb and bulbar muscles (Bäumer, Talbot, & Turner, 2014; Leigh & Ray-Chaudhuri, 1994). It is now recognized that extra motor parts of the CNS are also involved in MND and thus MND can be regarded as a multisystem disease whereby motor neurons are affected quickest and harshest (Wijesekera & Leigh, 2009).

The disorders occur in about one to two individuals per 100 000 and predominantly in middle aged and elderly patients (Shaw, 1999). Men have a relatively higher prevalence of the disease than women (1.5:1) although this seems to be turning towards a balanced prevalence in recent years (Logroscino et al., 2008). In most instances, onset is sporadic (90%) while heredity has also been reported (10%). MND patients have dire prognoses with median survival of approximately 3.5 years after onset of symptoms as a result of death due to paralysis of respiratory muscles (Leigh & Ray-Chaudhuri, 1994; Shaw, 1999).

Several hypotheses have been postulated as to the pathophysiology of MND including genetic predisposition, increased glutamatergic excitotoxicity, failure of axonal transport, mitochondrial dysfunction and oxidative stress (Turner et al., 2013).

Free Radicals and Oxidative Stress in Motor Neuron Disorders

Free radical-instigated oxidative stress is a significant portion of the already understood aspects of the pathophysiology of MND. Although familial MND is not fully understood, several point mutations in chromosome 21 gene product coding for the enzyme, copper-zinc superoxide dismutase (*SOD 1*), is responsible for 20% in different pedigrees of familial cases and 2% of all cases of MND (Rosen et al., 1993; Shaw, 1999). This ubiquitous antioxidant enzyme converts the superoxide free radical into less harmful hydrogen peroxide (H_2O_2) before it is taken care of by other antioxidant enzymes. Evidence suggest that the mutant enzyme exerts its damaging by an abnormal handling of hydrogen peroxide and peroxynitrite which cases elevated production of hydroxyl radicals and nitrotyrosine residues (Carrì, Valle, Bozzo, & Cozzolino, 2015; Cookson & Shaw, 1999; Shaw, 1999; Shibata, Hirano, Yamamoto, Kato, & Kobayashi, 2000). The mutated Cu/Zn SOD may also form neurotoxic intracellular aggregates

or release cytosolic Cu or Zn which then becomes neurotoxic (Shaw, 1999). The increased expression of Cu/Zn SOD in both axons and cell bodies of motor neurons in comparison to all other cells of the nervous system increases their susceptibility to damage by such genetic alterations. In addition, alterations in apurinic/apyramidinic (AP) endonuclease, an important enzyme for repairing oxidative damage to DNA and forming abasic sites, is also associated with ALS (Olkowski, 1998). Other genes have also been identified that increase the susceptibility to MND to various degrees aside SOD and AP endonuclease.

Neuronal injury instigated by free radicals is a key cause of several age-related neurodegenerative diseases because the effects of oxidative stress in neurons, which naturally are non-replicating, is cumulative. Given the effects of mutations in antioxidant enzyme SOD on the development of certain familial ALS, interest in free radicals and for that matter oxidative stress in MND has been high for a long time. Cultured fibroblasts of skin samples of both familial and sporadic motor neuron patients indicate an amplified sensitivity to oxidative insults (Aguirre et al., 1998; Wijesekera & Leigh, 2009). Also, post-mortem results points towards a change in expression of parts of the intracellular antioxidant defense mechanism. This has been recorded in ALS patients and signifies an attempted compensatory response to the increased oxidative stress (Shaw, Chinnery, Thagesen, Borthwick, & Ince, 1997).

The evidence to support an involvement of an aberrant oxidative damage management is also due to the observation that antioxidant molecule vitamin E exhibits beneficial effects in Cu/Zn *SOD1* mutated transgenics by delaying the onset of MND. Ghadge and colleagues (Ghadge et al., 1997) report that free radicals especially O_2^- are implicated in the mutant SOD-mediated cell death, owing to the fact that SOD and glutathione mimetics reversed this mortality. Their data also show that expression of mutant SOD escalates the vulnerability to oxidative stress and increases rate of accumulation of O_2^-. Cell death regulatory protein B-cell lymphoma 2 (BCl-2), which affects free radical production and for that matter cell survival, also protects the cells against mutant SOD-induced apoptosis (Hockenbery, Oltvai, Yin, Milliman, & Korsmeyer, 1993). These seem to explain an important involvement of free radicals and oxidative stress in ALS and MND in general.

Nonetheless, clinical trials involving potent antioxidant n-acetylcysteine showed non-significant correlates suggesting that the situation is not completely clear.

Huntington's Disease

HD is a devastating autosomal dominant ND with abnormal trinucleotide (CAG) expansion in the *huntingtin* (*HTT*) gene (Velusamy et al., 2017) which is characterized by impaired cognition, movement and psychiatric disorders (Ma et al., 2017). Usually, healthy individuals have 5-6 CAG repeats in exon 1 of the *HTT* gene but affected individuals have more than 36 repeats (Manoharan et al., 2016). The associated neuronal death has been attributed to the accumulation of mutant Huntingtin proteins as there is abnormal folding and protein function (Velusamy et al., 2017).

Oxidative stress is hypothesized as significant mechanism in the progression of this disorder with several studies confirming this hypothesis. For instance, the activity of the mitochondrial complexes II, III and IV have been found to be reduced in the striatum of HD patients' post-mortem (Lee, Gold, & Linker, 2012). It has been shown that in HD patients, there is elevation of biomarkers for oxidative stress such as malondialdehyde in the striatum, cortex and serum. The expansion of the CAG triplets has been shown to induce oxidative stress which causes damage to the cell membrane, DNA and other enzymes involved in adenosine triphosphate (ATP) production (Velusamy et al., 2017). This mitochondrial damage therefore provides a strong mechanism for initiating apoptosis in HD brains (Velusamy et al., 2017).

This is because under oxidative stress, there is the activation of glutamate receptors which leads to an increase in the influx of calcium ions. This increase leads to the translocation of proapoptotic Bcl-2 proteins to the mitochondrial membrane as well as the activation of caspase 8 thus initiating apoptosis (Bansal & Singh, 2017). Manoharan et al. (2016) hypothesized that, the causes of oxidative stress in HD include imbalance in oxidant-antioxidant status, higher lipid concentration and high energy requirement as well as poor antioxidant status. This has been supported by a reduced superoxide dismutase activity in the cortex and cerebellum in HD patients (Ma et al., 2017).

NADPH oxidase (NOX2) enzyme has been proposed to be involved in the increase in ROS in the progression of HD. For instance, elevated ROS levels in PC12 cells expressing huntingtin proteins are lowered by treatment with NOX inhibitors (Valencia et al., 2012). Again, higher levels of NOX activity was found in the brain of HD patients as compared to controls (Valencia et al., 2012).

Elevated 4-hydroxy-2-nonenal (4-HNE) adducts levels have been found in both clinical and preclinical models of HD (striatum of both human and mice HD brains) (Lee et al., 2011). Thus, 4-HNE is proposed to be a relevant marker for determining oxidative damage in HD. Data from this study revealed that 4-HNE immunoreactivity was co-localized with mutant huntingtin (mtHtt) inclusions in the striatal neurons of R6/2 HD mice suggesting the importance of 4-HNE as a possible target for therapeutic intervention (Lee et al., 2011).

Parkinson's Disease

PD is a ND which affects over 10 million people above the age of 65 worldwide (Schneider & Obeso, 2014). In PD there is degeneration of dopaminergic neurons in the substantia nigra pas compacta of the basal ganglia which control motor functions. PD exhibits both motor and non-motor symptoms including resting rigidity and postural instability, tremor, bradykinesia, and akinesia (Schneider & Obeso, 2014). Non-motor symptoms observed in PD include cognitive, mood, autonomic and sleep disturbances (Schneider & Obeso, 2014). James Parkinson and Charcot among others had reported several non-motor symptoms in their classic literature that include delusion, pain, fatigue, dysfunction of the bladder and cognitive deterioration (Garcia-Ruiz, Chaudhuri, & Martinez-Martin, 2014).

The etiology of PD remains unclear, but oxidative stress has been considered as one of the major pathophysiological mechanisms involved (Dias et al, 2013). The main mechanism identified leading to oxidative stress in PD include the dopamine oxidation which produces toxic semiquinones. Secondly, the enhanced catabolism of dopamine by monoamine oxidase B (MAO-B) may instigate increased production of hydrogen peroxide, superoxide anions, and-hydroxyl radicals and the accumulation of alpha-synuclein aggregates (Hwang, 2013). These free radicals reduce the activity of mitochondrial complex I, this in turn contributes to the production of more reactive oxygen species which leads to apoptotic cell death (Dias et al, 2013; Blesa et al., 2015).

Prion's Disease

PrD also referred to collectively as transmissible spongiform encephalopathies (TSEs) are uncommon fatal NDs that are acquired either by direct transmission, inheritance of dominant prion protein gene mutations and in about 85% of cases through idiopathic sporadic causes (Brown, 2005; Prusiner, 1991). A prion is a novel pathogenic particle made up of a self-propagating misfolded protein with an abnormal conformation (Sarnataro, Pepe, & Zurzolo, 2017). It is a cell surface glycosylphosphatidylinositol (GPI)-

anchored glycoprotein expressed by neurons, glial cells and several other cells in the body. Human TSEs include: CJD), Gerstmann-Sträussler-Scheinker (GSS) syndrome, kuru and fatal familial insomnia. TSEs are characterized by neuroamyloid formation and dementia and neuropathological changes including spongiform degeneration in the brain (Brown, 2005; Wong, Wang, Brown, & Jones, 1999).

CJD is an unusual but deadly disorder that causes swift-developing and progressive (Iwasaki, Mori, & Ito, 2012). CJD is caused by the transmissible proteinaceous infectious particle called "prion". This pathogen consists of a protein which transforms normal protein molecules into infectious molecules. CJD signs include rapidly declining memory, behavioral changes and ataxia (Iwasaki et al., 2012).

Similar to several NDs, the footprints of oxidative damage are readily identified throughout the brain of the affected patients (Brown, 2005; Elmallah, Borgmeyer, Betzel, & Redecke, 2013; Pamplona et al., 2008; Yun, Gerlach, Riederer, & Klein, 2006).

Methionine Oxidation of Prion Protein

The succinct underlying mechanisms in TSEs are unclear; however the footprints of oxidative stress exist in the aspect of pathophysiology of the disease that is understood. The chief event in the pathophysiology of TSEs is post-translational alteration of normal cellular prion protein (PrP^{C}) into an abnormal infectious and misfolded isoform known as scrapie (PrP^{Sc}) (Elmallah et al., 2013). Scrapie is protease resistance and can be passed between individuals (Brown, 2005; Elmallah et al., 2013). In sporadic TSEs, PrP^{C} is converted to the abnormal misfolded infectious isoform (scrapie) via a mechanism triggered by methionine oxidation (Elmallah et al., 2013; Younan, Nadal, Davies, Brown, & Viles, 2012).

Human PrP^{C} is soluble and has significant susceptibility to proteinase K (PK) digestion whereas PrP^{Sc} is an insoluble aggregated protein multimer with an enhanced PK resistance (Brown, 20050. Proteins with cysteine and methionine residues are the most vulnerable to oxidation by free radicals. This makes the mammalian PrP^{C} exceptionally prone to oxidation as a result of its high number of Met residues (Canello et al., 2008). Met-sulfoxide, the product of methionine oxidation, is often identified in brain deposited PrP^{Sc} isoforms and is deemed to be a specific marker for pathogenic prion proteins (Canello et al., 2008). Little alterations PrP polypeptide can initiate a misfolding cascade of PrP^{C} into scrapie. Methionine oxidation into methionine sulfoxide is a trigger that begins a series of events leading to PrP misfolding. In TSEs methionine oxidation is seen as the initial trigger signal in the conversion of PrP^{C} into scrapie and formation of toxic species—the main pathophysiology of sporadic TSEs. Oxidation of methionine within PrPC disturbs its hydrophobic core and leads to the formation of monomeric molton-like species with high aggregation capabilities (Colombo, Meli, Morra, Gabizon, & Gasset, 2009)

Loss of Antioxidant Defense in Transmissible Spongiform Encephalopathies

Oxidative damage accounts for a majority of the prion diseases which arises sporadically (Elmallah et al., 2013). Markers of oxidative stress are even observed in early preclinical stages of scrapie infection (Yun et al., 2006). In prion diseases, there is a significant loss of antioxidant defense. As PrP^{Sc} accumulates in the brain, an increase in oxidative damage end-products and a reduction in antioxidant defense is observed. Conversion of the normal cellular prion protein which has antioxidant properties to its protease resistant isoform leads to a loss of this antioxidant activity. This process is facilitated by oxidation of methionine by H_2O_2 to methionine sulphoxide (Younan et al., 2012).

There is now a preponderance of evidence that suggests that normal cellular prion protein (PrP^C) is associated with cellular response to oxidative stress and that oxidative, glycoxidative, lipoxidative and nitrative protein damage to it is observed in PrD (Brazier, Doctrow, Masters, & Collins, 2008; Brown, Schmidt, & Kretzschmar, 1998; Freixes et al., 2006; Pamplona et al., 2008; Wong et al., 1999). PrP^C itself exerts anti-oxidant properties by undergoing β-cleavage (cleavage of copper-binding octapeptide repeats in PrP^C by reactive oxygen species) to protect the cell from damage from free radicals (Wong et al., 1999). Therefore β-cleavage of PrP^C is an important step in the mechanisms by which PrP defends cells from oxidative stress (Watt et al., 2005). Antioxidant capacity of purified prion protein diminishes by up to 85% in the most common human prion disease, sporadic CJD (sCJD), and correlates to elevated of markers oxidative stress in the brains of sCJD patients. Cultured astrocytes and neurons from PrP^C-deficient mice are very vulnerable to oxidative damage (Brown, Schulz-Schaeffer, Schmidt, & Kretzschmar, 1997). Immunohistochemical studies of brain tissues of prion-infected mice indicate an extensive increase in neuronal markers for lipid oxidation and other neuronal oxidative stress indicators such heme oxygenase-1 and nitrotyrosine (Guentchev, Voigtländer, Haberler, Groschup, & Budka, 2000). This supports the assertion that, ROS-mediated neuronal damage is present in the neurodegeneration observed in TSEs (Rizzardini et al., 1997; Wong et al., 2001).

The exposure to neurotoxic peptide derivatives of prion protein induced elevation of oxidative stress markers cultured astrocytes (Rizzardini et al., 1997). In a human TSE experiment, nitrotyrosine positive neurons were found throughout the brain signifying that the occurrence of oxidative stress is widespread in TSEs and also affects most neurons in the CNS (Guentchev, Groschup, Kordek, Liberski, & Budka, 1998). Free radicals-instigated oxidative stress is linked to iron accumulation and both total iron and Fe^{3+} are substantially elevated in the cerebral cortex, striatum, and brainstem of PrP^{Sc} -infected mice in a scrapie model in addition to elevated malondialdehyde concentrations (Kim et al., 2000), thus implicating free radicals in TSEs.

Even though the *in vivo* function of normal prion protein still remains unknown (Sarnataro et al., 2017), it is now accepted that normal (PrP^C) has SOD-like activity when bound to Copper ions (Cu^{2+}) and thus may even be a marker of brain oxidative stress as it has significant antioxidant activity (Brown et al., 1999; Milhavet & Lehmann, 2002). That is why oxidative stress, due to impaired Cu^{2+} homeostasis may be a risk factor in the development of sporadic prion diseases (Requena et al., 2001). The conversion of PrP^C to PrP^{Sc} leads to a loss of this SOD-like activity and an accumulation of products of oxidative damage. PrP^C knock-out mice also show diminutive SOD activity (Brown, Schmidt, & Kretzschmar, 1997). These evidences augment the suggestion that oxidative stress is a significant contributor of neurodegeneration in prion diseases.

Spinal Muscular Atrophy

Spinal muscular atrophy (SMA) is a common neuromuscular disorder characterized by muscle weakness and paralysis. It is caused by a deficiency in the survival of the neuron gene (*SMN1*) that leads to a reduction in the levels of functional SMN proteins (Wan, Ottinger, Cho, & Dreyfuss, 2008). The SMN complex consists of SMN and other proteins called Germins (Wan et al., 2008; Zhang et al., 2008) required for the biosynthesis of small nuclear ribonucleoprotein particles (SnRNPs) (Fischer, Liu, & Dreyfuss, 1997; Yong, Wan, & Dreyfuss, 2004). SnRNPs play essential roles in processing pre-mRNA to mRNA (Yong et al., 2004). Even though the disease has been mainly classified as a motor neuron

disease, the SMN complex plays a key role in splicing regulation and thus making SMA splicing disease (Zhang et al., 2008).

ROS have been shown to inhibit the SMN complex (Wan et al., 2008). β-lapachone, a potent producer of ROS, along with other agents such as hydrogen peroxide, cumene hydroperoxide and environmental toxins which produce free radicals inhibit the effects of the SMN complex. This inhibition was shown to be dose dependent and the effect of the inhibition was shown to be of a functional deficiency equivalent to what happens in SMN protein deficiency. Thus, the SMN complex is very vulnerable to ROS (Wan et al., 2008).

Even though the direct role of mitochondria in the pathogenesis of SMA has not been fully elucidated, it has been shown in pre-clinical studies that, free radicals generation increases after SMN knockdown (Acsadi et al., 2009). SMN small interfering Ribonucleic acid (siRNA) transfection led to an increase in free radical production as compared to control at both 48 h and 72 h after SMN knockdown. This increase in free radicals may lead to mitochondrial DNA mutations and deletions (Acsadi et al., 2009). It was also realized that changes in mitochondrial function (which were observed as activity of caspase-3 and ATP levels) were observed before cell injury after SMN knockdown (Acsadi et al., 2009).

Traumatic Brain Injury

Traumatic brain injury (TBI) has been shown to be a major cause of death in young adults with one of its major causes being road traffic accidents (Ma et al., 2017). It has been projected by the World Health Organization that by 2020, road traffic accidents will be the third leading cause of death and disability worldwide (Finfer & Cohen, 2001) suggesting the concurrent increase in the incidence of TBI which will occur. However, in countries where there are low incidences of road traffic accidents due to safer roads and strict traffic regulations, TBIs are still reported due to falls (in the elderly) and violence suggesting that safer roads are not the only way to combat TBI (Maas, Stocchetti, & Bullock, 2008).

TBI refers to brain damage from a mechanical force (Choi et al., 2012; Maas et al., 2008) which can occur with or without loss of consciousness. Even though, some of the earlier manifestations of TBI have been managed effectively (thereby improving survival rate), most patients suffer from delayed neuronal death and cognitive impairment (Choi et al., 2012).

The initial damage from TBI is as a result of the mechanical injury which occurs at the time of impact; however secondary changes also develop later (Zhang et al., 2012). The initial injury results in skull fracture, cerebral contusions and epidural or subdural hematomas (Chakraborty, Skolnick, & Narayan, 2016). It has been shown that oxidative stress is important in the development of cerebral edema which is associated with TBI, the disruption of the blood brain barrier (BBB) and the resulting neuronal damage which occurs post-TBI (Ma et al., 2017). O_2^-, produced when an oxygen molecule obtains an electron from another molecule is the most common cellular free radical and the source of other ROS that leads to lipid peroxidation (Dohi et al., 2010). Excess O_2^-, causes tissue damage primarily through the formation of hydroxyl radical and peroxynitrite (Zhang et al., 2012). The reaction to form peroxynitrite is a diffusion-limited reaction with no requirements for enzymes. Both the $^{\bullet}OH$ and $ONOO^{\bullet}$ are powerful oxidants but with different biological implications as the hydroxyl radical is more promiscuous than the peroxynitrite in terms of substrate specificity (Pacher, Beckman, & Liaudet, 2007). These ROS can cause DNA damage and lipid peroxidation which could lead to inflammation in nearby tissues thus promoting apoptosis (Chakraborty et al., 2016). These reactive species can also oxidize polyunsaturated fatty acids in the cell membrane which leads to the formation of various reactive molecules including

HNE. HNE is very reactive and an increase in its levels is used as a specific marker of oxidative stress (Romano et al., 2017).

The mitochondria have been known to be the major source of superoxide anion after brain injury, however it has been recently shown that NOX also plays a role. NOX usually refers to the NOX2 isoform which was characterized first. NOX2 has been shown to be highly co-localized in neurons at 1 h after TBI suggesting its significance in this disorder (Zhang et al., 2012). NOX2 has been shown to be localized in the cerebral cortex and hippocampal CA1 region and its activation has been shown to be dependent upon formation of an active complex with several phox subunits (p47phox, p67phox, p40phox) and activated Rac1, which activated and translocated to the cytoplasm from the membrane to form an active enzyme complex (Zhang et al., 2012). NOX2 has also been found to be localized in microglia and hence can contribute to neuroinflammation (Zhang et al., 2012).

FREE RADICALS AND OXIDATIVE STRESS AS TARGETS OF DRUG THERAPY IN NEURODEGENERATIVE DISORDERS

Mechanism of Synthetic Drugs and Natural Products in Reducing Free Radicals and Combating Oxidative Stress

Neurodegenerative disorders are different in their manifestations but a single common underlying factor is the induction of oxidative stress by free radicals. Different therapies have been postulated to manage these disorders including the use of agents which scavenge free radicals in an attempt to rid the body of such chemicals. To slow the progression of neurodegenerative disorders, approaches utilized include preventive therapy, disease modifying therapy and hormone therapy. Preventive therapy aims at improving the redox status (in order to ensure homeostasis) as well as preventing the resulting sequelae from the primary insult (Losada-Barreiro & Bravo-Díaz, 2017). However, most of these remedies have been shown to be ineffective in clinical trials even though positive results were obtained in pre-clinical trials (Ma et al., 2017). Mechanisms which have been exploited as potential targets to combat the various neurodegenerative disorders are elaborated on below.

NADPH Oxidase Inhibition in Traumatic Brain Injury

Because initial injury cannot be reversed in traumatic brain injury, significant research targets preventing or minimizing secondary injury (Chakraborty et al., 2016). ROS generation has been implicated in impairment brain functioning neuronal death after TBI. Both prophylactic and curative treatment with apocynin, a NADPH oxidase (NOX) inhibitor, originally isolated from the roots of *Picrorhiza kurroa* (Maraldi, 2013), significantly decreased oxidative damage in the cortex and the hippocampus in rodents (Zhang et al., 2012). Pretreatment with a specific NOX2 inhibitor, *gp91ds-tat,* also greatly reduced the neuronal damage and edema after TBI (Zhang et al., 2012). Further evidence that NADPH oxidase is an important target to combat neurodegeneration by reducing oxidative stress is adduced by the observation that *gp91phos* (NOX2) gene deficient-mice exhibited reduced primary cortical damage and ROS levels at the site injury (Dohi et al., 2010). Also, pretreatment with intraperitoneal injection of apocynin led to reduced TBI-initiated oxidative produced neuroprotective effects as observed by decreased atrophy and neuronal loss in the CA3 region of the hippocampus in rats (Choi et al., 2012). The neuroprotective

plant extract, *Ginkgo biloba,* has also been shown to be an NADPH oxidase inhibitor which was able to reduce the activity of neutrophil-containing myeloperoxidase (Maraldi, 2013).

Oxygen Free Radical Scavengers as Neuroprotective Agents

Antioxidants produce their effects by donating their own electrons in order to counteract their effects of ROS. Generally their effects as classified by Losada-Barreiro & Bravo-Díaz (2017) may be to maintain the production of ROS to the minimum, scavenge produced ROS or restore damage ROS-target molecules.

Transcranial injection of the antioxidant glutathione, the powerful tripeptide antioxidant that efficiently scavenges the hydroxyl radicals as well as detoxifies H_2O_2, after head injury significantly reduced inflammation and meningeal cell death (Danta & Piplani, 2014). Also, administration of N-acetylcysteine (precursor to glutathione) both in patients and rodents have shown positive outcomes in mild and moderate traumatic brain injury (Corps, Roth, & McGavern, 2015). This is one of the few successful clinical trials involving antioxidants as therapy for a neurodegenerative disorder. It is important however to note that, the likely key in using antioxidants to management TBI is to initiate therapy as soon as possible so as to avoid lesion expansion and the subsequent sequelae which results (Corps, Roth, & McGavern, 2015).

Another antioxidant with positive outcomes in both pre-clinical and clinical trials is the potent antioxidant, vitamin E. In randomized controlled, double-blind clinical trials with vitamin E in moderately impaired AD patients, the progression of functional impairment was delayed. α-Tochopherol also slows the advancement of PD in both clinical and preclinical trials (Danta & Piplani, 2014). Natural products such as *Gingko biloba*, flavonoids, soybean isoflavones and nicotine have been shown to reduce the neurotoxicity that is predominant in Alzheimer's disease by reducing oxidative stress (Velusamy et al., 2017). Other natural products including luteolin derivatives, *Calendula officinalis* flowers, olive oil and melatonin have shown possible neuroprotective effects in Huntington disease (HD) models all due to their antioxidant properties (Velusamy et al., 2017). For example, *Ginkgo biloba* has been shown to reduce the rate of 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP)-induced neurodegeneration of dopaminergic neurons (Wąsik & Antkiewicz-Michaluk, 2017). This beneficial effect is due to its ability to scavenge superoxide free radicals. Additionally, *Ginkgo biloba* regulate glutathione reductase and other antioxidant systems, superoxide dismutase activity as well as its neurotrophic effects (Rojas et al., 2004). All these antioxidant therapies however are not effective as sole treatment but are effective against oxidative stress and slows the progression of HD (Manoharan et al., 2016)

Neuroprotective Steroids

Neuroprotective steroids are either synthetic or natural steroids that mainly protect the CNS or peripheral nervous system (PNS) from neurodegeneration. They include dehydroepiandrosterone, testosterone, estradiol, pregnenolone and progesterone. These agents act by mainly protecting neurons from oxidative stress, excitotoxicity and inflammation while promoting repair processes such as neurogenesis among others (Bansal & Singh, 2017). In AD, estradiol is known to regulate Aβ accumulation in the brain as well as protect neuronal cells from the resulting damage. It is also able to prevent the hyperphosphorylation of tau protein which is a hallmark of AD (Bansal & Singh, 2017).

Efficacy of Combatting Free Radicals in the Management of Neurodegenerative Disorders

The effectiveness of free radical scavenging agents as therapeutic agents is fraught with challenges. Thus the efficacy of some of these agents including apocynin in pre-clinical trials have not been translated in most clinical trials. Generally, this may be due to the inability of the agents to permeate the BBB or the fact that most of these agents do not target a specific oxidative mechanism (Ma et al., 2017).

One of the main challenges is the burden of off-target effects. For instance, diphenyliodonium (DPI) a very potent NOX inhibitor also has effects on cholinesterases, xanthine oxidase and calcium pump which may account for some of its adverse effects (Maraldi, 2013). Also, it has been shown that the use of NOX inhibitors targets both physiological and pathological effects of NOX and might lead to undesirable side effects. This will require the use of specific inhibitors which will help to reduce off-target effects as well as the need to selectively target only pathological NOX signaling (Ma et al., 2017).

Popular antioxidants like ascorbic acid and flavonoids as monotherapy or in combination have also not shown very positive results in human studies for the treatment of all neurodegenerative disorders (Ma et al., 2017). In certain conditions, where they prove to be beneficial, the nature of the formulation becomes a hindrance to their effective use. A perfect example is that of flavonoids which are highly polar molecules and hence are unable to cross the blood brain barrier effectively. Thus, for an antioxidant to be efficacious in ND management, it should have the following basic characteristics as classified by (Danta & Piplani, 2014):

1. The molecule must be able to accept electrons from reactive molecules and remain stable upon receipt of the electron
2. Be fairly lipophilic to facilitate crossing of the blood brain barrier and
3. Be fairly selective in order to prevent off-target effects

Future Research Directions Towards a Holistic Treatment of Neurodegenerative Disorders

Setbacks

There are currently no treatments for the complete amelioration of neurodegenerative diseases even though symptoms of some NDs can be partially assuaged using antioxidants. Positive results obtained in pre-clinical trials have not always been successfully replicated in humans during clinical trials (Ma et al., 2017). Oxygen-free radical scavengers have been used in clinical trials to manage several neurodegenerative disorders but mostly with no positive outcomes (Ma et al., 2017).

With the important role played by SOD in the pathology of several neurodegenerative disorders it was expected that SOD would ameliorate several neurodegenerative disorders (Chakraborty et al., 2016). However, upon administering pegorgotein, a conjugated form of superoxide dismutase with reduced antigenicity and prolonged half-life, there was no statistically significant difference in neurologic outcome or mortality between pegorgotein and placebo-treated groups in a traumatic brain injury clinical trials (Young et al., 1996). The effects of tirilazad, an amino steroid with antioxidant and lipid peroxidation inhibition properties was also studied in clinical trials and it was observed that there was no difference in favorable outcomes or mortality between treatment and placebo groups (Chakraborty et al., 2016).

Prospects

It has become imperative to look at other approaches for mitigating oxidative stress beyond the routine antioxidant approach recognizing the various failures to translate observations in preclinical data to clinical trials.

The Endocannabinoid System

It is now believed that targeting the endocannabinoid system to regulate oxidative stress-induced cell death may hold therapeutic potential in NDs from traumatic brain injury through AD and PD to amyotrophic disorders and HD. This is backed by the evidence from effects of interaction at both cannabinoid receptors (CB1 and CB2) (Paloczi, Varga, Hasko, & Pacher, 2017). CB2 expression in microglia appears upregulated in oxidative stress related NDs, such as AD, MS, or PD although how free radicals induce CB2 receptor expression is still elusive while CB2 agonists have exerted neuroprotective effects and attenuated of neuronal cell damage (Paloczi, Varga, Hasko, & Pacher, 2017).

Additionally, the neuroprotective role of CB1 nonselective receptor agonists (WIN55, 212-2 and HU210) has been reported in a murine PD model. Interrupting CB1 signaling led to reduced ROS production and suppression of NOX which culminated in increased survival of nigrostriatal dopaminergic neurons in the striatum (Chung et al., 2011). It has also be shown that the activation of CB1 receptor by anandamide protects hippocampal neurons from oxidative injury by decreasing intracellular ROS and lowering the expression of type 2 NADPH oxidase —effects that are abolished in the presence of CB1 antagonist AM251 or CB1-siRNA (Jia et al., 2014). Moreover, the non-psychoactive phytocannabinoid, cannabidiol, shows neuroprotection by diminishing ROS levels and lipid peroxidation products in vitro and in vivo in Alzheimer's disease models (Iuvone et al., 2004). With regard to traumatic brain injury, a positive correlation occurs between tetrahydrocannabinol intake and decreased mortality in adult TBI patients (Nguyen et al., 2014) while anandamide-CB1 receptor signaling reduces the progression of clinical symptoms in G93A-SOD1 transgenic mice model of ALS (Bilsland et al., 2006).

On the contrary, other studies have also demonstrated that CB1 receptor activation may promote ROS generation in other body systems and therefore the contribution of CB1 signaling may be cell-type dependent or an indirect consequence of various processes (Steffens & Pacher, 2015). This situation warrants further studies to evaluate the interaction of cannabinoids and ROS production in the disease progression of the various neurodegenerative disorders in order to understand the complex interactions and ultimately provide more efficacious cannabinoid-based therapies with minimal offset effects for neurodegenerative disorders in future

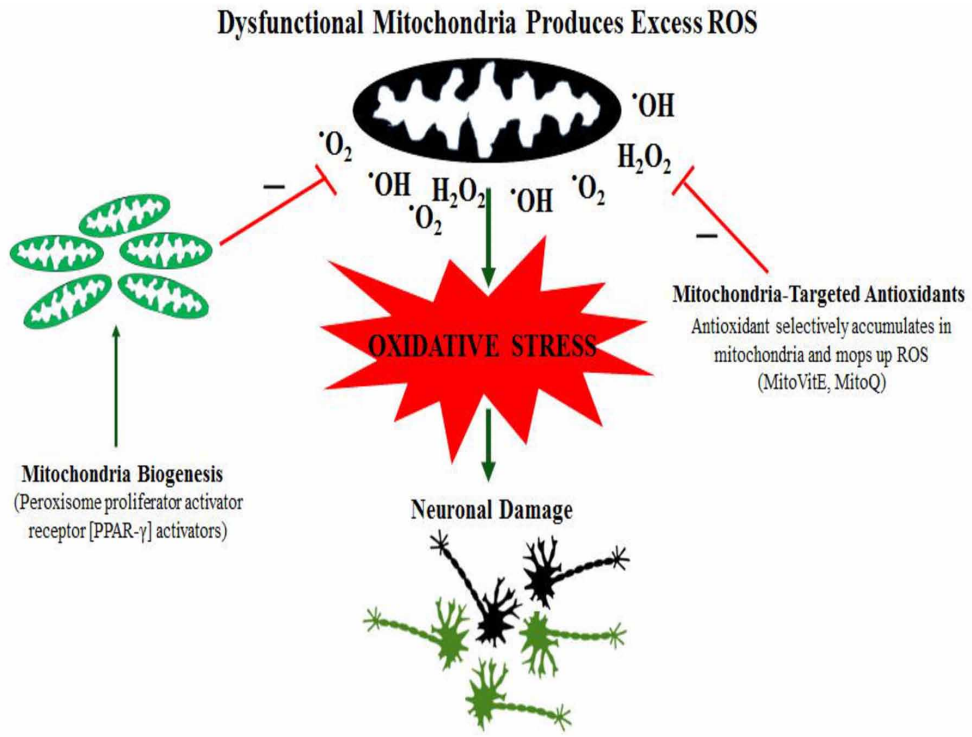
Mitochondria Targeted Antioxidant Therapy

The mitochondria's physiological actions include a variety of important cellular regulatory processes including ROS generation and detoxification. With the failure to translate pre-clinical success in antioxidant therapies to clinical trials, interest in mitochondria-targeted antioxidants therapy is increasing as a potential option to circumvent this challenge. The mitochondrion is an attractive target for drug-delivery strategies it is an important source of ROS.

This has led to the development of several investigational agents such as MitoVitE and MitoQ which are vitamins E and ubiquinone moiety of coenzyme Q10 derivative conjugated to the lipophilic cation triphylphosphonium respectively with the ability to cross the mitochondrial phospholipid bilayer, selectively accumulate in the mictochondria and mop up free radicals at their site of generation (Oyewole & Birch-Machin, 2015). The efficacy and toxicity of MitoQ have been evaluated in both pre-clinical and clinical trial for Parkinson's disease (Snow et al., 2010). MitoQ shows protection from MPTP-induced loss of behavioural activities and degeneration of dopaminergic neurons and terminals and demonstrated appreciable effects in phase I and II clinical trials (Jin et al., 2014; Snow et al., 2010). It has also been effective in mice models of Alzheimer's disease on mouse neuroblastoma (N2a) cells cultured with amyloid-β (Aβ) peptide (Manczak et al., 2010)

Another strategy of new interest is increasing mitochondria biogenesis. It is acknowledged that increases in neuronal mitochondrial numbers could compensate for bioenergetic dysfunction in neurodegeneration (Figure 1). Therefore, there is currently significant increase interest in peroxisome proliferator activator receptor (PPAR-γ) activators such as resveratrol, pioglitazone and rosiglitazone and the potential use to upregulate mitochondrial biogenesis and mitigate the increased oxidative burden seen in neurodegenerative disorders (Schapira, Olanow, Greenamyre, & Bezard, 2014).

Figure 1. Methods for mediating oxidative stress via reducing excess production of reactive oxygen species by dysfunctional mitochondria



CONCLUSION

In the battle to effectively manage NDs, it has been shown that free radical-induced oxidative stress is a major player hence this chapter provides an overview of the multiple roles played by ROS in different NDs. The various mechanisms which target the generation or end effects of ROS and are being used to alleviate the sequelae resulting from these diseases have been discussed. Antioxidant systems such as the enzymes and low molecular weight reductants are reviewed with their possible mechanisms of action in certain NDs highlighted. The interplay of diet in aging and oxidative stress is also highlighted. Mechanisms of synthetic drugs and natural products in combatting ROS are reviewed with emphasis on their effectiveness in clinical trials and associated challenges. Lastly, the chapter examines novel targets requiring further research such as the endocannabinoid pathway and the mitochondria-targeted antioxidants. These have been outlined to stimulate research into novel management strategies of NDs. Great strides have been made in understanding the mechanisms of NDs, however, there is still a knowledge void that needs to be filled. Current therapeutic agents cannot adequately to provide the desired therapeutic effect, hence additional research is required to deliver efficacious therapeutic agents with minimal off-target effects.

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