International Journal of Endorsing Health Science Research
Int. j. endorsing health sci. res.
Published by Advance Educational Institute and Research Centre

IJEHSR

Systemic Review

Oxidative Stress Mediated Neurodegeneration: A Cellular Perspective

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DOI:10.29052/IJEHSR.v7.i4.2019.192-212

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Received 02/04/2019
Accepted 20/09/2019
Published 01/12/2019

OPEN ACCESS

Abstract

Background: Environmental toxins, nutritional discrepancies, genetic predispositions, and lifestyle modifications induce a variety of stresses on the human brain and body. Such chronic stressors can influence the onset and progression of neurodegeneration via cellular alterations. In this systematic review, we have discussed the role of oxidative stress in causing neurodegeneration. Moreover, the chemical, metallic and other etiological factors that stimulate oxidative stress and results in the development of neurodegenerative disorders are also explored and summarized.

Methodology: A systematic review was conducted to investigate the impact of oxidative stress on the human brain in relation to neurodegeneration. The human studies focusing on neurobiology and cellular changes in brain, investigating the pathway of oxidative stress leading to neurodegeneration through mitochondrial dysfunction and cellular alterations, published during 1st January 2000 to 31st March 2019 were identified and included in this systematic review.

Results: Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, 13 out of 1169 studies met the eligibility criteria and were included in the quantitative synthesis and screening. These studies focused on the features like cellular factors, metal exposure, and aging, inducing oxidative stress-related neurodegeneration. Six studies described mitochondrial alterations resulting in oxidative stress due to an increase in the production of reactive oxygen species (ROS), oxidation of proteins, peroxidation of lipid and damages to the deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). While the data from five studies suggested the loss of mitochondrial activity in response to metal exposure. Two experimental studies specified the effect of aging and self-implication of oxidative stress in the brain.

Conclusion: Although there are sufficient evidence in favour of the hypothesis that stress is significantly associated with neurodegeneration but it is still not considered as a primary instigator in neurodegenerative disorders. However, it can be concluded on the basis of this review that it has been involved in the propagation of cellular alterations and mitochondrial dysfunction that further leads to neurodegeneration.

Keywords

Oxidative Stress, Neurodegeneration, Mitochondrial Dysfunction, Cellular Alteration.

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Introduction

Evidences suggest that the primary pathogenic factors associated with neurodegenerative disorders include oxidative stress, and mitochondrial damage[1]. The pathway of oxidative stress to neurodegeneration is linked to the overproduction of ROS[2], that stimulates mitochondrial DNA mutation, damages the mitochondrial respiratory chain, alters membrane permeability, Ca^{2+} homeostasis, and mitochondrial defense system. All these cellular changes not only cause amplification in the neuronal dysfunction but also triggers neurodegeneration[1,3,4]. It is a physiological fact that the nervous system is reliant on the energy supply by mitochondrial for normal functioning[4]. Therefore, damage to one or more of the mitochondrial respiratory chain complexes leads to the impairment of cellular ATP synthesis leading to energy dearth[5-7].

The altered ROS level, decreases capability of biological system to detoxify reactive species, impair restoration tendencies, and subsequent damage that leads to the generation of oxidative stress with subsequent outcomes including cellular destruction, tissue necrosis, depletion of ATP, and apoptotic cell death[8-10]. The alterations drastically threat neuronal integrity after proteins[8], lipids[11], and DNA damage that actually create an imbalance in the normal redox state via production of free radicals and peroxides which leads to toxicity[10,12]. Moreover, neurodegeneration is also linked to the excessive generation of nitric oxide (NO), and its toxic metabolite peroxynitrite (ONOO), that effects the mitochondrial respiratory chain ultimately resulting in neuronal cell death[13]. Alzheimer's Disease (AD), Parkinson's Disease (PD), and Amyotrophic Lateral Sclerosis (ALS), are few of the common neurodegenerative disorders that are caused by the mitochondrial dysfunction and oxidative stress while among the other less associated to oxidative damage are Multiple Sclerosis (MS), Huntington's Disease (HD), and Friedreich's Ataxia (FRDA)[14].

Oxidative stress and Neurodegenerative disorders

AD, PD, and ALS, are the common neurodegenerative disorders that are caused by the mitochondrial dysfunction and oxidative stress while among the other less associated to oxidative damage are MS, HD, and FRDA[14]. AD, PD, and ALS, are 90% sporadic, while only 10% exists in familial forms. The mixture of hereditary, environmental and lifestyle factors leads to the development of sporadic forms. In contrast, HD is inherited and strictly an autosomal disorder[10].

AD contribute to the progressive neuronal loss and cognitive decline by any damage to the structure, and components of mitochondria, increased oxidative stress, and diverse stressors, which is accountable for the degeneration in Alzheimer's brain[15]. Deficiency in various key enzymes of the Tricarboxylic Acid Cycle (TCA), involved in oxidative metabolism, and in the rate-limiting step of the TCA, cycle is responsible for reducing molecular oxygen, and cause consistent defect in mitochondrial components in brain[16]. Same as AD, ALS is found in both familial (fALS), and sporadic (sALS) forms with increased rate of sALS i.e. 90%. The familial form is less common and occurs due to the mutation in the gene encoding for enzyme Copper/Zinc (Cu/Zn)-Superoxide Dismutase (SOD-1)[17-19]. Being a multifactorial pathogenetic disorder, its etiology is not only restricted to oxidative stress but the excitotoxic reactions, formation of clumps, inflammation, deficiency of Growth Factor (GF), and disarrangements of neurofilaments precipitate the disease condition increasing the treatment complexity[20].

The second most common neurodegenerative disease after AD is PD[21]. PD pathogenesis involves the loss of mitochondrial Complex I

(CI) in nigral neurons[22,15], that may be due to decreased production of certain CI subunits, disassembly of CI, and self-inflicted oxidative damage[23-25]. It is evident that inflammation, and oxidative stress cause cessation of events involved in the generation of dopaminergic neurons leading to neurodegeneration[26,27].

The progressive decay of the caudate nucleus, putamen, and globus pallidus due to the loss of long projecting neurons is involved in HD pathogenesis[28]. It results from the mutation caused by the expansion of CAG (Cytosine, adenine, & guanine), repeated sequence in the gene encoding huntingtin protein on chromosome 4 which leads to the striatal as well as cortical atrophy[29]. As the CAG encodes for glutamine, however, a repeated sequence results in polyglutamine chain that causes an abnormal protein-protein interaction, and hence the mutant Huntingtin Gene (HTT) causes degeneration[30], which has been associated with defected mitochondrial metabolic activity resulting in impaired energy metabolism[31], increasing the oxidative damage though an increased production of free radicals.

Based on previous literature, MS pathogenesis is associated with oxidative/nitrosative stress that occurs due to excessive production of ROS and Reactive Nitrogen Species (RNS)[32]. ROS results in the upregulation of the genes involved in MS (such as tumor necrosis factor-α and nitric oxide synthase) through activation of Nuclear Transcription Factor-Kappa (NF-k) resulting in energy loss that leads to mitochondrial dysfunction, and calcium overloading[32]. Frataxin is responsible for mitochondrial Iron–Sulphur Cluster (ISC) synthesis, its deficiency leads to impaired synthesis of ISC which in turn causes iron overload in mitochondria, and multiple deficiencies related to ISC-containing proteins (ISPs)[33]. The resulting free radicals results in mitochondrial dysfunction, and activation of stress pathway leading to apoptosis, and energy deprivation[33].

All the above mention neurodegenerative disorders include oxidative stress as a primary key factor in their pathogenesis. An extensive research has been conducted previously, in order to understand the correlation between mitochondrial dysfunction, oxidative stress, and neurodegeneration. In this review, we have summarized the causes of oxidative stress, and the mechanism leading to various neurodegenerative, and neurological changes.

Methodology

A search strategy was employed on electronic databases including PubMed, and Google scholar to find associations between neurodegenerative conditions, mitochondrial dysfunction, cellular modifications, and oxidative stress. The terms such as oxidative stress, mitochondrial dysfunction, cellular modification, and neurodegeneration were utilized for search. Objectives, and outcomes of all articles were examined for potential relevance to the research question before inclusion. Furthermore, reference lists of the journal articles were thoroughly screened to identify additional studies that were relevant.

The articles fulfilling the eligibility criteria, published in between 1st January 2000 to 31st March 2019 were all included in the screening process. Original full-text articles, involving adult subjects within age group of 19 to 45 years or above were all included. While studies conducted on non-human subjects, pediatric studies, meta-analysis, case-reports, and duplicate publications, and studies with any risk of bias were excluded. The articles that correspond to the criteria were collected, and reviewed thoroughly for gathering information regarding the study aim. Only published studies were included to increase the robustness of the article.

The data was synthesized and a systematic summary was developed through extraction, and management of the studies, the results were then screened, and combined according to the PRISMA guidelines[34].

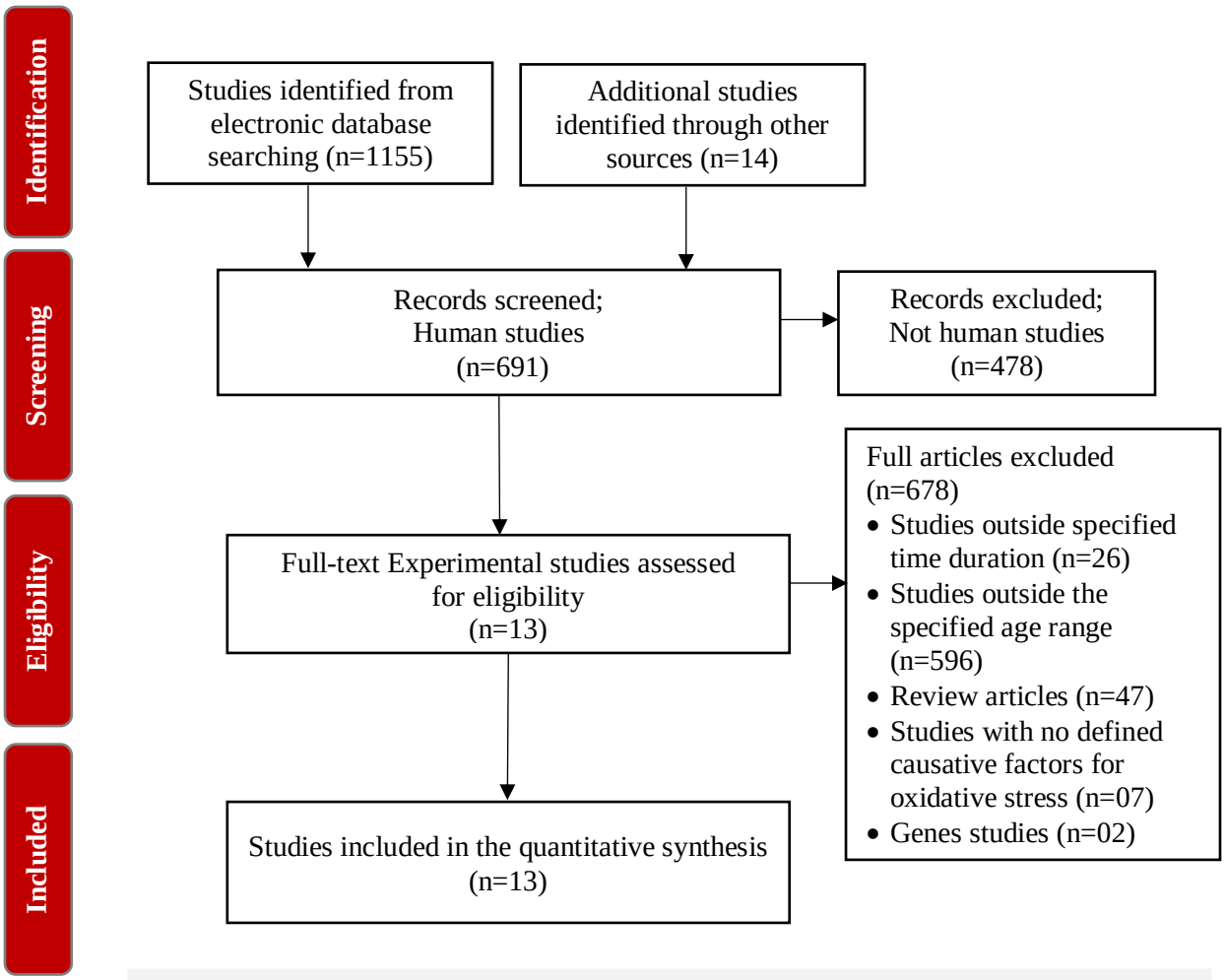

Figure 1: Flow diagram for study selection in systematic review (PRISMA Flow Chart)

Mechanism underlying oxidative stress involvement in neurodegenerative diseases

Numerous environmental, psychosocial, and physical factors stimulate the nervous system which then collectively generate stress response[35,36] mediated by the stress system, a part of which is located in the Central Nervous System (CNS), and also in the peripheral organs. The interconnected effectors of the CNS include the hypothalamic hormones arginine, vasopressin, corticotropin-releasing hormone (CRH), pro-opiomelanocortin derived peptides (POMC), locus ceruleus, and autonomic norepinephrine centers in the brainstem[36]. The executive, and cognitive reward, and fear systems, wake-sleep centers, growth system, reproductive and thyroid hormone axis, and the gastrointestinal, cardiorespiratory, metabolic, and immune systems are the targeted areas of the brain[36]. A profound effect of stress on brain development, and functioning is evident, it induces neurochemical changes, and disrupts normal neuronal circuitry. A wide variety of fundamental physiological processes are influenced by stress through the Hypothalamic-Pituitary-Adrenal (HPA) axis, and Glucocorticoid (GC) action[37]. Generating

stressful stimuli in the brain involves the activation of neurons of paraventricular nucleus of hypothalamus (PVH), which releases Corticotrophin-Releasing Factor (CRF), and arginine vasopressin. The anterior pituitary gland is then stimulated to secrete Adrenocorticotropic Hormone (ACTH) into the general circulation, which results in Cortisol (stress hormone) production by the Adrenal Cortex[37-39]. Excessive synthesis, and secretion of GCs due to stress-induced disruption of HPA axis can lead to altered neuronal connectivity, synaptic loss, and neuronal atrophy. Such modifications can alter brain function, and contribute to development, and progression of neurodegenerative diseases[40, 41].

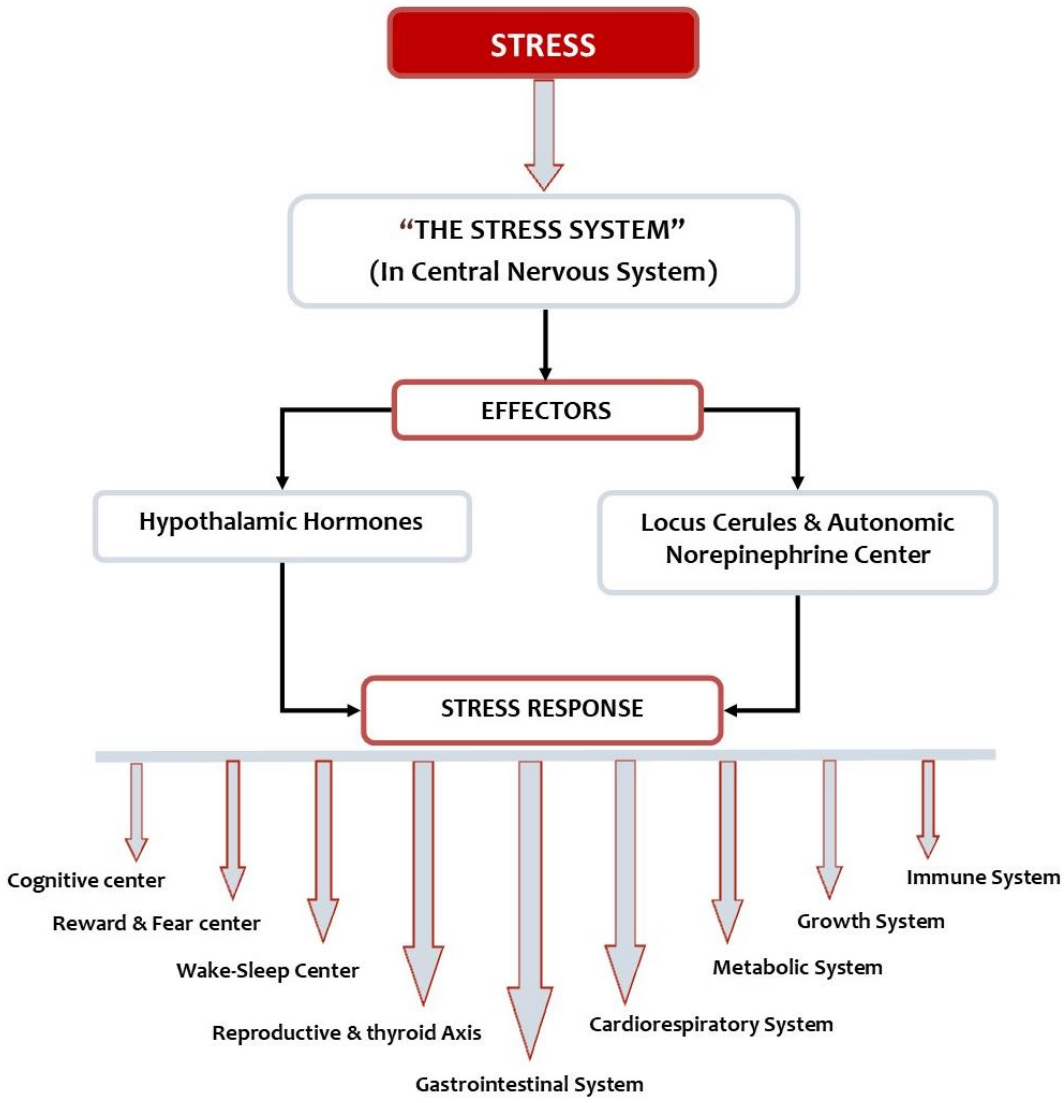

Figure 1: Schematic representation of the stress response network. Stress stimulates the stress system in the brain which in turn activates the effector organ which results in the release of hormones from hypothalamus and locus cerules and autonomic norepinephrine center in order to generate stress response by targeting areas for generating stress response.

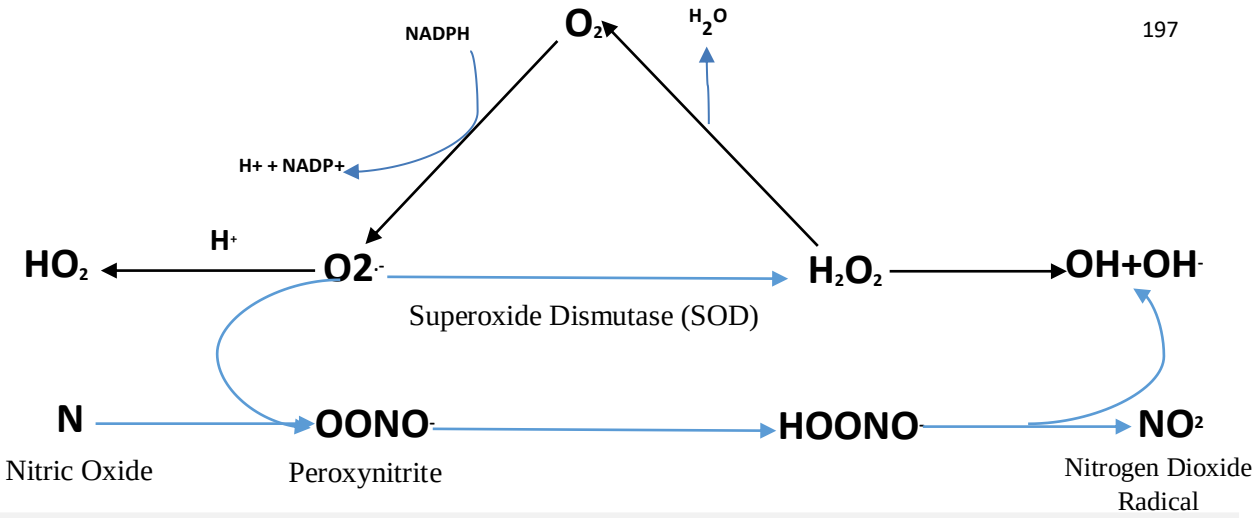

Figure 2: Metabolism of reactive oxygen species (ROS). O_2 by the action of NADPH oxidase results in the formation super oxide which forms hydrogen peroxide by the activity of superoxide dismutase (SOD). This hydrogen peroxide (H_2O_2) gives off hydroxyl radicals (OH) and hydroxyl anions (OH-) through fenton reaction.

Generation of Reactive Oxygen Species (ROS)

The source of ROS can be both exogenous and endogenous[42,43], among the exogenous sources environmental toxins, chemical metabolism, ultraviolet (UV) radiations, ionizing radiation, drugs whose activity is mediated by ROS production[43]. While the endogenous production is either associated with mitochondria or non-mitochondrial enzymes like Nicotinamide Adenine Dinucleotide Phosphate (NADPH) Oxidase (Nox), Xanthine Oxidase (XO), cytochrome P450, cytochrome b5, quinone oxidase, oxalate oxidase, amine oxidases, flavin oxidases etc., are involved in the production of ROS[42,43]. However, ROS is chiefly produced by mitochondria, and Nox system[44-46].

ROS exists in numerous partially reduced forms like Super Oxides (O2.-), Hydrogen Peroxide (H2O2), and Hydroxyl Radicals (OH.). ROS includes both oxygen radicals as well as non-radicals that can be easily converted into free radicals[47]. Moreover, evidences indicate that excessive generation of Nitric Oxide (NO), and its toxic metabolite Peroxynitrite (ONOO-) also plays significant role in neurodegeneration, it inhibits the mitochondrial electron transport chain leading to energy failure, and apoptotic cell death[48]. Brain cell display varying susceptibility towards NO/ONOO-, and is also affected by status of cellular antioxidants, and the maintenance of energy requirement ability[48].

Pathway leading oxidative stress to neurodegeneration

It is suggested that all the neurodegenerative diseases are to some extent multifactorial, and oxidative stress is inevitably intertwined with the disease mechanisms. It is intimately linked with an integrated series of cellular phenomena, which contribute to neuronal cell death, and neuronal atrophy[49]. Mitochondria is considered as the endogenous source of oxidative stress as it causes an increased production of ROS. Although much research has been conducted on the mechanism behind the increased ROS, and RNS production causing oxidative stress but still the researchers are involved in finding out the primary cause, and consequences associated with neurodegenerative process due to oxidative stress, as the etiology is multifactorial, and hence there is likelihood for deviation in the previous findings. ROS, highly toxic to neuronal cells had been associated with neurodegeneration[48]. Neurodegenerative disorders, such as PD, AD, and ALS clearly indicate increased ROS production which leads to neurodegeneration[49].

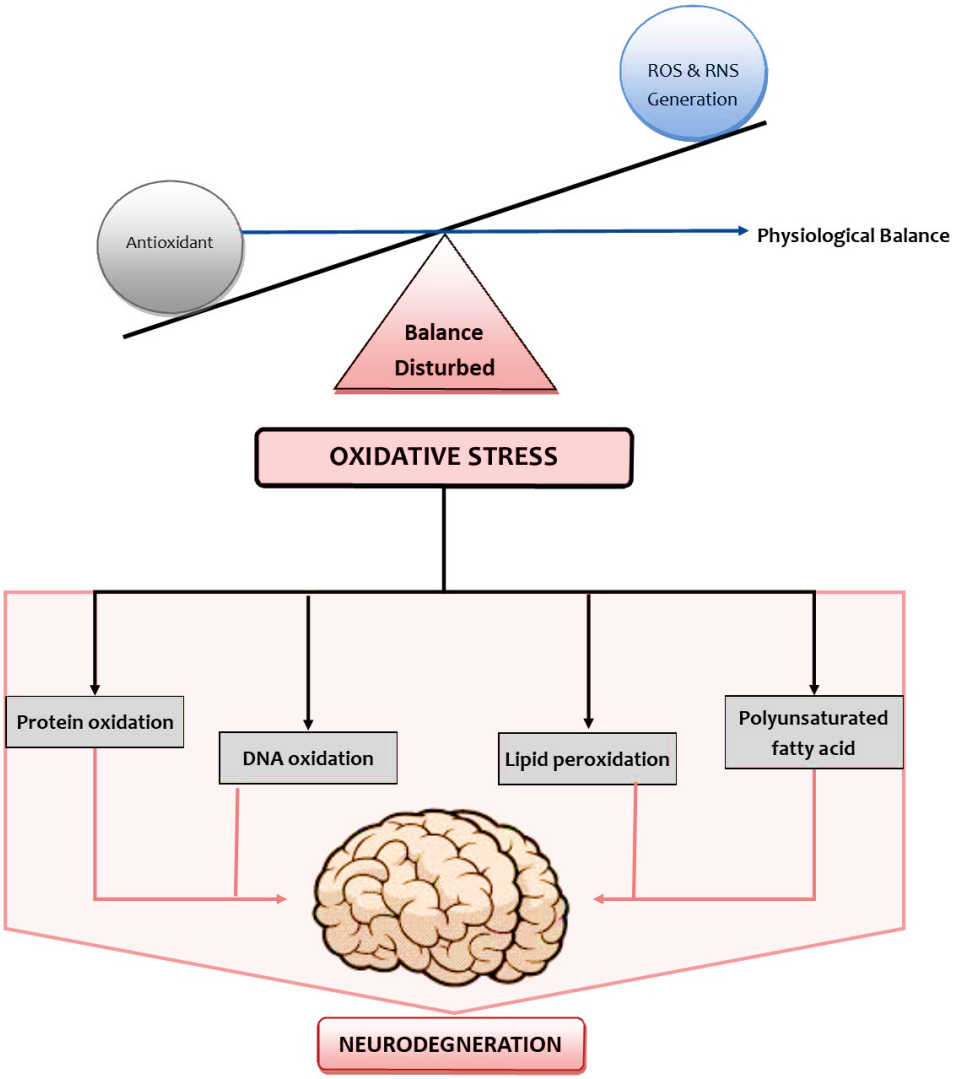

Figure 3: Stress response system. This figure shows stress response due to disturbance between reactive oxygen species and antioxidants, causing protein and DNA oxidation, lipid peroxidation and increased polysaturated fatty acid in brain that leads to neurodegeneration.

The disturbed balance between the production of ROS, and antioxidants level mainly results in the generation of oxidative stress which leads to cellular damage. The formation of free radicals by increased ROS generation, contributes to the development of neurodegeneration by modulating the function of several biomolecules at cellular level. Furthermore, ROS targets several different substrates within the cells, causing protein, DNA, and RNA oxidation, and lipid peroxidation. ROS attacks proteins, and oxidizes the backbone and the side chain. It further reacts with amino acid side chains to form carbonyl formations, and results in protein fragmentation, and cross linkages are formed[50].

Factors causing oxidative stress related neurodegeneration

According to past, and recent studies, it is evident that oxidative stress has a fundamental role in the pathophysiology, and pathogenesis of neurodegenerative diseases. There are numerous environmental toxins, nutritional discrepancies, genetic predispositions, and

changes in lifestyle that induce a variety of stresses on the brain, and body, ultimately resulting in cellular modification, and mitochondrial dysfunction. This section highlights some of the causative factors that cause oxidative stress, leading to mitochondrial alteration, cellular changes, and ultimately results in neurodegeneration.

Neurodegeneration associated with Cellular factors

Table I summarizes data for each study, including sample, cellular factors, alterations, and main outcomes of the studies included in this review. According to the findings, there are numerous cellular changes that occur within the brain producing homeostatic alterations in neurons, and causing neuronal cell death. One of the factors altering brain hemostasis is cholesterol. The CNS is rich in cholesterol, which is essential to neuronal development and survival, synapse maturation, and optimal synaptic activity. Alterations in brain cholesterol is strongly associated with neurodegeneration[51]. Amira Zarrouk, and her colleagues assessed the triggering capacity of oxysterols (cholesterol) for producing cellular modifications leading to neurodegeneration, by treating Human Neuronal Cells (SK-N-BE) with 7-ketocholesterol, 7α, and 7β-hydroxycholesterol, 6α-, and 6β-hydroxycholesterol, 4α-, and 4β-hydroxycholesterol, 24(S)-hydroxycholesterol, and 27-hydroxycholesterol (50-100 lM, 24h)[52]. The findings indicated that 7-ketocholesterol, 7β-hydroxycholesterol, 24(S)-hydroxycholesterol, and 27-hydroxycholesterol favor neurodegeneration by inducing mitochondrial dysfunction, oxidative stress, and/or cell death, associated with or without a rise in cytosolic calcium level[52].

Neurodegenerative disorders share a common pathogenetic mechanism involving aggregation, and deposition of protein aggregates[53]. These aggregates are formed due to the misfolding of the normal, soluble proteins which initiates a series of consequences associated with neurodegeneration[54] (Table I). Glutathione, an important antioxidant whose role has been proposed in the pathogenesis of some neurodegenerative diseases[55], is one of the important factors as discussed in table I. Findings from a study by F. Piemonte et al., in 2001 indicate the impairment of glutathione homeostasis in Friedreich's Ataxia, suggesting a prevalent role of free radical cytotoxicity, and deficiency of iron (Fe/Su)-containing proteins in the pathophysiology of neurodegeneration, inducing oxidative stress, and causing mitochondrial dysfunction[56].

Rotenone, an important chemical factor related to neurodegeneration, it alters cell viability, and causes mitochondrial dysfunction[57]. In 2018, Rekha, and her colleague observed that rotenone induces mitochondrial dysfunction, and generates endoplasmic reticulum (ER) stress by the inhibition of cell viability, dissipation of mitochondrial transmembrane potential, increases ROS level, and inhibits the activity of complex-I of mitochondrial electron transport chain[57]. Furthermore, increased rotenone reduces intracellular ATP concentration, and reduces glutathione level, which results in nuclear fragmentation, and destruction thus causing neuronal apoptosis, and necrosis[57,58].

Furthermore, salivary cortisol level also increases in response to acute stressful events and can be marked as a factor inducing oxidative stress[59]. Increased cortisol level in response to oxidative stress has been studied by various researchers, Aschbacher K. et al., 2013 studied three markers of oxidative damage including 8-Iso-Prostaglandin F2a (IsoP), 8-hydroxyguanosine (8-oxoG) and, 8-hydroxy-20-deoxyguanosine (8-OHdG)[60]. The results suggested that anticipatory stress arousal may accelerate the accumulation of oxidative damage, and biological aging, particularly

among chronically stressed individuals through anticipatory cortisol reactivity, and oxidative damage[60].

Drugs can induce a type of stress like in case of Methamphetamine (METH), it induces oxidative stress along with mitochondrial dysfunction, and cellular alteration. METH is a psychostimulant, highly addictive, and produces long-lasting, and strong euphoric effects[61,62]. METH addiction results in attention deficit, memory decline, and decreased decision-making abilities in human, its abuse is becoming a major public health concern[62]. Moreover, it results in the significant loss of dopamine in the striatum of the brain by causing damage to the dopaminergic neurons in the substantia nigra[63]. Borgmann, and Ghorpade reported that prolonged exposure to low level of METH can cause morphological dysregulation of mitochondrial astrocytes, and also effects their function, and hence increases antioxidant capacity, and oxidative burden which leads to oxidative stress associated with neurodegeneration[64].

It is suggested that the changes caused by oxidative stress in the functioning of mitochondrial leukocyte can be utilized for evaluation of bioenergetics health among individuals[65]. A study investigated the bioenergetics profiles of monocytes isolated from healthy human subjects, and the impact of the redox cycling agent, 2,3-Dimethoxynaphthoquinone (DMNQ) on it[66]. The results indicated that monocytes are affected by oxidative stress mediated by DMNQ. Furthermore, these monocytes displayed significant decrease in ATP-linked respiration, reduced reserved capacity, increased non-mitochondrial respiration, and a decline in Bioenergetics Health Index (BHI)[66].

Overall, there are 6 cellular factors discussed in Table 1. The outcomes of the studies show that all of these factors induce oxidative stress by mediating mitochondrial dysfunction that involves a decrease in mitochondrial respiration along with disruption in mitochondrial morphology. Furthermore, all the above discussed factors participate in the increased production of reactive species (ROS and RNS), and decreased ATP production.

Table 1: Results from the experimental studies evaluating the effects of different cellular factors on mitochondrial structure and cellular homeostasis

Author	Year	Sample	Factors	Alteration	Outcome
Amira et al[52]	2015	SK-N-SH human neuroblastoma cell	Cholesterol (7KC, 7α-OHC, 7β-OHC, 6α -OHC, 6 β -OHC, 4α -OHC, 4β -OHC, 24S-OHC and 27-OHC)	Mitochondrial dysfunctions, inhibition of cell growth, ROS overproduction, induction of a non-apoptotic mode of cell death.	Increased levels of 7KC, 7b-OHC, 24SOHC, and 27-OHC in various neurodegenerative diseases could contribute to neuronal loss.
Kirstin et al[60]	2013	Markers of oxidative damage: IsoP, lipid peroxidation, 8- oxoG and 8-OHdG	- Salivary cortisol	Anticipatory cortisol reactivity, oxidative damage	Anticipatory stress arousal may accelerate the accumulation of oxidative damage and biological aging, particularly among chronically stressed individuals.

Kathleen &Anuja[64]	2017	Human astrocytes	- METH	Increase oxidative damage, decrease oxygen consumption rate, decrease ATP level, enlarged mitochondria, decrease fission, increase fusion.	METH dysregulates astrocyte mitochondrial morphology and function, which in turn, concurrently increase both their oxidative burden and antioxidant capacity. Increase oxidative bundle can leads to oxidative stress associated with neurodegeneration.
Balu et al[66]	2016	Monocytes	- redox cycling agent, DMNQ.	Significant decline in ATP-linked respiration, decrease reserved capacity, non-mitochondrial respiration increases, and decline in bioenergetics health index (BHI).	Identified for the first time that the BHI is dynamically sensitive to oxidative stress mediated by DMNQ in monocytes from healthy human subjects.
Karamkolly & Ramu[57]	2018	SK-N-SH human neuroblastoma cell	- Rotenone (a pesticide)	Inhibit cell viability, increase ROS formation, dissipation of mitochondrial transmembrane potential, increase NOS level, inhibits the mitochondrial electron complex-I, reduced intracellular ATP concentration, elevated level of TBARS, reduce level of GSH, nuclear fragmentation and destruction, apoptosis, necrosis, mitophagy vesicle engulfment, damage mitochondria, protein expression levels of p-mTOR and AMPK increases	Treatment with rotenone decreased activities of enzymatic antioxidants such as SODs (Mn–SOD and Cu–Zn–SOD). The ER stress (UPR pathway) associated proteins, including PERK, IRE-1α and ATF6α levels were significantly increased in rotenone Treated cells, suggesting the presence of increased ER stress and inducing oxidative stress.
F. Piemonte et al[56]	2001	Erythrocytes	GSH	Decrease glutathione concentration, increase accumulation of hydroxyl radicals, deficiency of iron/sulphur-containing proteins, mitochondrial	Findings provide evidence of an impairment in vivo of glutathione homeostasis in Friedreich's ataxia suggesting a relevant role of free radical cytotoxicity

				dysfunction, and oxidative stress.	in the pathophysiology of neurodegeneration.

Abbreviations: 7α-OHC - 7α- hydroxycholesterol, 7β-OHC - 7β-hydroxycholesterol, 6α –OHC - 6α-hydroxycholesterol, 6β –OHC - 6β-hydroxycholesterol, 4α -OHC - 4α- hydroxycholesterol, 4β –OHC - 4β-hydroxycholesterol, 24S-OHC - 24(S)-hydroxycholesterol, 27-OHC - 27-hydroxycholesterol, 7KC - 7-ketocholesterol, ROS - reactive oxygen species, 8- oxoG - 8-hydroxyguanosine, 8-OHdG - 8-hydroxy-20-deoxyguanosine,METH – Methamphetamine, ATP – adenosine tri phosphate,DMNQ - 2,3 dimethoxynaphthoquinone,BHI - bioenergetics health index, NOS - nitric oxide synthase, SOD - superoxide dismutase, ER – endoplasmic reticulum, GSH - glutathione, TBARS - Thiobarbituric acid reactive substances, PERK - protein kinase R (PKR)-like endoplasmic reticulum kinase, IRE1α - inositol-requiring enzyme 1 α

Neurodegeneration associated with Metal Exposure

Metals are responsible for maintenance of cellular structure, neurotransmission, cell adhesion, regulation of gene expression, and metabolism of proteins and carbohydrates in human body[67,68]. There are numerous unfavorable events such as fragmentation of DNA, oxidative stress, mitochondrial dysfunction, misfolding of protein, apoptosis etc., associated with elevated metal exposure[69-71]. One of the metals discussed in Table 2 is manganese (Mn). Mn facilitates the activity of numerous enzymes like arginases, hydrolases, lyases, glutamine synthetases, and Superoxide Dismutase (SOD)[72].

Heavy, and transitional metal also have profound effects on the neurophysiology of brain. Lead (Pb), and cadmium (Cd) are non-essential heavy metals and a ubiquitously present pollutant in the ecosystem[67]. Chronic exposure to Cd, and Pb might restrict normal brain functioning[67]. To evaluate the relationships between oxidative stress, and heavy metal exposure, Xiaoyi et al., examined the health of female subjects belonging to an agricultural community in Japan. The results indicated that continuous exposure to heavy metals increases oxidative stress. Heavy metal exposure, and the concurrent presence of lifestyle factors, and age are significantly associated with oxidative stress[73]. Moreover, long-term exposure to heavy metals, such as Pb, contributes to the accumulation of peroxidative damage, lipid peroxidation, deteriorated cell membrane, and fibrillation of α-synuclein which leads to neurodegenerative cell death[74]. Similarly, transition metals are considered as the crucial players in the pathogenesis of neurodegenerative diseases[75]. A study by Marlene et al., demonstrated that redox-active Ferrous Ion (Fe^{+2}), Manganese Ion (Mn^{+2}), Cupric Ion (Cu^{+2}), and Zinc Ion (Zn^{+2}) ion-induces apoptosis in Peripheral Blood Lymphocytes (PBL) by Hydrogen Peroxide (H_2O_2)/ Hydroxyl Radical (·OH) generation, resulting in mitochondrial depolarization, activation of caspase-3, and NF-κB-independent nuclear fragmentation, and activation of p53 transcription factors[76].

Residual Oil Fly Ash (ROFA) is a particulate air pollutant generated from the combustion of fuel oil[77]. The chemical composition of ROFA includes sulfates, silicates, compounds containing carbon and nitrogen, and metals[78]. Jee Young Kim investigated the association between exposures to particulate matter, metal fumes, ROFA, and oxidative DNA damage, and repair in boilermakers working at a power plant. Acute lung injury, airways inflammation, and oxidative DNA damage by ROS were observed in the study subjects, indicating increased risk of developing oxidative DNA injury after exposure to high levels of metal-containing particulate matter[79]. Recently in 2019, the effect of particulate matters was also studied by Ying Wang, in which changes in

mitochondrial dynamics, Mitochondrial Permeability Transition Pore (mPTP), Mitochondrial DNA (mtDNA), and oxidative stress in human SH-SY5Y cells exposed to Particulate Matters (PM 2.5) was observed[80]. The changes induced by PM 2.5 includes swollen, and fragmented mitochondria, decreased ATP content, a decrease in mtDNA copy number in cells, increased ROS generation, decreased mitochondria SOD2 activity, triggers lipid peroxidation of mitochondrial membrane, and increases cell oxidative stress, Mitochondrial Amyloid Beta-42 (Aβ-42), and changes in the Mitochondrial RNA (mRNA), and protein expression of SH-SY5Y cells[80].

The studies in Table 2 demonstrated that excessive metal exposure in human body or brain results in neurotoxicity. Furthermore, it has also been evaluated that toxicity of metals in brain cause oxidative stress, mitochondrial dysfunction, and protein misfolding.

Table 2: Results from the experimental studies evaluating the effect of metals exposure inducing mitochondrial dysfunction and cellular alteration

Author	Year	Sample	Factor	Alteration	Outcomes
Jee et al[79]	2004	Urine sample (120ml).	Residual oil fly ash (ROFA) and metal fumes	acute lung injury, airway inflammation, oxidative DNA damage ROS	Boilermakers may experience an increased risk of developing oxidative DNA injury after exposure to high levels of metal-containing particulate matter.
Ying et al[80]	2019	Human SH-SY5Y cells.	- particulate matter (PM2.5)	Inhibit cell viability, swollen and fragmented mitochondria, decrease ATP content, decrease in mtDNA copy number in cells, increase ROS generation, decrease mitochondria SOD2 activity, triggers lipid peroxidation of mitochondrial membrane and cell oxidative stress, increased mitochondrial Aβ-42, Changes in the mRNA and protein expression of OPA1, Drp1, COX IV, CypD, SIRT3 in SH-SY5Y cells,	PM2.5 caused mitochondrial swelling, mPTP opening, MMP decline, mtDNA copy number decrease, ATP synthesis reduction, Ca2+ overload, and oxidative stress in SH-SY5Y cells, which is a vital reason of mitochondrial dysfunction and might be a pathological mechanism of neurological diseases caused by PM2.5.
Marlene et al[76]	2004	Peripheral blood lymphocytes (PBL).	Redox transition metals 50, 100, 250, 500, and 1,000 μM (Fe2_),	Apoptosis, highly condensed/fragmented chromatin, necrosis, generated H2O2 and	Redox-active (Fe2_), (Mn2_), (Cu2_), and (Zn2_) ion-induced apoptosis in PBL by

			(Mn2_), (Cu2_), and (Zn2_)-(SO4)	(·OH), depolarization of mitochondrial transmembrane potential, increase mitochondrial dysfunction, increase cell death	(H2O2)/(·OH) generation, resulting in mitochondria depolarization, caspase-3 activation, and nuclear fragmentation independent of NF-κB and p53 transcription factors activation.
Steven et al[74]	2006	Concentrations of tibial and calcaneal bone Pb stores.	- chronic occupational lead exposure	Accumulation of peroxidative damage and neurodegenerative cell death, lipid peroxidation, deteriorated cell membrane, fibrillation of α-synuclein.	Long-term exposure to heavy metals, such as Pb, contributes to the accumulation of peroxidative damage and neurodegenerative cell death that is observed in PD.
Xiaoyi et al[73]	2016	Blood and urine samples.	- Heavy metal exposure (lead [Pb] and cadmium [Cd]) - Co-factors such as physical activity and age	Increase free radicles production, ROS generation, increased oxidative stress.	Continuous exposure to heavy metals increases oxidative stress. Heavy metal exposure and the concurrent presence of lifestyle factors and age are related with oxidative stress.
Abbreviations: ROFA - Residual oil fly ash, DNA – deoxyribose nucleic acid, mtDNA – mitochondrial DNA, Aβ-42 – amyloid beta-42, NF-κB -Nuclear Factor kappa-light-chain-enhancer of activated B, p53 – tumor protein 53, PD – Parkinson disease, ROS - reactive oxygen species, ATP – adenosine tri phosphate, SOD - superoxide dismutase, mRNA – messenger ribonucleic acid, Pb – lead, Cd – cadmium, PBL – peripheral blood lymphocytes					

Neurodegeneration associated with increasing age

In the last 20 years, it has been recognized that oxidative stress plays an important role in etiology of a variety of onset of neurodegenerative diseases. Aging is by far the greatest risk factor for neurodegenerative diseases such as AD, PD, and ALS[81,82]. Most theories of aging centers suggest that increasing oxidative stress leads to mitochondrial mutation, mitochondrial dysfunction, and oxidative damage[70]. Oxidative stress increases with age in the brain, and neurons might particularly be affected because they are post-mitotic[83]. The ability of cells to respond to oxidative protein damage also seems to decline with age and possibly contribute to protein buildup[84]. A decline in induction of heat shock proteins (HSPs), for instance, can result in an increase in oxidatively damaged proteins that might be resistant to ubiquitinylation, and degradation by the 26S proteasome[49].

Table 3 summarizes the studies, showing association between age, and neurodegenerative diseases. Venkateshappa, and his colleagues, in their study demonstrated that the brain aging contributes to the vulnerability of midbrain to neurodegeneration in PD[86]. Increase in protein oxidation, loss of mitochondrial CI activity, increased astrocytic proliferation indicated by glial fibrillary acidic protein (GFAP) expression, decreased SOD activity, and low GSH level were observed during physiological aging

in human brain[85,86,87]. Furthermore, there was a significant protein oxidation, and nitration with increasing age. The findings of the included studies indicate that extensive oxidative damage, loss of antioxidant, and mitochondrial function during physiological aging are responsible for neurotoxic activity thus contributing to selective degeneration during evolution of PD[49]. Furthermore, the author continued in another study that a distinct increase in oxidative damage, and Glial Fibrillary Acidic Protein (GFAP) expression, decreased antioxidant response, and insignificant trend towards a decreasing activity of mitochondrial Complex I (CI) in hippocampus region of human brain with increasing age[88].

Table 3: Results from the experimental studies evaluating the effect of age in the progression of oxidative stress

Author	Year	Sample	Factor	Alteration	Main outcome
Venkateshappa C. et al[86]	2012	Oxidant and antioxidant markers	Aging	Increase in protein oxidation and protein nitration, increased glial fibrillary acidic protein (GFAP) expression, decrease in mitochondrial complex I (CI) activity, and decrease in antioxidant enzyme activities in HC and FC. Decrease SOD activity, decrease catalase activity.	A distinct increase in oxidative damage and GFAP expression, decreased antioxidant response and a non-statistically significant trend towards decreasing activity of CI in HC region of human brain with increasing age.
Venkateshappa C. et al[89]	2011	Oxidant and antioxidant markers	Brain aging	Increase in protein oxidation, loss of mitochondrial complex I (CI) activity, increased astrocytic proliferation indicated by glial fibrillary acidic protein (GFAP) expression, decrease SOD activity, low Glutathione (GSH)	Age related alterations in the status of oxidant and antioxidant markers in the SN with implications for mitochondrial dysfunction and astrogial proliferation thus differentiating this region from the CD and explaining the vulnerability of SN to neurodegeneration in PD. There was significant protein oxidation and nitration with increasing age while it was relatively unchanged in CD

Abbreviations:GFAP - Glial fibrillary acidic protein, SOD - superoxide dismutase, GSH – glutathione, CD – caudate nucleus, SN – substantia nigra,CI - complex I

Discussion

Neurodegenerative conditions associated with neuronal cell death has long been linked to oxidative stress but the primary events involved in the initiation of oxidative stress with neurodegeneration in PD, AD, and ALS is still uncertain[49]. Further research regarding mechanism behind neurodegeneration, and its possible link to oxidative stress with respect to the contributing factors is required for advancement in the field of molecular and cellular physiology.

In this review, we have highlighted the etiology behind mitochondrial dysfunction, and cellular alterations influencing the production of reactive species, and other associated events with respect to oxidative stress leading to neurodegeneration. Despite of the rapid scientific evolution, a number of stimulators that have shown association with oxidative stress, and neurodegeneration among animals are still unexplored in humans. A study discovered Menadione (Vitamin K3) as one of the important etiological factors for oxidative stress in animal model[89]. Rodrigues MD et al., measured the alterations induced by menadione in mitochondrial bioenergetics, redox homeostasis, and cell viability. Decreased activity of mitochondrial dehydrogenase, decreased Glutathione (GSH), reduced antioxidants, and Superoxide dismutase (SOD), while increased production of ROS and proinflammatory response was observed in cortical astrocytes of wild-type (Gcdh+/+) mice. The authors concluded that redox, and mitochondrial bioenergetics homeostasis is disturbed when triggered by menadione, and it therefore increases the death risk[89]. Though the indicator showed positive response but the study is limited to the animal species.

Many animal models have been utilized for exploring the connection of cellular factors with brain neuronal homeostasis[49]. α-Synuclein (ASN) oligomer is another widely studied fact in animals. ANS is a multifunctional E3 ubiquitin ligase that is associated with the pathophysiology of PD[90], its excessive release contributes to neuronal injury leads to neuronal cell death through oxidative-nitrosative stress induction, mitochondrial impairment, and synaptic dysfunction[91]. In 2018, Anna Wilkaniec investigated the effect of extracellular ASN oligomers on Parkin expression and S-nitrosylation activity by using rat pheochromocytoma (PC12) cell line treated with exogenous oligomeric ASN as well as PC12 cells with parkin overexpression, and parkin knock-down[92]. The study concluded that the ASN oligomers induce oxidative/nitrosative stress leading to Parkin S-nitrosylation, resulting in neuropathological changes[92].

This review also discussed the mechanism leading to neurotoxicity due to several metallic exposures. Entaz et al., showed Mn-induced neurotoxicity in SK-N-MC human neuroblastoma cell line by investigating the protective effect of Quercetin (QCT)[93]. Increased intracellular ROS level, decreased mitochondrial membrane potential, increased Inhibitory Protein Kappa-B (P-IkB), Nuclear Factor Kappa-B (NF-kB), Protein 65 Subunit (P65), Heme Oxygenase-1(HO-1) and Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2) proteins were observed in SK-N-MC cells[93,94]. Moreover, the neutrophils, macrophages levels were also altered, expression of inducible nitric oxide synthase (iNOS), and polymerase-I (PARP-I) protein expression, and decreased Copper/Zinc-SOD (Cu/Zn-SOD) activity were also associated with excessive metallic exposure therefore, carbonyl stress, mitochondrial apoptotic pathways, and inflammatory responses participate in Mn-induced neurotoxicity[95]. Furthermore, Dejan Milatovic et al, 2009 investigated the impact of neurotoxicity of Mn in cortical neurons of Dawley rats. The results

indicated altered concentrations of oxidative biomarkers including increased F2-isoprostanes (F2-IsoPs), and prostaglandin E2 (PGE2) level[96].

Altered calcium-independent phospholipase A2γ (iPLA2γ) level is one of the substantial causes of neurodegeneration, it results in increased mitochondrial lipid peroxidation, and dysfunction[97]. According to Chao H. et al., 2017, decreased functioning of iPLA2γ results in the reduction of dopamine, and its metabolites by stimulating the Parkinsonian phenotype, which subsequently results in locomotory deficiencies, and hypersensitivity to rotenone-induced oxidative stress[97]. Furthermore, it also escalates the ratio of mitochondrial irregularities, reducing ATP synthesis, and levels of glutathione[97]. Bianca Seminotti et al., 2014 evaluated the lysine induced oxidative stress, a marked increase in 2,7-Dichlorodihydrofluorescein (DCFH) oxidation was observed. Lysine overload decreases the brain antioxidant defense mechanism and induces protein oxidation by generating reactive species[95]. Glia Maturation Factor (GMF), a neuroinflammatory protein in the brain has been studied in relation to PD pathophysiology. Selvakumar GP et al., 2018 found that GMF increases oxidative stress, mitochondrial dysfunction, and results in apoptotic cell death by altering the expression of Peroxisome Proliferator-Activated Receptor γ Coactivator 1-α (PGC-1α) and inhibits the mitochondrial activity[98]. Which further causes decreased antioxidant enzyme function, increased intracellular ROS level, increased depolarization of mitochondrial membrane potential, and inhibition of Oxidative phosphorylation (OXPHOS) protein complex[98]. All these studies highlight impact of oxidative stress on human brain system, and its functions with regard to specific causative factors resulting in neuronal cell death or neurodegenerative disorders.

Conclusion

This review concluded that it has been made evident by research studies that oxidative stress is involved in the propagation of cellular alteration and mitochondrial dysfunction that further leads to neurodegeneration. Although the neurodegenerative diseases are multifactorial but the oxidative stress is inevitably associated with the disease mechanisms and itself is linked with an integrated series of cellular variations that all contribute to neuronal death. Moreover, cellular factors, exposure to excessive metals, brain injuries and aging have an important role in the progression of oxidative stress leading to neurodegenerative diseases.

Conflicts of Interest

None.

Acknowledgement

We would like to acknowledge the lab members of psychophysiology research lab, specifically Annah Askari, Syeda Farah Batool, Syeda Faiza Batool, Umme Hani Mustafa, and Minhal Akber for their help and support throughout the preparation of this article.

Funding

None.

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