GSC Biological and Pharmaceutical Sciences

eISSN: 2581-3250 CODEN (USA): GBPSC2

Cross Ref DOI: 10.30574/gscbps

Journal homepage: https://gsconlinepress.com/journals/gscbps/

(REVIEW ARTICLE)

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Review on various factors responsible for neurodegenerative disorders

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GSC Biological and Pharmaceutical Sciences, 2021, 16(01), 126–132

Publication history: Received on 13 June 2021; revised on 18 July 2021; accepted on 20 July 2021

Article DOI: https://doi.org/10.30574/gscbps.2021.16.1.0203

Abstract

Neurodegenerative disorders are nervous system disorders that result in the loss of neuronal structure and function. As shown in Alzheimer's and Parkinson's disease, these changes cause a loss of various capacities, including cognition and mobility. Several factors have been discovered to play a critical role in the etiology of common neurological illness es, including oxidative stress and protein misfolding. It's still unclear if these factors cause or contribute to the progres sion of the illnesses. Despite efforts to understand the molecular and pathophysiological mechanisms behind these pat hways, many aspects remain unknown. The goal of this review is to investigate the numerous factors linked to neurod egeneration.

Keywords: Oxidative stress; Mitochondrial dysfunction; Neurodegeneration; Excitotoxicity

1. Introduction

Neurodegenerative 'neuro' means neuron degeneration means "loss' disorders results impairment in loss of activity which performed by neuron, diagnosed as clinical indications of disorders related to neurons [1]. Some neurodegenerative disorders are degenerative disorder, Huntington's disease Alzheimer's, amyotrophic lateral sclerosis, frontotemporal dementia and therefore the spinocerebellar ataxias. These disorders are diversified in their pathophysiology to blame for cognitive impairments causing amnesia and affecting physical activity of somebody's wish to moving, speaking and breathing etc [2-4].

The environmental and genetic influences are most common factors causing disorders of nervous systems in Parkinson's and Alzheimer's, shows by accumulation of abnormal protein aggregate ends up in inflammation and oxidative stress within the CNS [5,6]

Neurodegenerative disorders caused by biological mechanism are oxidative stress, abnormal protein agrregation in neurons, low or improper biosynthesis of neurotransmitters, neurotransmitters degradation within the synaptic cleft by higher activity of enzymes, uncommon ubiquitination, mitochondrial dysfunction Ing, and neuronal excitotoxicity still as displacement or distruction of the BBB [7].

2. Etiology

Neurodegenerative disorders are characterized by progressive loss of functional characteristics of neurons and neuronal obstruction linked with extra and intracellular misfolded proteins accumulation. The main critical processes for abnormal protein function due to the lack of ubiquitin-proteosome-autophagy system, oxidative stress, free radical formation, mitochondrial dysfunctioning and impaired bioenergetics.

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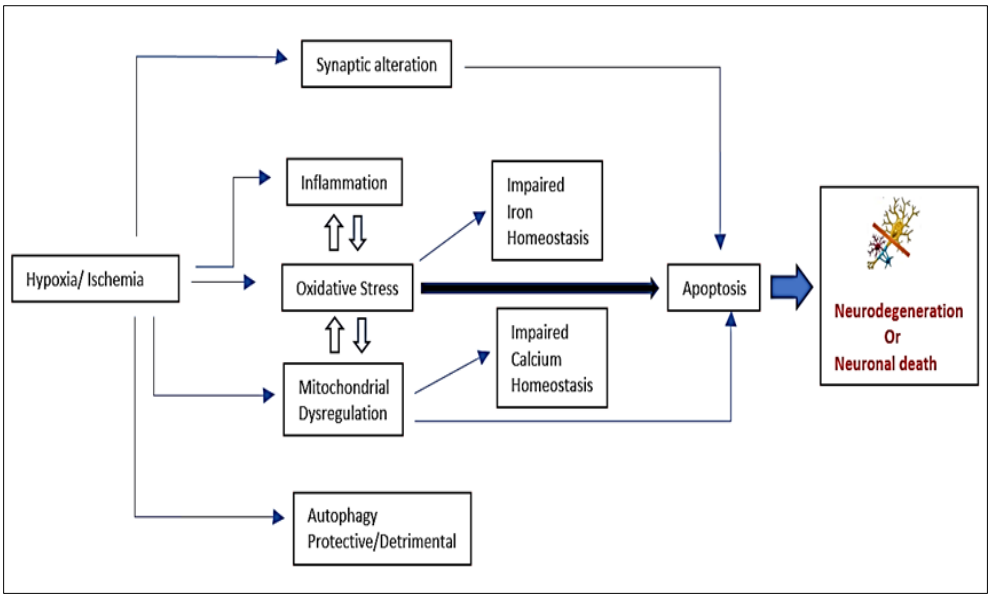

Figure 1 Pathway involve in development of neurodegenerative disorders

The secondary most process involves in dysfunction of neurotrophins (family of proteins that induces the survival, development, and function of neurons) is 'neuronal inflammation which interrupt the neuronal Golgi apparatus and axonal transport. The interconnected mechanisms leads to apoptosis (programmed cell death).

2.1. Protein aggregation

It plays a diverse of pathological characteristic involve in neurodegenerative disorders due to abnormal interactions between intracellular and extracellularly self-aggregating misfolded proteins with formation of high-ordered insoluble fibrils formed by a large number of proteins and peptides.

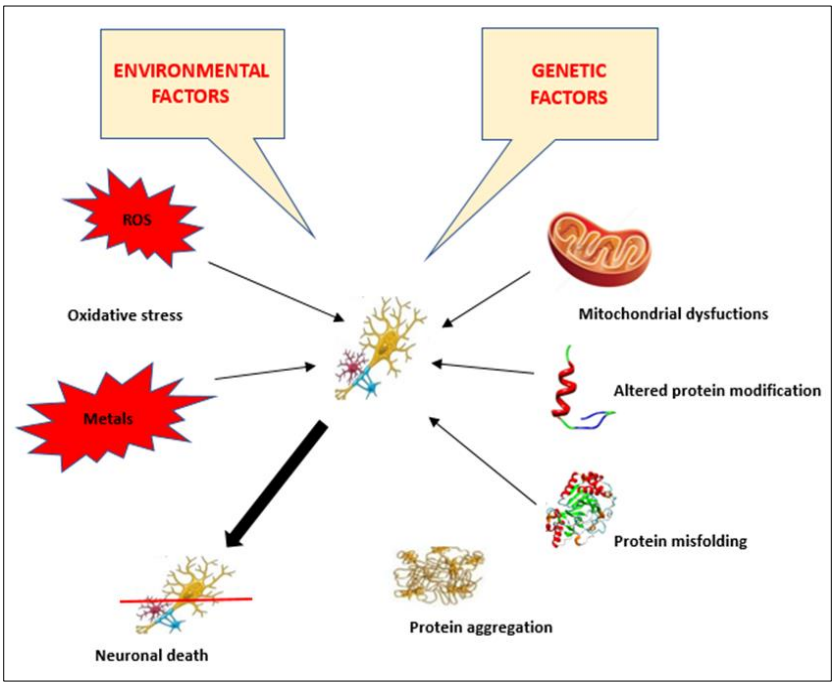

Figure 2 Different factors showing mechanism associated with neurodegenerative disease [8]

The basically process neurodegeneration involves the generation of various gene-gene complex and gene-environmental interaction with mutation within the genes encoding protein constituents. Whereas the disintegration

of neuronal networks rely upon functional loss and neuronal death further as glial cells, this is due to abnormal protein-protein interactions with its lesion that result from the assembly of vicious circles.

Protein aggregation responsible for inappropriate protein folding or misfolding protein results structural and functional changes of a normal protein [8].

2.2. Mitochondrial dysfunction, oxidative stress and ROS

Oxygen is required for the normal functioning, On the basis metabolic needs, different tissues have different oxygen demand. The brain's vast consumption of oxygen and glucose is mostly attributed to the two major groups of brain cells, neurons and astrocytes; moreover, the brain accounts for more than 20% of all oxygen absorption, beyond the fact that oxygen is required for life. Hyperoxia causes toxicity, which entails neurotoxicity. Unbalanced redox states may either contain too many reactive oxygen species (ROS) or cause the antioxidant system to malfunction, resulting in oxidative stress [9].

Mitochondria is known as power house of the cell, perform functions of ATP (Adenosine triphosphate) generation, maintains calcium homeostasis, regulating oxidative stress and neuronal survival. Mitochondrial dysfunction plays key role in pathogenesis of neurodegeneration, mitochondrial dysfunction give rise to neuronal death in case of neurodegenerative disease or disorders.

Under normal physiological environments, there is an equilibrium between mitochondrial fission and fusion, but any failure in these pathways triggers a defect in ATP (Adenosine Triphosphate) biogenesis, which contributes to the initiation of several NDs. Furthermore, mitochondria-mediated ROS may cause lipid and protein peroxidation, as well as an energy deficient state in neurons, which contributes to cell death and dysfunctional neurotransmission [10].

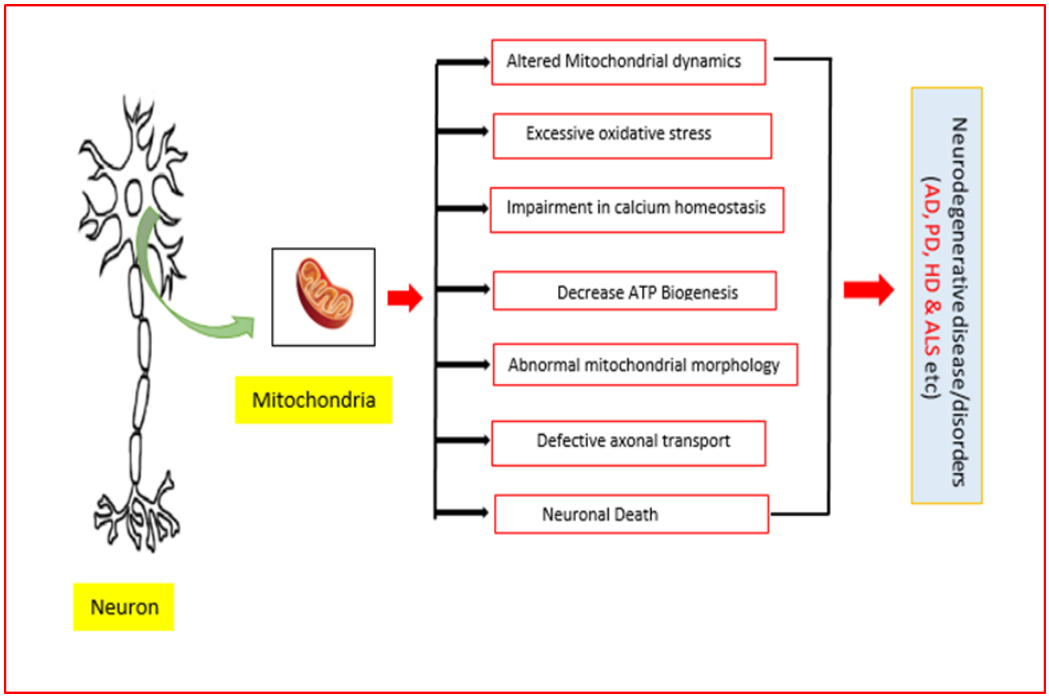

Figure 3 Mitochondrial dysfuction and neurodegenerative disorders [11]

2.3. Environmental Factors

Neurodegenerative disorders caused by environmental factors. Many metals like lead and mercury Show involvement in the pathogenesis of Alzheimer's disease these metals can increase the deposition of Aβ plaques and phosphorylation of tau protein which are characteristic of Alzheimer's disease. Chronic exposure to manganese and certain dangerous solvents have been associated with hallmarks of Parkinson's disease like mitochondrial dysfunction Ing and accumulation of α-synuclein. Even if these metals are very important in biological reactions, a disturbance in their homeostasis results in free radical production. An rise in the intracellular content of iron has been linked to an increase in oxidative stress. Intracellular iron is usually bound by ferritin in the form of an insoluble ferrihydrite centre. 6-hydroxydopamine (6-OHDA) is a neurotoxin that reduces iron to ferrous form, causing it to be released from the

ferrihydrite centre. The iron chelator deferoxamine can prevent this reduced form from facilitating lipid peroxidation. Studies have shown that occupational pesticide exposure causes neuronal damage in elderly people, demonstrating pesticides' toxic function [12].

Environmental factors responsible for Multiple sclerosis, such as exposure to the Epstein-Barr virus, low levels of vitamin D, and smoking [13]. The only environmental factor that is generally accepted to be associated with ALS is smoking. Some evidence supports US military service, lead exposure, physical activity, β-N-meth-ylamino-l-alanine (BMAA), head trauma, electromagnetic fields, agricultural chemicals, and heavy metals as possible factors [14].

2.4. Genetics and Hereditary

There has been great advancement in our understanding of the etiologies of hereditary neurodegenerative disorders in the last few decades, The discovery of various causative genes has aided in a better understanding of disease processes and has also resulted in the advancement of newer therapies. Completely penetrant mutations in three genes (APP, PSEN 1 and PSEN 2) cause hereditary early-onset AD in Alzheimer's disease. In experiments on Parkinson's disease, researchers discovered eight causative genes (α-synuclein, parkin, UCH-L1, PINK1, DJ-1, LRRK2, ATP13A2, and OMI/HTRA2), as well as four additional linkage loci (PARK3, PARK10, PARK11, and PARK12). SOD1, TDP-43, FUS, and TAF15, which cause ALS, caused mitochondrial dysfunction. [12] Mitochondrial dysfunction was caused by ALS-causing genes (SOD1, TDP-43, FUS, and TAF15).

Mutation & fragmentation of huntingtin (htt) results in transcriptional dysfunction, mitochondrial damage, Ca2+ homeostasis impairment , energy deficiency , increases oxidative stress leads to neuronal death [12]. Several genes are believed to play a role in the development of multiple sclerosis. The HLA-DRB1 gene mutations are the most powerful genetic risk factors for multiple sclerosis. IL7R gene mutations have also been attributed to a higher chance of developing multiple sclerosis [13].

2.5. Mediators in neuroinflammation

The activation neuroinflammatory mediators like, microglia and astrocytes and the subsequent release of inflammatory cytokines and prostaglandin responsible for neuroinflammation, which leads to pathogenesis neurodegenerative disorders [9].

3. Alzheimer's disease

Alzheimer's disease (AD) is now the most prevalent type of dementia and it is characterized by a progressive loss of episodic memory and cognitive ability, which contributes to verbal as well as visuospatial skills deficits, as well as behavioral disorders like apathy, aggression, and depression.

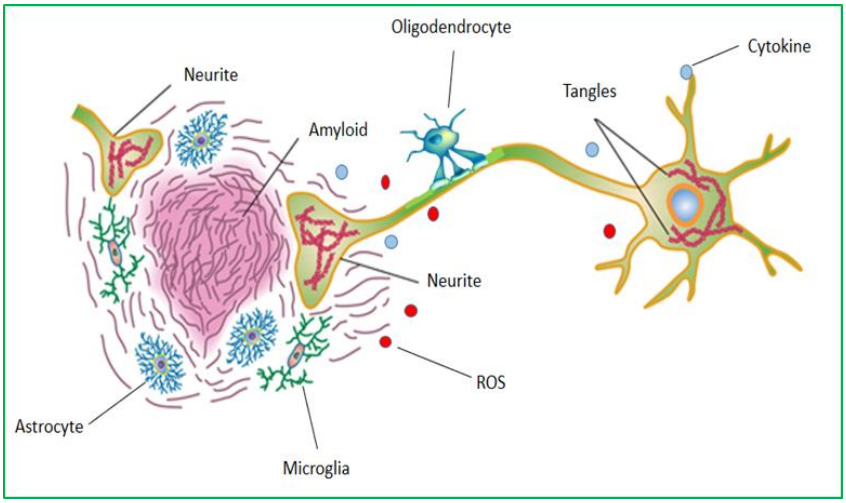

Figure 4 Schematic diagram of a neuron showing, In AD, neurons contain intracellular neurofibrillary tangles composed of hyper phosphorylated tau protein and extracellular plaques of amyloid β (Aβ). An induction of microglia and astrocytes, and the resulting development of inflammatory cytokines and reactive oxygen species (ROS), is important in the pathological processing of Alzheimer [21]

The presence of extracellular plaques of insoluble β-amyloid peptide (Aβ) and neurofibrillary tangles (NFT) containing hyperphosphorylated tau protein (P-tau) in the neuronal cytoplasm is a remarkable pathophysiological hallmark in AD [15]. Dementia of Alzheimer's disease is linked to neurodegeneration, which begins with synaptic injury [16–18] and progresses to neuronal death [19].

Many metals like lead and mercury Show involvement in the pathogenesis of Alzheimer's disease these metals can increase the deposition of Aβ plaques and phosphorylation of tau protein which are characteristic of Alzheimer's disease. Penetrant mutations in 3 genes (APP, PSEN 1 and PSEN 2) are responsible for familial early-onset of AD. [12]

ApoE4 is most prevalent genetic factor in AD. A number of signaling proteins, including fyn kinase; glycogen synthase kinase-3β (GSK3β) and cyclin-dependent kinase-5 (CDK5), are involved in the neurodegenerative progression of AD. Anti-aggregation compounds, pro-clearance receptors, and antagonists of hyperactive signaling pathways could all be useful in the treatment of Alzheimer's disease [20].

Oxidative stress, especially ROS, is caused by amyloid plaque, tau aggregation, excessive generation of ROS, mitochondrial dysfunction, iron accumulation, disrupted calcium homeostasis, and low antioxidant status in Alzheimer's disease. Enhanced oxidative alterations to β-amyloid protein lead to protein misfolding and protein aggregation which in turn causes exacerbation of neurodegeneration and death of neuronal cells in AD. The destruction of the cells leads to brain atrophy in AD [21].

4. Parkinson's disease

Parkinson's disease as a widely known neurologic ailment characterized by tremor and bradykinesia and is a progressive neurodegenerative disease. Motor as well as non - motor signs characterize PD. The classic findings of Parkinson's disease are motor symptoms. They include resting tremor, bradykinesia, postural instability, and rigidity [22].

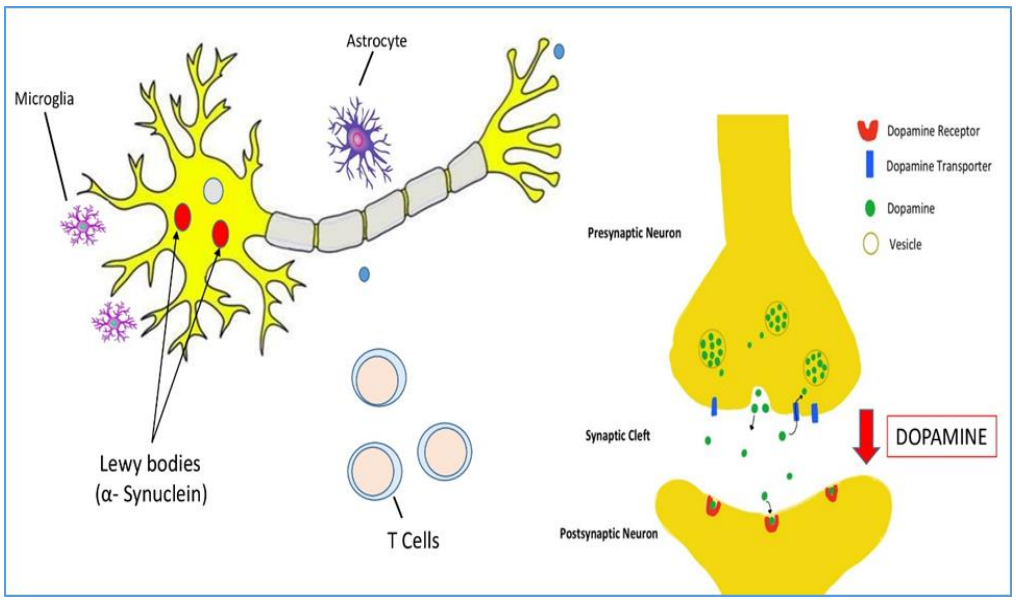

Figure 5 In PD, neurons contain α-synuclein aggregates, forming Lewy bodies. Neuronal loss leads to lower production of dopamine [21]

Accumulation of alpha-synuclein protein, impaired respiratory chain and somatic mitochondrial DNA mutations, iron accumulation, enhanced dopamine metabolism, increase in malondialdehyde and hydroperoxides in the substantia nigra, hydroxyl radical accumulation, and poor antioxidant status generates oxidative stress, particularly ROS in PD. Protein misfolding including aggregation are influenced by elevated oxidative changes to the -synuclein protein, which causes exacerbation of neurodegeneration, degradation of neurones, and loss of dopaminergic neurons in PD. The destruction of the cells and the reduced dopaminergic transmission in the substantia nigra leads to progressive loss of muscular coordination and balance in PD [21].

5. Huntington Disease

HD is an autosomal dominant ND caused by polyglutamine expansion in the gene encoding huntingtin caused by cytosine-adenine-guanine (CAG) repeats. It causes transcriptional dysregulation, making neurons vulnerable to oxidative damage, excitotoxic stress (neuronal stress caused by elevated calcium ions in neurons), energy deprivation, and pro-apoptotic signals. Huntingtin (htt) mutations and fragmentation cause transcriptional disruption, mitochondrial damage, Ca2+ homeostasis impairment, energy deficiency, and increased oxidative stress, all of which contribute to neuronal death [10].

Excessive mHTT aggregation leads to an abnormally high level of ROS production in neurons, as well as a mitochondri al OS. The accumulation of mHTT protein impairment in the electron transport chain and mitochondrial dysfunction, a n imbalance in oxidant-antioxidant status, higher lipid concentration and high energy demand, and low antioxidant levels all contribute to oxidative stress, particularly ROS in HD [21].

6. Amyotrophic lateral sclerosis (ALS)

ALS is one of the most common late-onset NDs, characterized by the gradual and selective loss of both upper and lower motor neurons in the brain cortex, which are linked to muscles fibres via the spinal cord and brainstem. Motor neuron damage causes gradual muscle denervation (muscle atrophy due to a lack of nerve supply), motor dysfunction, paralysis, speech impairment, and eventually death [10].

Oxidative stress, especially ROS, is caused by glutamate-induced excitotoxicity and mitochondrial dysfunction in ALS. Protein misfolding and protein degradation are caused by increased oxidative modifications to the SOD 1 protein, which induces exacerbation of neurodegeneration in ALS. Muscle fatigue is caused by the loss of motor neurons in ALS [21].

In neurodegeneration in HD & ALS, Its shows that mitochondrial oxidative stress increase in both HD & ALS , which results declined antioxidant status and leads to protein misfolding and further neurodegeneration [21].

7. Conclusion

Inflammatory mediators such as cytokinin, astrocytes, microglia, and prostaglandin are stimulated in neurodegenerative disorders such as Alzheimer's disease. Drugs which prevent inflammatory mediators, CNS excitotoxicity and decrease protein misfolding and tau protein aggregation in Alzheimer's disease, as well as inhibiting α- synuclein, which is a marker for Parkinson's disease, Huntington and ALS Treatment with the drug which attenuates the pathways by inhibiting NMDA excitotoxicity as well as acting as an antioxidant will show beneficial effect.

Compliance with ethical standards

Acknowledgments

We are thankful to those people who contributed generously their time to preparing this review paper. We would also like to thank and express our gratitude to the principal and teaching staff of Smt. Kishoritai Bhoyar College of Pharmacy, Kamptee, Nagpur.

Disclosure of conflict of interest

There was no conflict of interest in this study.

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