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Neurodegeneration: Factors Involved and Therapeutic Strategies

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Abstract: *Neurodegenerative disorders are disorders of the nervous system which are characterized by a loss of neuronal structure and function. These changes lead to a loss of several abilities that include cognition and movement as observed in Alzheimer's and Parkinson's. Several factors like oxidative stress and protein misfolding have been found to play a vital role in the etiology of common neurological disorders. Whether these factors contribute to the progression of the disorders or are a consequence still remains elusive. Inspite of attempts to elucidate the molecular and pathological mechanisms of these pathways, many aspects still remain unclear. However, newer areas of therapeutic interventions like stem cell therapy and anti-oxidant therapy are now being explored as potential treatments. The aim of this review is to study the various factors that are associated with neurodegeneration along with recent therapeutic strategies that are being employed in an attempt to treat neurodegenerative disorders.*

Keywords: *factors, neurodegeneration, treatment*

I. Introduction

The term neurodegeneration can be broken down into two terms , "neuro" that relates to the nerve cells and nervous system and " degeneration" which is related to the progressive loss of normal functioning and concurrent damage and deterioration. Thus, this term is applied to a large number of conditions which are characterized by a loss of neuronal structure and function. These changes lead to a loss of several abilities that include cognition and movement. Neurodegeneration is a central aspect of a large number of diseases that are broadly classified as "Neurodegenerative disorders." Disorders like Alzheimer's and Parkinson's have distinct features that are morphological and pathological. Studies have indicated that these disorders can arise due to several conditions like hereditary and genetics, environmental factors and impaired mitochondrial function to name a few. The aim of this review is to study these factors in detail and discuss the various therapeutic strategies that are employed in order to alleviate the symptoms and to prevent further progression of the disorder. Currently, there is no complete cure for most of the neurodegenerative disorders like Alzheimer's disease and thus, attempts are being made to understand the pathophysiological features of these disorders along with newer therapeutic interventions to explore new areas of treatment of neurodegenerative disorders.

II. Oxidative Stress And Reactive Oxygen Species

Studies have indicated the association of oxidative stress with neuronal death since a long time. However, whether it is a cause of neurodegenerative disorders or is an associated consequence still remains elusive.Although the etiology of Neurodegenerative Disorders has not been elucidated completely, there is increasing amount of evidence that suggests that oxidative stress is one common factor. Increasing oxidative stress leads to DNA damage and mitochondrial impairment which can potentially exacerbate neurodegradation. Due to the presence of the two unpaired electrons in the valence shell of oxygen, it is susceptible to the formation of free radicals. [1]. There are various free radical species like super oxides and hydroxyl ions. Cellular ROS can be generated by both endogenous and exogenous sources. [2]. Ultra violet radiations and ionizing radiations constitute exogenous sources of cellular ROS. ROS production can also be triggered due to stimulation by environmental toxins like pesticides. Mitochondrial enzymes and other enzymes from the endoplasmic reticulum like P450 are some of the endogenous sources of reactive oxidative species. Under healthy conditions, the body has various mechanisms to control the levels of the ROS and to maintain a state of equilibrium. Superoxide Dismutase plays a vital role in catalyzing the breakdown of highly reactive $O2^-$ to less reactive species. [3]. Glutathione is a tripeptide that is synthesized from glutamate, cysteine, and glycine and exerts a protective function against oxidative stress. [4].The normal levels of ROS play many regulatory roles in cellular signaling and in various pathways that are essential to cell survival. For example, the Nox- derived ROS play a role in cellular signaling that is related to cardiovascular systems. [5] Thus, this state of oxidative stress and imbalance occurs only when the anti -oxidant defense systems are unable to cope up with the reactive oxygen species accumulation and thereby leads to a state of oxidative stress.This oxidative stress can be related to various consequences like cell membrane damage that arises due to lipid peroxidation or protein misfolding due to protein oxidation. The DNA repair systems can also be damaged due to oxidative stress. There are various factors that make the brain more susceptible to oxidative stress. The brain has a high oxygen demand

and contains high levels of polyunsaturated fatty acids in the cell membranes which react as substrates for lipid peroxidation. [6]. Many metals like copper exist in large quantities in the brain and catalyze the process of formation of reactive oxygen species. It has also been reported that lower levels of glutathione, an antioxidant can make certain neurons more susceptible to oxidative stress. [7].

III. Environmental Factors

Several environmental factors can contribute to the progression of neurodegenerative disorders. Several metals like lead and mercury have been involved in the pathogenesis of Alzheimer's disease due to their ability to increase the deposition of Aβ plaques and phosphorylation of tau protein that are characteristic of Alzheimer's disease. Chronic exposure to metals like manganese and certain toxic solvents have been associated with hallmarks of Parkinson's disease like mitochondrial dysfunction and accumulation of α-synuclein. While these metals are very essential in biological reactions, a disturbance in their homeostasis results in free radical production. It has been found that an increase in the intracellular concentration of iron leads to an increase in oxidative stress. Normally, the intracellular iron is bound by ferritin in an insoluble ferrihydrite core. 6-hydroxydopamine (6-OHDA) is a neurotoxin that causes the release of iron from the ferrihydrite core by reducing it to the ferrous form. This reduced form then stimulates lipid peroxidation, which can be inhibited by adding deferoxamine, an iron chelator. Studies have shown how occupational exposure to pesticides has caused neuronal impairment in elderly people, thereby highlighting the toxic role of pesticides. [8] There is also evidence that regular consumption of nutritious food like fruits, vegetables and omega -3 rich oils may decrease the risk of dementia and AD, especially among APOE-ε4 non-carriers. [9].

IV. Role Of Protein Misfolding And Aggregation

Proteins can be defined as structurally complex biomolecules which regulate fundamental processes and are considered as the building blocks of our body. Every protein is synthesized as a long stretch of amino acid chains and these polypeptide chains are folded into three dimensional structures in order to attain a functional state. [10].The correct folding of proteins can be ensured in a narrow range of thermodynamic conditions inside the cell. [11]. There are various conditions like age, disease and oxidative stress that can alter the essential conditions and therefore lead to protein misfolding. The correct three dimensional folding is essential for the protein in attaining its biochemical functionality. If the proteins get partially folded, or misfolded, they can affect various cellular processes and can be toxic to the cell. The truncated or the misfolded proteins can lead to the exposure of hydrophobic regions which then have a tendency to form clumps or aggregates. [12]The protein misfolding is further followed by self-association of the proteins and subsequent deposition of the aggregated plaques in the brain tissues. Alzheimer's disease and Parkinson disease are protein misfolding diseases, which are caused by the presence and accumulation of abnormal proteins, and are associated with cell dysfunctions [13].They are very commonly referred to as proteinopathies due to the characteristic protein misfolding hallmark. The deleterious effects of protein misfolding are minimized in living systems by various protective systems like the quality control system of cell and molecular chaperons. There are two specific lines of defencethat ensure the regulation and maintainance of proteostatic equilibrium inside the cell. [14] Firstly, the protein chaperons bind to unfolded proteins and newly synthesized proteins, and through ATP hydrolysis, actively contribute to the attainment of the mature protein confirmation. Secondly, the pathway involving E1-, E2- and E3- ubiquitin ligases which are recruited by the chaperons, target proteins that are damaged beyond repair and clear them by proteolysis. The PQC pathways are compartmentalized spatially on the basis of the subcellular location of their misfolded substrates. [15] These protein misfoldings and aggregates can be recognized due to appearance of toxic folds or premature degradation that occurs. [16]

V. Genetics And Hereditary

In the last few decades, there has been great advancement in our understanding of the etiologies of hereditary neurodegenerative diseases. The discoveries of the various causative genes for these disorders have promoted a greater understanding of the mechanisms of the diseases and have also lead to the development of newer therapies. In case of Alzheimer's, fully penetrant mutations in 3 genes (APP, PSEN 1 and PSEN 2) are responsible for familial early-onset of AD. In a minority of cases, PD is inherited as a Mendelian trait. Studies have identified 8 causative genes (a-synuclein, parkin, UCH-L1, PINK1, DJ-1, LRRK2, ATP13A2 and OMI/HTRA2) and 4 additional loci of linkage across the genome (PARK3, PARK10, PARK11 and PARK12) pending characterization and/or replication. [17]. Thus, this knowledge has greatly impacted the development of newer therapies along with methods of diagnosis.

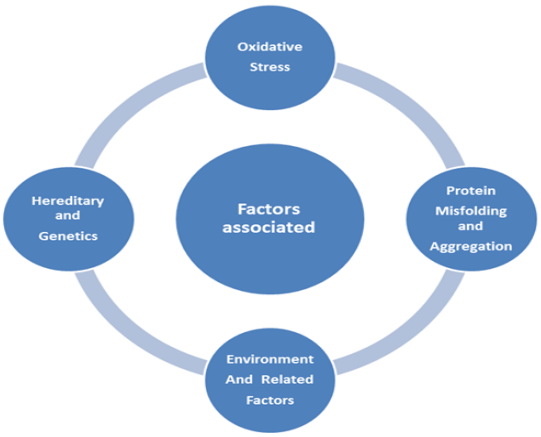

Fig. 1: Various Factors associated with Neurodegeneration.

VI. Therapies For The Treatment Of Neurodegenerative Disorders

There are various therapies that are being explored and are emerging as possible strategies for the treatment of neurodegenerative disorders that target specific pathways or aim to prevent the neuronal loss that is caused due to specific factors. For instance, the anti -oxidant therapy aims to inhibit the oxidative stress that occurs due to the release of free radical species. Areas like nanotechnology, immunotherapy and stem cell therapy are also being explored as potential cures for the neurodegenerative disorders.

6.1.1. Anti -Oxidant Therapy

The most commonly used anti -oxidants for clinical applications include vitamin E that acts as a scavenger of lipid peroxidation in the brain, vitamin C that acts as an intracellular reducing molecule and N-acetyl cysteine that acts as a precursor of glutathione. [18]. However, anti -oxidant therapy has still not been employed as a completely effective therapy for neurodegenerative disorders. This could be due to several reasons like the primary cause of the disorder not being oxidative stress. In such a case, if oxidative damage is occurring during the progression of the disease as a side effect, anti -oxidant therapy will not be successful. Secondly, there is a possibility that antioxidant therapy failed at causing a decrease in oxidative stress in patients with neurodegenerative diseases as the dose was insufficient or the therapy duration was inadequate. [19] Furthermore, there is a chance that a single antioxidant may not solely contribute to preventing the oxidative damage that occurs as oxidative stress is modulated by a complex system that comprises of both endogenous and exogenous antioxidants. [20] Thus, the benefit of this therapy can be explored in further detail by identifying central biomarkers for oxidative stress and detecting the benefits that are derived from this therapy along with further investigation with regard to the exact role and pathway of oxidative stress in a neurological disorder.

6.1.2. Immunotherapy

Immunotherapy is being explored extensively as a future prospect for neurodegenerative disorders, especially Alzheimer's disease. However, initial human trials of the Aβ vaccination were halted due to serious side effects (meningoencephalitis) that were witnessed in subjects.[21] However, rapid progress has been made towards the development of alternative and safer immunotherapeutic approaches. Many of these approaches are currently in clinical trials. Activeimmunization , passive immunization and T- cell mediated cellular immunotherapeutic approaches have been developed in attempts to target Aβ,α-syn and tau protein. Passive immunization in an attempt to coat Aβ plaques to enhance their phagocytic uptake by microglial cells in an area of great research. The major scope for future prospect lies in gaining a better understanding of the mechanisms involved in T- cell or antibody mediated clearance of the abnormal misfolded or hyperphosphorylated proteins in vivo, which should be facilitated by an impeccable array of transgenic animal models for neurodegenerative disorders.

6.1.3. Stem Cell Therapy

Stem cells have the ability of repairing injured nervous tissue by causing the replacement of damaged cells. They also play a neuroprotective role in creating an environment that is conducive to the regeneration of endogenous cells. Thus, cell replacement therapy and gene transfer may act as powerful and promising therapeutic strategies for neurodegenerative disorders. The stem cells are multipotent in nature and can contribute to the delivery of therapeutic factors which can aid in the replacement of dysfunctional cells. In Parkinson's disease, current therapies rely on the oral administration of L-dopa and dopamine receptor agonist [22]. Studies in patients suffering from Parkinson's disease after intrastriatal transplantation of human fetal

mesencephalic tissue, have shown results that indicate that the theory of neuronal replacement can work in the human brain[23]However, inspite of the effective pharmacological treatment, the development of side effects and gradual decrease in effectiveness are limitations in this therapy [24]. Thus, an alternative approach for restoration of the damaged dopaminergic system is the transplantation of dopaminergic-synthesizing cells. Human stem cells may provide sources of cells for use in the treatment of PD [25]. In case of Alzheimer's disease, stem cells can be modified genetically to carry new genes and exhibit a high migratory ability after brain transplantation, and could be used in place of fibroblasts for delivery of the nerve growth factor (NGF) to prevent degeneration of basal forebrain cholinergic neurons[26] The major advancements that are being made in the field of stem cell research provide possibilities for neural implantation for patients suffering from various disorders like Amyotrophic lateral sclerosis. However, the major challenge still remains in identification of the ideal stem cell type and route for administration for each neurodegenerative disorder. It is also difficult to control the proliferation and differentiation of the stem cells. Another drawback is that the animal models may not always fully predict the toxic effects of the stem cells and may not indicate immune responses completely. Thus, there can be a possibility of tumor formation or other immune responses occurring in the patients post transplantation. Finally, attempts are being made to explore less invasive methods of stem cell implantation across the blood brain barrier.

6.1.4. Nanotechnology

One of the major challenges that is involved in the treatment of neurodegenerative disorders is the interaction of the medicament with the blood brain barrier. Currently, nanomedicine is one of the most promising strategies, which exploits the mechanisms of transport without interfering with the normal functioning of the barrier. There are two broad mechanisms of this transfer, receptor mediated and adsorptive mediated.The field of nanotechnology finds it application in fields like the diagnosis and treatment of neurological diseases and also as a regenerative medicine strategy. Extracellular scaffolds have been used to facilitate neuronal attachment which contributes to the repair of damaged neuronal tissues. NT and nanofibres (NF) have been successfully exploited for regenerative medicine, due to similarities of their structure to those of cells. [27]. Nanotechnology is also involved in playing various neuroprotective roles. It is a widely known fact that excessive oxidative stress promotes neurodegeneration. Fullerenes have been suggested as radical "sponges" that make use of their delocalized double bond system in removing the superoxide radicals. [28]. Nanotechnology aids in measurement of known pathogenic markers like tau protein in human and thereby in the diagnosis of Alzheimer's disease. The recent advancement of nano-HPLC-MS has been used for phospholipid profiling of CSF which can help in monitoring lipid changes as possible additional pathogenic AD markers [29]. Nanoliposomes (NL) functionalized with phosphatidic acid or cardiolipin have demonstrated positive effects in the treatment of Alzheimer' disease. [30].Delivery and release of dopamine has been reported by nano – based approaches which can aid in the treatment of Parkinson''s disease. [31]. Chitosan NP that are adsorbed with dopamine have been studied for Parkinson's treatment [32] .Nanotechnology has also served as a tool for the in vitro diagnosis of Parkinson's disease. Au-doped TIO_2 nanotube arrays have been designed as immunosensors for α-synuclein detection. [33] .Inspite of all the technological advancements, there are still many challenges that are faced in the employment of Nanotherapy as an effective strategy. Firstly, the nano material should cross the BBB without causing any side effects. [34].The nano material should be biodegradable and must not promote an immunogenic response. Currently,very little is known about the potential toxic effects of the nano material on the CNS. [35]. Thus, more research and investigation is necessary in this field before the complete translation of this therapy occurs from pre-clinical to concrete clinical applications.

Fig 2: Therapeutic Strategies employed to treat Neurodegenerative Disorders.

VII. Conclusion

As discussed, several neurodegenerative disorders like Alzheimer's disease and Parkinson's disease appear to share various degenerative processes that can either contribute to or exacerbate neuronal death and dysfunction. This neuronal dysfunction can then lead to numerous impairments and can have deleterious effects on various processes like memory, learning and cognition to name a few. Due to the high prevalence of these disorders, attempts are being made to elucidate the role of the components that contribute to neurological disorders in greater detail. Inspite of great research being done in these areas, no effective cure for these neurodegenerative diseases has been identified. Most of the therapies that are employed provide symptomatic relief and do not target the actual cause of the disorder. Therefore, newer therapeutic strategies like use of Anti-Oxidant Therapy to relieve the oxidative stress, stem cell therapy to promote nerve cell growth and nanotechnology are being explored in an attempt to develop disease-modifying therapies that can effectively treat neurodegenerative disorders.

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