



Review Article

NEURODEGENERATIVE DISEASES: AN OVERVIEW

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ABSTRACT

Neurodegenerative diseases are traditionally defined as disorders with selective loss of neurons and distinct involvement of functional systems defining clinical presentation. The neurodegenerative diseases affect a significant number of individuals in all age groups. The common features of multiple neurodegenerative diseases, such as abnormalities in protein degradation pathways, mitochondrial dysfunction, compromised axonal transport processes and ultimately induction of cell death pathways. These aberrant processes originate in and in many cases remain restricted to, specific regions and cell types within the CNS. This review can provide impulsion for investigators to take on molecular mechanism with the ultimate hope of finding a cure for the devastating neurological diseases.

Keywords: Neurodegenerative disease, Molecular mechanism, Alzheimer's, Parkinson's

INTRODUCTION

Neurodegenerative disorders (NDD) is a hereditary or sporadic condition that results in slow and irreversible loss of neurons and their processes (axons, dendrites, synapses) with a corresponding progressive impairment in neuronal function¹. Etymologically, the word is composed of the prefix “neuro-,” which designates nerve cells (i.e. neurons), and “degeneration,” which refers to, in the case of tissues or organs, a process of losing structure or function.

Thus, in the strict sense of the word, Neurodegenerative disorders correspond to any pathological condition primarily affecting neurons. Examples of NDDs are Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, prion diseases, Pick's disease, corticobasal degeneration (CBD), progressive supra nuclear palsy, amyotrophic lateral sclerosis (ALS), front temporal dementia, spino-cerebellar ataxias (SCA), spinal muscular atrophy (SMA), motor neurone diseases (MND) and Friederichs's ataxia. Among these diseases AD and PD are the most prevalent diseases, where AD is known as an escalating dementia, while PD is primarily characterized as a movement disorder – affecting 5% and 1%, respectively, of individuals aged 65 and dramatically increase up to 35% and 5% at age 80 and above².

These NDDs are diverse in their patho physiology – with some causing memory and cognitive impairments and others affecting a person's ability to move, speak and breathe³. The major factors that contribute to the development of NDD are genetics, aging and environmental causes⁴.

The possible molecular mechanisms underlying NDDs are Proteosomal dysfunction (due to impairment in ubiquitin-proteasome-autophagy system (UPA)), oxidative stress, dysregulation in alternative splicing, free radical formation, mitochondrial dysfunction, DNA damage, Neuro-inflammatory process, dysfunction of neurotrophins, disruptions of Neuronal Golgi apparatus and Axonal transport. These mechanisms are interrelated in complex circles finally leading to cell dysfunction and neuronal cell death. Some of them are common for all NDD, such a neuro-inflammation, free radical production and oxidative stress, mitochondrial dysfunction, while others are more specific for a particular disorder. Neurodegenerative diseases, including AD, PD, MND, Huntington disease and prion disease share a common feature: accumulation of abnormally aggregated intracellular proteins like tau, amyloid-beta (A β), alpha-synuclein (α -syn), or TDP-43^{5,6}.

Several treatments are available for NDDs, but none of them are particularly effective in terms of fully overcoming the disease rather there are only drugs for symptomatic relief. This is because the symptoms and exacerbations of all these diseases are much different according to their specific pathways and mechanisms of cell death. Effective treatments are critically needed to treat neuro-degeneration at molecular level but only after understanding the deep underlying mechanisms of each neurodegenerative disorder.

However, this review mainly focuses on Biological pathways, pathological hallmarks along with recent findings of most common neurodegenerative diseases Alzheimer's and Parkinsonism in detail. Thus the objective is to improve the understanding of the underlying molecular mechanisms, thus

leading pathway for designing novel therapeutic strategies either to halt or at least slow disease progression rather than merely providing symptomatic treatment.

Alzheimer's disease

Alzheimer's disease (AD) is an irreversible brain disorder characterized by memory deficits and cognitive impairment. Initial symptom of AD includes short term memory loss that develops into profound memory failures at subsequent stages⁷ which finally leads victims to be bed-ridden, with loss of control in urinary and bowel movement and frequent epileptic attacks⁸. The biological pathway that underlies AD are Amyloid hypothesis, Tau hypothesis, APP Trigger Tauopathy, Cholinergic Hypothesis, Mitochondrial Cascade Hypothesis, The Metabolic Hypothesis, The Vascular Hypothesis, Neuroepigenetic Modification.

Common Neurodegenerative mechanism in Alzheimer's disease

In Amyloid hypothesis, the accumulation of A β plaques acts as an enhancer in the pathological cascade, including neurite damage and NFT formation via tau protein, which may result to neuronal dysfunction and cell death in AD⁹. Tau hyper phosphorylation appears as Neurofibrillary tangles (NFT) that includes paired helical filaments (PHFs) or related straight filaments (SFs). These findings suggested that mis-sorting of tau might induce tau pathology and could contribute to the cognitive and metabolic alterations in patients with AD¹⁰. Impairment of APP metabolism also triggers AD by starting with neuro-inflammation and then progresses through tau pathology¹¹.

Reduced cortical cholinergic neurotransmission due to neuron or synapse loss results in reduced coupling of Muscarinic M1 receptors to second messenger system that leads to NFT formation, reduced secretion of soluble APP, increased production of β -amyloid protein and decreased glutamate production. It is hypothesized that these changes give rise to the clinical symptoms of AD and contribute to the spread of pathology¹².

In mitochondrial cascade hypothesis, mitochondria sit at the apex of AD histopathology and ND. Many investigators, though, feel mitochondria do not play an upstream role in AD¹³. The abnormalities in neuronal glucose/energetic metabolism leads to deficit in ATP availability and abnormalities in the insulin signal transduction cascade causing an intracellular accumulation of A β . Furthermore, the hyper phosphorylation of tau protein and consequent formation of NFT is potentiated by insulin signal transduction abnormalities and low levels of ATP¹⁴.

The critical steps that turns normal aging into a cognitively dysfunctional vortex begins with the acquisition of vascular risk factors responsible for the persistent cerebral Hypo perfusion (CATCH) that later follows up. The process may take decades to develop until progressive ND appears and in time, AD. β - Secretase, Glycogen synthase kinase-3 β , Acetyl cholinesterase, Butyl cholinesterase and Rho Kinase are the common enzymes involved in dysregulation, one of the most common pathological scenarios of AD and involvement of such dys-regulation has been targeted in several therapeutic approaches for AD¹⁵.

Some pathological changes are attributed to neuroepigenetic alterations which make neuronal DNA to switch "on" or "off" certain genes which further contributes to the onset of pathological changes in some neurodegenerative disorders, such as Alzheimer's. The classical neuro-pathological hallmarks of

AD are senile plaques (containing deposits of A β protein) and NFT (consisting of hyper phosphorylated tau protein) and brain atrophy in specific brain areas confirms the presence of AD¹⁶.

Initial attempts to treat AD were not related to any of the currently known core patho-physiological abnormalities but were merely related to symptomatic treatment. On this basis, effective treatment for AD is achieved with drugs like Rivastigmine, donepezil, galantamine, Memantine.

Parkinson's disease

Parkinson's disease (PD) is the world's second most common neurodegenerative disorder, which can significantly impair the quality of life, create dependency and trigger premature mortality of affected individuals. It is characterized by diminished facial expression, stooped posture, slowness of voluntary movement, festinating gait, rigidity, and a "pill-rolling" tremor¹⁷. The most salient mechanisms involved in the development of PD include the accumulation of misfolded proteins aggregates, failure of protein clearance pathways, mitochondrial damage, oxidative stress, excitotoxicity, neuro-inflammation, and genetic mutations.

Common Neurodegenerative mechanism in Parkinson's disease

Dopamine (DA) deficiency occurs due to progressive neuronal loss in Substantia Nigra pars compacta (SNc) which leads to formation of abnormal protein-rich aggregates-known as Lewy bodies¹⁸. There are also number of genes identified and reported to be in association with inheritable PD which includes SNCA, Wnt, Parkin/PRKN, DJ-1/Park7, PINK1, and LRRK2 (leucine-rich repeat kinase)¹⁹. PD also includes accumulation of Tau leading to NFT formation, hallmark of the disease which is also found in AD.

Ubiquitin-Proteasome System (UPS) is the most efficient disposal system of cell, and is mainly responsible for degradation of short polypeptides into small intracellular and plasma-membrane proteins in normal cells²⁰. The Impairment or failure of this critical cellular system has been observed in the pathogenesis of PD, leading to aggregation of misfolded amyloid proteins, such as Lewy bodies, and an increase in neurodegeneration in the SNpc²¹.

Recently, the "prion hypothesis" is considered one of the most intriguing theories behind its onset. This theory posits that SNCA spreads throughout the CNS, similar to "prion proteins" and infect adjacent new, healthy neurons and that this cycle continues until most of the CNS neurons are infected. Therefore, "prion-like infection" of SNCA may be responsible for the progression and neurodegeneration of some types of PD²². One more promising theory in PD research, as well as other age-related neurodegenerative diseases, is the oxidative stress theory. This theory posits that the mitochondria are the "hot-spot" for degenerative processes²³. In addition, environmental toxins cause increased production of glutamate, leading to Ca⁺⁺ excitotoxicity which makes DA neurons vulnerable to neurodegeneration. There are no available therapies that alter the underlying neurodegenerative process. Only symptomatic therapies can improve patient quality of life, where therapy for PD is still under investigation. The current available drug treatment for PD includes Levodopa, Carbidopa, Dopamine agonist like Ropinirole, Pramipexole, MAO-B Inhibitors, COMT-Inhibitors.

RECENT DISCOVERIES IN NEURODEGENERATIVE DISEASES

In addition to the review on pathological mechanisms, this special collection showcases original research articles on Alzheimer's disease and Parkinson's disease that impact our understanding of neurodegenerative disease mechanisms.

Okamoto *et al.*, reported that Glutamate modulator, Riluzole significantly enhanced cognition and reduced A β 42, A β 40, A β oligomers levels, and A β plaque load in 5XFAD mice. Their findings showed that riluzole reversed many gene expression changes, specifically disease-associated microglia (DAM), as well as neurons and astrocytes in RNA-Sequencing. Central to the cognitive improvements observed, riluzole reversed alterations in NMDA receptor subunits gene expression, which are essential for learning and memory. Together, these findings suggest results that riluzole's regulation of the glutamatergic synapse plays a critical role in reducing A β levels and restoring expression of genes implicated in both microglial activation and synaptic transmission²⁴.

Bogie Jet. al., investigated on phytosterols and phytosterol-containing extracts that activate Liver X Receptor- β (LXRs) *in vitro*, to test their effect on memory performance and A β plaque pathology in an animal model of AD. They concluded that *Sargassum fusiforme* improves cognition and alleviates AD pathology which may be explained at least partly by 24(S)-Saringosterol-mediated LXR β activation²⁵.

Seok H *et al.* proposed the novel therapeutic potential of PPAR- γ agonist for AD treatment at a lower dose than the conventional clinical dose to treat diabetes. They reported that low-dose pioglitazone increased the expression of low-density lipoprotein receptor-related protein 1 (LRP1), which upregulates the clearance of A β , using human brain microvascular endothelial cells²⁶.

Wang C *et al.* findings predict a therapeutic potential of piperine against cognitive deficits in sporadic AD mouse. They concluded this effect might be due to its abilities to ameliorate oxidative-nitrosative stress, restore neurotransmission and reduce neuroinflammation²⁷.

Bhuvaneshxari S, *et al.* performed molecular docking study and showed that embelin binds well to active site of AChE with interaction energy of -65.75 kcal/mol which correlates with their *in vitro* results. From the findings of the study they conclude that embelin could be a suitable molecule to be further developed as therapeutic molecule for treatment neurological disorders particularly Alzheimer's disease²⁸.

Viswanathan, G.K. *et al.* has characterized a hit molecule as a modulator of Tau aggregation using *in vitro*, *in silico*, and *in vivo* techniques. The molecule named Purpurin, inhibited ~50% of PHF6 fibrillization *in vitro* at equimolar concentration and disassembled pre-formed PHF6 fibrils. *In silico* studies showed that Purpurin interacted with key residues of PHF6, which are responsible for maintaining its β -sheets conformation. The research concludes that Purpurin significantly ameliorated the AD-related neurotoxic symptoms of transgenic flies expressing plausibly by inhibiting Tau accumulation and reducing Tau Phosphorylation²⁹.

Abby L. Olsen studied about the enzyme poly (adenosine 5'-diphosphate-ribose) polymerase 1 (PARP1) and found it as a mediator of neuronal cell death in Parkinson's disease. His findings also provide support for a class of FDA-approved drugs

that inhibit PARP1, currently used in the treatment of certain breast and ovarian cancers, as candidate drugs for Parkinson's disease³⁰.

Gao G *et al.* opens a novel avenue that Gold nanoclusters (AuNCs) prevents α -Synuclein aggregation and fibrillation and improve cell viability in MPP⁺ lesioned cell PD model and points a new direction for AuNCs in medicinal applications³¹.

Gaba B *et al.* presented results that provided evidence for possible efficacy of a novel noninvasive intranasal delivery system of Vitamin E Loaded Naringenin Nanoemulsion for management of PD related symptoms in a 6-OHDA Parkinson's disease Model³².

Gerez *et al.* showed that insoluble α Syn fibrils, but not monomers or small oligomers, were internalized and accumulated in neuronal cells. Upon internalization, a specific iron-regulated ubiquitin ligase mediated α Syn fibril degradation. Promoting this ubiquitination counteracted Lewy bodies (LB) formation and spreading in mouse models of α Syn accumulation. The results suggest that the ubiquitin complex described here might be a potential target for treating disorders associated with LB formation³³.

Sardoiwala N *et al.* evaluated neuroprotective efficacy of bio-compatible polydopamine nanocarrier for metformin delivery (Met encapsulated PDANPs) by *in vitro*, 3D and *in vivo* experimental PD models. Their study divulges the neuroprotective role of Met loaded PDANPs by reversing the neurochemical deficits arbitrated by downregulation of phosphoserine 129 (pSer129) α -Syn, with reduction in oxidative stress, prevention of apoptosis and anti-inflammatory activities. This study also proved that neuroprotective mechanism is because of novel interaction of epigenetic regulator EZH2 mediated ubiquitination and proteasomal degradation of aggregated pSer129 α -Syn³⁴.

Kim KH *et al.* has previously demonstrated that subcutaneous administration of bee venom (BV) phospholipase A₂ (bvPLA₂) suppresses dopaminergic neuronal cell death in a PD mouse model. Now in their present study, they established administration of purified bvPLA₂ in a dose-dependent manner reversed motor deficits in PD mice by suppressing microglial activation as well as inhibited loss of dopaminergic neurons within the substantia nigra of PD mice³⁵.

Lee SB *et al.* elucidated the neuroprotective effects of Transcranial direct current stimulation (tDCS) on the mitochondrial quality control pathway in a MPTP-induced PD mouse model. tDCS improved the behavioral alterations, changes in tyrosine hydroxylase levels further attenuated mitochondrial damage, decreased mitophagy as indicated by diminished mitochondrial swelling and mitochondrial glutamate dehydrogenase activity in the PD mouse model. The study was concluded that neuroprotective effect of anodal tDCS with modulation of mitochondrial dynamics provides a new therapeutic strategy for the treatment of PD³⁶.

CONCLUSION

This review outlined the current concepts on multiple pathways that may lead to cascade of events leading to manifestation of NDDs. On the whole, it is the pathways and networks that can serve as vehicles for diverse findings on neurodegeneration. Therefore, there is a need for understanding the mechanisms of NDD in order to aid development of more effective therapeutics. The urge now is to understand the biological pathways in which

the disease progress. The challenge in the near future will be to determine effective drugs that can tackle the dysregulated biological pathways for the treatment of neurodegenerative diseases. Given lot of information on Neurodegenerative disease specially on Alzheimer and Parkinson's, we are sure that an ideal therapeutic drug will be discovered in the near future by targeting the specific pathways for neurodegenerative disorders.

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