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REVIEW ARTICLE

A Review on Biomolecular Mechanisms of Parkinson's Disease

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ABSTRACT

Degeneration of catecholaminergic (dopamine) neurons in the Substantia Nigra pars compacta of the basal ganglia results in Parkinson's disease (PD). The drug of choice is L-dopa, anticholinergics, amantadine, monoamine oxidase-B inhibitors, dopamine agonists, and catechol O-methyl transferase inhibitors are used. Therapeutic strategies are currently managing the symptoms of PD, but not curing the disease. This review draws insights on the molecular mechanisms driving the loss of brain cells in PD.

Keywords: Alpha-synuclein, excitotoxicity, free radicals, neuroinflammation, oxidative damage, protein degradation

INTRODUCTION

In all neurodegenerative disorders, Parkinson's disease (PD) has a negative impact on health quality. It has a worldwide impact on millions of people. The management of PD appears to be the most challenging aspect for neurologists. Several genes have been changed in recent decades to create greater understanding of the pathology of the disease. Early detection of signs and symptoms of PD is important in diagnosis. In PD affected individuals, the cell loss is particularly pronounced within substantia nigra that significantly affects the ventral part.

In a particular region of the affected population, the brain loses 50–70% of neurons compared to those unaffected. Parkinsonism has two types: Early onset of PD, which will see the early stages and late onset of PD, which will see the features when the disease extends. Both the first and last stages of PD have better treatment options based on their symptoms and signs. The combination of cellular and cellular pathways leads to the formation of PD in a way that makes treatment difficult.[1]

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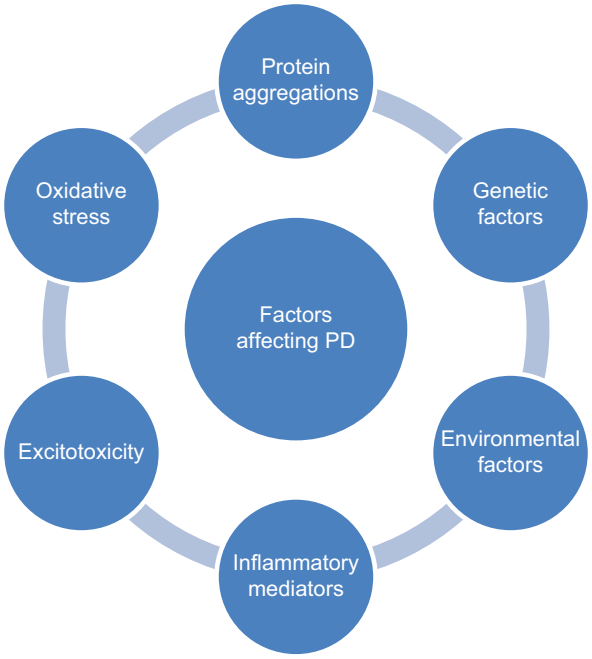
PD is affects more than a million people over the age of 55. Treatment for PD can be symptom control or neuroprotection. PD has both motor and non-motor features that are referred to as primary symptoms. Motor symptoms include tremors, stiffness, and slow movement while non-motor symptoms include the changes in blood pressure, mood, sleep, and weight. Secondary symptoms include difficulty speaking, vision problems, urinary problems, sexual dysfunction, and weight loss. Tremors and shaking are seen in the early stages of PD. As a result of this tremor, there is a slow movement of body that continues to leads to a lack of balance in walking. This is clinically referred to as Bradykinesia. Normal body movement is regulated by a neurotransmitter called dopamine, but in PD it leads to decrease in dopamine levels in the striatum.[2,3]

There is no known cause for PD occurrence. Many factors are involved. Studies have shown that the combination of environmental and genetic factors leads to the status of PD. Several mutations have been identified that cause changes in the type of PD development. The following mutations identified in PD: A gene encodes PARK1, PARK4 (SNCA), Parkin, Ubiquitin Carboxyl-Terminal Esterase 1 (UCHL 1), DJ-1, PTEN-induced kinase 1 (PINK1), Leucine-rich repeat kinase 2 (LRRK2), ATP13A2.

Pesticides, and natural herbicides also cause PD. A chemical called 1-Methyl-4-Phenyl-1,2,3,6 tetrahydro pyridine (MPTP) is also responsible for the formation of PD. Medications such as anti-psychotics also develop PD.[4]



Compared to other sensory conditions the prevalence of PD is higher. It is most common in men. The primary pathology is the aggregation of α-syn. Initially, the disease begins within the medulla and olfactory bulb. In the later stages, the disease progresses to Substantia Nigra pars compacta (SNpc). It is the stage at which we should diagnose the disease. There is also an advanced phase of PD where pathology reaches the cerebral cortices leading to mental and visual impairment. The pathology involves not only dopamine deficiency but also other neurotransmitters such as serotonin, nor-epinephrine, histamine, glutamine, and acetylcholine. Dopamine mainly affects motor impairment while other neurotransmitters affect mental retardation, mental illness, depression, and anxiety.

There are three types of PD subtypes:[5]

Subtypes	Mild	Intermediate	Malignant
Incidence (%)	49–53	35–40	9–15
Onset	Young age	Medium age	Adults
Symptoms	Mild	Intermediate	Worsen
Spread of disease	Slow	Intermediate	Rapid
Therapeutic response	Good	Better	Based on the condition of the patient

There are two approaches to PD management. The first way is to understand the etiology and pathophysiology of the disease and develop novel therapies to slow the disease or slow the progression of the disease. The second approach is to care for patients developed with PD. The aim is to reduce the risk of disease and to improve health.[6]

The motor symptoms of are controlled with dopaminergic drugs but due to non-motor symptoms the disease persists. After a diagnosis (within 5–6 years), it leads to problems such as post-traumatic stress disorder and dementia. Phenotypes present in the disease are the other causes for progression of the disease. In the patients dying of PD, the cause of death is not directly related to PD. Initially, the motor symptoms are controlled by dopamine agonists or levodopa. Patients given levodopa develops "'wearing-off" phenomena within a few years and dyskinesias during the "on" phase.

Dopamine agonists are used as the first-line treatment for PD, leading to the development of motor problems. Patients diagnosed with dopamine agonists or MAO-B inhibitors show better health compared to levodopa treatment. Catechol O-methyl transferase (COMT) inhibitors are also developed to treat PD. Recent drugs such as opicapone, a third generation COMT inhibitor and safinamide, the MAO-B inhibitor are helpful in treating both on and off mechanisms. The treatment of non-motor symptoms includes selective serotonin reuptake inhibitors, anti-cholinergic, and anti-depressants.[7]

Main text

The molecular mechanisms of Parkinsonism include the synthesis of proteins, particularly the synthesis α-synuclein protein and hyper phosphorylation of tau protein (P-tau). 18 specific chromosomal loci, denoted as denoted for chromosomal loci (PARK) sequential detection sequence (PARK 1 - PARK 18). Certain loci are not identified with these genes or with specific diseases. The genetic pattern of the disease is of two types: Autosomal dominant (AD) and autosomal recessive (AR). Protein degradation in pathways such as ubiquitin – proteasome system (UPS), molecular chaperones (heat shock proteins [HSP]), and autophagy lysosomal pathway (ALP)

causes Parkinsonism. Exposure to Environmental Toxins, such as MPTP, rotenone, paraquat, maneb, organochlorine pyrethroids, iron, manganese, heavy metals, and polychlorinated biphenyls (PCBs), is the subscription factors responsible for the development of Parkinsonism. Mitochondria are a major source of energy production and also produce free-radical superoxide anion. In Parkinsonism, mitochondrial dysfunction degrades dopaminergic neurons by the induction of oxidative stress. Another mechanism of degradation of dopaminergic neurons in Parkinsonism is neuronal excitotoxicity due to lengthened exposure of glutamate and its excessively associated calcium intake and bio-energetic changes, leading to the oxidative burden and apoptosis.

MOLECULAR MECHANISMS OF PD ARE

Aggregation of misfolded proteins

The combining of both the aggregation and misfolding of specific proteins into abnormal and toxic species is established in most of the neurodegenerative diseases.

Aggregation of α-synuclein protein

Composition of α-zsynuclein

α-syn, a small acidic protein consisting of amino acids and carboxy terminals. N-terminal is a lipid binding α-helix, amyloid binding domain and C-terminal is acidic tail. α-syn is present with α-helix in combination with phospholipids in the cytosol. According to its vital structure, play various roles in cell environment.[8]

N-terminal

It is positively charged region, including seven series 11-aminoacid repetitions, containing the highly conserved KTKEGV hexameric motif. This motif is exists in α-helical domain of the apolipoproteins. The ability of α-syn to interfere with bilayer lipids is associated with these recurrent sequences, with residues of 1–87. This replicates, reduces the tendency of α-syn to form β-structures, and is important for α-syn lipid interactions. The core region of α -syn (61–95 residues) known as non-amyloid component (NAC) is involved in the synthesis and formation of fibril as it forms cross β – structures.[9,10]

C-terminal

It is an acidic tail with 43-AA residues, contains 10 Glu and Asp residues. Due to its low hydrophobicity and high net negative charge, it is a random coil structure. *In vitro* studies revealed that the reduction in pH neutralizes these negative charges and induces aggregation of α – syn.[11,12] Connections within the C-terminal domain and NAC region of α-syn inhibit α-syn aggregation. In front of aluminum, the C-terminal of α-syn binds to metal ion, blocking the fusion of α -syn. The phosphorylation of serine 129 induces α-syn fusion.[13]

Synthesis of lewy bodies from α-synuclein

In a healthy individual α-syn is a wave like structure and in PD it wraps up badly forming a cohesive or toxic compound. The initial integration is still very reactive during this process and is believed to cause damage to cellular components. These clumps accumulate into large masses and are termed as lewy bodies. Therefore, the process involved in the synthesis of these integrated proteins may be the cause of PD.[14]

Functions of α-syn

General physiological functions of α-syn such as storage and recycling of neurotransmitters, physiological regulation of some enzymes, increase in the number of dopamine transporter (DAT) molecules, release of neurotransmitters, and interaction with synaptic soluble N-ethylmaleimide-sensitive factor attachment protein receptors complex. This is consistent with its role as a molecular chaperone.[15,16]

α-Synuclein aggregation and degradation

α-syn has many adaptations involving both internal and external factors that inhibit or promote fibrillation. Disease related mutations affect α-syn synthesis. Some of the adaptations of α-syn are monomers (essential for α-helical transformation),

oligomers (Soluble conformations of higher level in β-sheets), tetramers, and fibrils.[17]

The changes associated with PD, available on the N-terminal domain are Ala 53 Thr, Ala 30 Pro, His 50 Gln, Glu 46 Lys, Gly 51 Asp, and Ala 53 Glu. Modification of Glu 46 Lys, His 50 Gln, Ala 53 Glu promote α-syn to form aggregates, and oligomers. It may be due to the reduction in the N-terminal integration. Residues 68-78 (NAC core) and residues 47–56 (pre-NAC) showed that in some regions, these fibers are transmitted to sheets, which are common amyloid assemblies.[18]

Other types of oligomeric species create toxins by interacting with cell elements in a number of ways such as, alterations in cytoskeletal integrity, nuclear dysfunction, membrane disruption and pore formation, vesicle docking inhibition, ALP impairment, UPS dysfunction, chronic endoplasmic reticulum (ER) stress, and reduction of mitochondrial function.

Existing mechanisms involved in the production of α-syn

The various mechanisms underlying α-syn transfer activation through membrane fusion, fused exosomes, pre-exocytosis and endocytosis, excavated nanotubes (direct interactions between two cells), internal receptor translocation, axonal, and trans synaptic fusion.

The cellular signaling pathways involved in low α-syn utilization are: Overuse of microglial activation results in increase of pro-inflammatory cytokines (Tumor Necrosis Factor alpha [TNF-α], interleukin-1 beta [IL-1β], IL-6, and INF-γ), and activates the oxidative stress response. Toll-like receptors (TLRs) detect pathogen related cellular patterns and initiate immune responses through different signaling pathways such as activation of nuclear factor kappa-light-chain-enhancer of activated B cells and MAPK. TLR2 activation results in the fusion of α-syn. Ion channels are also involved in α-syn mediated microglial response.

Degradation of α-syn

α-syn phosphorylation is important in the neurodegenerative diseases. α-syn extracted from human Lewy bodies are phosphorylated at serine 129. Polo-like kinase is also involved in degradation. Alteration of α-syn forms of tyrosine nitrated monomers and dimers that affects α-syn depletion. Immune electroscopy studies have shown the presence of nitrated monomers and dimers in the amyloid fibrils. The integrated α-syn is also degraded by UPS and ALP.[19]

Hyperphosphorylation of tau protein

Tau protein

Tau proteins are processed using microtubule-associated protein tau. They are most active in the distal parts of the axons where they strengthen microtubules and provide flexibility. They work simultaneously with tubulin, globular protein to stabilize microtubules, and to support the synthesis of tubulin in microtubules. Tau proteins derive their control of microtubule stability through phosphorylation and isoforms. Hyper phosphorylation of tau proteins forms tangle filaments (neuro fibrillary tangles [NFTs]), which contribute to disease transmission in CNS.

Tau proteins regulate tubule chemical action that promotes polymerization, stabilization. Binding of tubules to signal molecules such as lipids, regulates nerve fiber growth, and diameter. It regulates adult neurogenesis, cellular response to heat stroke, and initiates neuronal polarity in growth.[20]

Structure of tau protein

The human tau protein, coded by chromosome 17q21, responsible for the functioning of tubules. Microtubule binding domain (MTBD) is accountable for the binding of the microtubules. MTBD replicates amino acid phosphorylates, leading to neural formation, and stability.[21]

Alternative splicing and isoforms

Several isoform structures are composed of a single gene 17q21, with a small variation of one or two inserts in its N-terminal region. There are 16 exons within the gene, the exons 4A, 6, and 8 are shown at the edges, and eight of the axons (1, 4, 5, 7, 9, 11, 12, and 13) are involved in the formation of tau protein. The other cut (splicing)

of exons 2, 3, and 10 is responsible for the six isoforms in the tau protein that differs from three or four tubulin binding domains in the C-terminal region. Isoforms separately regulates the dynamics of microtubule.[22]

Regulation of tau phosphorylation

The phosphorylation status of the tau protein is important in determining its functional capacity. In Parkinsonism tau accumulates in NFTs due to hyper phosphorylation of tau proteins. The phosphorylated and insoluble tau species are mainly associated with synaptic destruction and cell loss. Various kinases and phosphatases such as GSK3, Cdk5, AMPK, and CK1 are involved in the regulation of tau phosphorylation. An imbalance in the regulation of the activity results in hyper phosphorylation of tau.[23,24]

Phosphorylation sites

Tau is a phosphorous protein, which contains 85 sites of serine, threonine, and tyrosine phosphorylation. The abundance of the phosphorylated residues in tau exists in its proline content. There are 85 amino acids out there, 28 completely phosphorylated in AD brain, 16 – both phosphorylates in AD and brain control, 31 – phosphorylates in physiological conditions, and 10 – putative phosphorylation sites.[21]

Hyper phosphorylation of tau protein

Hyper phosphorylated tau protein accumulates and form filaments, influences its binding ability to microtubules, dissociates from microtubules and their aggregation results in NFTs[25] and ultimately proceed to their dysfunction, disintegration of microtubules, impairs axonal transport, and eventually cell death. Tau protein easily phosphorylates as it contains 85 potential sites for phosphorylation.[26]

The basic mechanism involved in the hyper phosphorylation is either upregulation of protein kinase activity or downregulation of protein phosphatase activity.[27] Hyper phosphorylation is an important step in fusion of tau and NFTs. Antibodies that attacks the tau protein detect tau isoforms in brain tissue, specifies the existence of hyper phosphorylated tau protein in NFTs. C-terminus of the protein starts tau aggregation.[28]

Genetic causes of PD

Genetic disorders are those that are passed on from one generation to another generation. Some genetic disorders are the result of the random mutations that can be inherited from their parents. Studies show that some cases of PD are genetically modified. The genetic causes of these diseases are rare. Only 15% of PD patients have a family history, the etiological feature for Parkinson's is usually unknown to the rest. Genetic studies help to understand the pathophysiology of PD.

Genetic classification of PD

There are 18 specific areas of chromosomal loci, defined as PARK, sequential detection sequences (PARK 1 - PARK 18), no specific loci have been identified for these genes and appropriate pathology. The genetic pattern of the disease lies in two types: AD and AR, in which autosomal states that the gene which causes the disease is located on one of the numbered or non-sexual chromosomes. AD means only one copy of the disease associated with the mutation of the disease is sufficient. AR means two copies (Homozygous or Heterozygous) are needed for the mutation to develop the disease.[29]

PARK1

Members of this group have a genetic mutation in the SNCA (A53T) at exon4, signaling for α-syn. The age of onset is 46 years. Repeated gene expressions such as triplications and duplications are also found to cause the disease. Gene triplication causes an earlier onset of disease compared to that of recurrence. This is the first mutation identified in PD patients.[30]

The SNCA gene is located in the fourth chromosome in the human genome. Single nucleotide polymorphisms have been found to be associated with increased PD. Modification of SNCA leads to the development of PD due to amino acid transfer

and changes in the activation of encoded protein. Three mutations of pathogenic missense point mutations in SNCA gene lead to the induction of amino acids effects on PD growth.[31]

Alteration of the first point mutation A53T results in the replacement of Alanine to Threonine at the position 53 of α-syn protein. The second point of altering A30P, led to the replacement of Alanine to Proline in the position 30 of the protein. A30P mutation has early onset of the disease when compared to that of A53T mutation. The modification of A53T and A30P increases the oligomerization of α-syn. A53T mutation increases the α-syn fusion and fiber formation when compared to that of A30P mutation. The modification of the third point mutation E46K, results in the incorporation of glutamic acid (E) to lysine (K) at position 46 of the protein. This leads to the effective aggregation of α-syn when compared to A53T and A30P mutations.[32]

PARK2

The PARK2 gene produces the protein Parkin that usually helps cells breakdown and recycle proteins. Parkin belongs to the family of Ubiquitin-like domain (UBL). The process of covalent attachment of lysine residue to a substrate protein is called Ubiquitination as it occurs through the transfer of ubiquitin (Ub) molecules by the activation of enzymes, which, in turn, determines their cellular fate. Parkin appears to do mono ubiquitination and poly ubiquitination with either lysine 48/lysine 63 linkages.

In Parkin gene, the disease causing mutations vary from single base pair substitutions to deletions. Many missense mutations also leads to the loss of Parkin function through impairment of proteasomal degradation, decreased catalytic activity, and ubiquitination. Parkin functions as an Ub E3 protein ligase.[33]

The amino terminal plays a key role in stabilizing the structure of Parkin. The Parkin gene has a unique structure with a UBL in the amino terminal and a RING (a family domain which are specifically clustered with histidine and cysteine residues, which helps in protein-protein interactions) finger motif in the carboxyl terminal. It consists of 12 exons in which the depletion is seen exon3. Here, the neuronal loss is restricted to Substantia Niagra and Locus Ceruleus.[34]

The main function of the Parkin is to regulate autophagy. PARK2 works in combination with PINK1 mitochondrial protein. In cellular events the depletion of inactive mitochondria there by stabilizes PINK1, which collects the plaque from cytosol and is active during the delivery to mitochondria, utilizes the function of PINK1 kinase and activates the parasite to initiate some autophagy of the damaged organelle. Thus, the link between Parkin and PINK1 controls the state of mitochondria.

The role of Parkin in dopaminergic synapse

Parkin was found to be with ubiquitinate and regulating the release of CDCrel-1, a protein related to synaptic vesicles and regulates their energy. Parkin mutations increase CDCrel-1 levels and inhibit the release of neurotransmitters. Parkin interacts with proteins involved in synaptic vesicle release and presynaptic Parkin regulates dopamine release.

Varying of dopamine levels by presynaptic Parkin depends on the binding between Parkin and the DAT, a neurotransmitter transporter located in the plasma membrane of dopaminergic neurons. Genetic mutations in the Parkin decrease dopamine levels at presynaptic sites.[35]

PARK5

It is due to heterozygous conversion of UCHL 1 to chromosome type 4p14. It belongs to the family of Ub C-terminal hydrolase of the deubiquitinating enzyme, which causes hydrolysis of polymeric chains of Ub. Because of its activity in catalytic hydrolase, this enzyme hydrolyzes peptide and recycles monomers of Ub for reuse in the same process. It also contains dimerization dependent ligase activity, which promotes α-syn aggregation. UCHL 1 in the form of a monomer, hydrolyzes the peptide bond between Ub molecules and as a dimer, it acts as a ligase. Two mis sense mutations are present in UCHL 1 gene associated with

PD: 193M and S18Y. 193M mutation is from cytosine-to-guanine transformation in codon93 of exon4. S18Y mutation is from cytosine-to-adenine at codon18 in exon3. S18Y has antioxidant protective function and decreased risk of PD. UCHL 1 dysfunction results causes a decrease in protein degradation, followed by accumulation of ubiquitous proteins leading to cell degeneration.[36,37]

PARK6

PARK6 gene encodes phosphatase and tensin homolog (PTEN)-induced kinase 1 (PINK1). It acts as a tumor antagonist with both lipid phosphatase and protein phosphatase activity. Over expression of PTEN activates apoptosis. It detects dysfunction of mitochondria and then signals Parkin to ubiquitinate damaged mitochondria selectively. PINK1 selectively sticks on damaged mitochondria for eliminating the flaggered mitochondria. PINK1 phosphorylates Ub leads to the activity of Parkin E3 ligase.

PINK1 would possibly accumulate in the damaged mitochondria because of increased synthesis/ decreased degradation of protein. PINK1 and Parkin are connected on a typical pathway in mitochondrial functioning and loss of their function leads to alteration in mitochondria leading to degeneration of dopamine neurons. The above genes in a combination control the clearance of dysfunctional mitochondria by ALP. PINK1 acts like a biosensor of mitochondrial proteins using pre-existing (TOM) protein translocases and mitochondrial membrane (TIM).[38,39]

PARK7

DJ-1 is encoded with PARK7 gene, an 189 amino acid protein and is dimeric under physiological conditions. Mutations of DJ-1 carry higher percentage of non-motor features. DJ-1 activity is affected by oxidative conversion. DJ-1 is a multidisciplinary protein, responsible for transcription, chaperone, anti-oxidative stress reaction, protease, and mitochondrial regulation. DJ-1 contains C46, C56, C106, and 3 cysteine residues. C106 is highly susceptible to oxidative stress and is oxidized as SoH, So2H, and So3H. Mutation of C106 leads to the loss of DJ-1 function.[40]

PARK8

PARK8 is encoded by the gene LRRK2, where the structure contains a combination of guanosine triphosphate (GTPase), Kinase, and Scaffolding domains. Seven mis sense mutations have been identified as pathogenic: R1441G, R1441C, Y1699C, G2019S, R1628P, G2385R, and I2020T. G2019S (substitution of glycine 2019 with that of serine) mutation augments the LRRK2 kinase activity, leading to impaired phosphorylation under MAPK and MKK, leading to the activation of neuronal death signal pathway. Mutations lead to decreased levels of dopamine in the caudate putamen, appearance of α-syn in the brain stem.[41] The isoforms of the following kinases MAPK, P38, JNK, and ERK are activated by stress (toxins and inflammatory agonists) in PD. Abnormal activation of one of these isoforms (MKK4) mediate cell death and degeneration of SNpc dopaminergic cells. LRRK2 is co-localized in early stages of aggregation of α-syn. LRRK2 dysfunction might contribute for the early formation of lewy bodies. Presence of LRRK2 protein in B cells rather than in T cells, indicates its role of neuro inflammation in PD.[42]

Protein degradation pathways in PD

Protein misfolding, fusion and deposition are common pathologies shared by a number of neurodegenerative diseases collectively called proteinopathies or disruption of protein synthesis. Accumulation of damaged or altered proteins causes disrupted cell function and ultimately leads to cell death. The steady state levels of any given protein are determined by its composition, modification of post-translational, downtime, and release. The main line of defense against condensed is to be synthesized by cellular chaperones, which strengthen or regenerate those proteins. A large portion of polypeptides cannot reach their endoplasmic reticulum folding state, so

it is improperly transported to the cytosol where it further degrades through a proteasome, known as endoplasmic reticulum associated degradation.

The two major proteolytic systems that regulate normal gain and removal of converted proteins from neurons are UPS and ALP.[43]

The quantity of any protein is determined by the balance of protein synthesis and protein degradation. The precise regulation of multiple proteins indicates a critical mechanism for cell regulation and is often determined by the same action pathways for protein synthesis and protein degradation. Protein depletion was initially thought to be a relatively inexplicable process. The invention of the UPS has profoundly altered this view.[44]

PROTEOTOXIC PRESSURE: COMBINATION AND MISHANDLING

Most neurodegenerative diseases share a common pathological process: The abnormal collection and processing of altered or damaged proteins. Protein synthesis, cellular response to abnormal proteins is the two phases of this process.

PD pathology is characterized by a tendency for excessively soluble neuronal protein to make continuous and proliferative mutations, leading to intracellular aggregation, a process associated with neuronal dysfunction and loss.[45]

UPS

It is a cellular, ubiquitous protein that is damaged or altered and degraded by the 26S proteasome. Ub is a smaller protein present in many tissues that help regulate the process of other proteins. The Ub molecule binds to a protein substrate, a process called ubiquitylation, which leads to a many different effects. Abnormal proteins are commonly targeted by ubiquitination, to the proteasome, where a decrease in ATP pathway occurs. UPS dysfunction may lead to the accumulation of damaged cytotoxic proteins that eventually lead to neuronal death.

Proteasomes, protein complexes degrade damaged by proteolysis. The enzymes that stimulate the reactions are called proteases. They are found in all Eukaryotes and archaea, as well as in other bacteria. Proteasome is a complex multi-subunit enzyme complex that plays a role in regulating proteins that regulate cell cycle progression and apoptosis.[46]

Ub has lysine (K) residues that aid in the assembly of Ub molecules. It is a small protein of seventy six amino acids. Human yeast and Ubs vary from three amino acid residues. It is found in all eukaryotes but not in prokaryotes. Ub is encoded in a polyubiquitin type code.

Signal transmission by ubiquitylation

It involves the synthesis of Ub and lysine residue of the target protein there by building a branch structure. This modifications works to stabilize protein degradation by 26S proteasome, when lysine-48 binds to many Ub molecules. Protein conjugation of Ub lysine-63 promotes the protein interaction between monoubiquinated substrate and the proteins with Ub binding domains. This modification may be temporary, because there are certain Ub proteases.[47]

Ub is often combined with lysine compounds, and since Ub itself contains seven lysine residues in which Ub can be absorbed, the further addition of Ub leads to the formation of polyubiquitin chains on substrates. The chains of Ub linked to K48 are clearly visible chains linked to lysine-48 to Ub, directing the substrates to the proteasome for destruction. Chains linked to K11 are also reported to target substrates in the proteasome.[48]

Most of the cellular proteins were degraded by UPS, which contains of both substrate-recruiting and degrading machinery. The ubiquitous protein process has three steps: The first step is E1 of polypeptide activation in an ATP-dependent manner. Second is transfer of the Ub network enzyme (E2) and the last to transfer of Ub-derived Ub protein ligase (E3) to a lower protein.[49]

Ub-proteasome pathway

Post-translational modification is important in normalizing cell homeostasis. The ubiquitination is the process of attaching Ub (76 amino acids) to

the underlying protein, which further demonstrates how to regulate the stability and function of cellular proteins. Ubiquitination is the main signal in each cell that regulates internal protein levels and plays a key role in vital cellular processes such as apoptosis, DNA repair, DNA replication, transcription, cell cycle progression, and immune responses by reducing the selective proteolysis by 26 S proteasome. The UPS system mainly consists of E3 ligases and deubiquinating nuclei (DUBs). They control apoptosis by controlling pro/anti-apoptotic proteins and determining cell survival/death. The pathway involves the combination of signaling signals that lead to cell survival/death.[50]

UPS failure results in dopaminergic neurodegeneration

Abnormal protein homeostasis can lead to the accumulation of toxic intracellular proteins, which are harmful to neuronal survival. Collection of combined and misfolded α-syn is believed to be the primary pathologic event in PD caused by mutations or repetitions of α-syn gene. Combined α-syn interacts with 19 S and inhibits the activity of the 26 S proteasome. The accumulation of certain substrates of Parkin can interfere with cellular functions and cause neurotoxicity in Parkin related – Parkinsonism. In the brains of PD patients, the substrates of Parkin, including CDCrel (proteins related to cell regulation) 1 and 2a, Pael-R (Parkin associated endothelin like receptor), cyclin E, and p38 are accumulated.

Ubiquitylation of Parkin substrates increases its benefit with UPS and accumulation of toxic substrate in the absence of active Parkin causing neurodegeneration. Mutations in Parkin alter solubility of proteins and improve their concentration in the cell.[51,52]

Autophagy – lysosomal pathway

Neurons use two main mechanisms to convert inactive proteins or organelles. The first is UPS, which destroys short lived proteins in the cytoplasm and nucleus. Second is the ALP that digests protein aggregates, longevity proteins, and RNA granules. Autophagy is a physical process within the body, which deals with destruction of the cells. It plays significant role in maintaining homeostasis through protein degradation.[53] Lysosomes are the major destructive sites of eukaryotic cells. Lysosome, unlike proteasome degrades a variety of substances such as nucleic acids, proteins, oligosaccharides, and lipids in to their building blocks. After entering the building blocks, the lysosomes left over, or with the help of the carriers. Blocks the building blocks of large molecules reused in cytosol and ensure lipid homeostasis.

Ub and the autophagy systems are intertwined, as ubiquitination serves as a symbol of choice. There is an link between autophagy and apoptosis process in response to cellular stress. ALP deficiency leads to the accumulation of abnormal protein aggregates and mitochondrial dysfunction that promotes oxidative stress and ultimately apoptosis.[54]

ALP in PD

Mutations of α-syn and increased intracellular concentrations of the non-mutant α-syn is implicated in the pathophysiology of PD. Diminished autophagic degradation of α-syn is an imperative mechanism of neurodegeneration in PD. α-syn is transmitted to lysosomes by selective CMA pathway. Binding of the mutant α-syn to their receptors obstructs the lysosomal uptake and prevents the degradation of mutant α-syn and other CMA substrates. Accumulated mutant α-syn and other CMA substrates continue to disrupt cell homeostasis and cause neuronal toxicity.[55]

Inherited genes and single factors account for 27% and 33% of the PD patients, respectively. Several genetic traits such as LRRK2, SMPD1, SNCA, GBA, PARK2 PARK7, PINK1, and SCARB2 are involved in ALP. Some of these genes encode lysosomal enzymes, while others are implicated in mitophagy, transport to the lysosome, or other autophagy related functions.[56]

HSP

HSP is a protein component, produced in response to physical, chemical or environmental pressure or after brief exposure to higher temperatures than normal growth temperature. HSPs synthesis is

common in plants and animals including humans. They are made of prokaryotic cells, namely, bacteria and Archean. They are also made up of toxins, oxidants, free radicals, heavy metals, and viruses and are sometimes called stress proteins. HSPs in cellular chaperones tend to enhance the binding of newly formed polypeptides of proteins in a local native structure, as well as their horizontal transport and signal transfer. A harmless increase in temperature in biological species above the body's processes inhibits protein formation within the cell, activates heat shock factor and stimulates the formation of heat shock genes, while fatal temperature triggers apoptosis.[57]

HSP in PD

HSP resources in regulating protein metabolism and preventing anti-apoptotic activity and represents a set of proteins involved in PD pathogenesis. HSPs included in PD are HSP 26, HSP 40, HSP 60, HSP 70, HSP 90, and HSP100. Some HSPs present in synapses and axons, are downregulated in PD and other neurodegenerative diseases. HSPs may bind to aggregated SNCA or pre-fibrillar structures or tau polymers and interact by forming soluble oligomers or higher insoluble structures that decrease their toxicity.[58]

Role of environmental toxins on PD

Pesticides that work by inducing oxidative stress and preventing mitochondrial complex-1 are likely to cause PD. Xenobiotics like annonacin produces symptoms of Parkinsonism in humans and loss of nigrostriatal neurons in animals. Exposure to a variety of metallurgy and industry can produce Lewy bodies or neuritis and cause loss of catecholaminergic neurons in the locus coeruleus and the substantia nigra.[59]

Rotenone

It is a plant based insecticide that is usually used to kill fish in dams. It is non-toxic to humans, but is a mitochondrial toxin, which inhibits the complex 1 of the electron transport chain (ETC)[60] and leads to further neurodegeneration and oxidative damage. Rotenone also causes phosphorylation, aggregation of tau and amyloid proteins.

Paraquat and maneb

Paraquat, a herbicide is an oxidative stressor. In nature, it is almost identical to that of the active metabolite of MPTP. Paraquat is often used with a fungicide Maneb, for additional effects. Paraquat causes tissue damage that produces free radicals of superoxide.[61] It improves glutamate efflux inducting excitotoxicity mediated by RNS.[62]

Organochlorines

They are used to control mosquitoes and are banned in US as they are toxic drugs related to PD. Dieldrin and β-hexachloro cyclohexane (HCH) are linked to PD, which are lipophilic compounds. Dieldrin induces mitochondrial dysfunction, creates oxidative stress by ROS. HCH even at nanomolar concentrations disrupt calcium homeostasis of dopaminergic cells.

Organophosphates

They produce acute neuro toxic effects, which is a major risk factor for PD. Many organophosphates mixed with blood in the form of toxic Oxon.[63]

Pyrethroids

These are a category of insecticides used as mosquito repellants. They indirectly augment the repetition of mediated DAT and lead to indirect apoptosis of dopaminergic cells.

Iron

Neuromelanin presents in substantia nigra neurons binds to iron and initiate lipid per oxidation and cell death through the production of free radicals. Iron also promotes auto-oxidation of dopamine.

Manganese

Manganese is a basal ganglia toxin associated with Parkinsonism.[64] It induces neurotoxicity by degrading Globus palladium, caused by the mitochondrial disruption due to formation of active ROS that induces apoptosis.

PCBs

PCBs are lipophilic compounds present in oily tissues of marine mammals. It regulates DATs, which by inflicting damage to the striatal dopamine system.[65]

Heavy metals

Heavy metals in the brain lead to oxidative stress and detrimental effects are seen in basal ganglia. They produce hydroxyl radicals from hydrogen peroxide under Fenton and Haber–Weiss reaction and damage neurons in SNpc.[66]

MPTP

MPTP is a synthetic neurotoxin, belonging to the group tetrahydro pyridine. It is formulated as a byproduct in synthesis of 1 - Methyl - 4 - Phenyl - 4 – Propionoxy piperidine (MPP). Exposure to MPTP produces free radicals that damages cells in pars compacta of the substantia nigra and locus ceruleus. Treatment with either paragyline, a common monoamine oxidase (MAO) inhibitor or Deprinil (selegiline), selective MAO – B inhibitor, prevents both pathological and the clinical outcomes of MPTP exposure.[67,68]

MPTP is combined with most active MPP^+ by the process of metabolism, which inhibits the complex-I activity of mitochondrial ETC. MPP^+ is transported by a DAT in dopaminergic neurons, MPP^+ accumulates in mitochondria and disrupts complex-I of ETC and reduced coenzyme Q-10 levels in mitochondria of the patients with PD.[69]

Mechanism of action

MPTP toxin is a prodrug to MPP^+. MPTP is highly lipophilic and crosses BBB easily, and in astrocytes it converts MPTP into its toxic metabolite, MPP^+.[70] MPP^+ is an excellent substrate for dopamine receptor site and therefore selectively targeted by dopaminergic neurons.[71] DAT, mediates reuptake of dopamine, has high concentration of MPP^+. The ventral tegmental area of the brain (VTA) also has uptake sites for dopamine. VTA survives due to the presence of calbindin. Calbindin regulates the availability of calcium within the cell.[72]

Systemic administration of MPP^+ does not harm central dopaminergic neurons, as it cannot cross BBB due to its charge. ATP decreases in striatum and SNpc regions of brain, which is more sensitive to MPTP. Mitochondrial MAO-B converts MPTP to MPP^+ and produces superoxide anion, nitric oxide (NO), hydrogen peroxide, and hydroxyl radical.[73] Superoxide radicals combine with NO to form peroxynitrite, a highly destructive process that damages the proteins by oxidation and nitration. The selective nitration process of tyrosine hydroxylase (TH) (restricts the enzyme in DA synthesis) does not use TH and later produces dopamine.[74] Mitochondrial apoptotic pathway involves the release of cytochrome - C from mitochondria that is associated with opening of the mitochondrial transition pore. MPP^+ opens the pore opening of mitochondrial transition by inhibiting complex-I and ROS production.[75,76]

Mitochondrial dysfunction and oxidative stress in PD

Mitochondrial dysfunction in PD

MPP^+ disrupts the activity of complex-I of the respiratory series leading to neurodegeneration.[77] Deficiencies of complex-I and complex-II are reported in Parkinsonian patients.[78] During oxidative phosphorylation electrons from NADH or FADH2 are transported through an ETC that incorporates complexes I - IV and creates a proton gradient on the inner mitochondrial membrane[79] which initiates the synthesis of ATP from ADP with the help of an enzyme called ATP synthase (complex - V).[80]

The main function of ETC is to generate cellular energy in the form of ATP. During oxidative phosphorylation, leakage of electrons from complex I and complex III and responds with oxygen to form superoxide radicals,[81] which are scavenged by superoxide dismutase enzyme. Mitochondrial dysfunction may be due to over production of superoxide anion, a cause for PD. Complex I deficiency is seen in SNpc, frontal cortex, peripheral tissues such as platelets, skeletal muscle of PD patients.[82]

Dopamine metabolism and Mitochondrial dysfunction

ROS produced during oxidation of dopamine by MAO, may have an inhibitory effect on mitochondrial respiratory proteins. Dopamine metabolite, dihydroxy phenyl acetic acid inhibits complexs I and IV.[83]

Genetic links and mitochondrial dysfunction[84-88]

Responsible genes	Mitochondrial dysfunction
SNCA	Increased levels of α-syn leads to production of ROS and mitochondrial fragmentation
LRRK2	DRP1 and MFN, mitochondrial proteins fragments mitochondria through the phosphorylation of LRRK2
VPS35	Decreased levels of MUL1 leads to increased production of DRP1 and ultimately causes mitochondrial fragmentation
Parkin	Proteasomal degradation

Oxidative stress in PD

In the structure of mitochondrial ETC, complex-I and to a lesser extent of complex-III are the main sites of ROS production. The primary ROS is superoxide radical, converted to H_2O_2 by superoxide dismutase, which is then detoxified by enzyme catalase. In the presence of ions such as Fe^{2+}, H_2O_2 converts to a highly reactive hydroxyl radical which causes acute oxidative damage to cellular components.[89] Increased ROS production is one of the leading causes for the death of dopaminergic neurons in PD.[90] ROS simultaneously destroys the ETC components specifically complex-I, leading to further inhibition and production of ROS. Elevated ROS damages all macromolecules such as proteins, lipids, and nucleic acids, leading to disruption of immune functions.[91]

Neuroinflammation in PD

Inflammation is the body's defensive mechanism to maintain homeostasis. Two pathological pathways responsible for death of neuronal cells are cell independent and non–cell-independent mechanisms. The integration of internal damage to degenerating neurons leading to their death is the first step. The latter describes indirect damage to the affected neurons caused by pathophysiological interactions with neighboring cells such as microglia and astrocytes and infiltration immune cells (i.e.., macrophages and lymphocytes).

Glial cells produce molecules such as microglia and astrocytes, causes signaling survival cascades in neurons to maintain brain homeostasis. The imbalance in homeostasis occurs in PD, leading to neuroinflammation.[92] Stress/infection is characterized by receptors such as TLR's and nucleotide oligomerization domain receptors and ultimately leads to apoptosis.[93]

Role of microglia in neuro inflammation

Various pathogens or stimuli activate microglia, and the CNS triggers an immune response. Microglia is present in a sleep-deprived state when there is no stimulus, done by immunosuppressant in CNS. Immunomodulatory molecules such as CX3CL1, CD22, CD200, CD47, CD95, and neuronal cell adhesion molecule present in microglia regulates neuro inflammation. Microglia are activated by changes in environmental and morphology, surface antigens, molecules of bacteria and virus, disease-related proteins (amyloid β and α-syn). Lack of CX3CL1, CD200 signaling dysfunction activates microglia.[94] Activated microglia transforms into reactive microglia, classified into two types: M1 (Pro-inflammatory) and M2 (anti-inflammatory).

Long-term activation of microglia upregulates inflammatory cell signals including MHC Class I and Class II, chemokine, and cytokine receptors, TNF-α, IL-6, IL-1β, and IFN-γ contributes to accelerating dopamine degeneration. Pro-inflammatory mediators, released by enlarged astrocytes increase microglial activation into an excited state. Others such as misfolded proteins, administration of MPTP induces microglia activation.[95]

Role of astrocytes in neuroinflammation

Astrocytes produce neurotrophic substances especially glial derived neurotrophic factor for the survival of dopaminergic neurons. Astrocytes respond to inflammatory substances such as IL-1β, lipopolysaccharide (LPS), and TNF-α.[96] The

mutant α-syn incorporates into astrocytes damages dopamine neurons. A glial scar is formed at the site of the injury due to the changes in active astrocytes. A1 astrocytes cause neuroinflammation, whereas A2 produces ischemia.

A1 astrocytes are induced by LPS stimulation, where LPS is microglia receptor through TL4. IL-1alpha, TNF secreted by active microglia, leading to neurodegeneration, and apoptosis.[97] The presence of A1 active astrocytes and those of active microglia contribute to neurodegeneration, in the event of neuroinflammation. Microglia and astrocytes are important brain homeostasis and their role in neuroprotection is lost under injury.

Genes associated with PD and neuro inflammation

Pathogenic strains of α-syn (SNCA) induce microglial response through TLR 2. Inflammatory stimuli such as LPS increase LRRK2 levels in microglia. Parkin promotes the development of astrogilosis, releases soluble factors. PINK1 is associated with the exchange of cytokines. PINK1 produces higher levels of pro-inflammatory cytokines. Astrocytes from DJ-1 producing higher levels of IL-6 and COX-2 represent a loss of DJ-1 activity. These are all the factors that contributes to PD.[98,99]

Excitotoxicity in PD

The cell death due to toxic effects of the excitatory amino acids, this phenomenon is called as excitotoxicity. Glutamate, a pleasurable neurotransmitter in the cerebral cortex and hippocampus plays role in body functions such as learning and memory, over work, or dysfunction leads to neurodegenerative diseases. Neuronal excitotoxicity generally refers to the death of neurons caused by prolonged exposure to glutamate and high concentrations of ions into the cell. It is due to intracellular calcium saturation and bio-energetic changes, leading to the oxidative stress and apoptosis activation.[100]

Glutamate receptors

Glutamate interacts with its receptors that contain cation channels. Over activation of these receptors leads to neuronal dysfunction, injury, and death. The beneficial effects of glutamate are produced by activating of three types of ionotropic receptors and various phases of metabotropic receptors linked to G-proteins. The three major ionotropic receptors produced by glutamate are N-methyl-D-aspartic acid (NMDA), kainic acid (KA) receptors, and α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA).[101]

Continuous activation of NMDA receptors (NR1/NR2B - subtype) leads to an increase in intracellular calcium load, leading to apoptosis or necrosis. These receptors are also active in the treatment of excitotoxic neuronal damage. AMPA receptors are a type of glutamate receptors that are most permeable to Ca^{2+} and this acceptance is determined by presence or absence of GluR2 subunit in the receptor complex. Low levels of GluR2 indicate high penetration of Ca^{2+} and promote neuronal degeneration. Increased glutamate receptor activity creates pro-apoptotic protein p53, leading to neuronal damage and death by apoptosis and autophagy.[102]

By stimulating the glutamate receptors, it increases the intracellular calcium by opening ion channels directly and second affecting calcium homeostatic pathways. Early activation of glutamate receptors not only allows Ca^{2+} but also causes membrane damage. This activated and activated Ca^{2+} which, in turn, increases in intracellular Ca^{2+}. Reduced sodium content in cell membranes reduces the ability of sodium gradient dependent anti-porter to remove Ca^{2+}. Excessive levels of calcium within cells cause neuronal damage.

Intracellular toxic incidents

Increased calcium levels activate a number of enzymes such as protein kinase C (PKC), phosphatases, calcium/calmodulin dependent protein kinase II, NO synthase (NOS), proteases, and endonucleases. Activation of phospholipase A induces platelet activating factor (PAF), arachidonic acid, and its metabolites. PAF has a direct impact on the harmful cascade by stimulating glutamate release. Arachidonic acid inhibits the glutamate reactivation from the synaptic space, activates glutamate receptors, and results in higher

arachidonic acid formation, and the formation of free radicals. Overactive stimulation of NMDA receptors promotes the excessive release of NO and superoxide ions, which can react and produce toxic peroxynitrite, leading to neuronal death.[103]

Mechanism of excitotoxicity in PD

The combination of non-invasive coordination and dyskinesias in PD is closely related to high glutamate levels in the basal ganglia. Increased glutamate in synaptic cavity further stimulates ionotropic and metabotropic glutamate receptors in post-synaptic components and facilitates excitotoxicity. With the use of AMPA and KA receptor, it reduces sodium infiltration and acute inflammation of nerve cells and mediates neuronal death.

Not only glutamate there are but also some others are involved in the excitotoxicity of PD. α-syn downregulates the function of N2RB-containing NMDA receptors. Glutamate stimulates Group I metabotropic glutamate receptors (mGluR), activates intracellular phospholipase C (PLC), and hydrolyze into IP3 and DAG, whereas IP3 promotes internal calcium release and DAG activates PKC and strengthen the calcium mediated NMDA receptor, inducing neuronal death. Glutamate accumulation in the synaptic cavity therefore plays a prominent role in the pathogenesis of PD.[104,105]

CONCLUSION

The incidence of PD is escalating day by day mainly in elderly population. Predicting or early detection of the disease is important. Several therapies are available but none of them are effective in curing and restoring the dopamine levels in substantia nigra. Understanding the cellular and molecular mechanisms of the disease can lead to the development of new drugs for the management of the disease.

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