



Cellular and Biochemical Changes in Neurodegeneration and Development of Parkinson Disease: A Review

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Abstract Parkinson disease is a multi-factorial neurological disorder instigated by a collapse in the dopaminergic pathways due to an inhibition in the normal flow of dopamine in the brain neurons. The prevalence of this disease is notable among people who are over 60 years and above. The ineffectiveness of most drugs currently in use with no definite treatment regimes is hinged on the lack of understanding of the cellular and molecular processes that transcends in the manifestation of its pathogenesis. Understanding the biochemical processes of the dopaminergic pathways is essential for specificities in drug design and discovery as drugs must be designed to target the missing functionalities thus avoiding drug failure. In this review, series of causative agents classified under genetic and environmental factors were discussed alongside their underlining cellular and molecular pathways that reveals failure of biochemical systems and release of harmful enzymatic activities.

Keywords Parkinson, disease, neurological, dopaminergic, pathways, pathogenesis, drugs, cellular, molecular, disorder

Introduction

Neurological disorders are usually caused by an alteration in the dopaminergic pathways of brain neurons responsible for transmitting dopamine; a neurotransmitter from one region of the brain to another. A common neurological disorder that is caused by the short flow of dopamine in brain neurons is known as Parkinson's disease which occurs due to the death of dopamine releasing brain cells. Parkinson's disease is a complex neurodegenerative disorder that is clinically characterised by impaired motor behaviour which is because of selective death of dopaminergic neurons of the midbrain [9]. It has an age-dependent and multi-factorial pathogenesis affecting 2% of the population over 60 years with an increasing 5% occurrence in people who are 80% and above [10]. The progressiveness of the disease causes the spreading of neurodegeneration to other regions of the brain [1]. The occurrence of this disorder is primarily classified into genetic and environmental factors with each having an



underlining cellular and molecular pathway that reveals failure of biochemical systems and release of harmful enzymatic activities.

The lack of understanding of the cellular and molecular process that result in the disease has led to a misguided information on the causative agents and factors that primarily trigger neurodegeneration thus hindering the development of effective treatments to affected patients. The purpose of this review is to identify the cellular and molecular mechanism behind the occurrence and progression of Parkinson disease which is a major neurodegenerative disorder.

Effects of Dopamine Biosynthesis in Parkinson Disease

Dopamine is a compound that is synthesised by dopaminergic nerve cells responsible for transmitting signals between nerve cells in the brain [25]. Under normal conditions, dopamine is formed when L-tyrosine is synthesised by tyrosine hydroxylase to produce L-DOPA which is synthesised by aromatic L-amino acid decarboxylase in the presence of tetrahydrofolic acid, ferrous iron and pyridoxal phosphate which acts as a catalyst in the production of dopamine. The inability of dopamine agonist to stimulate dopamine receptors which in turn activates alpha 1,2 and 3 regions of G-proteins leads to the progression of Parkinson disease. This is because the activated regions of G-proteins break-away to undergo series of events to alter the progression of the disease [28].

Dysregulation of Interlinked Molecular Pathways in Parkinson Disease

Prior to the onset of this disorder, Ubiquitin proteasome system present in the neuron under normal condition is responsible in controlling mitochondrial fission and fusion. The fission-fusion activity is important for the disintegration and expulsion of defective mitochondria that have been damaged due to cellular stress [18]. When there is decreased activity of ubiquitin proteasome system perhaps due to age or disease related factor, it leads to the deregulation of mitochondrial fission-fusion activity needed for removal of damaged copies of mitochondria. Damaged mitochondria and decrease in proteasomal activity often result in increased levels of reactive oxygen species (ROS). The increase in expulsion of reactive oxygen species from mitochondria will lead to increased protein damage with a potential reduction in the production of ATP by mitochondria thus affecting the efficacy of ubiquitin and chaperone. Failure in the activity of antioxidant defence mechanism such as superoxide dismutase and glutathione leads to further increase in protein damage thus resulting in the formation of inclusion and lewy bodies [23]. The presence of inclusion/lewy bodies triggers cell death. However, attempt made by cells to discard aggregating protein may involve autophagic and ubiquitin proteasome system activity. Released protein aggregate (α -synuclein) may be engulfed by immune cells or taken up by adjoining cells. Damaged or defective mitochondria in cells may be discarded by mitophagy catalysed by PARKIN and PINK1/DJ-1 which is dependent on its ability to bind to microtubules and its transport along axons to the cell body [1]. The stress response generated during any of this activity usually causes the activation of kinases (PINK 1 and LRRK2). However, reactive oxygen species can also act as signalling molecule thus leading to the activation of transcription proteins [12]. These proteins are needed to regulate increased stress relative to the activation of unfolded protein response triggered by protein misfolding and found within the endoplasmic reticulum or mitochondria [6].

Also, the size and structure of a neuron demands the transportation of subcellular organelles like mitochondria and proteins over a long distance within axons and the synaptic sections of the dopaminergic cells being abundant in mitochondria, dopamine and α -synuclein make it highly sensitive to adverse conditions [9]. The release of α -synuclein aggregate can also cause a reduction in proteasomal activity thus interfering with mitochondrial activity and calcium flux. When this occurs, it causes a blockage in series of chain reaction that are vital in maintaining the reverse transportation of aggregated α -synuclein and defective mitochondria for macro-autophagy [2]. Blockage in the free flow of sub-cellular organelles meant for synapses causes a loss in synaptic cell to cell contact and a retracted axon [18].



Role of α -Synuclein in Parkinson Disease

The protein α -synuclein has remained the most notably linked protein in the progression of Parkinson disease either through sporadic or hereditary factors [4]. It has been reported that duplication or triplication of the *SNCA* gene resulting in high level of α -synuclein leads to late and early development of the disease [14]. Since this protein is a major component of lewy body, it further depicts that an increase in levels of α -synuclein increases the formation of lewy body thus facilitating the progression of the disease. This protein is noted for its association with membranes and high levels can alter transportation of biomolecules from Endoplasmic reticulum to Golgi bodies [2]. For better understanding on the role of α -synuclein in the development of Parkinson disease, animal models were induced with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine to generate the parkinsonian effect through inhibiting the mitochondrial complex thus causing the release of reactive oxygen species within neural cells [16]. The release of ROS triggers apoptotic event and leads to the death of dopamine neurons. The ROS released from the mitochondrion as speed the formation of α -synuclein aggregates thus increasing the production of ROS through the toxic protofibrils. This event creates a cell death cycle for dopamine neurons. Oxidization of dopamine maintains the protofibrillary version of α -synuclein during fibrillization and causes an increase in the concentrations of protofibrils and ROS located within dopamine neurons [21].

Role of Parkin, PINK1 and 1/DJ-1 in Parkinson's disease

Recent studies have shown that the primary function of the Pink1/Parkin pathway is to regulate the fusion-fission mitochondrial machinery. However, for some genetic reasons, the genes responsible for synthesising active copies of these proteins undergo genetic mutation and lead to loss of enzymatic function or decreased enzyme activity due to protein misfolding. The activity of these genes; *PARK2* (encodes ubiquitin ligase parkin), *PINK1* (a mitochondrial kinase) and *PARK7* (codes for DJ-1 protein) are relatively responsible for mitochondrial dynamics and oxidative stress responses [26]. The *PINK 1/ Parkin* pathway regulates accurate folding and degradation of mitochondrial proteins through interaction with TRAP1 protein chaperone and the serine protease Omi/Htra2. Phosphorylation of TRAP1 by PINK1 leads to modification and mediates the protective role of PINK1 (22). Omi/Htra2 is indirectly phosphorylated by PINK1 through activation of p38 MAPK signalling pathway thus activating its protective function. Separation of damaged organelles from active mitochondrial network by profission GTPase Drp1 is achieved during mitochondrial depolarisation [5]. This event leads to recruitment of parkin by PINK1 to the outer mitochondrial membranes (OMM) where it directly or indirectly enhances ubiquitylation and proteasomal degradation of OMM proteins (Mfn1/2 and VDAC1). Degradation of Mfn1/2 protein hinders the refusion of damaged mitochondria with intact cellular organelles [27]. The proteasomal degradation event causes OMM breakage with subsequent autophaghic event [20]. However, where disease-linked mutations occur in PINK1, a blockage of *PINK1* gene activity in supporting the recruitment of Parkin is achieved. Also, mutations in *PARK2* gene either causes the non-recruitment of its protein by PINK1 or recruitment of inactive proteins that due not trigger mitophagy [22].

The primary function of *PARK7* gene is to synthesis DJ-1 proteins that acts as antioxidant thus protecting neurons from oxidative stress and apoptosis. Regulation of its activity is achieved through interaction with OXPHOS complex 1 [24]. DJ-1 undergoes chaperone activity which is controlled by BAG-1 (a cochaperone). Gene mutation in *PARK7* causes loss of protein activity due to the inability of DJ-1 to dimerized to form tertiary structures thus an inactive monomeric version of the protein is formed. This event is believed to contribute to the development of parkinsonian effects [26].

Role of LRRK2 in Parkinson's Disease

The leucine-rich repeat kinase 2 (LRRK2) is an enzyme that is encoded by *PARK8* gene and is actively involved in the development of both sporadic and hereditary forms of Parkinson's disease when an alteration in the gene function exist [15]. Under normal conditions, LRRK2 regulates autophagic event through a signalling pathway that is activated by the presence calcium ions. This event basically consists the following; activation of nicotinic acid adenine dinucleotide phosphate receptors, increased lysosomal pH and release of calcium from lysosomes [19].



LRRK2 activity is needed in the protein recycling retrograde pathway that occurs between lysosomes and Golgi bodies. Also, LRRK2 is known to phosphorylate proteins that are central to the disease. It is believed that healthy LRRK2 proteins easily penetrates the lysosome without hindrances thus allowing the free passage of other proteins like α -synuclein into lysosomes through pores. Mutation in the gene that encodes for the production LRRK2 proteins leads to synthesis of inactive and misfolded proteins [3]. The change in protein structure result in blockage of lysosomal pores and prevents the passage of other proteins (most significantly α -synuclein). This event causes a build-up of high levels of α -synuclein with subsequent aggregation and increases production of ROS which triggers neural cell death [19].

The Role of *HtrA2/Omi* Gene in Parkinson' Disease:

This gene encodes serine protease found within the mitochondria and is currently noted for its effects in neurodegeneration. It is essential for haemostatic regulation of mitochondrial dynamics and inactivation of mutations that triggers neuro-degeneration [27]. The protein is secreted from the mitochondria into cytosol during apoptotic event. However, mutations in HtrA2/Omi gene hinders its phosphorylation and affects the function of HtrA2/Omi protease in patients diagnosed of Parkinson's disease thus enhancing mitochondrial susceptibility to stress and neural cell apoptosis [7].

Overview on Primary Intracellular Mechanism Associated with Parkinson's Disease

The Human neuro-transmitting cascade typically comprises series of biochemical pathways that are classified into intracellular mechanism needed for effective neuro-transmitting cascade. These mechanisms are classified below;

Apoptosis: Apoptotic event involves the activation of capase and maintenance of cellular organelles. Poor regulation of apoptotic event has been described to be responsible for the death of hippocampal and cortical neurons in Alzheimer disease and dopaminergic neurons of the midbrain (Parkinson's disease). Apoptotic event associated to this disease is because of accumulation of α -synuclein.

Autophagy: This is an actively regulated mechanism that involves the degradation of damaged cellular components. Regulation of autophagic events prevents and eradicates inactive protease associated with the occurrence of neurodegeneration [21]. Transcriptional down regulation of this mechanism is noticeable during aging likewise mutations in *LRRK2* gene thus resulting in the impairment of its function with subsequent neurodegeneration [17].

Mitochondrial Dysfunction: Under normal cellular conditions, mitochondria are responsible for generating cellular energy through the catabolism of sugars, proteins and fats. However certain factors like gene mutations and oxidative stress can cause an imbalance in mitochondrial fission-fusion event with impaired axonal transport thus promoting abnormalities in hyper-phosphorylation of microtubule-associated protein [11]. This leads to accumulation of damaged mitochondria with subsequent activation of apoptotic event.

Oxidative DNA Damage and Repair Mechanism: Oxidative stress is a product of deregulation of generated toxic reactive oxygen species and DNA repair mechanism/glutathione system. The regulation of this event is important in the detoxification of ROS and in reversing ROS-triggered cellular damage. Dysfunction of this mechanism is related to mutations in Parkinson's related genes namely, PARK1, PARK2, PARK7 which function in the regulation of oxidative stress thus preventing neurodegeneration [13].

Ubiquitin Proteasome System: This system controls degradation of misfolded and aggregates of abnormal proteins. It typically involves the labelling of abnormal proteins by ubiquitin for transportation into proteasome and endoplasmic reticulum for degradation. Ubiquitin-dependent proteasomal degradation is more specific when compared to autophagy. Gene alteration and mutation is a major cause of dysfunction of the ubiquitin proteasomal degradation of damaged proteins and contributes to neurodegeneration [8].

Cell Adhesion: This involves the binding of cells to one another or to extracellular membranes using specific adhesion molecules. Cell adhesion pathways are essential for maintaining synaptic contact and effective in neurotransmission and intracellular signalling in the brain. It plays an active role in cell migration, signal transduction, memory formation and tissue development and repair. Cell adhesion within the neural environment



involves the active function of N-cadherin; a neural adhesion molecule that binds neurons to glial fibres and enables the transfer of force produced by intracellular actin network required for cell migration [24].

Summary and Conclusion

Parkinson disease is known as the most prevalent neurodegenerative disorder that is linked to failure and dysfunction in series of mechanisms and biochemical pathways that are meant to regulate the effectiveness of the neuro-transmitting cascade. The lack of accurate understanding of the mechanisms behind the development of this disease has hindered drug discovery and design needed to reverse missing cellular and protein functions. To successfully minimise and regulate mild neurodegenerative events, adequate understanding of the mechanisms and pathways relating to the development of this disorder is required. Although 10% of affected patients are diagnosed to have inherited the disorder due to transfer of faulty copies of genes involved in regulating the entire neural events. Interesting, studies carried out on these patients have further provided a better understanding of biochemical pathways relating to the onset of the disease and has also served as key to understanding the sporadic causes of the disease. The use of animal models has also proved useful in the management of this disease.

Conclusively, the neural cascade comprises series of unique cellular and biochemical event with distinct but inter-dependent biochemical pathways. Understanding the uniqueness in each pathway is essential for specificities in drug design and discovery because the drug must be designed such that it targets the missing functionalities thus avoiding drug failure and promoting the restoration of faulty and dysfunctional pathways where possible.

Abbreviations

PARKIN: Parkin RBR E3 ubiquitin protein ligase

PINK: PTEN induced putative kinase

LRRK: Leucine rich repeat kinase

HTRA: Htr A serine peptidase

ROS: Reactive oxygen stress

MFN1: Mitofusin-1 protein

OMM: Outer mitochondrial membrane protein

OXPPOS: Oxidative phosphorylation

TRAP: Parkinson disease symptoms; Tremor, Rigidity, Akinesia and Postural instability

DJ-1: Parkinson disease 7

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