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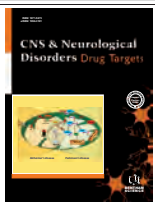
REVIEW ARTICLE

Autophagy and Mitochondria: Targets in Neurodegenerative Disorders



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Abstract: ***Background & Objective***: Cellular physiology and energy metabolism are maintained by the constant supply of energy furnished by the powerhouses of the cell called mitochondria. Cellular homeostasis depends on the timely clearance of damaged cellular organelles and proteins *via* pathways including autophagy. Mitochondria and mitochondrial autophagy play a vital role in cellular health and failure of these pathways can have a devastating effect on cellular homeostasis. Amongst the various cell types, neuronal cells are more vulnerable to bioenergetic depletion since most of their functions critically depend on the availability of energy derived from mitochondrial metabolism, thus making neurodegenerative disorders an obstinate issue. Research in the past few decades has shown that these neurodegenerative disorders are associated with mitochondrial dysfunction and compromised mitophagy leading to accumulation of protein aggregates which ultimately culminate in neurodegeneration.

Conclusion: Thus, targeting mitochondria and autophagy-related proteins and enzymes in neurodegenerative disorders may open the avenues for potential targets for discovering effective therapies. Here, we review the involvement of mitochondrial and autophagy dysfunction in neurodegenerative disorders specifically focusing on Alzheimer's, Parkinson's and Huntington's disease.

Keywords: Autophagy, mitochondrial dysfunction, mitophagy, Alzheimer's disease, Parkinson's disease, Huntington's disease.

1. INTRODUCTION

The current world is battling with the challenges of ageing population mainly due to increased life expectancy. This has inflated the incidence of age-related neuronal disorders which have been predicted to take over cancer and may become the second major cause of deaths by the year 2040 [1]. Unveiling the most affordable curative or prophylactic treatment for these diseases is important as they pose a major individual, social and economic burden. Despite years of meticulous endeavours to track the pathomechanisms behind these disorders, the current drugs available in the market provide only symptomatic relief. Hence future demands a better understanding of the primary cause and pathomechanisms of these diseases so as to bring forth an effective treatment regimen.

A broad array of symptoms ranging from dementia, cognitive and behavioral impairment to motor incoordination, tremors, bradykinesia, rigidity, chorea and dystonia which ultimately lead to incompetency in dealing with daily life activities designate the so-called menace of neurodegenerative disorders [2-5]. It has been previously postulated that neuronal atrophy in the specific areas of the brain in Parkinson's Disease (PD) and Alzheimer's Disease (AD) results in characteristic symptoms of these disorders. The molecular pathogenesis of neuronal atrophy is proposed to be due to genetic mutations, protein misfolding, accumulation of pathological protein aggregates and disturbed ubiquitin-mediated protein degradation [2, 6-8].

One of the predominant features overlapping among most of the neurodegenerative disorders is the accumulation of nonfunctional/dysfunctional protein aggregates *viz*. Aβ peptides in AD, mutated Huntingtin in HD, lewy bodies in PD *etc*. This may be partially or majorly due to the compromised or inefficient autophagy process, which is mainly involved in the clearance of these pathological protein aggregates [9-11]. Thus agents modulating autophagy process can be a major breakthrough for futuristic strategies for the treatment of these neurodegenerative disorders.

Neuronal cells demands and consume the bulk of our body energy pool, and thus, are very much dependent on mitochondrial health and functioning. Most of the neurodegenerative disease pathologies have been identified with a mutation in the mitochondria DNA and interaction of the

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disease-related proteins with mitochondria. The published reports suggest that mitochondrial dysfunction and oxidative stress contribute majorly to the pathogenesis of the disease and it occurs early before progression of the disease [12], hence targeting mitochondrial dysfunction is one of the strategies which can be pursued for future drug discovery and development. Here, we review the recent research providing corroboration of the contribution of mitochondrial dysfunction and autophagy in AD, PD and HD.

2. GENERAL PATHOMECHANISMS FOR MAJOR NEURODEGENERATIVE DISORDERS

Basic pathogenesis of HD involves elongation of cysteine-adenosine-guanine (CAG) repeat, on chromosome number 4 which encodes for polyglutamine in N-terminus of protein, Huntingtin (Htt) [13]. Normal CAG repeat at protein site coding for polyglutamine has the range of 6 to 26 and disease condition is associated with more than 36 repeats in the protein. Clinical features are seen if the number of repeats exceeds more than 40 [14]. Mutation in protein Huntingtin (mHtt) leads to its accumulation due to the disruption of protein degradation mechanism and forms' inclusions in the brain cells of the patients of HD. mHtt leads to neuronal dysfunction and loss of neurons in parts of the brain. Mechanisms involved in neuronal cell death include excitotoxicity, apoptosis, synaptic dysfunction, oxidative stress and impaired energy metabolism [15].

Amyloid hypothesis states that Aβ deposition and Tau (essential protein for microtubule assembly) is responsible for pathogenesis of AD [16]. β and γ-secretase act on the Amyloid precursor protein (APP) and cleave it in Aβ peptides in the size of 38, 40, 42 amino acids in length. Aβ-42 is the largest fragment that accumulates and oligomerises forming amyloid plaques outside the neurons [17]. Aβ-40 binds competitively to Aβ-42 in the monomeric and nontoxic state. It was observed that Aβ-40 prevents Aβ-42 fibril formation and lowered levels of Aβ-40 are associated with the plaque formation in APP transgenic mice. Aβ-40 has the protective role in the AD [18]. Tau gets phosphorylated inside the neurons which interacts with the other tau threads and forms neurofibrillary tangles mainly in the pyramidal cells [19]. Also, hyperphosphorylated tau interacts with the microtubule which is responsible for the shape and function of neurons. Tau hyperphosphorylation and aggregation are figured by Aβ aggregation. Hence Aβ aggregation concluded to initiate a neurodegenerative cascade leading to neuron loss and dementia termed as the amyloid cascade hypothesis. AD is a result of mutations in the APP, PS-1 or PS-2 which increases Aβ deposition [16].

The indicators of PD include the presence of dopaminergic neurodegeneration & intraneuronal Lewy bodies with advanced PD cases exhibiting neuronal loss in the cortex, subcortex, brainstem and peripheral autonomic sites. Mostly, PD is associated with genetic alterations like A53T, A30P, E46K mutations in γ -synuclein, triplication of non-mutant γ -synuclein which lead to excessive pathological protein accumulation. In addition, mutations in DJ-1, PINK1, and LRRK2 culminate in mitochondrial dysfunction and increase oxidative stress which reduces cellular ATP levels contributing to diminished proteasomal activity with reduced clearance of aggregated proteins. Moreover, parkin, UCH and ATP13A2 (gene encoding lysosomal ATPase) mutations also disturb the cellular protein degradation machinery [20]. The "double hit hypothesis" asserts that PD develops as an interaction between mutated genetic and environmental factors [21]. Besides these, excitotoxicity is a cardinal facet for the progression of PD. Thus, a combination of the deleterious effects of multiple genetic mutations ultimately leads to pathological protein aggregation, decreased ATP synthesis and death of dopaminergic neurons [22].

2.1. Available Treatment

Current treatment strategies only give symptomatic relief without treating the underlying cause.

Table 1. Current treatments of HD, AD & PD.

Drug	Class
Treatment for Huntington's	
Tetrabenazine	Dopamine depleting agent
Clonazepam	Benzodiazepines
Sodium Valproate, Levetiracetam	Anticonvulsants
Olanzapine, Quetiapine	Atypical neuroleptics
Treatment for Alzheimer's	
Donepezil, Rivastigmine	Cholinesterase inhibitors
Memantine	NMDA receptor antagonist
Paclitaxel, Epothilone D	Microtubule stabilizers
Ibuprofen, Flurbiprofen	γ-secretase modulators
Treatment for Parkinson's	
Levodopa	Dopamine precursor
Pergolide, Ropinirole	Dopamine agonists
Selegiline, Rasagiline	MAO-B inhibitors

3. AUTOPHAGY IN CNS DISORDERS

The equilibrium between the generation and degradation of cellular components like proteins is responsible for the maintenance of cellular homeostasis. Misfolded long-lived protein aggregates degradation is carried out by autophagy while short-lived proteins are handled by Ubiquitin Proteasome system (UPS) [20]. Autophagy has gained importance in late-onset neurodegenerative disease states, as it has been involved in stages and pathogenetic mechanisms of neurodegenerative diseases [23].

Autophagy, basically means "self-eating" in the context of cell organelles and proteins [24]. Autophagic protein degradation occurs *via* three routes [25]. Microautophagy, a non-selective process is less understood. It involves the retraction of the lysosomal membrane with small vesicles with the introduction of a small quantity of cytoplasm within lumen [23]. Chaperone-mediated autophagy (CMA) selectively involves the degradation of lysosomal proteins bearing

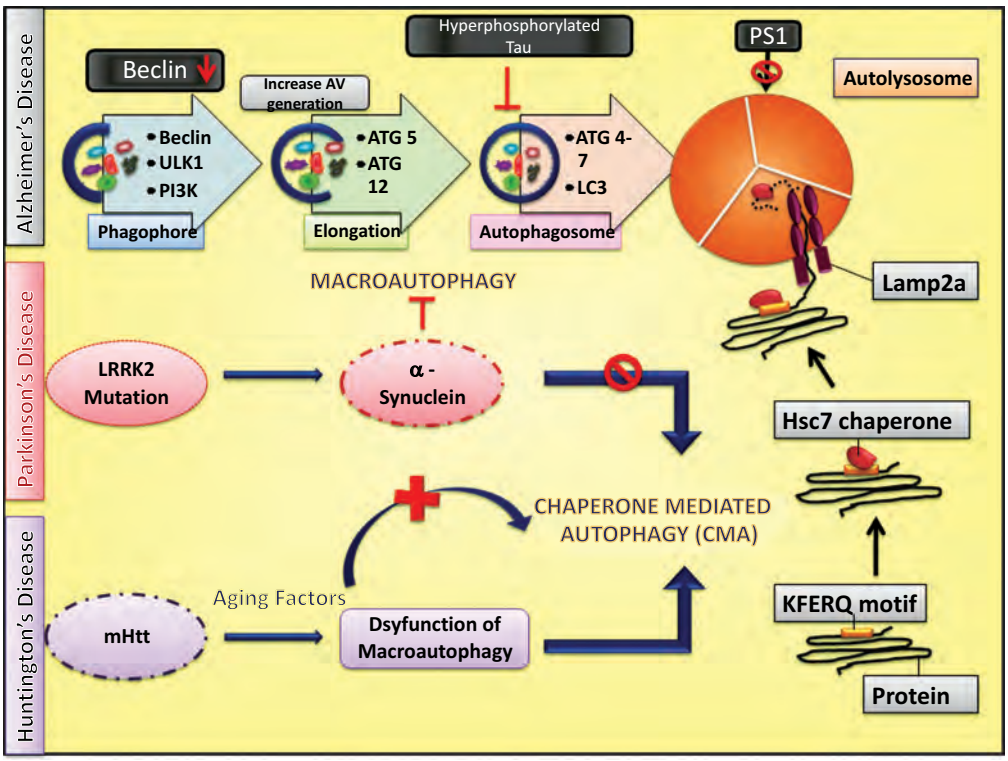

Fig. (1). Summary of altered Autophagy pathway in neurodegenerative diseases: Macroautophagy is altered in Alzheimer's Disease which involves downregulation of Beclin-1 resulting in generation of autophagic vacuoles (AVs), culprit for Aβ peptide generation. Even hyperphosphorylation of tau protein inhibits autophagosome formation. Additionally, mutation in presenilin-1 (PS-1) prevents autolysosome formation. In the case of Parkinson Disease, mutation in leucine-rich repeat kinase 2 (LRRK2) is responsible for mutation of α-synuclein, the root cause of PD which inhibits both macroautophagy and CMA. Furthermore, in Huntington Disease, mutation in huntingtin gene (mHtt) leads to dysfunctional of macroautophagy and also the progression of disease with age blocks CMA.

KFERQ related motif, that is identified by cytosolic chaperone [26]. Macroautophagy, being ubiquitous, causes protein degradation at a large scale. It involves engulfing of the cell components and organelles into the autophagosome followed by fusion with a lysosome. As a result, the engulfed material is degraded by lysosomal enzymes [27]. Different stress stimuli can be responsible for the induction of autophagic processes including endoplasmic reticulum stress, redox stress, energy and nutrient stress, hypoxia and mitochondrial damage [28].

4. AUTOPHAGY MACHINERY

Autophagy process involves initiation, maturation steps followed by fusion with lysosomes. The basic process is monitored *via* the mammalian target of rapamycin (mTOR) involving autophagy-related genes (ATGs) [29]. ATGs, firstly observed in yeast are involved in monitoring the sequestration process in autophagy [23]. Additionally, they play a major role in the formation of autophagosome membrane [30]. Under physiological condition, mTOR inhibits autophagy by suppressing ubiquitin-like kinases (ULK) activity [31]. The initiation process consists of ULK complex with ATG 1, ATG 13, ATG 17, ATG 9 and phosphatidyl inositol 3 kinase (PI3K) complex with Beclin-1 (ATG 6). Phosphorylation of ULK 1 involves its activation, regulated by AMPK. Activated ULK-1 complex recruits ATG proteins and phosphorylates beclin-1 with PI3K complex to initiate autophagosome formation. Elongation process is regulated by Beclin-1 complex dependent on ATG 12 and LC3 conjugation system. The complete autophagosome is marked by the release of LC3βII along with lysosomal fusion, forming autolysosomes where degradation of contents occurs [11].

5. ROLE OF AUTOPHAGY IN NEURODEGENERATIVE DISEASES

5.1. Alzheimer's Disease

Basic pathological features of AD, β amyloid plagues are formed by proteolysis of amyloid precursor protein (APP). Autophagy implies to be the major pathway for degradation of APP cleaved C terminal fragment (APP-βCTF) and Aβ peptides [32]. APP usually is internalized through endocytosis process *via* clathrin coated vesicles, which is further delivered to endosomes followed by β and γ secretase to generate Aβ peptides [33]. The clathrin mediated endocytosis process modulates through phosphatidyl inositol clathrin assembly protein (PICALM), which is a cytoplasmic adaptor protein along with adaptor protein 2 (AP2). It's binding to clathrin, AP2 and phosphatidyl inositol assists in the formation of clathrin coated pits [34]. PICALM/AP2 complex initiates the autophagic degradation process of APP-βCTF by shifting it from the endocytic pathway into the LC3

marked process that leads to fusion of autophagosome and endosome resulting in the APP-βCFT degradation, thus impeding the Aβ peptide generation. As PICALM is a key regulator of APP endocytosis, the decline in PICALM expression impacts clathrin coat formation resulting in Aβ generation and amyloid plaque pathogenesis associated with AD [32].

Deficiency of autophagy in AD was identified when a study revealed the immature accumulations of autophagic vacuoles (AVs) in the brains of AD subjects using electron microscopy and immunogold labeling [9]. These AVs are rich in γ-secretase and form Aβ peptide along with Presenilin-1 (PS-1) [31]. Accumulation of AVs provides evidence for the impairment of AVs transport and fusion of autophagosome, resulting in AD. Moreover, a mutation in PS-1, a component of the γ-secretase complex, promotes lysosomal pathway leading to an increase in Aβ pathology and neuronal loss. This mutation effect greatly influences neurons leading to apoptotic cell death [23]. In case of Tau protein, essential for stabilization of microtubule, autophagy dysfunction leads to the formation of tau aggregates and vice versa. This dysfunction greatly affects the phosphorylation of tau. Hyperphosphorylated tau causes instability and disintegration in microtubule that inhibit autophagosome-lysosome fusion, thus leading to the accumulation of immature autophagosomes [35].

5.2. Huntington's Disease

One of the neurodegenerative diseases, HD involves a mutation in the genes coding for the sequences of polyglutamine region of protein Huntingtin (Htt) [36]. Degradation of Htt is highly dependent on autophagic pathway [30]. In this case, a mutation in Htt (mHtt) actually initiates the degradation process leading to the activation of the autophagic pathway. Further, this mHtt increases autophagosome formation but disrupts its motility, ultimately preventing its fusion with lysosomes. Despite the increase in autophagosome formation, the mHtt and other cell organelles are not degraded that eventually lead to accumulation of mHtt and subsequent neuronal toxicity [10]. Additionally, Mamoru Shibata and his group proved the importance of beclin-1 expression, an essential gene in HD pathogenesis. The study shows that age-dependent decrease in the expression of beclin-1 is responsible for the accumulation of Htt. Moreover, mHtt on accumulation recruits beclin-1 and impairs its function in the autophagic pathway resulting in the progression of HD [37]. Contrary to the fact of macroautophagic dysfunction in HD, it has been shown that CMA is upregulated as a compensatory mechanism but it declines with the aging process and is responsible for cellular toxicity manifestations. Up-regulation of CMA is marked by the over-expression of lysosome-associated membrane protein type 2A (LAMP-2A), located on the lysosomal mem-

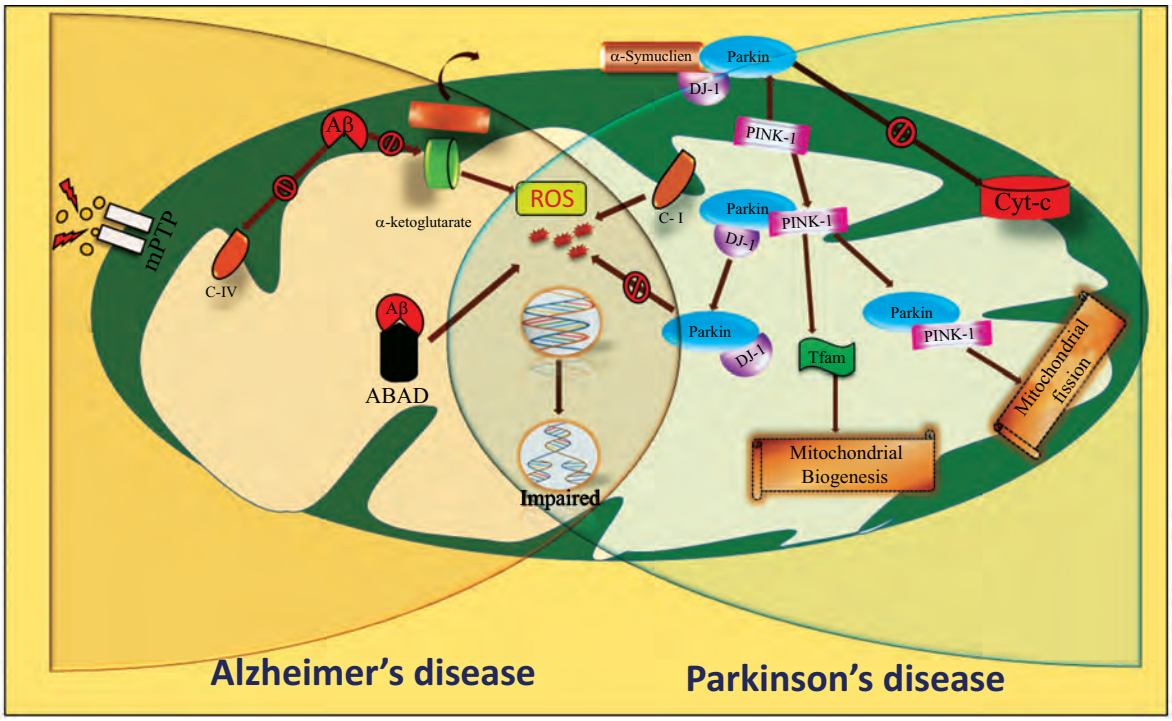

Fig. (2). Summary of mitochondrial dysfunction in AD and PD pathogenesis: In Alzheimer's disease, Aβ moves to the mitochondrial membrane where it leads to the excessive accumulation of the Ca^{+} resulting in the opening of the mPTP. Aβ inhibits complex IV of the ETC and also α-ketoglutarate dehydrogenase and binds to the Aβ alcohol dehydrogenase (ABAD). Both AD and PD involves alteration in the mitochondrial DNA. α-synuclein is the main protein involved in the PD pathogenesis. Overexpression of the α-synuclein results in the oxidative stress and mitochondrial dysfunction. Parkin is associated with the OMM and inhibits cytochrome c release, caspases activation and mitochondrial swelling. In the proliferating cells, Parkin moves inside and with the Tfam it causes mitochondrial biogenesis. Parkin acts downstream to the PINK1 and mutations in both of these results in the excessive mitochondrial fission and reduced fusion. DJ-1 acts as a redox sensor and protects against oxidative stress by acidifying its cysteine residue. LRRK2 mutation results in the excessive mitochondrial fission. Complex-activity is reduced resulting in the oxidative stress.

brane which serves as a binding site for the translocation of the substrate [38]. This alternatively upregulated CMA pathway proves to be advantageous over macroautophagic dysfunction for protein degradation, which helps in targeting therapeutics for the neurodegenerative diseases like HD [39, 40]. Unfortunately, disease progression halts the up-regulation process of CMA, which inefficiently removes the protein aggregates. Although the mechanism behind the age-dependent decline in CMA up-regulation is not clear, the possible interactions between the proteins and the regulators of the pathway could be the reason [38]. Moreover, it is identified that the factor responsible for age-dependent decline in up-regulation involves the instability of the LAMP-2A receptor along with some changes in lipid composition of the membrane that contributes to further decline in CMA [41].

5.3. Parkinson's Disease

PD is associated with the presence of Lewy bodies as well as increased intracellular concentration of non-mutant α-synuclein [20]. In normal physiology, α-synuclein protein is mainly cleared by the ubiquitin-proteasome system (clearance of soluble form) and autophagy (clearance of aggregated form). This specificity comes from the fact that the entry channel of the proteasome is narrow due to which, passage of very large aggregated proteins into it is prevented, diverting them to the autophagic pathway [42]. Finally, the activation of CMA occurs as α-synuclein contains the KFERQ motif identified by the Hsc70 chaperone complex [43]. Hsc70 chaperone further escorts α-synuclein into the lysosomes *via* binding to LAMP2A receptors. The mutant α-synuclein binds very tightly to these LAMP2A receptors preventing its translocation into the lysosomes. This also blocks the access to other CMA substrates to LAMP2A and halts their lysosomal degradation. This additively results in increased intracellular levels of oligomeric and aggregated α-synuclein along with increased levels of other oxidized, misfolded, aggregated proteins [43, 44]. In order to compensate for the functional loss of CMA to clear the aggregated proteins, neuronal cells activate the process of macroautophagy [45, 46]. This is evidenced by the presence of autophagic vacuoles (AVs) in PD patients and PD models [47]. Controversial opinions exist on whether these AVs are neuroprotective or would lead to neuronal damage. Most probably these AVs are responsible for cell survival as blocking macroautophagy at this stage results in reduced cell viability. But along the long run macroautophagy is not able to compensate for total clearance of accumulated toxic proteins as its efficacy is decreased by different factors like, decline in autophagic proteins due to increase in the age, mitochondrial dysfunction, increased presence of free radicals *etc*. [43]. Particularly in PD, different steps of the macroautophagic machinery are disturbed like the elongation of autophagosome membrane is incomplete due to mislocalization of the Atg9 complex, mutations in lysosomal ATPase like ATP13A2 increase the pH in lysosomes, preventing degradation of engulfed substrates. The LRRK2 mutations also lead to flaws in the endosomal-lysosomal trafficking, lysosomal pH and Ca^{2+} regulation, further preventing lysosomal degradation and leading to AVs accumulation [44, 48]. Also, the genes which are altered in PD are associated with the regulation of autophagy, for *e.g*. PINK1 which serves as a regulator of mitochondrial quality control phosphorylates Parkin in response to severe mitochondrial damage [48]. Parkin further polyubiquitinates Voltage-dependent anion channel 1 (VDAC1) and recruits p62 that binds to LC3 to sequester mitochondria in forming autophagosome. In parkinsonism associated with PINK1 and Parkin mutations, the normal physiology is terminated, leading to the accumulation of damaged mitochondria [31, 44].

6. MITOCHONDRIAL DYSFUNCTION

Many studies have realized the role of mitochondrial dysfunction and oxidative stress in the pathomechanism of neurodegenerative diseases such as AD,PD and HD. Accumulation of the ROS, byproducts of energy production of complex I & III, leads to the production of oxidative end products [49]. Neurons are highly dependent on the mitochondrial energy production as they need more energy. The decline in the activity of the respiratory chain complexes results in the reduced membrane potential and ATP formation which is associated with neurodegenerative diseases [50].

Impaired mPTP is a feature observed in most of the neurodegenerative disorders. Calcium ions as free radicals, lead to the opening of mPTP which then releases proapoptotic factors like Cyt *c* and apoptosis initiation factors [51, 52]. Hence, mitochondrial anomalies have a major role in the pathogenesis of neurodegenerative disorders. Mitochondrial dynamics is an important process having its role in neurodegenerative diseases which are characterized by reduced fusion, enhanced fission and altered morphology [53].

6.1. Alzheimer's Disease

In Alzheimer's disease, Aβ is translocated to mitochondrial membranes where it induces intracellular Ca^{2+} levels and promotes the excess accumulation of intracellular Ca^{2+} into mitochondria so as to open the mitochondrial permeability transition pore and to damage mitochondrial structure. This opening of the pore leads to fall of the electrochemical gradient, activation of apoptosis-inducing factors and caspases, finally resulting in apoptosis and progression of Alzheimer's disease [54]. It was observed that decreased interaction of Aβ with Cyclophilin D prevents the mitochondrial permeability transition pore from opening and preserves mitochondrial structure and function [54].

Oxidative phosphorylation causes the formation of H_2O_2,OH and O_2 [55]. When ETC gets inhibited, electrons accumulate in complex I and coenzyme Q, where they form superoxide radical O_2. Mitochondrial Mn superoxide dismutase gives H_2O_2 by detoxifying superoxide anion. Glutathione peroxidase converts H_2O_2 into the water. Also H_2O_2 undergoes Fenton reaction forming hydroxyl radical. This process is specified in the neurofibrillary pathology of AD and PD [56]. Oxidative stress activates signaling mechanism that affects the APP or tau phosphorylation *e.g*. oxidative stress activates c-Jun amino-terminal kinase and P-38 mitogen-activated protein kinase (MAPK) both of which are responsible for increasing the expression of β-secretase. Oxidative stress also activates glycogen synthase kinase-3 which increases tau phosphorylation. Proteomics study has shown

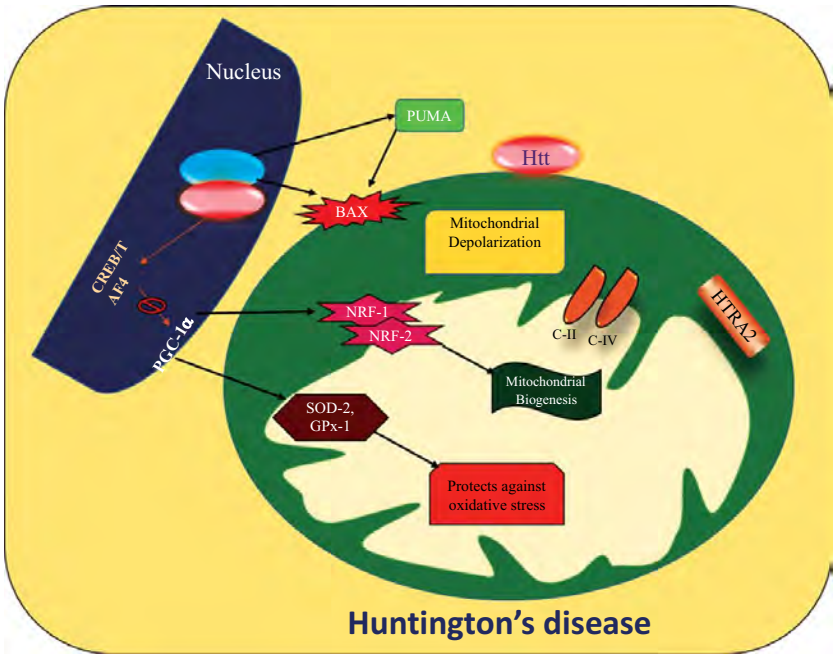

Fig. (3). Mitochondrial dysfunction in pathogenesis of HD: Mutant (Huntingtin) Htt can directly interacts with the mitochondria or with the other intermediate proapoptotic factors. Htt interaction with P-53 may cause activation of the PUMA. Mutant Htt bound P-53 gets upregulated leading to the mitochondrial depolarization. Mutant Htt inhibits the PGC-1α transcriptional activity hence alteration in the mitochondrial biogenesis and reduced protection against oxidative stress. HTRA-2 gets released from the mitochondria and resides into the intermembrane space where it inhibits IAP-1 resulting in the excessive apoptosis and neurodegeneration. Complex II and IV activities gets reduced in the HD.

shown that propyl isomerase PIN1 has its role in oxidative damage. PIN1 causes conformational changes in the proteins that affect APP processing & tau phosphorylation. Pin-1 knockout mice show increase intracellular Aβ levels in mice, tau hyperphosphorylation and neuronal degeneration.

Many reports suggest that there is a direct physical interaction between AD proteins and mitochondria. Aβ binds to the protein ABAD (Aβ-binding alcohol dehydrogenase) which is a mitochondrial matrix protein. When the interaction between Aβ and ABAD is blocked, it shows reduced Aβ induced neuronal apoptosis and free radical generation. However, in mice, over-expressing ABAD enhanced oxidative stress with impaired memory [57, 58]. It was observed that cytochrome oxidase activity was inhibited and free radicals were generated when Aβ directly interacted with mitochondria. Excessive amyloid β affects the proteins involved in the biogenesis causing its imbalance which leads to the excessive fragmentation and defective mitochondrial distribution inside the neurons [59].

Aβ inhibits α-ketoglutarate dehydrogenase and cytochrome oxidase which are two important mitochondrial enzymes found to be reduced in the brains of AD subjects [60, 61]. Presenilin-1 (PS1) is found to be mutated in the familial forms of Alzheimer's disease. At mitochondrial level, cells get sensibilized to the apoptotic stimuli generated due to these presenilin mutations. Presenilin forms an active γ-secretase complex by interacting with Nicastrin (NCT), APH-1 and PEN-2 and it is further responsible for breaking β-amyloid precursor protein (β-APP) [62]. In AD pathology, the enhanced Omi/HtrA2 protease activity in mitochondria leads to increased APP degradation through its association to mitochondrial γ -secretase and generating AICD fragments, therefore an appropriate Omi/HtrA2 protease activity in mitochondria might be significant for clearance of accumulated APP in mitochondria in AD brains [63].

6.2. Huntington's Disease

Biochemical studies in HD subjects showed decreased activities of complex II, complex III and complex IV of Etc. [64, 65]. Htt-knock-in mouse showed imperfect mitochondrial respiration and ATP production. 3NP is a succinate dehydrogenase inhibitor and malonate is a complex inhibitor. Both of these show similar clinical and pathological mechanism resembling HD [66, 67].

The mechanisms by which mitochondrial dysfunction occurs are as follows. In one study subfractionation of mitochondria from knockin HD mouse model showed HTT associated with OMM which shows that HTT may directly interact with mitochondria. When a genotoxic injury occurs, p53 activates BBC3 which is the proapoptotic factor of Bcl-2 family. Also, p53 can directly activate BAX by translocating to mitochondria. In one study, mutant huntingtin caused mitochondrial depolarization by the upregulation of p53 levels and its nuclear transcriptional activity. Further extirpation of the p53 protects HD cells from mitochondrial membrane depolarization [68].

PGC-1α interacts with the transcriptional factors such as NRF-1 and NRF-2 regulating mitochondrial fission and fusion [69]. PGC-1α knockout mice show deranged mitochon-

drial activity and features similar to those observed in the HD such as hyperkinetic movement disorder, striatal degeneration [70]. Mutant huntingtin prevents PGC-1a transcription by intervening with the transcription factors [71]. Not only reduced ATP synthesis but also cAMP levels exaggerate the early HD disease pathology by reducing CRE-regulated gene transcription and energy-dependent processes necessary for neuronal cell [72]. PGC-1α involved in the formation of SOD2, GPx1 which are the ROS detoxifying enzymes. ROS mediated cell death can be augmented with increasing PGC-1α levels. PGC-1α is a strong regulator of the ROS [73]. The study shows that in the mouse striatum and HD patients, PGC-1α expression is reduced [74]. In HD mice, crossbreeding of PGC-1a knockout (KO) mice with HD knock-in (KI) mice results in the augmented motor deformity and neuronal damage. In cultured striatal neurons, degenerative effects of mHtt were augmented by the PGC-1α [71].

The occurrence of mitochondrial dysfunction has been proved in a well-established R6/2 mice model which exhibits 155 CAG expansion with the expression of exon 1 of the huntingtin gene [75]. It shows a decrease in the kreb cycle enzyme such as aconitase and complex IV in brain regions. In HDR6/2 mouse model, reduced stability of mitochondria against calcium-induced mPTP opening has been observed [76]. In Huntington's disease, HTRA-2 which is a proapoptotic factor resides in the mitochondrial intermembrane space and is released from mitochondria. This HTRA-2 causes inhibition of the IAP-1(inhibitor of apoptosis protein-1) which leads to the enhanced apoptosis and neuronal degeneration [77]. In HD, mHTT interacts with Drp1 resulting in the fragmentation of mitochondria [78].

6.3. Parkinson's Disease

Mitochondria are first implicated in Parkinson's as MPTP which is complex I inhibitor, develops the same symptoms as that of the PD [79]. Substantia nigra of PD patients showed reduced activities of complex I and glutathione levels.

Genes which are found in the PD are also associated with the mitochondria in disease pathogenesis such as α-synuclein, Parkin, DJ-1, phosphatase and tensin homologue (PTEN)-induced kinase 1 (PINK1), leucine-rich-repeat kinase 2 (LRRK2). A mutated form of mt-DNA polymerase γ (POLG) causes impaired mtDNA replication leading to the familial form of PD [80].

In comparison with age-matched controls, PD patients have high levels of clonally expanded somatic mtDNA deletions [81]. These somatic mtDNA deletions induce the neuroprotective mitochondrial compensatory mechanisms that allow for maintenance of the function and integrity of the nigrostriatal system [82, 83]. It is found that several continent specific groups show the cluster of polymorphism called as mtDNA haplogroups which may reduce the risk of PD *e.g*. Europeans have haplogroup cluster UJKT which reduces PD risk [84].

In the PD, impediment of the respiratory chain occurs leading to the formation of the ROS mainly superoxide. SOD2 from mitochondrial matrix converts the superoxide into H_2O_2. This superoxide causes damage inside the mitochondria and H_2O_2 exerts oxidative damage both inside and outside the mitochondria. In the neurons and glial cells, NO is generated from the NOS. This NO reacts with the superoxide leading to the formation of the peroxynitrite which causes depletion of glutathione, DNA strand breakage, lipid oxidation and protein nitration. SOD2 and respiratory chain complexes get nitrated by the peroxynitrite and reactive nitrogen species. Superoxide causes the oxidation and decrease in the activity of the Fe-S comprising enzymes such as aconitase resulting in the formation of Fe^{2+} and H_2O_2, which after entering into the Fenton reaction, form the hydroxyl radical ($^{\cdot}OH$) which oxidizes proteins, DNA and lipids resulting into the mitochondrial dysfunction [85].

Mn-SOD has an important role in the mitochondrial dysfunction and oxidative stress. When Mn-SOD is too low, superoxide anion accumulates within the mitochondria. If the Mn-SOD is too high, hydrogen peroxide accumulates inside the mitochondria as hydrogen peroxide is formed by the reaction mediated by the Mn-SOD; hence, for maintaining the levels of the free radicals, the Mn-SOD should be in optimal levels. In sporadic PD cases, Mn-SOD levels found to be raised [86]. In mice model, it was found that mitochondrial activity is impaired due to the overexpression of α-synuclein, which enhances oxidative stress [87, 88]. SNCA overexpression blocks the ER- Golgi trafficking by sequestering Ypt1p which is vesicle trafficking protein. Overexpression of Ypt1p and its ortholog Rab1 attenuates SNCA induced toxicity [89]. Other pathomechanisms indicate that the scaffolding protein septin 4 (Sept4) clump up with α-synuclein in Lewy bodies. Dopaminergic neurons lacking Sept4 are more prone to deterioration in PD [90].

Parkin codes a ubiquitin E-3 ligase. Parkin mutations cause oxidative stress and mitochondrial dysfunction. Parkin null Drosophila causes mitochondrial wreckage and enhances ROS. Parkin lacking subjects show reduced complex I activity [91, 92]. Parkin connects with the OMM and averts the apoptosis as well as mitochondrial swelling; these protective effects are inhibited by the mutations in the Parkin [93]. In case of proliferating cells, Parkin gets localized into its mitochondria where it combine with the mitochondrial transcription factor-A thereby promoting mitochondrial biogenesis [94, 95]. Parkin acts downstream to the PINK-1. Mutation in both of these genes results in the excessive mitochondrial fission and reduced fusion. PINK-1 excerbates the mitochondrial pathology associated with the α-synuclein accumulation by dysregulating the mitochondrial calcium flux [96].

DJ-1 mutation is associated with the autosomal recessive juvenile PD. DJ-1 interacts with α-synuclein, Parkin and PINK-1. It protects against cell death induced by oxidative stress. DJ-1 acts as a redox sensor: Cysteine residue (C 106) gets acidified due to oxidative stress and relocalised into mitochondria. C-106 mutation prevents this and impairs the cell's ability to combat cellular stress [97]. HTRA-2 has its role in the mitochondrial quality control of proteins and acts as a proapoptotic factor after being liberated from intermembrane space. Homozygous Htra-2 knockout mice develop mnd-2(motor neuron degeneration) which has the same features as that of the Parkinson's disease. HTRA2 p.G399S is

responsible for hereditary essential tremor and that homozygote for this allele develops Parkinson's disease [98]. Alterations in Drp1 enhance mitochondrial fragmentation which can also be seen in cell models of PD [99].

LRRK2 is involved in the common pathway with the protein products of the other genes like α-synuclein and tau. Patients with the LRRK2 mutations have tau lesions and loss of dopaminergic neurons. Hence, LRRK2 acts upstream to the α-synuclein and its aggregation in the Lewy bodies. WT LRRK2 expression causes mitochondrial fragmentation that is further exacerbated in neurons expressing PD-associated LRRK2 mutants. Elevated mitochondrial DLP-1 recruitment due to LRRK2 and its interaction with DLP1 enhances the mitochondrial fission and slows down the mitochondrial fusion process. Hence, LRRK2 mutation results in the excessive fragmentation which results in the mitochondrial dysfunction and neurodegeneration [100].

7. FUTURE PERSPECTIVES

Since autophagic dysfunction has come into spotlight as a crucial factor contributing to the pathogenesis of various neuronal protein conformational disorders, ample research has been done in this field yielding preclinically efficacious pharmacological enhancers of autophagy which are now gradually making their way into clinical trials. Yet autophagy is a double-edged sword regulating cell survival as well as cell death, the optimistic use of these agents in neurodegenerative diseases will be possible only with the innovation of new techniques to ascertain when (for *e.g*. either due to reduced autolysosomal membrane formation or due to reduced autolysosomal clearance), how (either by using agents to induce autophagosomal membrane formation or by using agents to enhance autolysosomal degradation) and how long (for time adequate enough to clear toxic proteins but not so intense as to cause degradation of normal cellular organelles) to enhance autophagy. Thus the future calls upon an exigent need for clinically applicable biomarkers and assays to quantify autophagic turnover in situ in specific brain cell populations [20, 44, 101].

CONCLUSION

Mitochondrial dysfunction and oxidative stress occur early in AD, HD and PD. There is testimony that it has a chief role in the pathogenesis of these diseases. Many disease proteins interact with the mitochondria *e.g*. Aβ, presenilin, ABAD, DJ-1, PINK-1, PARKIN, a-synuclein, HTRA-2, Htt. A study needs to be carried out to explore the interaction between the disease proteins and mitochondrial proteins. It has been proved that many mitochondrial enzymes have been reduced in these diseases *e.g*. SOD-2 reduced in the Huntington's disease. We can target the pathways which are responsible for impairment of these enzymes. Htra-2 plays an important role for further progression of the disease; however in all the diseases, it acts differently and until now, we only have a crude idea in this sector. Current treatments only give the symptomatic relief, most of them are antioxidants which are found to be effective in the clinical trials but not targeting the generation of ROS and up-regulation of the antioxidant defense system. Interaction of the disease proteins and mitochondria open the doors for the new targets in this arena such as preventing the interaction between Aβ and cyclophilin D in AD so as to maintain mitochondrial structure and function.

Knowledge of neurodegenerative diseases has been progressed rapidly and the field holds a great promise for developing our understanding and the eventual treatment of these illnesses.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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