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Autophagy of Mitochondria: A Promising Therapeutic Target for Neurodegenerative Disease

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Abstract

The autophagic process is the only known mechanism for mitochondrial turnover and it has been speculated that dysfunction of autophagy may result in mitochondrial error and cellular stress. Emerging investigations have provided new understanding of how autophagy of mitochondria (also known as mitophagy) is associated with cellular oxidative stress and its impact on neurodegeneration. This impaired autophagic function may be considered as a possible mechanism in the pathogenesis of several neurodegenerative disorders including: Parkinson's disease (PD), Alzheimer's disease (AD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS) and Huntington disease (HD). It can be suggested that autophagy dysfunction along with oxidative stress are considered main events in neurodegenerative disorders. New therapeutic approaches have now begun to target mitochondria as a potential drug target. This review discusses evidence supporting the notion that oxidative stress and autophagy are intimately associated with neurodegenerative disease pathogenesis. This review also explores new approaches that can prevent mitochondrial dysfunction, improve neurodegenerative etiology, and also offer possible cures to the aforementioned neurodegenerative diseases.

Keywords

Autophagy; Mitophagy; Neurodegeneration; Oxidative stress

Introduction

Autophagy is an evolutionary conserved pathway that engulfs dysfunctional organelles and/or misfolded proteins in a double membrane compartment known as an autophagosome [1]. The formation of the autophagosome drives a progressive process involving a regulation of signal which triggers the formation of a phagophore. When the membrane edges of this phagophore fuse, a autophagosome is formed [2]. Autophagosomes are thought to play an important role in the pathogenesis of a number of common neurodegenerative disorders including: Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD) and Amyotrophic lateral sclerosis (ALS) [3]. Autophagosomes are now recognized as a

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Conflict of interest

Authors having no conflict of interest

potentially important contributing factor to the pathogenesis of neurodegenerative disorders. Autophagy systems cause increased oxidative stress and free radical formation, impaired bioenergetics and mitochondrial dysfunction, disruption of neuronal Golgi apparatus transport, and impaired molecular chaperones [4]. Neurons are metabolically active cells with high energy demands that are mainly dependent on mitochondrion which is confirmed by the link between diseases of mitochondria and their common neurodegenerative component [5]. In recent years, a growing number of collective data has inferred the role of mitochondria in the pathogenesis of neurodegenerative disorders and apoptotic processes [6]. Reactive oxygen species (ROS) concentration is mediated by mitochondrial antioxidants such as manganese superoxide dismutase (SOD) and glutathione peroxidase (GPX) which are normal byproducts of the mitochondrial respiratory chain. In addition to the generation of ROS, mitochondria are also involved with calcium homeostasis, apoptosis and lipid peroxidation which are central features of the majority of neurodegenerative disorders [7,8].

Recent reports have highlighted that neurons are reliant particularly on the dynamic properties of mitochondria. They engage in repeated cycles of fusion and fission, which serve to inter mix the population of mitochondria [9]. In addition, mitochondria are actively recruited to subcellular sites, such as the axonal and dendritic processes of neurons. Finally, the quality and health of the mitochondrial population is maintained through mitophagy, a form of autophagy, in which defective mitochondria are selectively degraded. In this review we will focus on the involvement of mitochondria, autophagy and oxidative stress in common neurodegenerative disorders (Fig.1.) and offer possible therapeutic approaches for cures.

Autophagy

Autophagy is characterized by the presence of autophagic vacuoles, autophagosomes, and acts as an arbiter of neuronal survival and death decisions amongst neurodegenerative diseases [10, 11, 12, 13]. The increased autophagy in the brains of patients with neurodegenerative disorders suggest that it contributes to the pathogenesis of these neurodegenerative diseases by causing cell death [14, 15, 16, 17, 18]. Autophagy also plays an important role in neuroprotection as well as in neurodegeneration as supported by in vitro and in vivo models [19, 20, 21].

Micro Autophagy

Microautophagy is somewhat similar to macroautophagy and it is reported that the lysosomes directly engulf cytoplasm by passing the need for autophagosome and autophagolysosomal formation [22]. Microautophagy is active in the resting state and is responsible for the appropriate removal of selective organelles and the continuous turnover of intracellular constituents. Interestingly, microautophagy is not activated by nutritional deprivation or stress.

Macro Autophagy

Macro autophagy is the most abundant type of autophagy and it is conserved from yeast to mammals. Non-selective autophagy is induced by withholding essential nutrients and

selective autophagy ensues to clear unwanted or damaged organelles, including mitochondria [23]. In this process an isolation membrane (known as phagophore) surrounds a portion of the cytoplasm or an organelle forming a double membranous structure called the autophagosome. Mitochondria are removed by a form of macroautophagy (called mitophagy) in which the core machinery of bulk macroautophagy is harnessed for the selective clearance of mitochondrion [24].

Mitophagy

The term mitophagy came to describe the selective degradation of mitochondria by autophagy [25]. Reactive oxygen species (ROS), particularly superoxide anion ($O_2^{\cdot-}$), hydrogen peroxide (H_2O_2), and hydroxyl radical ($OH^{\cdot}$) are toxic byproducts of normal oxidative phosphorylation. Damaged mitochondria release high levels of Ca^{2+} and cytochrome c into the cytosol and thereby trigger apoptosis [26, 27] and neurodegenerative diseases [28]. Mitochondria have their own proteolytic system whose function is to maintain health, both internally and externally by interacting with other mitochondria, by degrading unfolded membrane proteins on the inner and outer mitochondrial membrane [29, 30, 31]. In addition to proteolytic and proteosomal degradation recent evidence points to a lysosomal pathway in which vesicles bud from mitochondrial tubules, sequester selected mitochondrial cargos, and then deliver those mitochondrial components to the lysosome for degradation [32]. Mitophagy pathways account for degradation of mitochondrial proteins and the specific control of mitochondrial morphology has a significant impact on mitochondrial function [33]. Mitochondrial fusion was suggested as a route for the rapid exchange of metabolites, mitochondrial DNA (mtDNA) and membrane components [34]. Fission, however, is thought to facilitate the segregation of mtDNA and isolation of mitochondria from the network to allow their degradation [35]. Through this, mitochondrial fission and fusion influences nearly all aspects of mitochondrial function, including respiration, calcium buffering, and apoptosis [36].

Mitochondria and Redox Stress

Neurons and astrocytes, the two major types of brain cells, require more than 20% of the total consumption of oxygen [37]. Oxidative stress is a condition in which the balance between production of ROS and level of antioxidants is significantly altered, leaving high levels of ROS which eventually damages cells. ROS contribute to the development of neurodegeneration by modulating the function of biomolecules [38, 39]. ROS may target several different substrates in the cell causing protein, DNA, RNA oxidation, or lipid peroxidation. Overproduction of ROS in mitochondria or in other sources can also cause changes in the antioxidant system which leads to imbalance and induces oxidative stress and neurodegeneration [40].

Mitochondrial dysfunction and increased oxidative damage are often associated with AD, PD, ALS and HD and several other neurodegenerative disorders suggesting that oxidative stress may play an important role in the pathophysiology of these diseases [41]. It has become dogma that mitochondria are a major source of ROS and also a target of ROS. In pathological conditions this organelle actually produces less-free radicals than other

cytosolic enzymes such as NADPH oxidase [42]. However mitochondria (electron transport chain-ETC), in contrast to other cellular producers of ROS, generate free radicals constantly. Mitochondria, which harbor the bulk of oxidative pathways, are packed with various redox carriers that can potentially leak single electrons to oxygen and convert it into a superoxide anion [43]. ROS in mitochondria can also be generated by several enzymes including aconitase and α -ketoglutarate dehydrogenase complex [44, 45, 46]. The production of superoxide by the ETC in mitochondria is dependent on the value of mitochondrial membrane potential. In addition to being generated during cellular metabolism in mitochondria, ROS can be produced in response to different environmental stimuli such as growth factors, inflammatory cytokines, chemical oxidants and chemotherapeutics. Dependent on cell types ROS have been found to function as signaling molecules in cell proliferation and cellular senescence [47], or cell death [48]. The observation of increased autophagy in the brains of patients with AD, PD and HD suggests that autophagy contributes to the pathogenesis of these neurodegenerative diseases; a possible cause is increased cell death [49] because of the constant production of free radicals in mitochondria and changes in the antioxidant system which leads to imbalance, oxidative stress, and neurodegeneration [40].

The excessive Ca^{2+} uptake into mitochondria can be lethal to neurons. Intracellular stress such as Ca^{2+} overload and oxidative stress leads to cell death [50]. This causes mitochondria to swell and leads to rupture of the outer mitochondrial membrane releasing proteins from the intra membrane space, e.g. cytochrome c, into the cytosol [50]. This results in mitochondrial depolarization, uncoupling of oxidative phosphorylation, and overproduction of ROS to the cytosol which eventually leads to cell death [51]. Physiological mitochondrial Ca^{2+} concentrations do not induce mitochondrial transition pore (MTP) opening, but will work in synergy with pro-apoptotic stimuli [52].

Alzheimer's disease

Mitochondria are significantly reduced in various types of cells obtained from patients with Alzheimer's disease (AD) and their dysfunction has also been associated with the pathophysiology of AD [53]. The most consistent defect in AD is the deficiency in cytochrome c oxidase which is in the family of mitochondrial electron transport enzymes [54]. This deficiency leads to an increase in ROS production and a disturbance in energy metabolism [7]. AD brains also show evidence of ROS mediated-injury as in there are increased levels of malondyaldehyde and 4-hydroxynonenal in the brains and cerebrospinal fluid of AD patients compared to controls [55, 56]. The amyloid β -protein ($\text{A}\beta$) is involved in mitochondrial function and pathology of AD [57] and is also responsible for mitochondrial mutations in AD development. In AD there is massive accumulation of autophagosomes within large swellings along dystrophic and degenerating neuritis which is primarily due to deficits in the maturation of autophagosomes and their retrograde transport towards the neuronal cell body [49].

In general autophagy is considered to be activated in AD primarily because of impaired clearance of autophagosomes that contain both amyloid precursor protein (APP) and its processing enzymes thereby increasing the propensity to generate toxic $\text{A}\beta$ peptides [58].

Normally, most A β formed during autophagy are degraded within lysosomes via macroautophagy, but in disease, A β accumulates within the large pool of autophagosomes in dystrophic neurites and becomes a major intracellular reservoir of toxic peptides in AD brains [59]. Accumulation of autophagosomes in neurons contributes to A β generation within plaques and with that, increased autophagy [60]. Consistently oxidative stress induced autophagy of accumulated amyloid β -protein in AD causes permeabilization of the lysosomal membrane, pyramidal neuronal loss, neuronal cell death and a further neuronal subjection to autophagic degradation which summate into causing neurodegeneration [36, 26].

Parkinson 's disease

Parkinson's disease (PD) is the second most common progressive disorder of the central nervous system which is characterized prominently by a loss of dopaminergic neurons in the substantia nigra and formation of intraneuronal protein aggregates α -synuclein [61, 62, 63]. PD is associated with multifactorial causes having features of autophagosome-like structures and a pattern of neurodegeneration [64, 65, 66]. The first evidence in support of a significant role of autophagy in PD came from the demonstration that α -synuclein, which is a major constituent of Lewy bodies found in PD, is degraded by macroautophagy [30]. Besides the degradation of α -synuclein the autophagic pathway is also involved in the turnover of mitochondria. Mutations in genes such as PARKIN and PINK1 are known to cause autosomal recessive forms of PD and have been implicated in the control of mitochondrial morphology and function [67]. Recently PARKIN was found to facilitate macroautophagy of impaired mitochondria [68]. In support of a role for autophagy in the clearance of defective mitochondria in PD, knockdown of PINK1 expression induces mitochondrial fragmentation, followed by activation of autophagy/mitophagy [69, 70]. Furthermore, PARKIN, whose loss of function mutation causes early onset PD has been found to promote autophagy of depolarized mitochondria [71, 68] suggesting that a failure to eliminate damaged mitochondria by mutant PARKIN is responsible for the pathogenesis of PD.

Altered mitochondrial respiration and increased production of ROS causes a loss of dopaminergic neurons in human and animal models which strongly suggests a link between oxidative stress, mitochondrial dysfunction, and PD pathogenesis [72, 73]. It is reported that there is an increase in common deletions of mitochondrial DNA in the surviving dopaminergic neurons in PD substantia nigra. These DNA deletions are believed to be the result of oxidative stress [74, 75]. Protein oxidative damage in the form of protein carbonyls is evident in PD brain compared to controls and there is some evidence to suggest a role for nitration and nitrosylation of certain proteins due to reactive nitrogen species in PD brain [76]. Consistent with this concept, a significant decrease in the activity of complex I in the electron transport chain is observed in the substantia nigra from PD patients [72]. Genetic studies of PINK1 and PARKIN further support the role of mitophagy in pathogenesis of PD [77, 78].

Huntington's Disease

Huntington's disease (HD) is another hereditary neurodegenerative disorder that affects muscle coordination and leads to cognitive decline and dementia. HD is caused by an autosomal dominant mutation in the Huntingtin (HTT) gene [79, 80]. Mutant HTT is known to induce endosomal and lysosomal activities [81]. Morphologic defects of mitochondria, such as reduced mitochondrial movement and alterations in mitochondrial ultrastructures have been observed in patients with HD or in transgenic HD mouse models [33, 82]. In addition, expression of mutant HTT leads to impaired energy metabolism, abnormal Ca^{2+} signaling and mitochondrial membrane potential [83], and drastic changes in mitochondrial ultrastructures [84, 85, 86]. Postmortem brains of patients with HD have and increase in endosomal and/or lysosomal organelles and their multivesicular bodies express characteristic features of autophagy [87]. It is recently proposed that mutant HTT conveys its neurotoxicity by evoking defects in mitochondrial dynamics, mitochondrial fission and fusion, and organelle trafficking which in turn result in bioenergetic failure and HD associated neuronal dysfunction [33, 88].

Amyotrophic Lateral Sclerosis Disease

Amyotrophic lateral sclerosis (ALS) is characterized by extensive loss of motor neurons functioning in the spinal cord and brain stem, atrophy of ventral roots, degeneration of upper motor neurons in the motor cortex and corticospinal tract, somatic and axonal inclusions of aberrant neurofilament proteins, and reactive astrogliosis [89]. Mitochondrial dysfunction may cause motor neuron death by predisposing them to calcium-mediated excitotoxicity by increasing generation of ROS and by initiating the intrinsic apoptotic pathway [90]. The specific mechanism of ALS still needs to be investigated, but the findings are significant because they implicate cells other than neuron cells in neurodegeneration [91]. But accumulating evidence suggests that mitochondrial dysfunction is involved in the pathogenesis of ALS [92]. It has been reported that abundant autophagosomes and associated increases in autophagy proteins and their activation is detrimental for the survival of motor neurons [93]. However, other studies have found an increase in the LC3II macroautophagy marker protein and a decreased ratio of phosphorylated mTOR-positive motor neurons shows defective autophagy accompanied with motor neuron loss in ALS [94]. Mutant SOD1 was found to be preferentially associated with mitochondria and the subsequent impaired function suggests that axonal transport of mitochondria along microtubules is disrupted in ALS [95]. Furthermore, new evidence suggests that mitochondrial fission and fusion as well as mitophagy clearance may also be affected by mutant SOD1 [96]. A key to answering the question of whether mitochondrial dysfunction plays a crucial role in motor neuron degeneration are therapeutic approaches aimed at modulating mitochondrial function and protecting mitochondria from the pro-apoptotic effect of mutant SOD1. A better understanding of the etiology of ALS is needed to develop effective therapies for the treatment of this fatal neurodegenerative disease.

Multiple Sclerosis

Multiple sclerosis (MS) is a chronic, unpredictable, and often disabling disease that attacks the central nervous system [97]. In MS disease the neurological function starts gradually deteriorating from the onset of the disease [98]. Currently available therapeutic agents are not effective in preventing or reducing the relentless accumulation of neurological deficits during the progressive phase of MS [99]. Although the pathological substrate of disease progression is regarded as axonal degeneration, recent evidence identifies axonal dysfunction as an additional and possibly important contributor to the neurological disability during the progressive phase of MS [100]. The mitochondrial changes in axons lacking healthy myelin sheaths as well as redistribution of sodium channels suggest that demyelinated axons would be more vulnerable to energy deficits than myelinated axons [99]. The axons with dysfunctional Na^+/K^+ ATPase or without Na^+/K^+ ATPase will no longer be able to efflux sodium, maintain resting membrane potential, or conduct nerve impulses [100]. A recent study identified the lack of Na^+/K^+ ATPase in approximately half of chronically demyelinated axons in MS [101]. A dysfunction of mitochondria in lesions as well as in the normal-appearing white and grey matter is increasingly recognized in MS and could be an important determinant of axonal dysfunction and degeneration.

Prevention of Mitochondrial Dysfunction

The alterations of mitochondrial function lead to a plethora of diseases. However, targeting mitochondrial linked pathways and using different approaches can revert or prevent mitochondrial dysfunction, these approaches are: minimizing ROS generation, cellular antioxidant pathways, calcium flux, electron transport chain, anti-apoptotic mechanisms, and mitochondrial permeability transition pore (mPTP) (Figure.2). Several studies have reported therapeutic molecules that could be used as potential mitochondrial dysfunction reverting agents, these are: CDDO-ethyl amide, CDDO-trifluoroethylamide, pioglitazone, rosiglitazone, resveratrol, 5-aminoimidazole-4-carboxamide ribonucleoside (AICAR), coenzyme Q10, and bezafibrate. A compiled table of these molecules along with their mode of action, structure, trade name, and references has been given (Table-1). Exploring these agents along with other novel agents/approaches could help in preventing mitochondrial dysfunction and in improving neurodegenerative etiology.

Future direction and conclusions

It is evident from recent findings that mitochondrial abnormalities are actively engaged in the pathogenesis of neurodegenerative diseases. Evidence from the collected data suggested that mitochondrial-DNA mutations, autophagy, and oxidative stress are contributory factors for multiple neurodegenerative diseases. Autophagic dysfunction and oxidative stress occur early in all major neurodegenerative diseases and there is strong evidence that this dysfunction has a causal role in disease pathogenesis. Autophagy represents a major route for degradation of toxic proteins and dysfunctional organelles. Alterations in autophagy processes play a significant role in the pathogenesis of many neurodegenerative diseases. Since the autophagy pathway may be compromised in various neurodegenerative disorders, understanding the autophagy pathways in each neurodegenerative disorder could explain

differences in the course of these pathologies and will be essential to developing targeted therapeutic approaches for each disease. In our opinion a better understanding of the cellular response to oxidative stress, mitochondrial dysfunction, and its relation to autophagy will lead to new therapeutic approaches for the prevention and amelioration of neurodegenerative diseases. The future challenges are to devise models to better understand the common pathways and relative contribution of mitochondrial dysfunction to the pathogenesis of neurodegenerative disorders as well as to identify therapeutic approaches that target mitophagy and its consequences.

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Abbreviations

AD	Alzhiemers disease
PD	Parkinson disease
ALS	Amyotrophic lateral sclerosis
HD	Huntington's disease
ROS	Reactive oxygen species
MS	multiple sclerosis

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Figure 1.
Figure showing the autophagy associated common neurodegenerative disease and their molecule.

Figure 2.

Figure showing the different target of drugs, molecules and chemical compounds in Mitochondria. These drugs and chemical compound are also used for study of molecular mechanism of various neurodegenerative disease.

Table.1

Table showing the different chemical compounds, drugs and their targets in mitochondria. These drugs and chemical compounds targeting the oxidative stress pathways, neuroinflammatory pathways, some of targeting electron transport chain. These drugs and compounds are widely used for the study of neurodegenerative disease.

S. No.	Compounds	Mechanism	Structure	Trade name	References
1	CDDO-Ethyl amide	Target Nrf2/ARE (NF-E2-related factor 2/antioxidant response element) signaling pathway		Not assigned	[102, 103]
2	CDDO-Trifluoroethylamide	Target Nrf2/ARE (NF-E2-related factor 2/antioxidant response element) signaling pathway, attenuates mitochondria I dysfunction		Not assigned	[102, 103]

S. No.	Compounds	Mechanism	Structure	Trade name	References
3	Pioglitazone	Activate peroxisome proliferator-activated receptors (PPARs), provide neuroprotection, attenuates mitochondria I dysfunction by improving mitochondria I DNA (mtDNA) content, levels of mtDNA and nuclearencoded electron transport chain subunit proteins, increased oxygen consumption, and elevated complex I and complex IV V max activities	<chem>CC1=CC=C(C=C1)COC2=CC=CC=C2CC3C(=O)NC(=O)S3</chem>	Actos Piomed Pioneer	[104, 105]

S. No.	Compounds	Mechanism	Structure	Trade name	References
4	Rosiglitazone	Activate PPAR gamma activators, attenuates mitochondria l dysfunction.		NA	[106]

S. No.	Compounds	Mechanism	Structure	Trade name	References
5.	Resveratrol	Antioxidant, anti-inflammatory, and metalchelating effects, prevent mitochondria l dysfunction		Not assigned	[107].

S. No.	Compounds	Mechanism	Structure	Trade name	References
6.	5-aminimidazo le-4-carboxamide ribonucleoside (AICAR)	Block proinflammatory cytokines, inhibit ROS generation, deplete glutathione, prevent oxidative stress		Huapin	[108].

S. No.	Compounds	Mechanism	Structure	Trade name	References
7	Coenzyme Q10	Improve respiratory chain dysfunction, oxidative stress and neurodegeneration		Rite Aid Coenzyme Q-10	[109, 110]
8.	Bezafibrate	Anti-inflammatory, neuroprotective role, attenuate astrogliosis, improve peroxisome proliferator-activated receptor (PPAR)- γ		Bezalip Beza-XL Fenolip Globez	[111, 112]