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Review Article

Mitochondrial Diseases of the Brain

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ABSTRACT

Neurodegenerative disorders are debilitating diseases of the brain, characterized by behavioral, motor and cognitive impairments. Ample evidence underpins mitochondrial dysfunction as a central causal factor in the pathogenesis of neurodegenerative disorders including Parkinson's disease, Huntington's disease, Alzheimer's disease, Amyotrophic lateral sclerosis, Friedreich's ataxia and Charcot-Marie-Tooth disease. In this review, we discuss the role of mitochondrial dysfunction such as bioenergetics defects, mitochondrial DNA mutations, gene mutations, altered mitochondrial dynamics (mitochondrial fusion/fission, morphology, size, transport/trafficking, and movement), impaired transcription and the association of mutated proteins with mitochondria in these diseases. We highlight the therapeutic role of mitochondrial bioenergetic agents in toxin and in cellular and genetic animal models of neurodegenerative disorders. We also discuss clinical trials of bioenergetics agents in neurodegenerative disorders. Lastly, we shed light on PGC-1α, TORC-1, AMP kinase, Nrf2-ARE, and Sirtuins as novel therapeutic targets for neurodegenerative disorders.

Contents

Abbreviations: PD, Parkinson's disease; AD, Alzheimer's disease; HD, Huntington's Disease; ALS, Amyotrophic Lateral Sclerosis; TAR DNA, binding protein TDP-43; TCA, tricarboxylic acid cycle; ROS, reactive oxygen species; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydrodropyridine; KGDH, alpha-ketoglutarate dehydrogenase; PGC-1α, proliferator-activated receptor-gamma coactivator-1alpha; MMP, mitochondrial membrane potential; mtDNA, mitochondrial DNA; Tfam, mitochondrial transcription factor A; PCr, phosphocreatine; Drp1, dynamin-related protein 1; UCP-1, uncoupling proteins; BAT, brown adipose tissue; MFN, mitofusin; 6-OHDA, 6-hydroxydopamine; CK, creatine kinase; CoQ10, coenzymeQ10; PPARs, peroxisome proliferator-activated receptors; AMPK, AMP-activated protein kinase; TORC, Transducers of Creb-related binding protein; MPP+, 1-methyl-4-phenylpyridinium

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Neurodegenerative disorders are set of late-onset, progressive, age-dependent brain disorders, characterized clinically by the impairment of cognitive functions, motor co-ordination, dyskinetic movements, and irreversible changes in behavior and personality. Pathological hallmarks of these disorders including Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's Disease (HD) and Amyotrophic Lateral Sclerosis (ALS) are accumulations of mutant proteins such as α-synuclein, amyloid-β (Aβ), mutant huntingtin (Htt), TAR DNA binding protein (TDP-43) and superoxide dismutase (SOD) respectively in the affected brain regions. Oxidative stress, inflammation, mitochondrial dysfunction, excitotoxicity, and impaired transcription have been identified as causal factors for neurodegenerative disorders. Amongst these, mitochondrial dysfunction takes center stage in the pathophysiology of chronic neurodegenerative disorders. Mitochondria, a tiny and dynamic organelles often referred as "powerhouse of the cell" and "ATP reservoir", are required for the tremendous energy demands of the brain cells including neurons. In the mitochondria, ATP is produced by tightly regulated processes including tricarboxylic acid cycle (TCA) or Krebs cycle and oxidative phosphorylation (OXPHOS/respiratory chain complex I-IV). Any defect of proper functioning of brain mitochondria may lead to severe energy deficiency as well as increased generation of reactive oxygen species (ROS) in neuron and ultimately neuronal demise. In this review, we will discuss the role of mitochondrial dysfunction, mitochondrial bioenergetics, mitophagy, mitochondrial fusion/fission and transcriptional dysregulation in the pathogenesis of neurodegenerative diseases of the brain Figs. 1–4.

Mitochondrial dysfunction in Parkinson's disease (PD)

PD is a chronic, progressive, age associated and often debilitating neurodegenerative disorder characterized by selective degeneration of melanin containing dopamine producing, neurons and the presence of intraneuronal protein inclusions of aggregated α-synuclein termed Lewy Bodies in the nigrostriatal neurons as well as other affected nuclei. Several studies implicate mitochondrial dysfunction in dopaminergic neurons in PD pathogenesis. However, mitochondrial dysfunction in PD is not restricted only to the dopaminergic neurons but is also observed in non-dopaminergic neurons Table 1.

Bioenergetic defects in PD

Several lines of evidence imply a role for mitochondrial dysfunction in the pathophysiology of PD[1–3]. Parkinson like symptoms in humans occurred following accidental infusion of the meperidine analogue 1-methyl-4-phenyl-1,2,3,6-tetrahydrodropyridine (MPTP), a selective inhibitor of mitochondrial complex-I of the electron transport chain, which suggested a specific role of mitochondrial dysfunction in the pathogenesis of PD [4,5]. Other more potent complex-I inhibitors such as pyridaben, rotenone, fenazaquin, tebunfenpyrad, trichloroethylene and fenpyroximate cause degeneration of dopaminergic neurons and parkinsonian symptoms in rodents, fly and cell models, further suggesting involvement of mitochondrial dysfunction in PD pathogenesis[6–13]. Short term systemic rotenone infusion causes decreased respiratory activity, increased mitochondrial permeability transition and concomitant cell death in substantia nigra neurons in the rat brain [14]. Ingestion of another mitochondrial complex-I inhibitor annonacin, found in the fruit and leaves of the plant Annona muricata, caused atypical parkinsonism in rodents and humans [15,16]. Importantly these mitochondrial toxins not only inhibit complex-I activity, but also reduce mitochondrial movement [17]. Paraquat causes electron transport chain complex-III mediated ROS production in rat brain mitochondria [18]. Rotenone and pyridaben also decrease mitochondrial nitric oxide synthase (NOS) functional activity with NAD-dependent substrates, suggesting involvement of mitochondrial complex-I [19].

More direct evidence for involvement of mitochondrial dysfunction in PD pathogenesis comes from studies of complex-I activity in PD patients. Activity of complex-I and immunohistochemicalcomplex-I

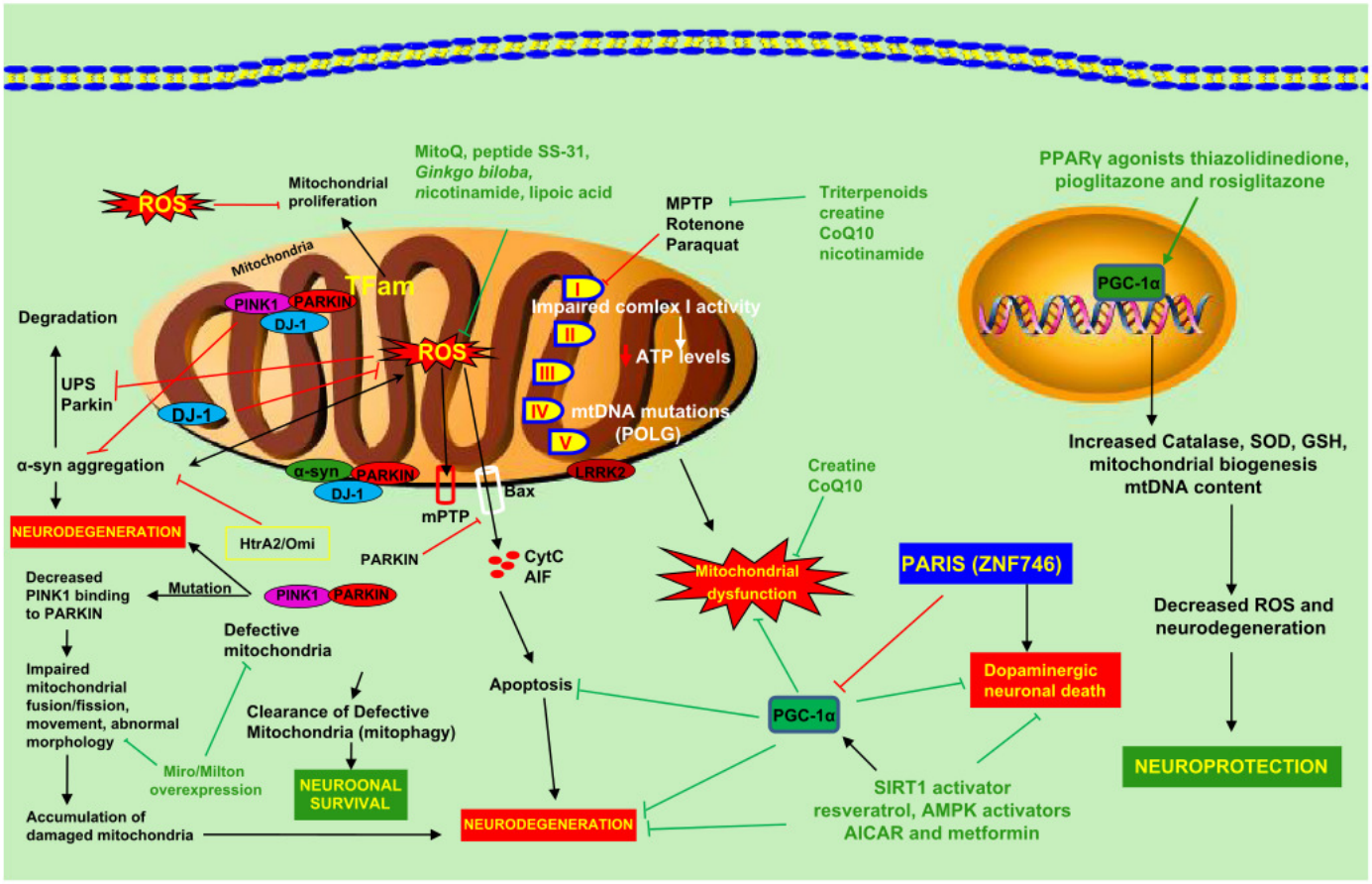

Fig. 1. Mitochondrial dysfunction and therapeutics in PD: Oxidative stress, apoptosis, mitochondrial dysfunction, and inflammation are the common factors for PD pathogenesis. Pathogenic mutations in α-synuclein, DJ-1, parkin, PINK1, Omi/HtrA2 and LRRK2 are the causal factors for mitochondrial dysfunction, oxidative damage and PD pathogenesis. DJ-1 plays a protective role by inhibiting ROS generation, while Parkin enhances mitochondrial proliferation by increasing Tfam expression. Mutations in DJ-1 and Parkin lead to increased ROS levels and decreased mitochondrial proliferation respectively. Mitochondrial DNA mutations also cause mitochondrial dysfunction. Enhanced ROS levels cause decreased mitochondrial proliferation, decreased activity of the Ubiquitin proteosome system (UPS), increased mitochondrial transition pore opening, and enhanced Bax mediated CytC release from the mitochondria, which ultimately lead to neurodegeneration. Mitochondrial toxins MPTP, rotenone and paraquat cause mitochondrial dysfunction through inhibition of mitochondrial complex-I, which leads to decreased ATP levels and neurodegeneration. PINK and Parkin act in co-ordinated manner for regulation of mitochondrial dynamics. PINK recruits Parkin to defective mitochondria for their clearance by mitophagy. Mutations in PINK and Parkin cause decreased binding of PINK to parkin, leading to Impaired mitochondrial fusion/fission, movement, abnormal morphology and accumulation of damaged mitochondria. Parkin interacting substrate, PARIS (ZNF746) represses the expression of PGC-1α and NRF-1 by binding to the PGC-1α promoter, leading to selective loss of dopaminergic neurons. PPAR agonists such as Thiazolidinedione, Pioglitazone and Rosiglitazone activate PPAR and PGC-1α, which regulate the expression of several target genes involved in mitochondrial biogenesis, ROS defence system, cell survival and neuroprotection. Activation of PGC-1α by SIRT1 activator resveratrol and AMP Kinase activator AICAR and metformin, blocks MPTP mediated cell death and inhibits mitochondrial dysfunction. Over expression of Miro/Milton enhances clearance of defective mitochondria and reduces defects in mitochondrial dynamics. MitoQ, mitochondrial targeted antioxidant peptide SS-31, Triterpenoids, *Ginkgo biloba*, Nicotinamide *and* Lipoic acid reduce mitochondrial dysfunction by inhibiting ROS levels.

subunits are decreased in the brains of idiopathic PD patients, suggesting disease specific and drug independent impairment of complex-I activity [20–26]. Morphometric and immunohistochemical analysis suggested defects of complex-I in the substantia nigra of PD patients[27]. There is also evidence that mitochondrial complex-I subunits are functionally impaired, misassembled and oxidatively damaged in postmortem PD brain [12]. Impairment of mitochondrial complex activity is not only restricted to the brain but also reported to be decreased in peripheral tissues such as skeletal muscle, lymphocytes and platelets of PD patients[28–35]. Mitochondrial respiratory chain failure is also observed in skeletal muscle of PD patients[36]. Recently, the levels and functions of the mitochondrial neuronal survival factor MEF2D and ND6, which regulate the activity of complex-I were found to be decreased in a mouse model of PD and postmortem brain tissue of PD patients[37]. Thus, mitochondrial complex-I activity and its regulation by transcription factors are both altered in PD patients[37]. Reduced staining of the rate limiting enzyme of TCA cycle mitochondrial alpha-ketoglutarate dehydrogenase (KGDH) is reported in the brain of PD patients[38,39]. These studies suggest involvement of bioenergetic defects and reduced mitochondrial complex activity in PD pathogenesis.

Mitochondrial DNA defects in PD

Reduced complex-I activity and an increased susceptibility to MPP+ were also observed in cytoplasmic hybrid ("cybrids") containing mitochondrial DNA (mtDNA) from PD patients, suggesting mtDNA encoded defects in PD[40–42], although in one study no significant reduction in complex-I activity was found[43]. Further, these studies also suggested that defects in complex-I activity are transferable from PD patients to mitochondria deficient cell lines to form "cybrids", and recipient cells also developed reduced mitochondrial membrane potential (MMP), mitochondrial respiration, variable mitochondrial biogenesis and abnormal Ca^{2+} handling[40–42,44,45]. PD cybrids show similar molecular genetic and mitochondrial respiratory properties to observations made on mitochondria in PD brain[46]. PD cybrids also have reduced SIRT1

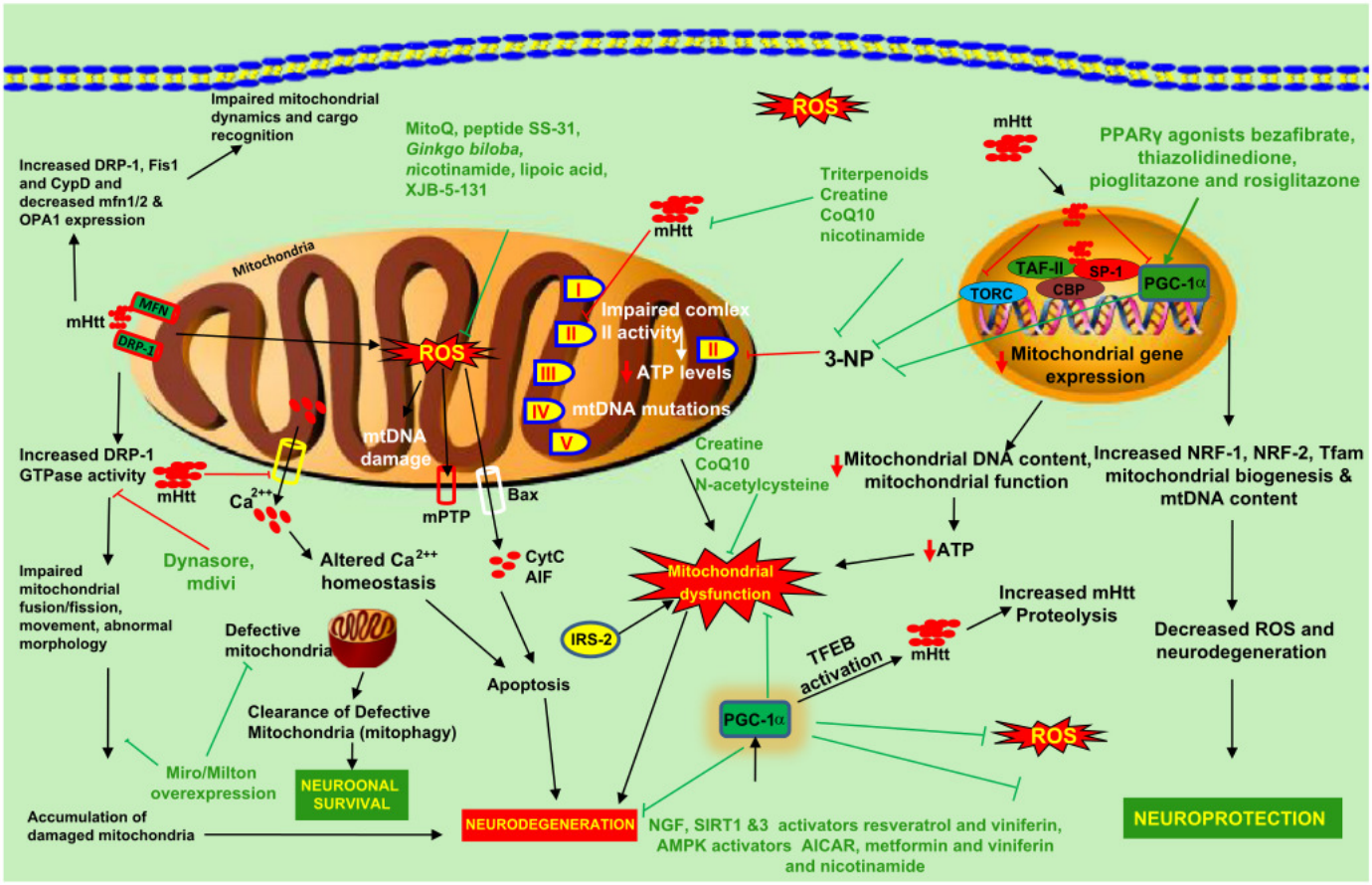

Fig. 2. Mitochondrial dysfunction and therapeutics in HD: Mutant huntingtin (mHtt), the pathogenic protein in HD, causes mitochondrial dysfunction by several mechanisms. It results in inhibition of the activity of succinate dehydrogenase (SDH), a component of complex-II of mitochondria, which leads to increased ROS generation and decreased ATP levels. Mutant huntingtin impairs mitochondrial Ca^{2+} handling ability, enhances mitochondrial permeability transition pore opening, and increases CytC release. It also binds to the several transcription factors including TAF-II, CBP, and SP-1 in the nucleus. PGC-1α, a transcriptional co-activator, involved in regulation of cellular respiration and mitochondrial biogenesis is implicated in HD pathogenesis. Mutant Htt protein directly binds to PGC-1α and reduces the expression of its downstream target genes involved in mitochondrial biogenesis and normal mitochondrial function. Mutant Htt binds to the CREB/TAF complex of the PGC-1α promoter, or directly represses PGC-1α and TORC1 transcription and function, leading to decreased mitochondrial biogenesis, reduced mitochondrial DNA content and enhanced mitochondrial dysfunction. Mutant Htt abnormally binds to mitofusin (MFN) and mitochondrial fission protein DRP1. This leads to increased DRP-1 GTPase enzymatic activity, impaired mitochondrial fusion/fission, movement, abnormal morphology and enhanced accumulation of defective mitochondria and ultimately neuronal demise. Mutant huntingtin also increases DRP-1, Fis1 and CypD expression and decreases mfn1/2 & OPA1 expression, resulting in Impaired mitochondrial dynamics and cargo recognition. The mitochondrial toxin 3-NP causes mitochondrial dysfunction through inhibition of mitochondrial complex-II activity. Over expression of TORC1 and PGC-1α inhibits 3-NP mediated toxicity and reduce mitochondrial dysfunction. The PPARγ agonists bezafibrate, thiazolidinedione, pioglitazone and rosiglitazone increase PGC-1α expression and mitochondrial biogenesis and reduce mitochondrial dysfunction. Nerve growth factor (NGF), SIRT1&3 activators resveratrol and viniferin, AMPK activators AICAR, metformin and viniferin and nicotinamide activate PGC-1α expression, which leads to decreased ROS levels and reduced mitochondrial dysfunction and enhanced neuronal survival. MitoQ, peptide SS-31, *Ginkgo biloba*, Nicotinamide, Lipoic acid and XJB-5-131 provide neuroprotection by reducing ROS levels and inhibiting mitochondrial dysfunction. Increased PGC-1α expression leads to TFEB activation and enhanced mutant Htt degradation. Over expression of Miro/Milton enhances clearance of defective mitochondria and reduces defects in mitochondrial dynamics. Small molecules dynasore and mdivi reduce DRP-1 GTPase activity and prevent dysfunction in mitochondrial dynamics.

phosphorylation, reduced peroxisome proliferator-activated receptor-gamma coactivator-1alpha (PGC-1α) levels, reduced cellular respiration and increased NF-kB activation [47]. Another study suggested that PD cybrids have less ATP, altered mitochondrial morphology, depolarized mitochondria, less mitochondrial cytochrome c and higher susceptibility to the mitochondrial complex-I inhibitor MPP+[48,49]. Interestingly transfer of mtDNA from commercially available human genomic DNA to PD cybrids restores mitochondrial dysfunction[50]. In this study, recombinant human mitochondrial transcription factor A (Tfam) having a SOD2 mitochondrial localization signal was used to transport mtDNA bound to Tfam in the mitochondria of PD cybrids, having impaired respiration and reduced mtDNA genes[50]. Following mtDNA transfer increased mtDNA gene copy numbers, Tfam and ETC proteins, cell respiration, and mitochondrial movement velocities were observed in PD cybrids [50]. Cybrid models of sporadic PD are being widely used to understand the role of mitochondrial dysfunction in PD pathogenesis [44,51]. Altogether studies in PD cybrids suggest direct involvement of mitochondria in the progression of PD.

Mitochondrial DNA mutations and polymorphisms in PD:

Besides the mitochondrial complex-I defects, a number of studies suggested that mutations in mtDNA [52–54] and polymorphism[55] play an important role in PD pathogenesis. Quite a few clonal and somatic mtDNA mutations have been observed in the substantia nigra of PD patients, implicating a role of mtDNA mutations in mitochondrial dysfunction and dopaminergic cell death [56–60]. Recently we found that mtDNA mutation levels were significantly elevated in the substantia nigra of early stage PD patients [61]. Genetic variations in NADH dehydrogenase ubiquinone flavoprotein 2, encoding a subunit of mitochondrial complex-I, were possibly associated with idiopathic PD [62]. Similarly, heteroplasmic mutations in a narrow region of NADH: ubiquinone

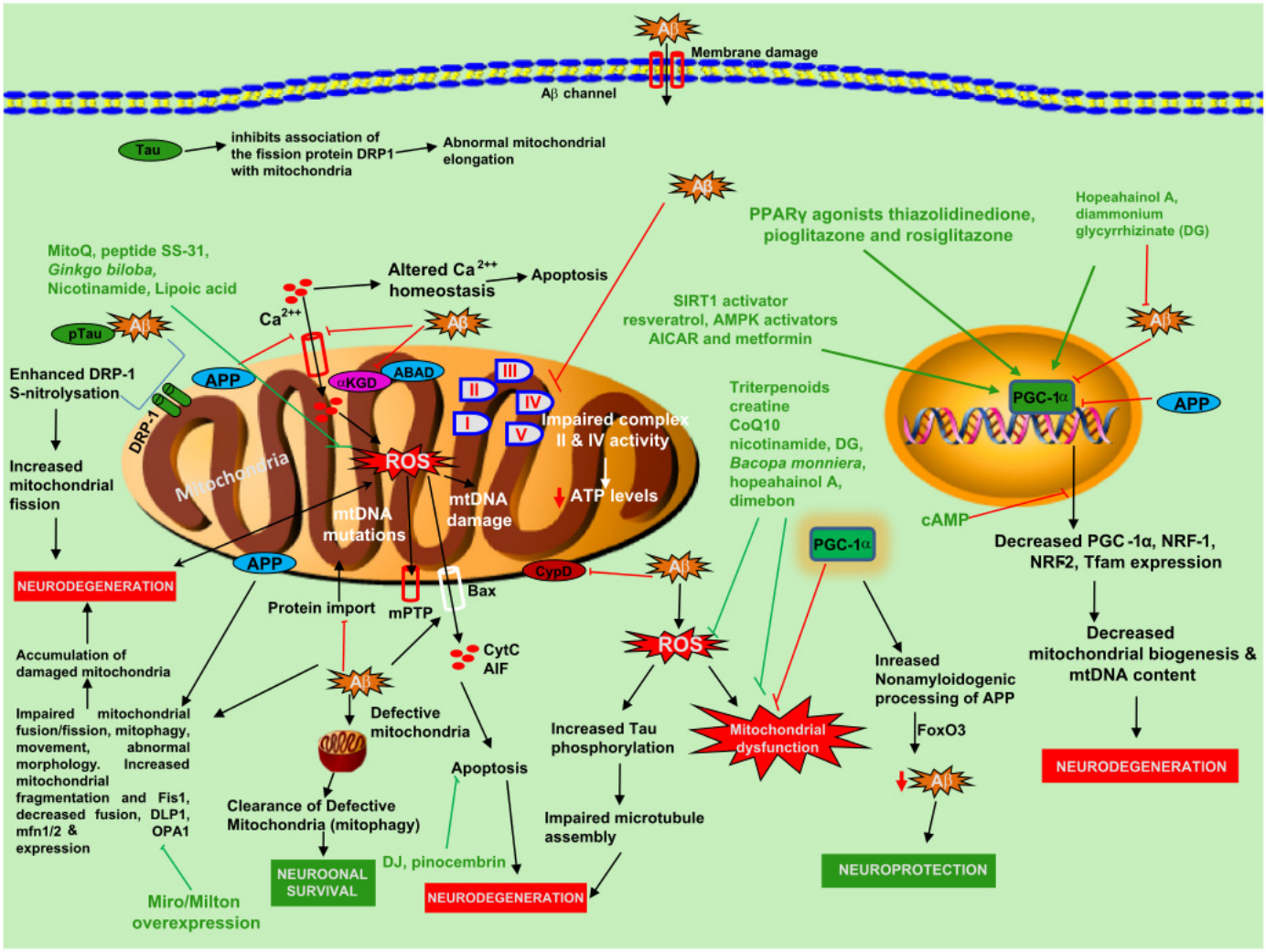

Fig. 3. Mitochondrial dysfunction and therapeutics in AD: Accumulation of amyloid-β (Aβ) causes mitochondrial dysfunction in AD. Aβ inhibits the activity of mitochondrial complex-II and IV, leading to decreased ATP levels and increased ROS generation. Aβ also reduces the activity of α-ketoglutrodehydrogenase (αKGD) and Aβ alcohol dehydrogenase activity (ABAD) and cyclophilin D expression. Aβ enhances mitochondrial dysfunction and apoptosis by impairment of mitochondrial Ca^{2+} handling ability, altering Ca^{2+} homeostasis, mitochondrial permeability transition pore opening and enhancement of CytC release. Aβ inhibits protein import inside the mitochondria. Amyloid precursor protein (APP) also alters Ca^{2+} homeostasis leading to apoptosis. Mitochondrial DNA mutations and mitochondrial DNA damage are also involved in pathogenesis of AD. Phosphorylated Tau and Aβ causes enhanced nitrosylation of DRP-1 leading to increased mitochondrial fission and neurodegeneration. Aβ and APP impair mitochondrial fusion/fission processes, mitophagy, mitochondrial movement, abnormal morphology. Aβ and APP also cause increased mitochondrial fragmentation and Fis1, and decreased fusion, mfn1/2 & OPA1 expression. Impaired mitochondrial dynamics ultimately leads to decreased clearance of defective mitochondria and neurodegeneration. Pathogenic protein Tau inhibits association of the fission protein DRP1 with mitochondria, which causes abnormal mitochondrial elongation. Aβ and APP reduce the expression of PGC-1α, which leads to decreased mitochondrial biogenesis, mitochondrial DNA content and enhanced neurodegeneration. Activation of PGC-1α by PPARγ agonist (bezafibrate, thiazolidinedione, pioglitazone and rosiglitazone), resveratrol, AICAR, metformin, hopeahainol A, diammonium glycyrrhizinate (DG) reduces Aβ induced mitochondrial dysfunction and neurodegeneration. Triterpenoids, Creatine, CoQ10, Nicotinamide, DG, Bacopa monniera, hopeahainol A, MitoQ, peptide SS-31, *Ginkgo biloba*, nicotinamide and lipoic acid reduce mitochondrial dysfunction through inhibition of ROS levels. PGC-1α causes increased nonamyloidogenic processing of APP and FoxO3 mediated reduction in Aβ levels, leading to increased neuronal survival. Over expression of Miro/Milton enhances clearance of defective mitochondria and reduces defects in mitochondrial dynamics.

oxidoreductase ND5 (a mitochondrial gene encoding a complex-I subunit) are detected in the brains of PD patients [63,64]. Increased mtDNA deletions/rearrangements were found to be associated with neurodegeneration in PD [59,65]. The presence of increased clonally expanded mtDNA deletions are associated with respiratory chain deficiency in the substantia nigra of aged PD patients [66,67]. Importantly, the frequency of mtDNA deletions was significantly higher in the substantia nigra, than in the putamen or frontal cortex of PD patients, suggesting dopaminergic neurons are more vulnerable to mtDNA deletions [68]. Mutations in mtDNA polymerase gamma (POLG) were identified as an important cause of inherited parkinsonism in five ethnically distinct finish families [69,70]. However, a study by Tiangyou et al., 2006 did not find a role of dominant POLG mutations in a large number of PD patients[71]. We observed G11778A mtDNA point mutation in a subunit of mitochondrial complex-I in a family with parkinsonism and multisystem degeneration [72]. We also identified high levels of somatic mtDNA point mutations in elderly PD patients [58]. Recently mutations in the mitochondrial chaperone mortalin, which has a regulatory role in mitochondrial biogenesis and mitochondrial homeostasis, were reported in PD patients [73,74]. Another compelling piece of evidence for mitochondrial dysfunction in PD has come from conditional knockout "MitoPark" mice, which have a disrupted Tfam gene in DA neurons. These mice show reduced mtDNA expression, reduced respiratory chain function in DA neurons, and a progressive PD phenotype, consistent with involvement of respiratory chain dysfunction in PD pathogenesis[75]. Further, there is evidence of reduced mitochondrial mass and size in mouse substantia nigra DA neurons as compared to non-DA neurons, suggesting selective vulnerability of

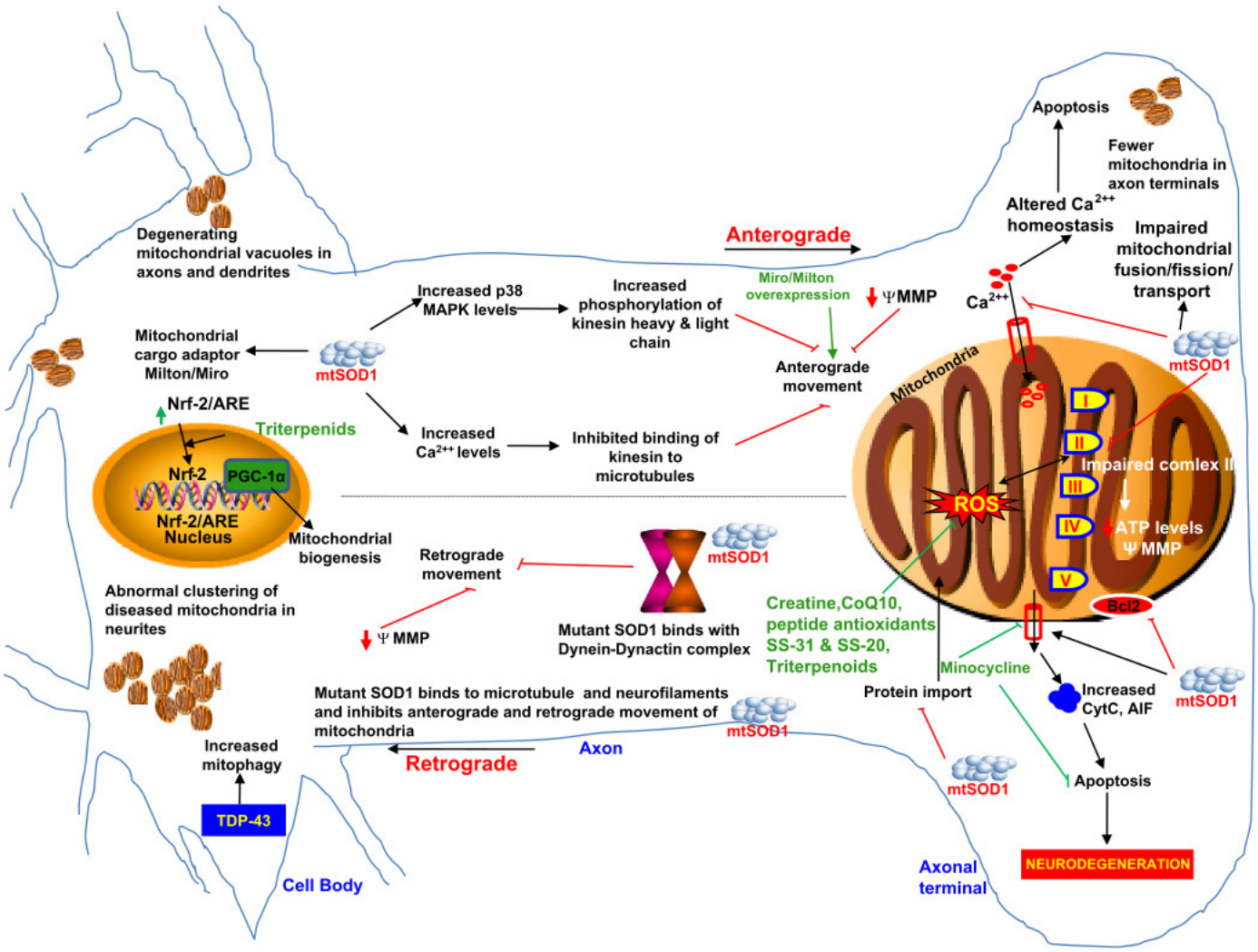

Fig. 4. Mitochondrial dysfunction and therapeutics in ALS: Mutant SOD1 (mtSOD1) localizes in the outer membrane, and in the matrix of mitochondria, and impairs mitochondrial morphology and bioenergetic functions. After association with mitochondria, mtSOD1 causes mitochondrial dysfunction by several mechanisms. It may damage mitochondrial membranes, leading to loss of mitochondrial membrane potential and swelling of the important organelle including mitochondria. It directly inhibits the activity of mitochondrial respiratory complex-II, which leads to disrupted redox homeostasis and decreased ATP production. Mutant SOD1 inhibits Ca^{2+} handling of mitochondria by impairing Ca^{2+} homeostasis, leading to activation of apoptosis of motor neurons. Impaired Ca^{2+} homeostasis, excitotoxicity, impaired respiratory complexes activity and increased ROS generation by mtSOD1 are not isolated but interrelated mechanisms, leading to mitochondrial dysfunction and motor neuron degeneration in ALS. Mutant SOD1 also sequesters the anti-apoptotic protein Bcl-2, and enhances cytochrome c release, and release of pro-apoptotic proteins from mitochondria. It also inhibits protein import inside the mitochondria. Mutant SOD1 also disrupts slow axonal transport of proteins and organelles such as mitochondria. Mutant SOD1 impairs mitochondrial movement in anterograde and retrograde directions by an interaction with the anterograde motor protein kinesin-2 complex via kinesin-associated protein, and the retrograde motor protein complex dynein-dynactin respectively. Mutant SOD1 also binds to microtubules and neurofilaments. Mutant SOD1 reduces the levels of the mitochondrial cargo adaptor proteins Miro/Milton. Mitochondria with abnormal morphology such as fragmented network, swelling, increased cristae, and degenerating vacuoles have been observed in the soma, axons and dendrites of motor neurons in ALS. There is also abnormal accumulation of diseased mitochondria in the neurites of motor neurons. TDP-43, another pathogenic protein in ALS, causes increased mitophagy in the neurons. Expression of PGC-1α and mitochondrial biogenesis are significantly decreased in ALS. MitoQ, mitochondrial targeted antioxidant peptide SS-31 and Triterpenoids reduce ROS levels and mitochondrial dysfunction.

DA neurons may be due to the mitochondrial dysfunction in PD[76].

Gene mutations implicate mitochondrial dysfunction in PD:

In addition to mtDNA mutations, pathogenic mutations in several genes including α-synuclein, parkin, UCHL-1, DJ-1, PINK-1, LRRK-2, NURR-1, tau, and HtrA2 also directly or indirectly implicate a role of mitochondrial dysfunction in familial PD pathogenesis [2,3,77–80]. Missense mutations, duplication and triplications in α-synuclein, a component of Lewy Bodies are associated with a rare form of autosomal dominant familial PD [77,78,81–83]. Several studies have suggested that α-synuclein is localized to mitochondria[77,84,85]. Mitochondrial import and accumulation of α-synuclein causes increased ROS generation and impairment of complex-I in the substantia nigra and striatum of PD brain[86]. α-synuclein localization on mitochondrial membranes causes increased release of cytochrome c, increase of mitochondrial calcium and nitric oxide, and oxidative modification of mitochondrial components in α-synuclein overexpressing cells [87]. Direct interaction of α-synuclein with mitochondrial membranes resulted in enhanced mitochondrial fragmentation [88]. Quantitative proteome analysis in a presymptomatic A53T α-synuclein PD Drosophila model suggested dysregulation of proteins involved in normal mitochondrial function [89]. Human α–synuclein gene over expressing transgenic mice and neuronal cells exhibit impaired mitochondrial function, increased mtDNA damage, and

Table 1
Mitochondrial Thereapeutic approaches in neurodegenerative disorders.

Bioenergetic agent	Disease	Treatment	Effects
Creatine	PD	Rat in vitro ventral mesencephalic neuron cultures, creatine (5 mM)	Significantly increased TH-IR cell density; crea
Creatine	PD	Primary cultures of E14 rat ventral mesencephalon dopaminergic neurons (creatine 5 mM for 7 days)	Creatine exerted significant neuroprotection f neurons against MPP^+ and 6-OHDA
Creatine	PD	Cyclooxygenase 2 inhibitor rofecoxib and creatine coadministered in MPTP mouse model of PD	Significant protection against striatal dopamir of substantia nigra tyrosine hydroxylase imm
Creatine	PD	Oral supplementation of creatine or cyclocreatine in MPTP mouse model of PD	Significant protection against MPTP-induced d and TH-immunostained neurons in the substantia
Creatine	PD	6-OHDA PD rats received a 2% creatine-supplemented diet for 1 month before L-DOPA therapy	Attenuation of L-DOPA-induced dyskinesia
Creatine + CoQ10	PD	Treatment with combination of CoQ10 and creatine in MPTP mouse model of PD	Combination of creatine + CoQ10 produced a neuroprotective effects against dopamine depl and loss of TH neurons and reduced α-synucl
Creatine	HD	Dietary supplementation of 2% creatine in N171-82Q HD transgenic mice	Significantly improved survival, slowed motor onset of weight loss, reduced brain atrophy a intranuclear inclusions
Creatine	HD	Creatine administration started after onset of clinical symptoms in HD R6/2 transgenic mice.	Significantly extended survival, improved mot reduced neuronal atrophy and huntingtin agg brain concentrations of creatine and ATP
Creatine + CoQ10	HD	Treatment with a combination of CoQ10 and creatine in HD R6/2 transgenic mice and 3-NP rat model of PD	Additive neuroprotective effects in reducing s produced by 3-NP; improved motor performa survival in transgenic R6/2 HD mice
Creatine	ALS	Oral administration of creatine in G93A transgenic mouse model of ALS	Dose-dependent improvement in motor perfo extended survival in G93A transgenic mice and of motor neurons
Creatine	ALS	Long-term creatine supplementation in G93A mice	Decreased cortical glutamate concentrations
Creatine	ALS	Creatine in combination with cyclooxygenase 2 in G93A transgenic mouse model of ALS	Additive neuroprotective effects and extended significantly improved motor performance, a loss
CoQ10	PD	In vitro pretreatment of SHSY-5Y cells with water-soluble formulation of CoQ10 containing polyoxyethanyl α-tocopheryl sebacate before paraquat exposure	Pretreatment with CoQ10 significantly reduce DNA fragmentation and prevented ROS gener mitochondria and collapse of MMP
CoQ10	PD	MPTP PD mouse diet supplemented with CoQ10 (200 mg/kg/day)	Increased striatal dopamine concentrations a caudal striatum
CoQ10	PD	MPTP PD mouse diet supplemented with CoQ10 and reduced CoQ10 (ubiquinol)	Neuroprotective effects against DA depletion, and induction of α-synuclein inclusions in the
CoQ10	PD	Water-soluble formulation of CoQ10 in drinking water before and during paraquat treatment in paraquat-induced PD rats	Reduced neurodegeneration and increased ro
CoQ10	ALS	Oral administration of CoQ10 in a transgenic mouse model of ALS	Significantly increased life span and increased mitochondrial CoQ10 concentrations
CoQ10+ remacemide	HD	Oral administration of CoQ10 and the NMDA antagonist remacemide in HD transgenic mice	Combination treatment resulted in increased ventricular enlargement, and reduced motor d
CoQ10+ Vit E	HD	Prior administration of antioxidants CoQ10 + Vit E in 3-NP-treated aged rats	Decreased 3-NP toxicity and increased brain e
CoQ10	HD	Dietary supplementation with CoQ10 in a slowly progressing transgenic mouse model of HD	Improved early behavioral deficits and norma deficits without altering huntingtin aggregate
CoQ10 and minocycline	HD		No behavioral improvement

Table 1 (*continued*)

Bioenergetic agent	Disease	Treatment	Effects	Reference
		Oral administration of CoQ10 and minocycline in HD transgenic mice		
CoQ10 and minocycline	HD	CoQ10 and minocycline in R6/2HD transgenic mice	Combination treatment enhanced beneficial effects, ameliorating behavioral and neuropathological alterations, extended survival, and improved rotarod performance	[381]
CoQ10	AD	In vitro primary cultured cortical neurons treated with CoQ10 and/or Aβ(25–35)	Neuroprotective effects of CoQ10 on Aβ(25–35) neurotoxicity	[482]
CoQ10	AD	Oral treatment of CoQ10 in AD transgenic mice	Reduced amyloid pathology and improved behavioral performance in the Tg19959 mouse model of AD	[483–485]
Mitochondria-targeted peptides	PD	Treatment of SS-31 and SS-20 peptides in MPTP mouse model	Significant neuroprotective effects on dopaminergic neurons against MPTP-induced toxicity	[418]
Mitochondria-targeted peptides	ALS	Antioxidant peptide SS-31 treatment in vitro and in ALS transgenic mice	Significant improvement in survival and motor performance	[417]
Mitochondria-targeted peptides	AD	In vitro SS-31 and MitoQ treatment in neurons from transgenic AD and neuroblastoma cells treated with Aβ	Significant neuroprotection against Aβ-induced neurotoxicity	[408]
MitoQ	AD	Treatment with MitoQ in transgenic AD mice	Reduced Aβ-induced pathology, reduced cognitive decline, Aβ accumulation, astrogliosis, synaptic loss, and caspase activation	[411,486]

impaired activity of cytochrome oxidase[90,91]. Over expression of human α–synuclein gene harboring the A53T mutation in these mice made them more susceptible towards MPTP and paraquat mediated neurodegeneration [90]. Electron microscopic studies suggested increased mitochondrial damage in mice over expressing α–synuclein after MPTP administration [91]. Primary cortical neurons over expressing mutant A53T α-synuclein showed increased mitochondrial autophagy, bioenergetic deficits and neuronal degeneration[92]. Interestingly, α–synuclein knockout mice are resistant to mitochondrial respiratory chain inhibitors such as MPTP, 3-nitropropionic acid (3-NP) and malonate, thus implicating mitochondria in α-synuclein mediated toxicity [93,94].

Parkin (PARK2) mutations are mostly involved in early onset autosomal recessive juvenile PD, and rarely with sporadic late-onset PD [95]. Recently, using phase analysis approach heterozygous deletions of the Parkin gene were observed in early-onset PD patiensts[96]. Single-nucleotide polymorphisms were also observed within the parkin core promoter in late-onset idiopathic PD patients [97]. Expression of truncated Q311X mutant parkin in mice recapitulates hallmark features of PD [98]. Parkin null mice and flies exhibit decreased abundance of a number of proteins important in mitochondrial function, reduction in several subunits of complexes I and IV, reduced respiratory capacity, loss of mitochondrial integrity and enhanced susceptibility to the complex-I inhibitor rotenone [99–101]. Parkin is a ubiquitin E3 ligase, which under normal conditions is selectively recruited to dysfunctional mitochondria, promoting mitophagy and mitochondrial clearance by catalyzing mitochondrial ubiquitination [100,101]. Pathogenic mutations in Parkin cause impaired recognition, transport and ubiquitination of defective mitochondria, increased mitochondrial aggregation, and reduced mitophagy [102].

Mutations in PTEN induced kinase 1 (PINK1; PARK6) were found to be responsible for an autosomal recessive familial form of early-onset parkinsonism [77,103]. Mutations in PINK1 are associated with mitochondrial dysfunction in PD patients[104]. PINK1 is also detected in Lewy Bodies in the brains of sporadic PD patients and PD associated with heterozygous mutations in the PINK1 gene [105]. Polymorphisms in the mitochondrial translation initiation factor 3 (MTIF3), an interactor protein of PINK1, are also associated with PD [106]. We recently found that mutations in PINK1, or PINK1 knock-down caused deficits in mitochondrial respiration and ATP synthesis, and increased α-synuclein aggregation in cell based PD models[107]. PINK1 mutants are defective in their ability to regulate opening of the mitochondrial permeability transition pore, MMP and cytochrome c release [108,109]. Recently it was suggested that PINK1 induces mitochondrial dysfunction by disturbing Ca^{2+} homeostasis in neuronal cells [110]. PINK1 localizes to the human and rat brain mitochondrial membranes and protects cells against stress and the mitochondrial toxin MPTP [103,105,111,112]. Fibroblasts isolated from familial PD patients having PINK mutations, exhibit reduced respiratory activity [113]. PINK1 knockout mice have decreased mitochondrial respiration activity, mitochondrial dysfunction, and enhanced susceptibility to oxidative stress and PD phenotypes [113,114]. PINK1 binds to and colocalizes with a mitochondrial molecular chaperone TNF receptor-associated protein 1 (TRAP1) in the mitochondria. After binding, PINK1 phosphorylates TRAP1 and protects cells against oxidative stress by suppressing cytochrome c release from mitochondria. PINK mediated TRAP1 phosphorylation and cell survival is impaired by PD associated mutations in PINK1 genes, suggesting mitochondrial dysfunction in PD [115]. PINK1 functions upstream to the Parkin, but both interact genetically and act in a common pathway to maintain mitochondrial integrity and normal mitochondrial function [116,117]. A reduction in mitochondrial membrane potential leads to expression of PINK1 on the outer mitochondrial membrane and phosphorylation of Parkin, which

then ubiquitinates mitochondria, and targets them for removal by mitophagy.

Loss-of-function mutations in the DJ-1 (PARK7) locus cause rare autosomal recessive early-onset PD, which account for 1-2% of all early onset PD [77,80,118]. Mutations in DJ-1 include homozygous and heterozygous point mutations, deletions and truncations [77]. The levels of DJ-1 and dissembled DJ-1 high molecular weight complex are decreased in the mitochondria from autopsied PD patient brain[119]. A recent study suggests that DJ-1 functions in synergy with the PINK1/Parkin pathway and regulates mitochondrial function and mitophagy [120]. DJ-1 knockdown leads to enhanced susceptibility to cell death mediated by oxidative damage in rodents and flies, while DJ-1 over expression provides cytoprotective effects against cell death [121,122]. Mitochondria isolated from DJ-1 knockout mouse brains produce increased levels of ROS [121]. DJ-1 knockout mice are more susceptible to dopaminergic degeneration and oxidative stress induced by MPTP and paraquat [123,124]. Lymphoblast derived from DJ-1 patients, DJ-1 knockout cells and mice display increased mitochondrial dysfunction, which can be abrogated by the expression of PINK1 and Parkin [121]. Moreover, cells from DJ-1 knockout mice and human carriers of the DJ-1 E64D mutation have impaired mitochondrial respiration, increased mitochondrial ROS, reduced MMP, altered mitochondrial morphology and accumulation of defective mitochondria [125]. DJ-1 exerts its neuroprotective effects through binding on mitochondrial complex-I and maintaining its activity, by acting as a transcriptional coactivator, a protease and a molecular chaperone [77,126]. DJ-1 protects against MPTP induced neurodegeneration by activation of the AKT pathway [127]. DJ-1 also maintains Nrf2 transcriptional activity, which activates both antioxidants and protein chaperones [128].

Gain of function mutations in leucine-rich repeat kinase 2 (LRRK2; PARK8) cause sporadic and autosomal dominant early and late-onset PD [129]. We and others created LRRK2 gain of function transgenic mouse and fly models that recapitulates cardinal features of PD [130,131]. Mutations in LRRK2 affect other proteins which are implicated in PD pathogenesis such as α-synuclein[132]. A recent study found decreased MMP and total intracellular ATP levels in fibroblasts from PD patients with the G2019S mutation in LRRK2 [133]. Caenorhabditis elegans LRRK2 mutants and DA neurons derived from induced pluripotent stem cells harboring G2019S-LRRK2 mutations, display mitochondrial dysfunction and are more susceptible to mitochondrial toxin mediated oxidative stress [134,135]. The Omi/HtrA2 is a serine protease mitochondrial protein localized within the mitochondrial intermembrane space and involved in protection against cellular stress. Loss of function mutations in Omi/HtrA2 gene have been identified in PD patients, associated with defective activation of the protease activity of Omi/HtrA2 [136,137]. Omi/HtrA2 knockout mice exhibit cardinal features of PD such as rigidity and additional features including ataxia, muscle wasting and premature death [138]. Omi/HtrA2 deficiency in mice, flies and humans leads to accumulation of ROS, altered mitochondrial morphology, and increased levels of the mitochondrial fusion protein OPA[139]. Therefore, multiple lines of evidence suggest a pathogenic role of familial PD linked mutations in compromising normal mitochondrial function in PD pathogenesis.

Impaired mitochondrial movement, mitochondrial □ssion/fusion and mitophagy in PD

Mitochondrial dynamics properties such as mitochondrial fission/fusion, trafficking, biogenesis and mitophagy are critical for normal neuronal function and survival. Mitochondrial fusion is tightly regulated by proteins such as OPA1, Mfn1, and Mfn2, and fission mediated by the proteins Fis1 and Drp1. A balance of fusion and fission processes is very critical for normal mitochondrial function. Enhanced fusion causes abnormal mitochondrial elongation, while excessive fission leads to increased mitochondrial fragmentation and formation of small round defective mitochondria, leading to impaired function of mitochondria. Several studies have provided convincing evidence of altered mitochondrial trafficking, reduced mitochondrial biogenesis and impaired balance of fusion-fission in AD, PD, HD and ALS.

Recently, dysregulation of mitochondrial dynamics processes have been linked to the pathogenesis of PD [54,140,141]. Recent studies suggested involvement of mutations in both LRRK2 and α-synuclein in impairments of normal mitochondrial fission/fusion processes in neurons [142–144]. PINK1 a mitochondria-targeted Ser/Thr kinase, regulates mitochondrial fusion/fission processes through Drp-1 and Drp1-interacting protein Fis1 [145]. Similarly another recent study found that mutations in DJ-1 causes impairment of mitochondrial dynamics through modulation of DRP1 expression [146]. Several studies have provided compelling evidence that parkin and PINK1 proteins regulate mitochondrial integrity, promote clearance of dysfunctional mitochondria by mitophagy and regulate axonal transport of mitochondria [147–149]. Interestingly, PINK selectively accumulates on diseased/damaged mitochondria and recruits them to parkin for ubiquitination and mitophagy [150]. Similarly, PINK and parkin by enhancing Miro phosphorylation and degradation, quarantine damaged mitochondria before mitophagy, by arresting their movement [151]. The ubiquitination of mitochondrial proteins such as mitofusins 1 and 2 is very important for identification of damaged mitochondria for degradation and mitophagy. Parkin and PINK act in a co-ordinated manner, where as Parkin requires PINK1 for mitochondrial translocation and ubiquitination of mitofusin, which leads to labeling of terminally damaged mitochondria for degradation by autophagy [152]. PINK1 and parkin ubiquitinate mitofusins 1 and 2 for selective removal of damaged mitochondria in dopaminergic cells, and inhibition of this pathway may lead to the accumulation of defective mitochondria in dopaminergic neurons [153]. Recent studies suggested involvement of Voltage-dependent anion channels (VDAC1) and p62/SQSTM1 in PINK1 and Parkin mediated mitophagy [154–156].

These studies show that involvement of PINK1 and Parkin play a crtical role in the regulation of mitophagy. Therefore disease causing mutations in PINK1 and Parkin may interrupt PINK1-parkin induced mitophagy processes in PD [101,157,158]. Moreover, PINK1 and parkin were directly implicated in abnormal mitochondrial dynamics in fly, rat and mouse models of PD [140,141].

Mitochondrial dysfunction in Huntington's disease (HD)

HD is an autosomal-dominant devastating neurodegenerative disorder characterized by lesions in the striatum of the brain, progressive development of involuntary choreiform movements, behavioral and cognitive impairment, neuropsychiatric symptoms, and premature death. HD is caused by the abnormal triplet expansion of a CAG repeat in exon-1 of the *HD* gene, resulting in elongated polyglutamine stretches in the protein product known as mutant Htt[159]. In HD, mutant Htt is expressed ubiquitously, but selective neuronal loss is observed in the brain, particularly in the striatum. How the mutant Htt protein elicits its toxic effects remains elusive, but several mechanisms have been postulated including transcriptional dysregulation, abnormalities in mitochondrial energy metabolism, protein aggregation, and oxidative damage[160,161]. Various lines of evidence suggest an important involvement of mitochondrial dysfunction in HD[162].

Impaired bioenergetics and decreased mitochondrial complexes activities in HD

Evidence for mitochondrial dysfunction and bioenergetics defects in HD pathogenesis comes from the presence of remarkable weight loss in HD patients, despite a normal diet[160]. PET imaging shows reduced glucose metabolism in the basal ganglia and cerebral cortex of symptomatic HD patients and presymptomatic gene carriers, suggesting a bioenergetic defect [163–165]. 1H Nuclear magnetic resonance (NMR) spectroscopy demonstrated decreased N-acetylaspartate and increased levels of lactate in the basal ganglia of symptomatic and some pre-symptomatic HD patients[166–169]. These studies found that mitochondrial dysfunction and bioenergetics defects are present even in the asymptomatic HD carriers, suggesting these defects may initiate disease onset. Using NMR spectroscopy we and others found widespread bioenergetics defects in the skeletal muscle of HD patients [167,169,170]. Reduced activity of key components of oxidative phosphorylation and the TCA cycle, mitochondrial complexes II-IV and aconitase is observed in the HD patients, with no alterations in complex-I activity[160,169,171–173]. Increased glucose utilization relative to oxygen utilization was found in the striatum of early HD patients[174]. Inducible yeast model of HD expressing a human Htt fragment showed decreased cell respiration, an altered amount and function of the mitochondrial respiratory chain complexes II +III and altered mitochondrial morphology and distribution[175].

Bioenergetics defects in HD were not confined only to the brain, but were also observed in the peripheral tissues such as muscle and platelets[167,169,170,176,177], and knockin Htt striatal cells[178]. Lymphocytes derived from HD patients displayed decreased MMP and increased mitochondrial mediated apoptosis [179]. Reduced ATP/phosphocreatine (PCr) ratio, decreased PCr/inorganic phosphate ratio, low ATP levels and impaired complex-I activity were evident in the muscle of symptomatic and presymptomatic HD patients, suggesting bioenergetic disturbances [162,167,170,176]. Recently we found reduced mitochondrial respiration and cytochrome oxidase expression in myoblasts from HD patients, and brain and muscle from NLS-N171-82Q HD transgenic mice, these defects were exacerbated in chronic energy deprivation conditions [180,181]. Another recent study found increased lactate synthesis and striking mitochondrial structural abnormalities in the muscle from symptomatic HD patients[182]. These studies suggest that mutant Htt may affect other cell types, with high energy demand. Lymphoblasts from HD patients and brain mitochondria from HD transgenic mice display decreased MMP, impaired Ca^{2+} homeostasis[183], and altered morphology [184]. Peripheral mitochondrial defects in HD are evident from a study showing that HD patient–derived lymphoblastoid cell lines have decreased ATP/ADP ratios[185]. Similarly, mouse immortalized striatal cells expressing endogenous mutant Htt (STHdhQ111) also showed decreased ATP levels and ADP uptake, suggesting that bioenergetics defects in the peripheral tissues emulate the defects in the brain[185]. Further, mitochondrial respiration and ATP production are significantly impaired in the striatal cells from mutant Htt knock-in mouse embryos[178]. Reductions in the FAD subunit (SDH-A) and the iron-sulfur cluster subunit (SDH-B) of complex-II were found in the HD caudate and putamen, suggesting that complex-II subunit reductions are associated with neuronal death[186]. Expression of pathogenic N-terminal Htt fragment in cultured striatal neurons caused decreased complex-II enzymatic activity and selective reductions of SDH-A and B. Interestingly, over expression of complex-II subunits in striatal neurons expressing Htt171-82Q restored complex-II activity and blocked mitochondrial dysfunction and cell death, suggesting involvement of complex-II dysfunction in HD pathogenesis[186]. Moreover, the mitochondrial toxins 3-NP and malonate, which selectively inhibit complex-II, induce a pathological phenotype similar to HD in rodents, primates, and humans further implicating a role of mitochondrial dysfunction in HD pathogenesis [159,160,187,188]. The 3-NP induced model of HD also show decreased State 3 respiration and complex-I+II inhibition and decreased succinate dehydrogenase activity[189]. Mutant Htt makes cells more susceptible to 3-NP induced mitochondrial dysfunction and cell death [190].

mtDNA mutations and polymorphisms in HD:

A large body of evidence suggests involvement of mtDNA mutations in the pathogenesis of HD. Lymphocytes, leucocytes and cortical tissues from HD patients have higher frequencies of mtDNA deletions as compared to controls [191–193]. Variations in mitochondrial haplogroup H are associated with altered ATP levels, mitochondrial dysfunction, and age of onset in HD[194]. The severity of HD phenotypes is directly related to the size of the CAG repeats expansion in patients[191,192]. Increased mtDNA damage has been reported in the 3-NP induced and the R6/2 transgenic mouse model of HD [195]. Cybrids harboring mtDNA from HD patients display impaired mitochondrial function and enhanced mitochondrial mediated apoptosis, suggesting that mitochondrial defects from HD patients are transferable[196].

Mitochondrial localization of mutant huntingtin in HD

Mutant Htt plays an important role in mitochondrial dysfunction in HD through several mechanisms. Mutant Htt may directly bind to the mitochondria. Studies from both a HD transgenic mouse model, and from HD striatal cells (STHdhQ111), showed localization of mutant Htt to the outer mitochondrial membrane [183,197]. Htt aggregates were found to be localized to the mitochondria in the brains of transgenic HD mice, suggesting that mitochondrial dysfunction contributes to the disease[198]. Electron microscopy studies found localization of N-terminal mutant Htt on neuronal mitochondrial membranes[183].

Altered mitochondrial calcium handling

There is defective mitochondrial Ca^{2+} homeostasis in HD. Mutant Htt enhances the susceptibility of mitochondria to the Ca^{2+} induced permeability transition and cytochrome c release [183,199]. Enahnced suscepetibilty towards Ca^{2+} induced inhibition of complex-I dependent respiration, a lower sensitivity to Ca^{2+} activation, and deficient respiration were observed in the mitochondria from HD transgenic mice [200,201]. Huntingtin striatal cells displayed Ca^{2+} induced decrease in cellular respiration, reduced mitochondrial Ca^{2+} uptake capacity and enhanced MMP [202,203]. Mitochondria from huntigtin striatal cells and from HD transgenic mice are unable to handle large Ca^{2+} loads and more susceptible towards Ca^{2+} induced oxidative stress[203,204]. Incubation of mitochondria isolated from normal lymphoblasts with mutant Htt recapitulates mitochondrial dysfunction seen in HD patients and HD transgenic mice, suggesting that the mitochondrial defects in HD are a direct effect of the mutant Htt[183].

Altered mitochondrial dynamics and traf□cking in HD

Mutant Htt also impairs *in vitro* and *in vivo* trafficking of mitochondria in neurons, leading to loss of mitochondrial motility and eventually mitochondrial dysfunction[205–208]. There is increased expression of Drp1 and Fis1 and reduced expression of

mitofusins and OPA1 in cellular models of HD, and HD postmortem brain tissue and mutant Htt binds to Drp1 and increases its mitochondrial fission enzymatic activity [209–213]. Mitochondrial fragmentation, presence of disrupted cristae, swollen mitochondria and increased suscepetibility towards apoptotic stimulai are obserevd in transgenic mice and cellualr models of HD[214,215]. Increased vacuolization, disturbed cristae, and the presence of giant mitochondria were observed in the skin fibroblast and muscle tissues from HD patients[216]. This evidence comprehensively indicates a role of mutant Htt in mitochondrial Ca^{2+} handling defects, respiratory deficits, and impaired mitochondrial movement, which may play important roles in the mitochondrial dysfunction which occurs in HD.

Transcriptional dysregulation in HD

Mutant Htt may also impair mitochondrial function by altering transcription. Aberrant transcriptional regulation occurs due to binding of mutant Htt to several transcriptional regulators, and interfering with their function. Mutant Htt directly interacts and down regulates the activity of several transcription factors including p53, cAMP response element binding protein (CREB), TAFII130 and SP1 [217–223]. Binding of Htt to these transcription factors leads to alteration of expression of several genes involved in mitochondrial respiration and normal mitochondrial function. Htt binding to p53 causes up regulation of the downstream target genes BAX and PUMA, which leads to increased mitochondrial membrane depolarization[224]. Mutant Htt also represses the expression of CREB by a direct interaction with CREB binding protein [219,223,225]. Expression of CREB is reduced in the brain and muscle of HD transgenic mice and in HD cell models [180,181,218]. CRE dependent transcription is also reduced in HD [217,226]. Over expression of CBP rescued polyglutamine-induced neuronal toxicity [219]. CREB knockout mice show extensive apoptosis of post mitotic neurons and exhibit a phenotype similar to that in HD transgenic mice[227]. Recently, an interaction of mutant Htt with PGC-1α has been implicated in HD pathogenesis [228]. PGC-1α is a coactivator of several transcription factors, and a key regulator of mitochondrial biogenesis, energy homeostasis, adaptive thermogenesis, and glucose metabolism[229]. PGC-1α expression and activity are impaired in the brain and muscle tissues from HD patients, and in transgenic mouse models of HD [180,181,228,230,231]. Mutant Htt protein directly impairs the ability of PGC-1α to activate downstream target genes involved in mitochondrial biogenesis and adaptive thermogenesis [231]. Collectively, these data support a role for PGC-1α transcription interference in the degeneration of the striatum in HD. Of particular interest is the finding that the expression of PGC-1α is reduced several fold in medium spiny neurons but increased almost 50-fold in nNOS interneurons from knock-in HD mice [228]. This suggests that the selective vulnerability of medium spiny neurons and the resistance of interneurons, which are spared in HD, may be a consequence of altered PGC-1α expression and mitochondrial dysfunction. Down-regulation of PGC-1α significantly worsened behavioral and neuropathological abnormalities in a PGC-1α knock-out/ HD knock-in mouse model (PGC-1α KO/KI)[228]. Over expression of PGC-1α in the striatum of R6/2 mice results in a significant increase in mean neuronal volume, indicating that PGC-1α over-expression prevents neuronal atrophy [228]. PGC-1α is rapidly induced in response to cold exposure and has been shown to regulate key components of adaptive thermogenesis including the uncoupling of respiration via mitochondrial uncoupling proteins (UCP-1), resulting in heat production in BAT. Significant hypothermia at both baseline and following cold exposure was observed in both N171-82Q and R6/2 HD mouse models. Following cold exposure, UCP-1 expression is decreased in BAT from N171-82Q transgenic HD mice relative to wild type controls, implicating impaired PGC-1α function in these mice. This failure to induce UCP-1 and other PGC-1α target genes is further demonstrated in pre-adipocyte cells and primary brown adipocyte cells from N171-82Q mice. In brown fat adipocytes, there is also evidence of reduced ATP/ADP ratios and mitochondrial numbers similar to the findings in PGC-1α KO mice [232], N171-82Q BAT shows marked abnormalities including increased lipid vacuolation. The finding that UCP-1 expression is reduced but not PGC-1α strongly indicates that mutant Htt blunts the response of PGC-1α in HD models [228,231].

Mutant Htt also binds to the CREB/TAF4 complex which impairs activation of the PGC-1α promoter, and transcription of its target genes [228,230]. Impairment of PGC-1α function, and down regulation of its mitochondrial target genes, leads to abnormalities in mitochondrial function and energy metabolism, and ultimately neuronal demise [230]. PGC-1α activates a diverse set of metabolic programs in different tissues by forming complexes with several transcription factors, including nuclear respiratory factors (NRF-1 and NRF-2) and nuclear hormone receptors (PPARα, PPARγ, ERRα and thyroid receptor) [229,233]. It also regulates the activity of several nuclear encoded mitochondrial genes including Tfam and cytochrome c [233,234]. PGC-1α KO mice exhibit mitochondrial dysfunction, defective bioenergetics, a hyperkinetic movement disorder and striatal degeneration, which are features also observed in HD [232,235]. We and others found that over expression of PGC-1α in muscle and brain tissues reduces mitochondrial dysfunction, and enhances mitochondrial biogenesis in transgenic HD mice [180,228]. Selective ablation of PGC-1α leads to increased striatal neuron degeneration, and increased susceptibility to the mitochondrial toxin 3-NP in HD transgenic mice [228]. Furthermore, polymorphisms in PGC-1α and its downstream target genes such as NRF-1 and Tfam modulate the age of onset of HD, providing further evidence that it plays an important role in HD pathogenesis [236–239]. Impaired PGC-1α transcription and activity impacts the oxidant enzyme systems that combat ROS. This leads to down regulation of ROS defense genes encoding SOD1, SOD2, and glutathione peroxidase, resulting in increased oxidative damage and neuronal death [240]. We observed significantly decreased expression of PGC-1α and its downstream target genes, and impaired mitochondrial biogenesis in the muscle tissue of HD transgenic mice, myoblasts and muscle biopsy tissue from HD patients [180]. Adenoviral vector mediated over expression of PGC-1α in the muscle tissue resulted in increased PGC-1α expression, mitochondrial biogenesis and increased numbers of oxidative muscle fibers in HD transgenic mice [180]. We also observed a significant decrease of PGC-1α expression, increased gliosis and increased Htt aggregates in the striatal tissue of HD transgenic mice [181]. In HD striatal neurons there is a significant pathologic grade dependent reduction in numbers of mitochondria, which correlates with reductions in PGC-1α. Taken together there is a large body of evidence which shows that both mitochondrial dysfunction and oxidative damage contribute to the pathogenesis of HD which may be a consequence of impairment of PGC-1α, and other transcriptional pathways, which regulate mitochondrial biogenesis and expression of antioxidant defenses.

Mitochondrial dysfunction in Alzheimer's disease (AD):

AD is a late-onset, progressive, age-dependent neurodegenerative disorder, characterized by the progressive cognitive decline. The pathology of AD involves intraneuronal accumulation of amyloid plaques (aggregates of Aβ) and neurofibrillary tangles (aggregates of tau). Several studies suggested mitochondrial

dysfunction as a significant contributing factor to onset and progression of AD. According to the "mitochondrial cascade hypothesis" mitochondrial dysfunction is the primary event in pathogenesis of AD[241].

Mitochondrial bioenergetics impairment in AD

Soluble forms of Aβ cause reduced MMP and ATP levels in the brains of AD transgenic mice harboring mutant APP and mutant PS1 (tgAPP/PS1)[242]. Similarly APP, Tau and PS2 triple transgenic AD mice displayed decreased mitochondrial protein levels mainly related to complexes I and IV of the electron transport chain, reduction of the MMP and decreased synthesis of ATP[243]. Interestingly Tau and Aβ act synergistically to impair oxidative phosphorylation, where dysregulation of complex-I both at the protein and activity levels was tau dependent, and dysregulation of complex-IV was Aβ dependent[243]. Intrahippocampal stereotaxic injection of Aβ in rats caused damaged mitochondria, decreased Ca^{2+} ATPase activity and MMP, and increased Ca^{2+} levels[244]. Full length APP binds directly to the mitochondria in cortical neuronal cells from AD transgenic mice and causes mitochondrial dysfunction and impaired energy metabolism [245]. APP also causes mitochondrial dysfunction by accumulation in the mitochondrial import channels (TIM23 and TOM40) of AD brain[246].

PET imaging showed decreased resting-state brain glucose metabolism, decreased blood flow and metabolic failure in AD brains[247,248]. Decreased expression of genes involved in glucose delivery, oxidative phosphorylation, and energy consumption in the brain were observed in AD[249]. The activities of TCA enzyme complexes, pyruvate dehydrogenase, isocitrate dehydrogenase, and KGDH were found to be impaired in postmortem AD brain and fibroblasts from AD patients [250–252]. Levels of ATP and activities of cytochrome oxidase and mitochondrial ATP synthase are decreased in platelets and brain tissue of AD patients [253–255]. Similarly, reduced respiratory chain complexes I, III, and IV activity were found in platelets and lymphocytes from AD patients and AD postmortem brain tissue[253,256–258]. Fibroblasts derived from AD patients show decreased cytochrome c oxidase (complex-IV) activity [259]. A Genome-wide transcriptomic study showed reduced expression of nuclear encoded mitochondrial electron transport genes in carriers of AD[260]. The expression of cytochrome oxidase subunit II (COX II) was decreased in AD brain[261]. The protein levels of complex I-IV subunits were also decreased in AD[260]. Mitochondrial proteome analysis found dysregulated protein levels of citric acid cycle, oxidative phosphorylation, pyruvate metabolism, glycolysis, and mitochondrial protein synthesis pathways in the triple transgenic mouse model of AD which has APP, PS1 and Tau mutations[262]. Over-expression of APP intracellular domain in human neuroblastoma cells causes decreased MMP and altered mitochondrial morphology and distribution[263]. Hippocampal and cortical mitochondria isolated from Aβ transgenic mouse models of AD, have impaired mitochondrial respiration rates, ROS production, MMP, and cytochrome c oxidase activity[264].

Mitochondrial localization of A□ impaired mitochondrial dynamics and trafficking in AD

In addition to a direct mitochondrial respiratory chain defect, more recently, increased autophagic degradation of mitochondria has also been observed in AD[265]. A recent study showed increased mitochondrial fragmentation and decreased mitochondrial biogenesis in Aβ transgenic AD mice[266]. Several studies suggested defective mitochondrial fusion/fission, mitochondrial movement, altered mitochondrial dynamics and mitophagy in AD transgenic mice and AD patients [267–269]. A critical balance of mitochondrial fusion and fission, which is required for normal mitochondrial functioning, was found to be impaired in AD brain [270]. In the neurons, synapses are the sites of highest energy demand and increased bioenergetic activities. Synaptic mitochondria from Aβ AD transgenic mice are more susceptible to Aβ induced mitochondrial dysfunction as compared to non-synaptic mitochondria[271]. Synaptic mitochondria show increased age associated accumulation of Aβ, mitochondrial dysfunction, increased mitochondrial permeability transition, decreased mitochondrial respiration and cytochrome c oxidase activity[271]. Aβ also causes altered mitochondrial distribution and trafficking, reduced mitochondrial movement and length, and increased synaptic degeneration [271,272].

There is ample evidence suggesting that mitochondria are prime targets for amyloid precursor protein (APP), which affects mitochondrial import channels and for Aβ which interacts with numerous mitochondrial proteins and leads to mitochondrial dysfunction[273]. Aβ causes mitochondrial dysfunction by directly interacting with Aβ binding alcohol dehydrogenase (ABAD) in the mitochondria of AD transgenic mice and patients[274]. Inhibition of this interaction leads to attenuated mitochondrial dysfunction and decreased Aβ mediated toxicity in AD transgenic mice[275]. Decreased mitochondrial respiration, decreased pyruvate dehydrogenase protein levels and increased Aβ-ABAD interactions were observed in AD triple transgenic mice[276]. Aβ from mutant APP transgenic mice also binds to mitochondria and causes mitochondrial dysfunction[277].

The pathogenic protein Aβ may induce mitochondrial dysfunction by directly binding to mitochondria[278,279] and mitochondrial proteins such as omi/HtrA2[280]. Aβ accumulates in the mitochondria, reduces the enzymatic activity of complexes III and IV and decreases mitochondrial respiration[277,281]. A recent study found that intraneuronal and oligomeric forms of Aβ co-localize with Drp1 in the AD brains and Aβ precursor protein transgenic mice, and co-localization is increased as the disease progresses [267]. Further, expression of genes involved in mitochondrial fission (Drp1 and Fis1) and mitochondrial fusion (Mfn1, Mfn2, Opa1 and Tomm40) is altered in AD brain[267]. This abnormal interaction resulted in increased mitochondrial fragmentation and abnormal mitochondrial dynamics[267]. Over-expression of APP and Aβ in neuronal cells leads to alterations in mitochondrial morphology and distribution and impaired modulation of the mitochondrial fusion/fission machinery [282]. Another recent study suggested that Aβ mediated impairment of mitochondrial anterograde and retrograde axonal transport in neurons[272]. Aβ caused decreased mitochondrial numbers, mitochondrial velocity, and mitochondrial length[272]. Dynamin-like protein-1 (DLP1) a member of the dynamin large GTPases family, regulates mitochondrial fission and the normal distribution and morphology of mitochondria. The levels of DLP1 were found to be decreased, and they were associated with abnormal mitochondrial distribution and the presence of elongated mitochondria in fibroblasts from sporadic AD patients[283]. Mitochondrial dysfunction and cognitive impairment in AD transgenic mice are directly proportional to the levels of mitochondrial Aβ[264].

mtDNA encoded defects in AD

Cybrid cell lines with mtDNA from AD patients display the same pathology and phenotype observed in the AD brain [284,285]. Trans mitochondrial cybrid neuronal cells displayed reduced mitochondrial movement, reduced numbers of moving mitochondria, decreased MMP, altered mitochondrial morphology and synaptic degeneration[49,286]. Cybrid cells were more susceptible to Aβ induced toxicity and displayed enhanced MMP,

increased cytoplasmic cytochrome c levels, elevated caspase-3 activity and enhanced cell death[287]. AD cybrids also have increased secretion of Aβ and intracellular Aβ levels with Congo red-positive Aβ deposits[285].

Several studies suggest that mtDNA mutations also play an important role in mitochondrial dysfunction in AD pathogenesis. Recently, variations in mtDNA were found to be associated with AD pathogenesis[288]. Heteroplasmic somatic mtDNA control region mutations were observed in AD patients, which caused reduced mtDNA ND6 transcript expression and reduced mtDNA copy numbers[289]. Somatic mutations in the mtDNA control region accumulate in the brain and blood of AD patients and the frequency of mutations increased with age[289,290]. Point/missense mutations in the mitochondrial-encoded cytochrome c oxidase subunits I, II, and III genes were observed in AD patients [291–294], however direct sequencing of the complete mtDNA coding region has not identified disease specific mutations[295]. Recent studies suggested an association of polymorphism in Tfam and in the regulatory region of the presenilin-2 gene, with late onset AD [296,297].

Mitochondrial dysfunction in Amyotrophic lateral sclerosis (ALS)

ALS is a fatal motor neuron disease, characterized by a progressive and selective degeneration of upper and lower motor neurons in the spinal cord, brainstem, and motor cortex, leading to leading to muscle weakness, paralysis and death[3]. ALS is either sporadic or familial in origin, 90% of cases are sporadic with an unknown cause and 10% are familial. Approximately 20% of familial ALS cases are associated with mutations in SOD1, the gene encoding Cu/Zn-SOD. Mutations in RNA Transactivation response DNA-binding protein 43 (TDP-43) and FUS/TLS are also associated with familial ALS[298]. TDP-43 transgenic mice recapitulate the features of ALS[299,300]. Transgenic TDP-43 mice expressing full-length human TDP-43 showed abnormal juxtanuclear aggregates of mitochondria and decreased expression of mitofusin 1, involved in mitochondrial fusion[301]. Several different pathogenic mechanisms have been identified in the CNS and peripheral tissues during the disease course in ALS, but mitochondrial and bioenergetic defects are implicated widely in ALS pathogenesis[2]. Sporadic ALS patients have increased levels of 8-hydroxy-2'-deoxyguanosine in the CSF, suggesting increased oxidative damage[302,303]. Altered respiratory chain enzyme activities and CNS energy hypometabolism were observed in ALS spinal cord and motor cortex[304–308]. SOD1 over expressing G93A ALS transgenic mice displayed altered mitochondrial morphology as primary pathologic changes followed by decreased mitochondrial respiration [306,309,310]. Motor neuron cell lines expressing mutant SOD1 displayed decreased ATP levels and impaired respiratory chain enzyme activities [311,312]. We found decreased oxygen consumption, mitochondrial Ca^{2+} loading capacity, respiratory chain complex activities and ATP synthesis in the brain and spinal cord mitochondria from mutant SOD1 transgenic mice [313,314]. A recent study found that over-expression of mutant human SOD1 (G37R) in neuronal cells resulted in morphological abnormalities of mitochondria, reduced activity of the oxidative phosphorylation complex I, II and IV, reduced MMP and decreased levels of cytosolic ATP[315,316]. Mitochondrial abnormalities such as morphological alterations, decreased MMP, reduced mitochondrial depolarization, respiratory chain defects, increased Ca^{2+} signaling and increased apoptosis are observed in platelets[317,318] and muscle[319–321] of mutant SOD1 transgenic ALS mice and ALS patients. An ALS transgenic mouse model expressing a mutant SOD1 gene with G93A mutation selectively in skeletal muscle, displayed muscular atrophy, reduced muscle strength, altered muscle contractile ability, increased mitochondrial dysfunction and increased oxidative stress[322]. Over expression of mutant SOD1 with the G93A mutation in neuronal cells caused impairment of mitochondrial calcium handling[323].

Interaction of mutant SOD1 with mitochondria in ALS

Pathogenic mutant SOD1 appears to exert its pathogenic properties and induce mitochondrial dysfunction by direct interactions with mitochondria. Several studies found localization of mutant SOD1 in the mitochondrial intermembrane space, outer mitochondrial membrane and matrix [324,325]. It also selectively associates with the outer mitochondrial membrane in spinal cord motor neurons[324–326]. We found that mutant SOD1 forms macromolecular aggregates and compartmentalizes into the mitochondrial matrix[327,328]. It has been suggested that mutant SOD1 fails to fold properly, and forms aggregates, and disturbs the physiological regulation of mitochondrial import and retention[328]. However, the mechanism by which mutant SOD1 forms aggregates on the outer membrane, or in the matrix of mitochondria, and the etiology of the selective association with spinal cord motor neuron mitochondria are obscure[324,328]. After binding to the mitochondria, mutant SOD may cause mitochondrial dysfunction by several means. Mutant SOD damages the mitochondrial membrane that leads to decreased MMP, and swelling, and vacuolar degeneration of mitochondria[329,330]. It also causes impaired respiratory complex activity, decreased ATP production, impaired calcium and redox homeostasis, and increased mitochondria mediated apoptosis [298,310,331–333]. Mutant SOD1 caused clustering of axonal mitochondria in ALS transgenic mice[334]. Mutant SOD1 over expression in NSC34 cells resulted in increased fragmentation of motor neuron mitochondria, and inhibition of specific components of the mitochondrial electron transfer chain [316,335]. Mutant SOD1 binds with the mitochondrial anti-apoptotic protein Bcl-2 in mouse and human spinal cords [326]. Formation of the toxic mutant SOD1/Bcl-2 complex leads to conformational changes in Bcl-2, and mitochondrial dysfunction including altered mitochondrial morphology, reduced mitochondrial membrane integrity and increased release of cytochrome c[336]. Mutant SOD1 impairs fast axonal mitochondrial transport in the anterograde direction in motor neurons derived from SOD1 G93A transgenic mice[337]. Another study reported impaired mitochondrial transport in both anterograde and retrograde directions in differentiated NSC34 cells over expressing mutant SOD1[338]. These studies suggest that mutant SOD1 is associated with mitochondrial dysfunction in the pathogenesis of ALS.

There is more limited information linking sporadic ALS to mitochondrial dysfunction. However studies in muscle biopsies in sporadic ALS patients have shown abnormal mitochondrial function, reduced neuronal NOS, and impaired functions of mitochondrial enzymes [339]. Others studies found respiratory chain defects, mitochondrial alterations and impairment of mtDNA in muscle and dorsal root ganglion cells of sporadic ALS patients[319,320,340,341]. Muscle biopsies of individuals with sporadic ALS also show increased mitochondrial volume and calcium levels within the mitochondria[342]. Another study showed reduced cytochrome oxidase activity in anterior horn motor neurons of patients with sporadic ALS[307]. A recent study found decreased mRNA expression of PGC-1α and downstream genes involved in mitochondrial biogenesis in muscle tissues of human sporadic ALS patients [343]. These studies provide some insight about role of mitochondrial dysfunction in pathogenesis of sporadic PD. However, exactly what percentage of sporadic ALS patients has mitochondrial pathology is not known since in many cases they have not been studied and needs to be investigated.

Mitochondrial dysfunction in Friedreich's ataxia (FA)

FA is an autosomal recessive disorder which is the most frequent hereditary ataxia. It is characterized by progressive gait and limb ataxia, decreased vibration sense, absence of tendon reflexes, lower-limb areflexia, and muscular weakness in the legs. FA is caused by a GAA triplet repeat expansion due to loss of function mutations in intron 1 of the Frataxin (FXN) gene[344]. The FXN protein is mitochondrial chaperone and is mainly involved in iron metabolism, biogenesis of enzymes with Fe-S clusters, and detoxification of excess Iron. Deficiency of FXN leads to an accumulation of iron in the mitochondria, enhanced cellular iron uptake and impaired activity of Fe-S cluster enzymes[2]. Defective mitochondrial complex I, II, and III activities, decreased ATP content and mitochondrial dysfunction are observed in conditional FXN knockout mice, yeast mutants and patients with FA [344–348]. These studies suggest a central role of mitochondrial dysfunction in FA pathogenesis

Mitochondrial dysfunction in Charcot-Marie-Tooth disease (CMT)

CMT is the most common form of hereditary peripheral neuropathy, characterized by loss of muscle tissue and touch sensation. The evidence for involvement of mitochondria in CMT is mostly for the axonal form of the neuropathy which is CMT type 2A (CMT2A). CMT2A is mainly caused by mutations in the Mitofusin 2 (MFN2) gene, which encodes a mitochondrial membrane protein involved in mitochondrial fusion[349]. Transgenic mice having a mutated form of the human MFN2 in neurons have decreased mitochondrial complex activity, decreased ATP synthesis and a phenotypes similar to CMT2A[350,351]. There are other mutations such as ganglioside-induced differentiation-associated-protein 1 gene (GDAP1), and DHTKD1 which affect mitochondria and involved in pathogenesis of CMT. Mutations in the ganglioside-induced differentiation-associated-protein 1 gene (GDAP1), are associated with the recessive forms of CMT (CMT4A) and rarely with the autosomal dominant forms (CMT2K)[352]. GDAP1 encodes a protein localized to the mitochondrial outer membrane, and plays a role in mitochondrial dynamics by promoting mitochondrial fission. Mutations in GDAP1 lead to mitochondrial dysfunction, mitochondrial complex-I deficiency, altered mitochondrial dynamics and impaired energy generation[352,353]. Mutations in the neurofilament light gene cause CMT type 2E (CMT2E) which affects axonal mitochondrial transport[354].

Mitochondrial therapeutics for neurodegenerative diseases

Several studies suggest that bioenergetics defects, altered mitochondrial dynamics, impaired mitochondrial trafficking, and transcriptional dysregulation play an important role in the mitochondrial dysfunction which occurs in neurodegenerative disorders. Thus, agents which enhance mitochondrial bioenergetics are attractive potential therapeutics for amelioration of mitochondrial dysfunction in neurodegenerative diseases. We have summarized the potential therapeutic effects of bioenergetic agents in animal models and clinical trials for neurodegenerative disorders.

Creatine

Creatine is a guanidino compound found primarily in meat products and involved in energy supply to the muscle and nerve cells. In the body, creatine is found as free creatine and phosphocreatine (PCr) which together make the total creatine pool. In tissues with high energy requirements such as skeletal muscle and brain, creatine gets transformed into PCr by cytosolic and mitochondrial creatine kinase (CK). CK is an important enzyme, which maintains cellular homeostasis by reversibly converting creatine into PCr, thus creating a pool of PCr for ATP generation. Creatine exerts neuroprotective effects in several animal models of neurodegenerative disorders including PD, AD, HD, and ALS [355,356]. It also protects neuronal cells against 3-NP, MPP+, and 6-hydroxydopamine (6-OHDA) mediated toxicity and glucose and serum deprivation[161]. We found reduced degeneration of dopaminergic neurons in the substantia nigra and reduced depletion of dopamine levels in a MPTP induced mouse model of PD, following creatine administration[357]. Creatine supplementation was protective against a variety of neurotoxic injuries such as NMDA, malonate, Aβ and the neurotoxin ibotenic acid induced neuronal death [161]. Creatine alone exhibited neuroprotective effects, however it produced additive neuroprotection when co-administered with either nicotinamide, a cyclooxygenase-2 inhibitor or minocycline[161]. Creatine also produced additive neuroprotective effects in MPTP treated PD mice and in a transgenic mouse model of ALS, when given in combination with either a cyclooxygenase-2 inhibitor or minocycline [358–360]. We also found that creatine mediated protection of motor neurons and extended the survival of G93A transgenic ALS mice [361]. Creatine supplementation was also neuroprotective in several transgenic mouse models of HD. Oral dietary supplementation of Creatine reduced motor deficits, brain atrophy, Htt aggregates in the striatum, reduced mitochondrial dysfunction and enhanced survival in HD transgenic mice[362–364]. Combination therapy of creatine with the bioenergetic compound CoQ10 produces additive neuroprotective effects in rodent models of PD and HD[365]. These studies suggest that creatine has significant neuroprotective potential in both *in vitro* studies and in a variety of toxin and genetic models of neurodegenerative disorders.

Clinical trials with creatine in PD

In a randomized, double-blind, placebo-controlled cross over study in patients with mitochondrial cytopathies, we observed beneficial effects of creatine[366]. A small pilot trial with creatine in PD patients suggested benefical effects of creatine on patients mood but not on the Unified Parkinson's Disease Rating Scale (UPDRS) scores[367]. A creatine dose of 4 g/day was found to be safe and well tolerated in a placebo controlled randomized clinical trial in aged PD patients[368]. Creatine supplementation enhanced muscle endurance and upper body strength in PD patients, when given with resistance training[369]. The NINDS NET-PD investigators carried out a randomized, double-blind, Phase II futility clinical Neuroprotective Exploratory Trials (NET) of creatine and minocycline in early PD patients and found reduced UPDRS scores with significant tolerability for creatine and minocycline with no futility[370]. Further, NET-PD investigators carried out an add on phase II futility study of 10 g/day creatine and 200 mg/day minocycline for 18 months in early PD patients, and found that creatine was safe and tolerable[371]. Thereafter, NINDS with the NET-PD investigators initiated a double-blind placebo controlled phase III clinical trial [355,372]. This trial is examining 1,720 patients with early stage PD, randomized to 10g of creatine or placebo at 51 medical centers in the United States and Canada. The patients will be studied for the next 5 to 7 years. Altogether these clinical trials suggest a possible protective role of creatine in PD patients.

Clinical trials of creatine in HD

Several clinical trials with creatine have been carried with promishing outcomes. We carried out a 16-week, randomized,

double-blind, placebo-controlled phase II clinical trial in HD subjects to assess the safety and tolerability of creatine[373]. We found that a dose of 8g/day of creatine for 16 weeks was safe and well tolerated, and decreased serum 8-hydroxy-2-deoxyguanosine a marker for oxidative stress back to baseline levels in HD patients. Higher doses of creatine (30g/day) showed significantly improved clinical outcomes including slowing of the ongoing cortical atrophy in HD patients in an open-label add on clinical trial. Recently a double blind placebo controlled phase III clinical trial with creatine was initiated by the Huntington Study Group. This clinical trial is currently ongoing at a large number of centers, where maximum tolerated dose of creatine and UHDRS scores, cognition, and quality of life will be studied in HD patients. Taken together, these clinical trials suggest that creatine is a promising neurotherapeutic agent in a variety of neurodegenerative disorders.

CoQ10

CoQ10, is an endogenous biological substrate for the electron transport chain and an important anti-oxidant in mitochondrial membranes. It exerts neuroprotective effects in *in vivo* and *in vitro* models of neurodegenerative disorders[161]. CoQ10 protects dopaminergic neurons against MPTP mediated neurotoxicity [374,375]. CoQ10 reduces mitochondrial dysfunction and provides neuroprotection against a wide range of toxicants including paraquat, rotenone, and iron in dopaminergic neurons[161]. We found that CoQ10 mediated protection of dopaminergic neurons, increased dopamine levels, and reduced α-synuclein aggregation in a chronic MPTP model of PD[376,377]. We and others found that CoQ10 reduces the mitochondrial dysfunction, reverses the disease pathology, reduces pathogenic protein aggregation and increases survival in transgenic mouse models of ALS and HD[365,378–380]. CoQ10 exhibits marked neuroprotective effects against aminoxyacetic acid and the mitochondrial toxins malonate and 3-NP and reduces striatal lesions in rats[161]. CoQ10 in combination with minocycline or remacemide (a NMDA antagonist) significantly reduces behavioral deficits, reduces neuronal atrophy and increases survival in transgenic HD mice [379,381,382]. The combination of CoQ10 with creatine and also exerts additive neuroprotective effects in the MPTP model of PD[365]. CoQ10 is water insoluble, to increase its bioavailability, a water soluble formulation of CoQ10 was prepared by combining CoQ10 with polyoxyethanyl α-tocopheryl sebacate in 1: 2 mol/mol (1: 3 w/w) ratio, which can be diluted with aqueous solutions[383]. This formulation of CoQ10 found protective against paraquat induced degeneration of dopaminergic neurons and behavioral impairments in rats[383]. Several studies suggest that water soluble formulation of CoQ10 increases mitochondrial activity in neuronal cells[384,385].

Clinical trials with CoQ10 in HD

Multiple in vitro and in vivo animal studies found a potent neturoprotective role of CoQ10 in neurodegenerative disorders. Therefore, several clinical trials with CoQ10 have been initiated in PD, HD and ALS[386]. Oral administration of CoQ10 (360mg/day) resulted in significantly decreased levels of elevated cortical lactate in HD patients, which were reversed by withdrawal of CoQ10[167]. Animal studies showed additive significant neuroprotective effects of cthe ombination of CoQ10 with remacemide in HD transgenic mice, therefore Huntington's Study Group carried out a CARE-HD trial with CoQ10 and remacemide combination in HD patients. CoQ10 and remacemide combination treatment resulted in a 14% decrease in disease progression[387]. A phase III trial of 2400 mg of CoQ10 daily has recently started in HD. A phase II trial of CoQ10 in presymptomatic gene positive HD patients (PREQUEL) has also recently been completed.

Clinical trials with CoQ10 in PD

Several early stage clinical trials have been carried out with encouraging behavioral improvements in PD patients[386]. A open label phase-I pilot trial was carried out to assess the safety and tolerability of CoQ10 in 15 PD patients [388].. This study suggested that CoQ10 at doses 400, 600 and 800mg/day for 1 month was safe and well tolerated, and prroduced significant and dose-dependent increases in plasma CoQ10 levels in PD patients. However, there was no significant improvement in UPDRS scores. Interestingly CoQ10 administration in this study showed a trend toward an increase in complex-I activity in the PD subjects[388]. Next, a multicenter, parallel-group, placebo-controlled, randomized, dosage-ranging, double-blind and phase II (QE2) clinical trial of CoQ10 in early PD patients was carried out by the Parkinson's Study Group [389]. In this study, CoQ10 was given at doses of 300, 600, or 1,200 mg/day for 16 months to PD patients. CoQ10 was safe and well tolerated at dosages of up to 1200 mg/day and cauesd a significant dose-dependent reduction in UPDRS score in PD subjects [389]. A dose of CoQ10 360 mg/day for 4 weeks exerted significant improvement in the UPDRS score with no improvement of motor symptoms in PD patients in a monocenter, parallel group, placebo controlled, double-blind trial[390]. Similarly, 1000mg/day and 1500mg/day CoQ10 treatment for 3 months in an open label clinical trial exerted significantly improved motor performance in PD patients[391]. However, CoQ10 administration at 100 mg three times/day for 3 months did not show any improvement in the UPDRS score, behavioral symptoms and motor performance [392,393].

We have carried out CoQ10 dose escalation (1200, 1800, 2400, and 3000 mg/day with vitamin E (alpha-tocopherol) 1200 IU/day) open label clinical trial in PD patients. CoQ10 dosages up to 3,600 mg/day were safe and well tolerated, and plasma CoQ10 levels reached a plateau at the 2400 mg/day dosage, and did not increase further at the 3000 mg/day dosage in PD patients [394]. A NINDS sponsored double-blind, randomized, calibrated futility clinical trial with 2400mg/day CoQ10 and GPI-1485 in early untreated PD patients did not meet futility criteria[395]. However, phase III QE3 trial of 600 early stage PD subjects treated with placebo, 1200mg or 2400mg of CoQ10 daily was recently halted when an interim analysis showed futility in its outcome. These results therefore do not support a neuroprotective effect of CoQ10 in PD.

Clinical trials with CoQ10 in ALS, AD and Friedreich□s ataxia

An open label placebo controlled clinical trial found that 3000mg/day COQ10 dose safe and well tolerated in ALS patients [396]. Recently a multicenter, two-stage, bias-adjusted, randomized, placebo-controlled, double-blind, Phase II CoQ10 clinical trial was conducted by QALS study group[397]. No significant difference in ALS Functional Rating Scale-revised (ALSFRSr) improvement was observed between CoQ10 and placebo [397]. A double-blind, randomized, placebo-controlled, phase II trial of CoQ10 (5 mg/kg/day) for six weeks in progressive supranuclear palsy patients, showed an increased ratio of high-energy to low-energy phosphates in the occipital lobe, and a significant improvement in the PSP rating scale and frontal assessment battery[398]. Similarly, a double blind, randomized pilot study of CoQ10 and vitamin E in Friedreich's ataxia patients found improvement in the International Co-operative Ataxia Ratings Scale scores compared to cross-sectional data[399].

Idebenone

Idebenone, an analogue of CoQ10 act as a powerful anti-oxidant and biochemically also known as ubiquinone. Idebenone chemically belongs to the quinone family of compounds has very similar chemical structure to CoQ10. Idebenone showed neuroprotection against Aβ induced toxicity in cells and rodents[161]. Two multicentre, placebo controlled clinical trials of idebenone in patients with AD, showed statistically significant improvement in the Alzheimer's Disease Assessment Scale (ADAS) score [400,401]. Idebenone was safe and tolerable up to 360 mg/day and slowed progression of cognitive deficits in small trials in patients with AD [402,403], however a larger multi-dose trial by the AD collaborative group in 536 patients showed no benefit [404]. Idebenone clinical trials in Friedrich's Ataxia are very promising and showed clinical improvements [405,406].

MitoQ and Mitochondrial targeted peptides

MitoQ is a form of coenzymeQ ubiquinone linked to triphosphonium ions through covalent attachment, which results in its selective membrane potential driven accumulation within mitochondria. It shows neuroprotective effects in several *in vitro* and *in vivo* models of ischemia reperfusion injury, Aβ induced toxicity and neurodegeneration[407–409]. MitoQ protects Friedrich's Ataxia fibroblasts from oxidative stress[410]. In a recent study MitoQ protected against Aβ induced impairments in hippocampal synaptic plasticity in AD transgenic mice[411]. MitoQ reduces mitochondrial fission and inhibits the translocation of the pro-apoptotic protein Bax to the mitochondria in 6-OHDA induced cell model of PD [412]. However, a double blind clinical trial with two doses of MitoQ for 12 months in 128 newly diagnosed untreated patients with PD did not show any significant improvement in UPDRS scores and PD progression as compared to the placebo control[413].

The novel antioxidant SS (*Szeto-Schiller*) peptides are cell-permeable synthetic tetrapeptides that can selectively localize to the inner mitochondrial membrane [414,415]. These peptides carry 3+ net charge at physiologic pH and decrease mitochondrial ROS production, and inhibit mitochondrial swelling and cytochrome c release in isolated mitochondria [415]. Addition of a tyrosine or modified tyrosine residue increases their free radical scavenging properties, and these analogs potently inhibit ROS-induced cell death [416].

Peptide antioxidant (SS-31 and SS-20) targeted to the inner mitochondrial membrane, reduce inhibition of the mitochondrial electron transport chain, and inhibit apoptosis and oxidative stress. These peptides also decrease mitochondrial ROS production, inhibit the MPT and mitochondrial swelling, and reduce cytochrome c release. We found that SS-31 protects neuronal cells from toxicity mediated by mutant Cu/Zn superoxide dismutase (SOD1)[417]. We also showed that SS-31 and SS-20 provide neuroprotection and decrease oxidative stress in the MPTP induced model of PD, and in G93A ALS transgenic mice[417,418]. The Mitochondrial antioxidant (TEMPOL) coupled to gramacidin localizes into mitochondria (XJB-5-131), and causes enhanced mitochondrial function, improved behavior and enhanced survival and significant neuroprotective effects in a transgenic mouse model of HD[419]. These findings strengthen the growing view that mitochondria-targeted antioxidants/peptides have a potential therapeutic role in neurodegenerative disorders.

Nrf2/ARE pathway/Triterpenoids

Mitochondrial dysfunction and ROS mediated damage to the mitochondria plays a pivotal role in pathogenesis of major neurodegenerative disorders, therefore therapies targeting the Nrf2/antioxidant response element (ARE) pathway to combat mitochondrial ROS are gaining much attention. Synthetic triterpenoids (TP) are **derivatives** of oleanolic acid, and inhibit oxidative stress and cellular inflammatory processes, by potently activating the antioxidant response element (ARE)-Nrf2-Keap1 signaling pathway. Activation of Nrf2 by TP causes dissociation of Nrf2 from Keap1 and translocation to the nucleus and binding to the ARE promoter sequences. This promoter binding leads to coordinated induction of a battery of cytoprotective genes, including antioxidant and anti-inflammatory genes. Recently, synthetic triterpenoids such as CDDO were found to potently induce the transcriptional activity of Nrf2, and markedly enhance the expression of NQO-1, HO-1, glutathione transferases, and other cytoprotective enzymes [420,421]. These triterpenoids may act as Nrf2 inducers by their involvement in Michael reaction to reactive cysteine residues on the KEAP1 protein[422]. The synthetic triterpenoid, CDDO-methyl amide (2-cyano-*N*-methyl-3,12-dioxooleana-1,9(11)-dien-28 amide; CDDO-MA), is at least 200,000 times more potent as an inducer of NQO-1 or a suppressor of iNOS than its naturally occurring oleanolic acid. We found that CDDO-MA is a very potent and selective activator of the neuroprotective Nrf2/ARE pathway [423,424]. Several studies implicate a neuroprotective role of synthetic TPs in neurodegenerative disorders.

Neuron derived from the Nrf2 knockout mice are more susceptible towards mitochondrial electron transport chain complex inhibitors such as MPP+ and rotenone mediated oxidative stress [425]. 3-NP causes increased motor deficits and striatal lesions in the Nrf2 knockout mice, which were protected by adenoviral mediated over expression of Nrf2[426]. We found that the synthetic triterpenoid CDDO-MA potently activates Nrf2/antioxidant response element (ARE) signaling and exerts significant neuroprotective effcets in the 3-NP rat model and the MPTP mouse model [418,424]. The neuroprotective effects of synthetic TP against MPTP induced neurodegeneration were dependent on Nrf2, since treatment with TP in Nrf2 knockout mice did not provide protection against MPTP mediated neurotoxicity and induction of Nrf2-dependent genes[424]. CDDO-MA in our studies activated Nrf2 dependent genes in wild type fibroblasts, but not in Nrf2 deficient fibroblast [423]. CDDO-MA treatment resulted in significantly reduced ROS generation, decreased MPTP induced neurodegeneration and, dopamine depletion and reduced 3-NP induced striatal lesions[418]. We found that TPs also improve the behavioral phenotype and survival in transgenic mouse models of AD, HD and ALS[427–429]. These studies suggest that targeting Nrf2/ARE pathway through synthetic TPs could be a better therapeutic approach in neurodegenerative disorders.

Lipoic acid, Carnitine, Nicotinamide, and □-hydroxybutyrate

Lipoic acid found naturally in the mitochondria and has antioxidant effects. We observed significant neuroprotective effects of α-lipoic acid in transgenic mouse models of HD and ALS[366,430,431]. The combination of α-lipoic acid and acetyl-L-carnitine protects neuroblastoma cells against rotenone induced toxicity by increasing mitochondrial biogenesis,and reducing ROS through up-regulation of PGC-1α[432]. Carnitine and β-hydroxybutyrate protect dopaminergic neurons against MPTP induced toxicity[161]. Nicotinamide is a substrate for complex-I of the electron transport chain. It prevents MPTP induced neurodegeneration in mice[375].

PGC-1□ and PPARs

PGC-1α, a transcriptional co-activator is a new therapeutic target for neurodegenerative disorders[230]. PGC-1α regulates several important biological functions including regulation of

mitochondrial biogenesis, adaptive thermogenesis, antioxidant defences and cellular respiration, by activating downstream target genes including NRF-1, NRF-2, Tfam and antioxidant enzyme genes[230]. Several studies have suggested impaired expression/function of PGC-1α and downstream target genes in the neurodegenerative disorders including HD, PD, AD and ALS [180,181,228,230,231,343,433–435]. HD transgenic mice displayed impaired thermoregulation during cold exposure, due to impaired activation of PGC-1α and mitochondrial UCP-1 in brown adipose tissue [231].

Crossbreeding of PGC-1α knockout mice with HD knockin transgenic mice resulted in an increased susceptibility of striatal neurons towards 3-NP, enhanced neurodegeneration, and motor symptom impairment in HD mice[228]. Lentivirus mediated over expression of PGC-1α in the striatum prevented atrophy of striatal neurons in the R6/2 HD transgenic mice [228]. Impairment of PGC-1α transcription is not restricted only to the brain in HD, but is also observed in peripheral tissues. We found impaired PGC-1 transcription in muscle and liver of HD transgenic mice[180]. We injected β-guanidinopropionic acid (GPA) in HD transgenic mice to create an artificial energy deprivation condition. GPA depletes PCr and ATP levels and activates expression of AMPK and PGC-1α. We found that GPA administration caused increased expression of PGC-1α and its downstream target genes in the muscle and brains of wildtype mice, while in HD mice this response was blocked [180]. This suggests that activation of PGC-1 and AMPK by an energy stresser is significantly impaired in HD transgenic mice. Further, adenoviral vector mediated over expression of PGC-1α in the muscle reversed this blunted response[180].

PGC-1α knockout mice are more susceptible to MPTP induced neurodegeneration, suggesting involvement of PGC-1α in PD pathogenesis [240]. Genome wide expression studies in SN dopaminergic neurons of symptomatic PD patients, showed alterations in PGC-1α target genes regulating cellular bioenergetics [436]. PGC-1α regulates the expression and activities of ROS scavenging antioxidant enzymes and therefore combats aginst oxidative stress [240]. PGC-1α over expression protects neural cells and mouse model of PD, from oxidative stress induced by mitochondrial toxins[240,437]. The parkin interacting substrate, PARIS (ZNF746) represses the expression of the PGC-1α by binding to the PGC-1α promoter leading to selective dopaminergic neurodegeneration in the SNPc[438]. PARIS mediated dopaminergic neurodegeneration was reversed by over expression of PGC-1α and parkin in the SNPc [438]. Over expression of PGC-1α protected cells against mutant α-synuclein and rotenone mediated toxicity by increasing the expression of mitochondrial respiratory chain subunits genes [436]. PGC-1α expression was also found to be decreased in the postmortem brain tissue of AD patients [434].

These studies suggest an involvement of PGC-1α in the pathogenesis of neurodegenerative disorders, therefore pharmacological/transcriptional activation of PGC-1α may serve as a new therapeutic strategy[2,230]. Several compounds which induce PGC-1α and oxidative phosphorylation have already been identified [439]. PGC-1α reduces Aβ production in a PPAR dependent manner [435]. Dietary supplementation with nicotinamide riboside improves both cognitive function and synaptic plasticity by enhancing PGC-1α mediated BACE1 degradation, and thus preventing Aβ production in AD mouse models[419]. Diammonium glycyrrhizinate (DG), the salt form of Glycyrrhizin, having anti-inflammatory properties, was found to protect against Aβ induced neuronal death, mitochondrial dysfunction and improve cognitive impairment by upregulating PGC-1α in Aβ (1-42) induced AD mice [440]. PGC-1α over expression in SOD1 transgenic (TgSOD1-G93A/PGC-1α) mice leads to significantly improved motor function, restoration of mitochondrial electron transport chain activities, protection from motor neuron loss and enhanced survival of SOD1-G93A mice [441]. However, over expression of PGC-1α solely in muscles of SOD-1 ALS mice improves muscle function throughout disease course, without extending the survival [442]. PGC-1α over expression in HD transgenic mice promoted htt turnover and degradation by activating transcription factor EB (TFEB), a master regulator of the autophagy-lysosome pathway, thus ameliorating HD neurodegeneration [443]. Another potential approach to activate the PGC-1α and downstream target genes, and to reduce mitochondrial dysfunction is via activation of peroxisome proliferator-activated receptors (PPARs). The PPARs are nuclear receptors that act as ligand-modulated transcription factors and regulate gene-expression programs of metabolic pathways such as oxidative phosphorylation and mitochondrial biogenesis.

The PPARγ agonist thiazolidinedione (TZD) treatment in R6/2 HD transgenic mice resulted in reduced Htt aggregates and thereby decreased recruitment of PPARγ into Htt aggregates [444]. TZD also enhanced the expression PPARγ and downstream genes including PGC-1α, and several mitochondrial genes. Similarly, another PPARγ agonist rosiglitazone protected a neuroblastoma cell line (N2A) from mHtt mediated mitochondrial dysfunction [444]. We found that administration of the pan-PPAR agonist bezafibrate in the diet potently induced transcription of PGC-1α and downstream genes, and increased survival in HD transgenic mice [445]. Bezafibrate also reduced neuronal atrophy and increased the numbers of mitochondria [445]. The PPARγ agonists rosiglitazone and pioglitazone provide neuroprotection in models of PD, ALS, AD and HD [229,446–451]. Ganoderma lucidum (GaLu) extract increases PGC-1α expression and mitochondrial biogenesis in the 3-NP induced cellular and animal models of HD [452,453].

Altogether these studies suggest that PGC-1α expression can be modulated by several pharmacological agents/genetic approaches in neurodegenerative disorders. However, PGC-1α over expression needs to be carefully regulated, as sustained overexpression of PGC-1α in the substantia nigra of rats, causes impaired dopaminergic function and reduction in striatal DA content [454].

Transducers of Creb-related binding protein (TORC)

Recently we have identified TORC as a novel therapeutic target for HD. We found significantly decreased TORC1 transcription/function in HD striatal cells, transgenic mice, and in striatal tissue from HD patients[455]. TORCs are co-activators of CREB, which enhance CREB dependent gene transcription[455,456] and strongly regulate PGC-1α promoter activity, transcription and mitochondrial biogenesis [457]. TORC1 over expression resulted in significantly increased CREB expression, PGC-1α promoter activity, mRNA expression of mitochondrial biogenesis genes, and mitochondrial DNA content in HD striatal cells. TORC1 over expression increased the resistance of striatal cells to 3-NP mediated toxicity by enhancing mitochondrial activity and MMP in striatal neurons. TORC1 knock down resulted in decreased PGC-1α expression, and increased susceptibility to 3-NP induced toxicity and enhanced neurodegeneration in HD transgenic mice. These studies implicate TORC1 as a new therapeutic target in HD.

AMP Kinase

AMP-activated protein kinase (AMPK) is a Ser/Thr kinase that serves as an energy sensor for whole body energy regulation during energy deprivation conditions (reduced ATP) such as starvation, ischemia and chronic metabolic stress. During low energy states, AMPK gets activated which results in increased glucose transport, fatty acid oxidation and mitochondrial biogenesis. AMPK activation also increases the phosphorylation of

PGC-1α. 5-aminoimidazole-4-carboxamide ribonucleoside (AICAR) is an AMPK agonist, which activates PGC-1α through AMPK. AICAR blocked LPS/Aβ induced inflammatory processes by blocking the expression of proinflammatory cytokines and by reducing numbers of astroglial cells [458]. Activation of AMPK by AICAR resulted in significantly decreased Aβ production in neuronal culture [459]. Activation of AMPK by metformin resulted in significantly prolonged survival and decreased hind limb clasping in male HD transgenic mice. However, metformin showed no beneficial effects on survival in LAS transgenic mice [460]. Recently, Viniferin (a natural product) was found to activate AMPK and SIRT3 and provide neuroprotection in cellular models of HD [461].

Sirtuins (Sir2) and resveratrol

Sirtuins are members of the NAD+ dependent histone deacetylase family mainly involved in regulation of several important biological functions such as cellular metabolism, energy metabolism, gluconeogenesis, cell survival and aging. Pharmacological activation of sirtuins may serve as a potential neuroprotective stretegy in several neurodegenerative disorders. The mammalian Sirtuin gene family has seven homologues (SIRT1-7) and SIRT1 is a potent inducer of PGC-1α. A recent study suggested that NAD-dependent deacetylase SIRT1 over expression reduces the production of Aβ and plaques in a mouse model of AD, by activating transcription of the gene encoding the alpha-secretase, ADAM10 [462]. SIRT2 knockdown resulted in increased α-synuclein toxicity and enhanced dopaminergic cell death in cellular and fly models of PD[463]. Administration of resveratrol, a potent activator of SIRT-1, resulted in increased survival of motor neurons in ALS transgenic mice, and reduced learning and neurodegeneration in AD mice[464]. Furthermore, lentiviral mediated over expression of SIRT1 in the hippocampus, leads to significant neuroprotection in AD transgenic mice [464]. Resveratrol was found to provide neuroprotection against 3-NP induced motor and behavioral deficits [465]. Resveratrol decreases PGC1α acetylation, which causes increased PGC1α activity, increased mitochondrial biogenesis and improved motor function in mice [466]. SIRT1 is activated by increased intracellular NAD+ concentration in the brain following caloric restriction, which leads to decreased amyloid pathology in an AD mouse model [467]. Over expression of SIRT1 deacetylase, and SIRT1 activation by resveratrol significantly protects against microglia-dependent Aβ toxicity [468]. We observed that dietary supplementation with resveratrol resulted in reduced Aβ accumulation, motor improvement and reduced disease pathology in transgenic mouse models of AD[469]. We also found decreased peripheral pathology, decreased behavioral impairments and reduced mitochondrial dysfunction in HD transgenic mice following resveretrol supplementation[470]. These studies suggest that targeting of Sirtuins may be an attractive therapeutic approach in neurodegenerative disorders.

Conclusion and future perspectives

There is increasing evidence, which suggests a pivotal role of mitochondrial dysfunction in the pathogenesis of major neurodegenerative disorders. The bioenergetic defects, mtDNA mutations/polymorphism, altered mitochondrial dynamics, transcriptional dysregulation, and altered Ca^{2+} homeostasis are associated with mitochondrial dysfunction in neurodegenerative diseases. Studies in cybrids suggest direct involvement of mitochondria in the progression of neurodegenerative disorders. In some neurodegenerative diseases such as Friedreich's ataxia, there is direct involvement of the product of the pathologic genetic defect with mitochondria. In other neurodegenerative disorders such as PD and AD involvement of mitochondria in disease pathogenesis is more indirect. In AD, the pathogenic protein Aβ may induce mitochondrial dysfunction by directly binding to the mitochondria and mitochondrial proteins such as ABAD and omi/HtrA2, leading to reduced enzymatic activity of complexes III and IV and mitochondrial respiration. In PD, α-synuclein and LRRK2 cause mitochondrial dysfunction by association with the mitochondria. DJ-1 plays an important role in antioxidant defenses against oxidative damage and thus protects against mitochondrial dysfunction. PINK1 and Parkin regulate mitochondrial integrity, promote clearance of dysfunctional mitochondria by mitophagy and regulate axonal transport of mitochondria. PINK selectively accumulates on diseased/damaged mitochondria and then recruits parkin, which ubiquitinates mitochondria which then target them for mitophagy. Parkin ubiquitinate mitofusins 1 and 2 for selective removal of damaged mitochondria. Genetic mutations in PINK1, Parkin, DJ-1 and LRRK2 lead to impaired defense against oxidative stress, reduced mitophagy, enhanced accumulation of damaged mitochondria and impaired mitochondrial dynamics in the brain. The mutant SOD1 protein in ALS exerts its pathogenic properties by direct interactions with mitochondria. Several studies found localization of mutant SOD1 in the mitochondrial intermembrane space, outer mitochondrial membrane and matrix in spinal cord motor neurons. Mutant SOD1 caused clustering of axonal mitochondria and impaired fast axonal mitochondrial transport in the anterograde direction. Mutant Htt plays an important role in mitochondrial dysfunction in HD by directly binding to the mitochondria.

There is also evidence for abnormalities in mitochondrial dynamics, which are involved in trafficking and turnover of mitochondria, in neurodegenerative diseases. Mutant Htt impairs *in vitro* and *in vivo* trafficking of mitochondria in neurons. Mutant Htt binds to Drp1 and increases its mitochondrial fission enzymatic activity, which leads to enhanced mitochondrial fragmentation. Aβ impairs mitochondrial anterograde and retrograde axonal transport in neurons. Aβ caused decreased mitochondrial numbers, mitochondrial velocity, and mitochondrial length.

Lastly, there is increasing evidence that mitochondrial dysfunction may be a consequence of transcriptional alterations. In the case of HD, mutant Htt impairs mitochondrial function by altering transcription. Mutant Htt directly interacts and down regulates the activity of several transcription factors including p53, CREB, TAFII130 and SP1. Recently, an interaction of mutant Htt with PGC-1α has been implicated in HD pathogenesis. PGC-1α is a coactivator of several transcription factors, and a key regulator of mitochondrial biogenesis, energy homeostasis, and adaptive thermogenesis. Recently, PGC-1α expression and activity were also found to be impaired in AD, PD, and ALS. In PD there is reduced PGC-1α expression in dopaminergic neurons of sporadic cases, as well as a decrease in association with Parkin mutations due to an increase in PARIS, which inhibits PGC-1α expression.

Agents which enhance the mitochondrial bioenergetics can be attractive potential therapeutics for amelioration of mitochondrial dysfunction in neurodegenerative diseases. Therefore, a number of mitochondrial-targeted therapeutics have been studied in several animal models and clinical trials for the neurodegenerative diseases. Creatine is a guanidino compound involved in energy supply to the muscle and nerve cells. Creatine exerts neuroprotective effects in several neurodegenerative disorders including PD, AD, HD, and ALS. It protects against degeneration of dopaminergic neurons in the substantia nigra and reduced dopamine levels in a MPTP induced mouse model of PD. Creatine protects motor neurons and enhances survival of G93A transgenic ALS mice. Creatine supplementation was also neuroprotective in several transgenic mouse models of HD. Several clinical trials with creatine have been carried out by the NINDS NET-PD investigators

in PD patients. Creatine was found safe and tolerable and caused reduced UPDRS scores in PD patients. Similarly, creatine provided promising effects in HD patients and is now in phase III clinical trials.

Coenzyme Q (CoQ) is a component of the electron transport chain as well as an important antioxidant in mitochondrial and lipid membranes. CoQ10 has been shown to be neuroprotective against toxin and/or genetic models of PD, AD, HD and ALS. Several phase III clinical trials were commenced to study its efficacy in PD and HD, although the PD trial was halted due tofutility. In animal studies the combination of Creatine with CoQ10 provided additive neuroprotective effects. Idebenone, a synthetic analogue of CoQ10 also found neuroprotective in AD small trials, although not in a larger phase 3 trial. Idebenone and CoQ10 clinical trials showed promising clinical improvements in Friedrich's Ataxia.

Several mitochondria targeted antioxidants such as MitoQ have been developed. MitoQ, a form of coenzymeQ ubiquinone linked to triphosphonium ions through covalent attachment, which results in its selective accumulation within mitochondria. MitoQ and other novel peptide antioxidants (SS31 and SS20) found neuroprotective in cellular and animal models of neurodegenerative diseases. Activation of Nrf2/ARE pathway by synthetic triterpenoids, which regulate antioxidant enzymes and mitochondrial biogenesis, showed neuroprotective effects in transgenic mouse models of AD, HD and ALS. Dimethyl fumerate which activates the Nrf2/ARE pathway was recently approved for the treatment of multiple sclerosis [471]. Dimethyl fumerate improves cellular redox status, glutathione, ATP levels, and mitochondrial membrane potential [472]. Activation of PGC-1α, SIRT1, AMP kinase and PPAR through genetic and pharmacological approaches were found to exert neuroprotection and reduce mitochondrial dysfunction in a number of different transgenic mouse models of neurodegenerative diseases including HD. Recently TORC, which enhances the transcription/function of PGC-1α, was implicated in HD pathogenesis. There are a large number of compounds, which are under development for the treatment of neurodegenerative diseases, which target mitochondrial dysfunction and oxidative damage, and which show great promise.

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