

Review

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Review

Mitochondrial Bioenergy in Neural Disease: Huntington and Parkinson

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Abstract: Much evidence suggests a correlation between degeneration and mitochondrial impairment. Typical cases of degeneration can also be observed in physiological phenomena (aging) as well as in neurological neurodegenerative diseases and cancer. All these pathologies have as a common denominator the dyshomeostasis of mitochondrial bioenergy. Even neurodegenerative diseases show a bioenergetics imbalance in their pathogenesis or progression. Huntington's chorea and Parkinson's disease are both neurodegenerative diseases, but while Huntington's disease is a genetic, and progressive disease with early manifestation and severe penetrance, Parkinson's disease is a pathology with a multifactorial aspect. Indeed, there are different types of Parkinson/Parkinsonism. Many forms are early onset diseases linked to gene mutation, others can appear in young adults and senescent only post-injury, and a final group is idiopathic. Huntington's was defined as a hyperkinetic disorder, while Parkinson's is a hypokinetic disorder; but in the middle, there are a lot of similarities as well as neuronal excitability, the loss of striatal function, psychiatric comorbidity, etc. In the review, we would embrace the theories that both diseases start and develop in light of mitochondrial dysfunction. These dysfunctions act on energy metabolism and reduce the vitality of neurons in many different brain areas.

Keywords: movement disorders; mitochondria; energy metabolism; synaptic plasticity; basal ganglia; calcium

Introduction

The Mitochondrion is an evolutionary organelle that originates from alphaproteobacteria that are entered into eukaryotic cells and have established a symbiotic ratio. It led during mitotic cell divisions to stabilize the host as an organelle [1]. In light of this hypothesis, it is possible that mitochondria have enabled the development of life as we know it and represents the common factor through which many organisms function or are dysfunctional [2]. Mitochondria are well-known as energetic units of the eukaryotic cells. They supply energy in the form of ATP to support all cellular functions. They provide for the aerobic respiration, a complex biochemical pathway by which starting from pyruvate and adding different co-factors, mitochondria synthesized ATP molecules. Moreover, mitochondrial proteomes, aggregates of more than 1000 proteins, can realize a wide variety of critical biochemical processes, including amino acid metabolism, nucleotide metabolism, protein synthesis, and fatty-acid catabolism [3]. There is abundant evidence in literature associating mitochondrial disruption with neurological and neurodegenerative diseases [4–7]. The brain requires high-energy consumption in the form of ATP; it was estimated that a cortical neuron in the human brain could utilize 4.7 billion molecules of ATP/sec. In addition, the ATP used at rest corresponds to about 5.7 kg per day [8]. The brain's highenergy demand supports many important functions, such as neurotransmission, cellular activities required for learning and memory, neural plasticity, and synapse development [9]. Since the mitochondrion, through oxidative phosphorylation and the

production of ATP, meets all the energy demands of the nervous system, even with a rapid turnover [10], mitochondrial dysfunction with consequent loss in the energetic capacity and may represent a neurodegenerative trigger. Severe bioenergetic dysfunction makes neurons very vulnerable to oxidative stress and predisposed to neuronal cell death [11]. Additionally, neurodegeneration can be seen as an energy disorder, which manifests indifferent aspects depending on the severity of the process and the area involved [12]. This energetic disorder can lead to different pathologies with sometimes-opposite symptoms, such as hypokinetic and hyperkinetic disorders. The purpose of the present review is to emphasize how mitochondrial dysfunctions, which may be associated with phenomena as inflammation and degeneration, are actually a common element in two major neurodegenerative diseases, one purely genetic and the other resulting from a combination of genetic and environmental factors: Huntington's disease (HD) and Parkinson's disease (PD).

Role of Mitochondria in Brain Energy Metabolism, Calcium Homeostasis, and Signal Transduction

Mitochondria are organelles responsible for several critical processes in neuronal function and dysfunction, including energy metabolism, calcium homeostasis, and signal transduction [13]. The brain consumes 20% of total oxygen respired to meet the high metabolic demand of neurons that must maintain ionic gradients across membranes, transport of molecules from the soma along axons and dendrites, as well as for neurotransmission [14]. The metabolic activities to generate ATP rely mainly on mitochondrial oxidative phosphorylation (OXPHOS). During OXPHOS, enzymes of the Krebs cycle utilize acetyl-coenzyme A to reduce the cofactors nicotinamide adenine dinucleotides (NADH) and flavin adenine dinucleotides (FADH₂) that serve in energy transfer to the electron transport chain (ETC), embedded within the extensive inner mitochondrial membrane [15,16]. The ETC consists of four complexes which transfer electrons from NADH and FADH₂ to O₂. Ultimately, the energy released by electron's transfer is used to allow the thermodynamically unfavorable pumping of protons against their concentration gradient from matrix to the intermembrane space and generate an electrochemical gradient, known as mitochondrial membrane potential ($\Delta\Psi_m$), essential in the process of energy storage. The protons accumulated in the intermembrane space are allowed to move, according to a concentration gradient, back into the matrix by passing through one of the domains of the enzyme ATP synthase (or Complex V), which finally harnesses the released energy to phosphorylate ADP molecules into ATP [15]. Proper neuronal functioning is strongly linked to the retention of mitochondrial membrane potential and ATP levels [17]. Indeed, mitochondrial functions go beyond the primary role of ATP production because these organelles are intimately involved in numerous processes operating within the cell, including calcium homeostasis, generation of free radical species (ROS), steroid synthesis, apoptosis, and participate in cell signaling pathways [18]. The direction of the mitochondrial membrane potential (negative internal) has important implications as it elicits the thermodynamic force supporting the accumulation of metal cations, in particular the calcium (Ca²⁺), in the mitochondria [19]. Mitochondrial Ca²⁺ homeostasis undertakes a key role in cellular bioenergetics and signaling [20]. Ca²⁺ passage across the outer mitochondrial membrane (OMM) is mediated by the VDAC channel, whose different selectivity for cations or anions is voltage-dependent [21]. At low potentials (10 mV), the VDAC channel is highly permeable to anions and able to maintain low Ca²⁺ flux. Conversely, increases in the membrane potential (20-30 mV) result in the conformational change that allows a 4- to 10-fold increase in Ca²⁺ influx [22]. In comparison, the inner mitochondrial membrane (IMM) has considerable Ca²⁺ permeability: the mitochondrial calcium uniporter (MCU) contributes to the potential-dependent Ca²⁺ influx into the mitochondrial matrix while the mitochondrial Na⁺/Ca²⁺ exchanger (NCLX) is one of the main units involved in Ca²⁺ extrusion [23]. In general, cytosolic calcium uptake by mitochondria will occur only if they are exposed to elevated Ca²⁺ concentrations [24,25]. Within the cell, however, Ca²⁺ is compartmentalized and the average resting cytosolic concentration is remarkably low [26–28]. One of the main stores of cellular calcium is the endoplasmic reticulum (ER), which contributes to orchestrating cellular Ca²⁺ homeostasis through its interaction with mitochondria [29]. Notably, Ca²⁺ uptake in mitochondria probably occurs only at proximity sites between the ER and

mitochondria [20]. Neuronal mitochondria, unlike those in non-neuronal cells, have a considerably lower threshold for Ca^{2+} uptake. In addition, ER-mitochondria contacts are critical for Ca^{2+} uptake in dendritic mitochondria but not in axonic mitochondria [30]. This property of axonal mitochondria is due to the presence of the brain-specific uniporter, MICU3, which unlocks axons from the constraint of relying on intracellular Ca^{2+} storage. In the absence of MICU3, synaptic function is impaired [31]. Mitochondrial calcium signaling in neurons regulates metabolism and energy production, which are crucial for neurotransmission and sustaining synaptic plasticity [32]. In addition, mitochondrial Ca^{2+} also drives the production of reactive oxygen species (ROS) [33]. Mitochondria are the primary sources of ROS in cells and actively participate in cellular redox regulation and ROS signaling [34]. ROS, in the form of superoxide, are natural byproducts of normal mitochondrial activity, naturally converted to H_2O_2 , in turn scavenged, by the enzyme catalase, into water [34]. Under normal conditions, through the generation of ROS and redox signaling, mitochondria can control cell metabolism and physiology, as well as inflammatory response, immune function, autophagy, and stress response [35–37]. Indeed, ROS, and in particular hydrogen peroxide, at low concentrations, act as important signaling molecules in the cell, activating several protein kinases, such as PKA, PKC, PI3K, and p38 [38]. Moreover, in immune cells, mitochondrial metabolites and ROS finely regulate signaling pathways and cell fate, orchestrating the immune response [39]. The immune system comprises a diverse family of cells with multiple roles during homeostasis and inflammation, capable of using distinct metabolic programs to undertake their functions. For example, during the immune response, effector T cells promote aerobic glycolysis while, in contrast, memory T cells and regulatory T cells promote fatty acid oxidation [40]. Particularly, mitochondria can modulate the metabolic and physiological states of different types of immune cells [41] and stimulate the innate immune signaling cascade that can intensify inflammation following cytotoxic stimuli or microbial infection [42]. For example, the innate immune receptor NLRX1, a member of the Nod-like Receptor (NLR) family, is located in mitochondria and undertakes an important role in maintaining cellular homeostasis following acute mitochondrial injury [43,44]. In addition, it has recently been discovered that mitochondria play a central role in initiating and regulating the NLRP3 (nucleotide-binding domain, leucine-rich-repeat containing family, pyrin domain-containing 3) inflammasome [45]. This multiprotein complex, activated upon infection or cellular stress, leads to the secretion of proinflammatory cytokines such as interleukin- 1β (IL- 1β) and IL-18 that trigger an inflammatory form of cell death called pyroptosis [46,47]. Although the mechanisms of NLRP3 inflammasome activation are still debated, it is widely believed that changes in the mitochondrial membrane potential, permeabilization of the outer mitochondrial membrane, and increased formation of mitochondrial ROS are crucial factors in inducing the cytosolic translocation of mitochondrial molecules, such as cardiolipin and mitochondrial DNA, which are capable of activating the inflammasome [45]. Indeed, the overproduction of ROS and dysregulation of the redox signaling system results in oxidative stress that can lead to mitochondrial damage, induce mitochondrial DNA mutations, damage the respiratory chain, alter membrane permeability, and affect the Ca^{2+} homeostasis and mitochondrial defense systems [48]. Accumulating evidence suggests that oxidative stress, and mitochondrial injury can result in cellular DNA damage and degradation of proteins and lipids as well involved in the pathogenesis of neurodegenerative diseases [49,50]. Nevertheless, cells have an accurate endogenous antioxidant defense system that can maintain cellular redox homeostasis between ROS production and elimination that ensure normal cellular signaling and redox regulation [51]. The nuclear factor erythroid 2–related factor 2 (Nrf2) is an emerging therapeutic target since it is involved in cellular resistance to oxidants. In detail, Nrf2 controls basal expression of genes coding for enzymes and proteins involved in antioxidant and detoxifying action, repair and removal of damaged proteins and organelles, inflammatory response, and mitochondrial bioenergetics [52,53]. Additionally, malfunctioning mitochondria can be selectively removed through a conserved cellular recycling process known as mitochondrial autophagy or mitophagy. Efficient elimination of damaged mitochondria prevents activation of cell death pathways, protects against ROS overproduction, and maintains efficient ATP production [54]. Damaged mitochondria are swallowed into autophagic vesicles that subsequently transport them to lysosomes for destruction.

Mitophagy is a strictly regulated process, modulated by mitochondrial fission and fusion proteins, BCL-2 (B-cell lymphoma 2) family proteins [55], and the PINK1/Parkin pathway [56]. As all other defense mechanisms fail, the neuron can orchestrate its self-destruction by activating an intrinsic suicide program otherwise known as apoptosis [57]. The underlying mechanisms of apoptosis are very sophisticated and engage an energy-dependent cascade of molecular events. In addition, it can follow different molecular pathways, one of which, known as the intrinsic pathway, involves the mitochondria [58]. Indeed, these organelles represent the site where antiapoptotic and proapoptotic proteins interact and the origin of signals that initiate the activation of caspases, the cysteine proteases capable of cleaving many cellular substrates to disrupt cellular contents [59].

It is therefore understood that mitochondrial integrity and homeostasis are prerequisites for proper cellular functioning, most notably for neurons, which are polarized, complex cells with high energy demand [60]. Not surprisingly, neurons have the highest content of mitochondria compared to other cell populations. Mitochondrial functionality is essential for ensuring membrane excitability and performing the complex neurotransmission and plasticity processes. First, mitochondria provide the energy needed to undertake a wide range of neuronal functions: the maintenance of resting membrane potential, the restoration of ionic balance after depolarization, the cycling of synaptic vesicles, as well as the transport of proteins and organelles from the soma to distal sites. Interestingly, mitochondria in axons and dendrites have different morphologies, small and sparsely distributed in the former and elongated and densely distributed in the latter. In addition, axonal and dendritic mitochondria differ in movement, metabolism, and responses to neuronal activity [61]. Second, several lines of evidence support the role of mitochondria in the mobilization and recycling of synaptic vesicles [62]. Neurotransmission is underpinned by endocytosis and the local filling of synaptic vesicles in the presynaptic terminal [63]. Third, mitochondria support synaptic activity through cytosolic calcium reabsorption, a critical buffering mechanism for establishing and maintaining synaptic activity and preventing neuronal toxicity and excitotoxicity. Nevertheless, mitochondrial calcium buffering appears necessary at the synapse even when the neuron is at rest: synaptic terminals lacking mitochondria show a higher frequency of spontaneous release of neurotransmitter-containing vesicles [64]. Overall, the importance of mitochondria in neurons is unequivocal, and it is not unexpected that mitochondrial dysfunction has emerged as a critical factor in a plethora of conditions, from impaired neuronal development to various neurodegenerative diseases.

Role of Mitochondria in Degenerative Disease

A great deal of evidence supports the role of mitochondrial dysfunction in degenerative diseases [65] diseases caused by mitochondrial alterations often show a neurodegenerative component involving the nervous system and, similarly, mitochondrial defects are frequently observed in tissue samples taken from patients with a neurodegenerative disorder. This evidence found a common goal in the high-energy requirements for all biological processes. The continuous increase in energy demand, mainly due to excess food consumed daily, the constant increase in energy required for thermoregulation, and the increase in energy needed to counteract the environmental toxicity caused by human them self, require an overwork of the mitochondria resulting in impaired bioenergy efficiency [66,67]. It was demonstrated that the cells exposed to an opulent nutrient environment are inclined to have their mitochondria in a fragmented state. Moreover, mitochondria observed in cells below malnourishment are apt to remain for a longer time in the associated state [68,69]. This is evidence that mitochondria can change their architecture and therefore their bioenergy capacity according to external events. A degenerative disease is defined as a type of un-physiological condition whose origins in a tissue or organ worsen over time. Energy failure was linked to degenerative processes as well as cancer, aging, neuroendocrine disease, neurodegenerative disease, and inflammatory diseases. In agreement, a great deal of evidence supports the involvement of mitochondria in neurodegenerative particularly in PD [70–74]. The story of MPTP toxin first highlighted the role of mitochondrial complex I dysfunction and neurodegeneration in PD [1]. In association with other more used toxins as well as rotenone and Paraquat, MPTP offered a new

scenario to define the effective role of mitochondrial bioenergy in neurodegeneration [75]. Indeed, more than five thousand manuscripts dealing with the association between Parkinson's disease and mitochondrial alteration can be found on Pubmed. In addition, due to studies on PD, particularly genetic Parkinsonism, all mitochondrial dysfunction leading to cell death has been well defined [76]. PINK1 gene mutation, responsible for an early onset Parkinsonism, is an example [77]. This gene codifies for the mitochondrial protein phosphatase and tensin homolog serine/threonine-protein kinase 1 (PTEN-induced kinase 1) [78]. PTEN- protein can protect the cells against oxidative stress, proton chain dysfunction, and bioenergy failure [77,79] Silvestri et al., 2005). The PINK1 gene has been also identified, the first, as an oncogene with tumor suppressor properties [78,80,81]. Additionally, PINK1 protective role is observed in many disorders characterized by progressive inflammation and neurodegeneration, such as Alzheimer's disease, multiple sclerosis, amyotrophic lateral sclerosis, and HD [78]. In physiological conditions, PINK1 is translocated inside the mitochondria in its mature isoform with the scopes to withstand the activity of the mitochondrial chain and to produce (at the level of complex I) the molecules of ATP showing the maximal bioenergetics efficiency. Moreover, PINK1 is located, also, in the inner mitochondrial membrane and can interact with the chaperone TRAP1 (recognized also, as an interactor of the type 1 tumor necrosis factor receptor), to maintain important bioenergetics and proteostatic functions [78,82]. Clivate PINK1 can interact with other chaperon proteins and when it is located in the cytosol can activate the m-Tork/Atk pathway. Besides, PINK1 can mediate the phosphorylation of another important gene for PD: Parkin. The coupled action of PINK1 and Parkin may induce mitochondrial fusion with the scope to cause the elimination of dysfunctional mitochondria. PINK1 is also involved in the formation of an autophagosome complex by the activation of beclin protein and may regulate the apoptotic process [78]. The role of the PINK1 gene in PD was well investigated by the use of animal models and cellular culture by human fibroblast [83–88]. These studies have confirmed the role of bioenergetics efficiency in the maintenance of health state or the progression of neurodegeneration. The absence of PINK1 results in low bioenergetic efficiency and programmed cell death after each minor stress [87,89]. It is very interesting to note that PINK1 has not only a key role in degeneration in general, in oncological degenerative processes, and neurodegenerative PD, but also neurodegeneration found in HD. PD and HD are two different neurological diseases involving the central nervous system. The symptomatology of both is quite similar (cognitive impairment, limb inflexibility, and problems in walking or talking), but while PD results from a combination of genetic and environmental factors, HD is only an inherited genetic disease. Both pathologies have a common denominator: the loss of bioenergetics efficiency [78,90]. HD is an incurable degenerative disorder caused by a mutation in the huntingtin gene where the CAG sequence is excessively repeated. This mutation alters numerous cellular processes and leads the cell to apoptosis. One important alteration is caused by the impairment of mitochondrial metabolism. In a study conducted on the fly model was found the formation of abnormal ring-shaped mitochondria; this particular shape was previously identified in mitophagy-blocked cells in which PINK1 overexpression was able to rescue the regular shape and function of mitochondria. PINK1 over-expression was able to improve bioenergetics efficiency (increasing ATP levels) and rescue neuronal integrity in the adult drosophila model of HD [91]. HD is a degenerative pathology caused by pathological expansion of CAG repeats in the Huntington gene codifying for the Huntingtin protein. The gene is located on chromosome number 4 and is characterized by a high level of polymorphisms. Unlike PD, HD has an age of onset of around 35-44 years and an estimated post-onset life span of 15/18 years; and is characterized by advanced motor disability including chorea [92]. Many pieces of evidence suggest that the mutation may cause alteration in mitochondrial trafficking, increase in oxidative stress, dyshomeostasis in intracellular calcium content, alteration in bioenergetics, and alteration in a respiratory mitochondrial chain [93–96]. HD, PD, and Alzheimer's diseases are three-neurodegenerative diseases that have 37 common genes and about 40 % of whose product acts at the mitochondrial level [97]. These neurodegenerative diseases are coupled to a physiological, but equally degenerative process called aging or senescence that starts at mitochondrial levels and results in reduced bioenergetics efficiency [98]. Cellular senescence is characterized by heavy changes in cellular metabolism and by an increase

in pyruvate utilization that may produce differences in phosphorylation state increasing the activity, of the mitochondrial pyruvate dehydrogenase complex; and the increase of ROS production [99,100]. These features may lead to an impairment of cellular function that induces degeneration equal to cancer or neurodegenerative processes [101]. Moreover, recent data have demonstrated that key oncogenes and tumor suppressors modulate mitochondrial metabolism and dynamics. Indeed, different types of cancer result in more or less sensitivity to the modulation of mitochondrial function in the function of the lesion caused by the tumor [102]. Therefore, mitochondria play a cardinal role in many degenerative processes and it is only in animal models, even before humans, that they can make us understand their importance.

Mitochondria Bioenergy in Parkinson's Disease, Huntington Disease Rodents Animal Models

In PD and HD are both neurodegenerative diseases with multiple mitochondria bioenergy alterations related to metabolism oxidative stress, dynamics biogenesis transport, and mitophagy. Since there is a close relationship between neurodegeneration and mitochondria bioenergy, one might presume that mitochondria homeostasis changes, with the release of calcium and NO as well as reactive oxygen species (ROS), will affect the unfolded protein response modulating specific signalling molecules and reprogramming mitochondria bioenergy. The mice models of PD e HD provide a valuable tool to define the role of mitochondria bioenergy in pathogenic mechanisms in these diseases.

Parkinson Disease

PD animal models are associated with multiple mitochondrial defects [103–106]. The current view is that abnormalities in more related mitochondrial factions such as membrane potential, energy production, disruption of mitochondrial-ER Ca^{2+} homeostasis, inhibition of mitochondrial dynamics, and induced mitochondrial pro-apoptotic protein cytochrome c release led to neurodegeneration [107–109]. In fact, the neurotoxin MPTP, rotenone, and paraquat block mitochondrial bioenergetics in dopaminergic neurons and induce Parkinsonian syndrome [110–116]. However, it is important to consider that overexpression of α -synuclein or agent that generates stress or cytosolic acidification shows translocation of α -synuclein into the mitochondria or in the mitochondrial membrane [117–119]. α -synuclein is a presynaptic neuronal protein that is linked to familial and idiopathic PD [120] both over-expression or loss-of-function of SNCA gene contribute to disease manifestation [121] according to the “ α -synuclein cascade hypothesis” [122]. Experimental studies in A53T mutant mice, a transgenic animal model that expresses human α - synuclein, develop mitochondrial DNA damage and degeneration with an apoptotic-like death of neocortical, brainstem, and motor neurons [123]. In the same animal model, the mitochondrial complex IV activity was reduced significantly in the spinal cord [123]. Additionally, in vivo human α -synuclein expression is associated with a decrease of Drp1 (Dynamin-related protein 1), the major player in the regulation of mitochondrial dynamics and plays a critical role in the maintenance of their proper function [124]. The dysfunction of Drp1 in the mitochondria is associated with enlarged neuronal mitochondria [124].

Other protein that facilitate mitochondrial fusion are decreased in these models, Mfn1 (Mitofusin1) [124], which correlates with the mitochondria bioenergy dynamic changes. Previous studies in A53T mice suggest that α -synuclein distress the mitochondrial morphology and reduces both Mfn1 and Mfn2 in an age-dependent manner [125]. In vivo study in midbrain dopaminergic neurons suggested that α -synuclein predominantly accumulates in the central mitochondrial membrane and interacts with the complex I resulting in the impaired activity of the mitochondrial electron transport chain [126]. Consistent with these findings other experimental analyses show that after post-inoculation of human α -synuclein in rats, lends its accumulation in striatal dopaminergic terminals from the SNpc and early synapse loss [127]. To explain this early synapse loss a proteomic analysis using a real-time cell metabolic method and isolated synaptosomes was used to investigate functional and molecular mechanisms. Upon injection, in isolated striatal synapses was found multiple dysfunctions of mitochondrial bioenergetics and morphology were with the upregulation

of PRKAG2 and TTR, respectively sensor protein of the cell energy status and marker of oxidative stress [127]. Moreover, ultrastructural examination of subsequent human α -synuclein accumulation shows an altered expression of Rab5 endocytic and LC3 autophagic proteins that potentially reflect an accumulation of autophagic vesicles [127]. This study has allowed the evaluation of an interesting aspect such as the contribution of oxidative stress and the mitochondria bioenergy alteration in both dopaminergic neuron death and striatal neurons, which could be responsible together for the induction of Parkinsonian syndrome. The neurons are high- energy consumers and employ most of the energy at the level of the synapse to preserve and restore ionic gradients, and for the uptake and recycling of neurotransmitters [128]. Various mouse lines expressing a different type of α -synuclein present impaired dopamine neurotransmission and striatal synaptic plasticity [129]. In rodents, the injection of α -synuclein with an adeno-associated viral vector blocks the induction of long-term potentiation (LTP) long-term depression (LTD) that is normally expressed in medium spine neuron (SPNs) [116,130–132] that are associated to early memory and motor alterations. There is a relatively large body of evidence that α -synuclein misfolding and aggregation lead to mitochondrial stress that appears to be related to the dysfunction of synaptic plasticity. Another interesting aspect is that α -synuclein overexpression promotes by the endoplasmic reticulum (ER) Ca^{2+} transfer in the mitochondria, while its silencing impairs mitochondrial function by loosening the ER-mitochondria interface [133].

Although, the precise mechanism by which α -synuclein accomplished pathological characteristics and specific cell death remain to be delineated more clearly. However, it is important to note that α -synuclein plays a role as pro-apoptotic in different neuronal cells [134]. The wild-type α -synuclein can defend neurons from apoptosis by inhibition of caspase-3 and the mutant α -synuclein loses this activity [134]. Caspases-3 exerts its actions trigger general damage and degeneration, aggregates in synapses, and persists in neurons without causing acute cell death [135–137]. Furthermore, the discovery of many genes related directly or indirectly with mitochondria to PD underlines the implication of mitochondria bioenergy in its pathogenesis features. For instance, genes linked to early-onset recessive PD include Parkin [84], PINK1 [77] and DJ-1 [138], these genes have been powerfully implicated in the morphology, damaged and mitochondria degradation via mitophagy [139], involved in the mitochondrial activity and quality control mechanisms [78,140–143]. Parkin encodes a protein localised in the cytoplasm that contains an N-terminal ubiquitin-like domain with a function as E3 ubiquitin-protein ligase [144–146]. Parkin knockout (KO) mice show alteration of the levels of different proteins involved in detoxification, stress-related chaperones, without neuronal degeneration [147]. Parkin has neuroprotective effects through the regulation of different cellular processes or pathways such as mitochondrial swelling and cytochrome c release [148–150]. Normally, Parkin resides in the cytoplasm but can translocate to depolarized or damaged mitochondria to mediate their removal by mitophagy in cooperation with PINK1 and potentially other factors [151]. In a model mouse of Parkin KO was reported to cause a decrease of subunits of complexes I and IV with redaction of peroxide reductases. In addition, the serum presents a redaction of antioxidant capacity and increased protein of lipid peroxidation [152]. Other studies in Parkin-deficient mice show an increase in the content of dopamine in the striatum and consequently redaction of the excitability of striatal SPNs [153]. Deficits in glutamate neurotransmission and amphetamine-induced dopamine release were also observed in other parkin mutant mice with an increase in the metabolism of dopamine (MAO) [154]. Functional analysis of striatal SPNs showed an impairment of bidirectional corticostriatal synaptic plasticity, with the loss of the LTD and LTP in Parkin KO mice, while synaptic plasticity was not altered in the hippocampus of these animals [155]. The dopaminergic defect [153,154] may explain a selectively enhanced sensitivity to striatal group II metabotropic glutamate receptor in cortically-evoked excitatory postsynaptic potentials recorded from SPNs, this reinforcing effect is an adaptive change [79]. Recent evidence in Parkin KO rats offers the suggestion that lack of Parkin is also necessary for the maintenance of postsynaptic endocytosis of AMPARs, even decreased expression of the postsynaptic protein Homer1, which is essential for coupling AMPA receptor endocytic zones with the postsynaptic density [156]. On the other hand, changes to the numbers or function of ER-mitochondrial contact sites may also affect mitochondrial

calcium homeostasis regulated by Parkin [157], calcium uptake into the mitochondrial matrix results in enhanced respiratory function, tuning synaptic activity [158,159]. Recent work showed that conditional knockout of Parkin in adult animals expresses the progressive loss of dopamine neurons. Moreover, overexpression of PGC-1 α leads to the selective loss of DA neurons in the substantia nigra [160].

One more gene linked to early-onset recessive PD is PINK1 which encodes a protein with a serine/threonine kinase catalytic domain cytosolic or mitochondrial-associated [78]. Mice models of PINK KO exhibited significant functional impairment of synaptic plasticity and mitochondria morphology, without motor deficits or dopaminergic neuronal loss [84]. Consistent with these findings, PINK KO mice models generated with the silencing of the PINK1 gene did not develop dopaminergic neurodegeneration [161]. PINK1 heterozygous KO mouse show selective impairment of LTP with a normal expression of LTD [162], nevertheless, low doses of rotenone has been sufficient to induce severe alterations of the corticostriatal LTP and LTD [85]. This led to the proposal that the PINK1 homozygous KO model represents a good model to study the effect of gene- environment interaction. While PINK1 KO rats show mitochondrial alteration, locomotor deficits, and α -synuclein aggregates in several brain regions such as the cerebral cortex, dorsal striatum, and degeneration of substantia nigra [163–166]. However, this model presents clear symptomatic deficits that occur at 9 months old and at 4 months are asymptomatic [165]. In the same model, using magnetic resonance spectroscopy, the mitochondrial metabolomic alterations arise in the cortex and striatum, during the asymptomatic period, which coincides with the metabolic alterations [165]. Functional, bioenergetics experiments revealed that mitochondrial alteration in PINK1 KO rats is due to impaired complex I respiration carrying a dysfunction in ATP synthase and reduced substrate oxidation [164]. New scientific research performed in animal models with the deletion of PINK1 mice provides an indication that lack of PINK1 results in impaired synaptic plasticity caspase-mediated [86]. Caspase-3 presents an additional role in neuronal processes, including the regulation of synaptic function, and pruning [136,167,168]. Previous studies in PINK1 KO show a loss of LTP and LTD with alteration on dopamine release [84]. Indeed, low activation of the caspase-3 is critical to restoring cortical-striatal LTD [86] although chronic activation is involved in degenerative processes [168]. In PINK1 KO mice analysis with electron microscopic and functional studies in the striatum revealed significantly enlarged mitochondria shape and impaired activity [169]. Indeed, functional examination showed impaired mitochondrial respiration and aconitase activity in the striatum but not in the cerebral cortex [169]. Additional independent studies in PINK1 KO mice show a decreased dopamine release in the dorsal striatum in an age-dependent manner with impairment of basal mitochondria respiration [170].

DJ-1 gene mutations cause autosomal recessive early-onset PD. DJ1 encodes a protein of the superfamily which belongs to the ThiJ/PfpI-like. normal conditions, DJ-1 is confined throughout then cytoplasm of neurons with a small amount localised to the mitochondrial matrix and intermembrane space [171] indicating a role in the balance in mitochondrial physiology [19]. DJ-1 KO mice studies fail to express PD features such as substantia nigra degeneration or formation of protein inclusions similar to PINK1 and Parkin KO mice [141]. Recent experiments in DJ-1 KO mice show increasing facilitation of calcium influx into the neuron during its activity, creating basal mitochondrial oxidant stress [172,173]. Functional analysis in isolated mitochondria shows increased ROS and decreased aconitase activity in DJ-1 KO mice [180]. Additionally, DJ-1 gene deletion reveals a deficit in scavenging because the loss DJ-1 pathway loses atypical peroxiredoxin-like activity [174]. In contrast, in an independent study of DJ-1 KO mice present an increase in mitochondrial respiration-dependent H₂O₂ consumption and increase mitochondrial Trx activity, total glutathione (GSH and GSSG respectively) levels, mitochondrial glutaredoxin (GRX) activity and a decrease in mitochondrial glutathione reductase (GR) activity [175]. Furthermore, new research of the semi-quantitative measurement of cerebral metabolites in DJ-1 knockout mice detect significantly increased glutathione (GSH) level and GSH/glutamate (Glu) ratio in prefrontal cortex [176] (Table 1). It is important to note that the GSH system is the more important antioxidant system in ROS detoxification in the brain [177–179]. Accumulated scientific information allowed the hypothesise that the increased sensitivity

to oxidative stress in DJ-1 KO mice and dopaminergic neuronal cells is related to a decrease in ROS scavenging arising from deteriorated peroxidase-like scavenging with a deficient Nrf2 transcriptional factors and increased mitochondrial dysfunction due to complex I deficiency [180–184]. Although, DJ-1KO mice had normal corticostriatal LTP but the LTD was absent [185]. Overall, the data from animal models provide a framework that suggests that genes linked to early-onset recessive PD are important for maintaining normal mitochondria bioenergy function. Gradually, the mutation protein described above related to the mitochondrial bioenergy activates the response to mitigate the mitochondrial alteration. Indeed, genetic inactivation PINK1/Parkin/DJ-1 with a triple KO mouse exhibit abnormalities in mitochondrial pathway and morphology or activity without PD-related phenotype [85] (Table 1).

Huntington Disease

For HD several mouse lines of transgenic and knock-in mice have been engineered to address specific pathological characteristics [186]. Accumulation of scientific information implicates that gain and/or loss of function mutant HTT leads to impaired mitochondrial bioenergy with alteration of oxidative stress, dysfunction of mitochondrial trafficking, and mitochondrial calcium dyshomeostasis [187]. In fact, malonate and 3-nitropropionic acid (3-NPA) are considered potent neurotoxins and are used to induce experimental pharmacological models of HD in rodents [188]. These oldest models provided the first piece of evidence that mitochondria bioenergy, targeting the electron transport chain, is involved in the pathophysiology of HD. However, degenerating mitochondria have been identified in different areas, brain, liver, and muscle in genetic mouse models of HD [189–191] (Table 1).

The R6/1 and R6/2 both strains express a single copy of a human genomic fragment that contains 116 and 144 CAG repeat HTT under the control of the human HTT promoter [192]. These mice express relatively rapid onset and progression of symptoms that include motor defects and neurodegeneration. Another major contribution to the research was the generation of knockin mice models where CAG is repeated extensively (CAG94 and CAG140), compared to the human transgene, for developing HD-associated phenotypes [186]. The R6/2 model mice have been the most widely utilised because the disease starts earlier with a rapid progression compared to the YAC, BAC, and other knock-in lines [193]. Transgenic animal models expressing the amino (N)-terminal fragment of the mutant form of HTT (R6/2) show an increase of 8-hydroxy-2-deoxyguanosine OH(8)dG in the late stages of the illness [194], thus, oxidative stress occurs in the striatum before the onset of motor symptoms. Biochemical analysis performed in the striatum of R6/2 mice at 12 weeks shows a significant reduction of mitochondrial complex IV activities and a decrease in aconitase in the cerebral cortex [195]. In accordance with these data, new scientific research using synaptosomes isolated from R6/2 mice shows a decrease in mitochondrial mass with increased ROS production and antioxidant levels in the striatum compared to the cortex [196] indicating oxidative stress. Additionally, in the same model through depolarization conditions the oxygen consumption rates in synaptosomal were significantly amplified, which was accompanied by a clear increase of mitochondrial proton leak of the striatal synaptosomes [196], indicating synaptic mitochondrial stress. Indeed, synaptic dysfunction occurs in various mouse models of HD, appears to involve, with dysfunction of LTD, and displays a physiological LTP but lost synaptic depotentiation. These have been directly connected with the onset of cognitive deficits in HD models [197–201]. Using the brain slices from R6/1 mice, at different ages, presents a significant increase of Ca^{2+} content after glutamate stimulation, such alterations impact in mitochondrial dysfunction with a decrease in NAD(P)H fluorescence and loss in Mitochondrial membrane potential ($\Delta\Psi^m$) [202]. Several groups characterise the reduction of N-acetyl aspartate in R6/2 mice, similar to symptomatic HD patients [203–207] fluctuations in some metabolite suggest the impairment in cellular metabolism and mitochondrial bioenergy [208]. Another interesting contribution to assessing the deficits of mitochondrial function and redox deregulation is the experimental data performed with PET in YAC128 transgenic mice [209]. PET analysis displays a specific accumulation of $[^{64}\text{Cu}]\text{-ATSM}$ in the striatum with concomitant alteration of mitochondrial respiration and ATP production, and increased complex II

and III activities. In turn, an increase in mitochondrial H_2O_2 levels in YAC128 mice and defects in Ca^{2+} handling [209] support an early increased striatal susceptibility of mitochondrial. Furthermore, functional assays revealed impairment of mitochondrial respiratory capacity in the striatum and cortex of R6/1 mice. It is important to note that N-acetylcysteine administration delayed the onset and progression of motor deficits in R6/1 mice [210] which may reduce both excitotoxicity and oxidative stress in the striatum. Recent work established that voluntary wheel running reduces hindlimb clasping in the R6/1 mouse model. Chronic exercise in the R6/1 showed the clasping phenotype with normal mitochondrial respiration in the cortex and striatum, suggesting mitochondrial dysfunction is not necessary for the progression of symptoms [211]. At the molecular level, different studies pointed to considering the contribution of mitochondria in their role in apoptotic cell death processes with an elevated caspase activity in HD mice models [189,212]. HTT has been shown to be involved in vitro for caspases-1,2,3 and [213–215]. In fact, immunostaining analysis of YAC72 mice displays an increase of caspase-2 in the SPNs in the striatum, with concomitantly decreased levels of a brain-derived neurotrophic factor in the cortex and striatum at 3 months [213], demonstrating that caspase-2 participates selective on the neurodegeneration of SNPs in the striatum. In YAC128 model mice, to contrast the cognitive dysfunction such as performance on the rotarod, swimming T-maze, the lacking caspase-2 produce a protection from the well-validated motor and cognitive features of HD [216]. Moreover, previous studies in transgenic mice expressing exon 1 of the human HTT demonstrate that intracerebroventricular administration of a caspase inhibitor 1 delays the disease progression of the disease [215] (Table 1).

In conclusion, while HD animal models have not yet provided definitive evidence whether or not mitochondria bioenergy is critically involved in htt-induced disease symptoms compared to PD animals models genes, mitochondrial bioenergy defects are nonetheless a major component for both disease progression. On the other hand, the creation of HD mouse models using different strain backgrounds and expressing only a portion of the htt protein leads to increased difficulty in understanding compelling findings that instead were obtained with the genetic models of PD.

Mitochondria Bioenergy in Parkinson's Disease, Huntington Disease, Human Evidences

Assessment of mitochondrial activity (or dysfunction) is not easy in CNS of living patients. However, analyzing peripheral tissues and fluids can offer a reliable measure. Albeit the core pathology in PD and HD is central, a number of substantial abnormalities result at the systemic or peripheral level. Peripheral blood mononucleate cells (PBMCs) are one of the most reliable “in vivo PD model”. PBMCs present several alterations in critical metabolic pathways and accumulate α -synuclein pathological forms, well recapitulating PD-related neuropathology [217,218]. In a recent work, PBMCs mitochondrial bioenergetics from PD patients was assessed by the Seahorse Bioscience technology, showing a peculiar pattern of mitochondrial respiration, including normal basal respiration, significant augmentation of the maximal respiratory capacity and spare respiratory capacity, and a tendency to higher ATP production. The increased spare respiratory capacity was found to follow the disease duration and the severity of motor disturbances, revealing some mitochondrial adaptations to the higher bioenergetics requirements occurring at later disease stages [219]. Similar, consistent findings of greater mitochondrial respiration were also observed in different cell lines obtained from PD patients, such as lymphoblasts (immortalized blood lymphocyte-derived cells) [220] and fibroblasts [221,222]. It is thus reasonable that, in PD patients, oppositely from animal models, the mitochondrial activity may increase in a compensatory manner. Indeed, the “nuclear factor erythroid 2-related factor 2” (Nrf2) pathway, a master regulator of the cellular defence and mitochondrial activity, can be overexpressed in PD patients’ PBMCs proportionally to the disease duration, suggesting a systemic defensive response to the PD clinical-pathological progression [218]. Otherwise, changes in respiratory activity could reflect defects in mitochondrial structures, metabolism, or respiratory proteins functioning [223]. Indeed, another study also found in PD patients’ PBMCs increased glycolysis and deficits in superoxide dismutase, together with a peculiar mitochondrial vulnerability in monocyte subpopulation [224]. Substantial evidence also arises from the assay of mitochondrial dysfunction biomarkers in PD patients’ fluids. There are metabolomic

studies performed in blood and cerebrospinal fluid (CSF) disclosing various abnormalities in metabolic pathways related to mitochondria (in alanine, branched-chain amino acids, fatty acids, and acylcarnitines levels; in steroidogenesis; in glutathione cycle) [225–227]. Likewise, the redox balance-related biomarker levels, such as uric acid [228–231] catalase and total glutathione [232], nonmercaptalbumin (oxidized form of albumin) [233], oxidized glutathione [218], oxidized DJ-1 [234], α -klotho [235], lactoperoxidase [236], and heme-oxygenase-1 [237] were altered in the same fluids. Genomic studies on peripheral blood showed the down-regulation of genes critical for mitochondrial functions (COX4I1, ATP5A1, and VDAC3) [238], while the analysis of blood-circulating extracellular vesicles demonstrated the reduction of mitochondrial components (i.e., ATP5A, NDUFS3, and SDHB) in PD patients [239]. Analysis of mitochondrial bioenergetics has also been performed in peripheral tissues of HD patients with some controversial findings depending on the matrix or the experimental technique. Indeed, mutant huntingtin is expressed out of the CNS as well, accounting for the substantial impairment in multiple cellular pathways related to mitochondria and redox balance [240]. It has been observed that skin fibroblast may show some energetic, respiratory, redox, and morphological abnormalities [241,242]. Likewise, several functional or structural mitochondrial defects have been found in HD patients-derived lymphoblasts [243] (Figure 1). Finally, increased oxidative damage, reduced antioxidant capacity, and mitochondrial abnormalities have been tracked even in HD patients' blood through different fluid markers [244].

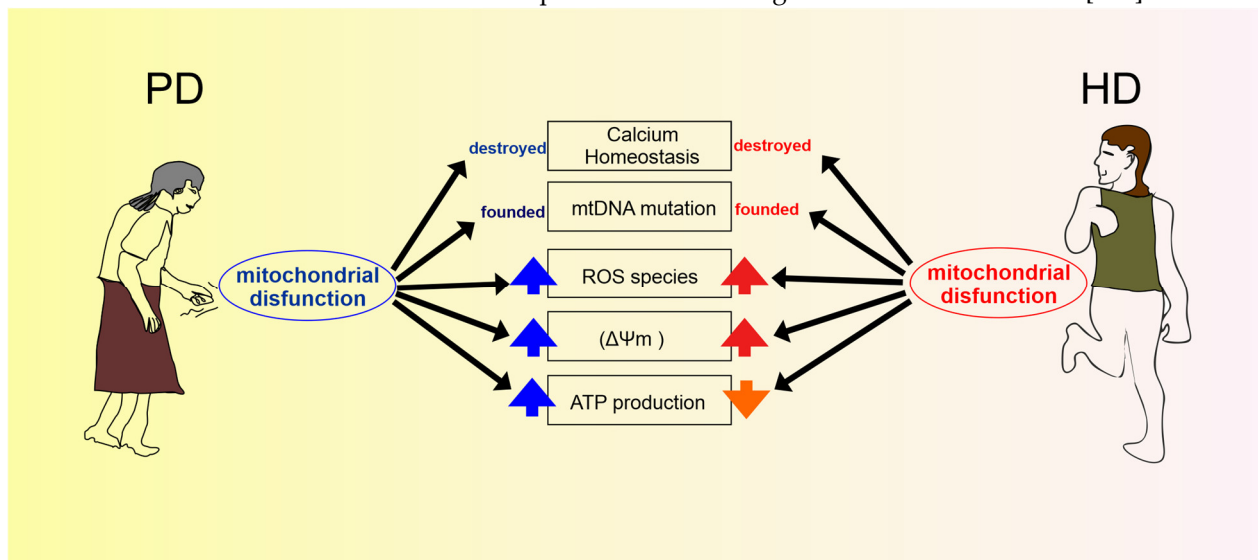


Figure 1. mitochondrial dysfunction in MP and HD. Characteristic features for both disease.

Discussion

Degenerative diseases show as a common point the mitochondrial impairment. Mitochondria represent the major source of bioenergy for the cell and, as a consequence, their putative failure leads to a lack of energy. Daily energy metabolism for a human and also for an organism is the sum of daily energy expenditure and daily energy intake. Daily Energy Expenditure may be divided into diverse workings: 1) energy spent on basal metabolism; 2) energy by thermic increment following food intake; 3) energy spent on thermoregulation; 4) energy spent during daily activities. In particular, energy metabolism is the process of generating energy (ATP) from nutrients, and mitochondria are the headmaster in the powerhouses of the cell. To produce energy in the form of ATP and GTP, all the cells, and in specific the neurons, devour glucose, amino acids, and fatty acids [245]. These nutrients are processed and transferred into the tricarboxylic acid (TCA) cycle, and electrons are stored in the reducing equivalents NADH and FADH₂, through iterative oxidations. NADH and FADH₂ represent the carrier molecule that withdraws electrons into the electron transport chain (ETC); protons flow down to generate ATP [246]. The capacity of mitochondria to supply at the request of ATP, defined as bioenergetics efficiency may change, during life for the effect of environmental stress, aging, or pathologies. During aging, for example, mitochondria go through

alterations in their capacity to produce ATP. This is due to the release of a great number of reactive oxygen species (ROS). ROS are able to increase spontaneous DNA mutations and can start the processes that lead to cancer [247,248]. Mitochondria from aging people show different features [249]; they swell while their numbers dwindle, unable to replace themselves as quickly in their dysfunctional state [250]. Failure in mitochondria is the starting phase of the neurodegenerative process [251]. It was demonstrated in both PD and HD that the presence of environmental stress can increase the production of oxidative species and also can modify the structure of protein and DNA inside mitochondria and its nucleio [252]. Usually, HD is considered a hyperkinetic disorder, despite the presence of hypokinetic features in the motor symptoms [253]. Conversely, PD is judged a hypokinetic disorder in which the resultant speech motion disease may be classified as hyperkinetic or hypokinetic dysarthria [254,255] (Figure 1). Both are defined as neurodegenerative disorders causing the gradual loss of neurons. In addition, both disorders result in a deficit at the level of the basal ganglia, with peculiar references to striatal [256] and hippocampal areas [257]. These areas are deputized to movement and cognitive ability; for this reason, it is not a surprise that both diseases can affect cognitive or thinking abilities and motor functions. Studies on rodent models of PD show the impairment in bioenergetics pathway and a block of function in mitochondrial complexes I and III. Also, in genetics in phenotypic models induced by toxin exposure, in the early stages of the disease as well as in the developmental stage [4,86,103,105,106,173]. While, study on animal models of HD, show an evident alteration in mitochondrial complexes II and III, and describe a reduction of bioenergetics efficiency that was described essentially in the early pathogenic mechanism [258]. The confirmation of this evidence comes from translational studies in man in which the association between mitochondrial deficit and biomarkers of PD and HD is shown [253]. Actually, there is no cure for both pathologies, and neither exists drugs to modify the development and gravity of the diseases. For all these reasons the knowledge of pathogenetic mechanisms and the similarities in the disease can help us to revise the traditional approach and can help in understanding new scenarios. New pharmacological approach considering mitochondria target agents could be used in the future to cure degenerative and in particular neurodegenerative pathologies that although different show so many common elements.

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