

Review Article

Electron Transport Disturbances and Neurodegeneration: From Albert Szent-Györgyi's Concept (Szeged) till Novel Approaches to Boost Mitochondrial Bioenergetics

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Impaired function of certain mitochondrial respiratory complexes has long been linked to the pathogenesis of chronic neurodegenerative disorders such as Parkinson's and Huntington's diseases. Furthermore, genetic alterations of mitochondrial genome or nuclear genes encoding proteins playing essential roles in maintaining proper mitochondrial function can lead to the development of severe systemic diseases associated with neurodegeneration and vacuolar myelinopathy. At present, all of these diseases lack effective disease modifying therapy. Following a brief commemoration of Professor Albert Szent-Györgyi, a Nobel Prize laureate who pioneered in the field of cellular respiration, antioxidant processes, and the roles of free radicals in health and disease, the present paper overviews the current knowledge on the involvement of mitochondrial dysfunction in central nervous system diseases associated with neurodegeneration including Parkinson's and Huntington's disease as well as mitochondrial encephalopathies. The review puts special focus on the involvement and the potential therapeutic relevance of peroxisome proliferator-activated receptor-gamma coactivator 1-alpha (PGC-1 α), a nuclear-encoded master regulator of mitochondrial biogenesis and antioxidant responses in these disorders, the transcriptional activation of which may hold novel therapeutic value as a more system-based approach aiming to restore mitochondrial functions in neurodegenerative processes.

1. The Man Amused by the Dance of Electrons

"The fuel of life is electron, or more exactly, the energy it takes over from photons in photosynthesis, and gives up gradually while flowing through the cellular machinery."

This imagination originates from Professor Albert Szent-Györgyi, a Hungarian physician and biochemist, former chair of the Department of Medical Chemistry and the Department of Organic Chemistry at the University of Szeged from 1930 and 1935, respectively, until the end of World War II in 1945. His early research activities in Groningen and later in Cambridge conducted on biological combustion, cellular respiration, and energy production of plants lead

to the discovery of a reducing substance called "hexuronic acid," a substance that is able to lose and regain hydrogen atoms and capable of protecting plants from "browning," an injury that he characterized as oxidative damage due to the excessive activity of an enzyme, peroxidase. This "antioxidant" substance was later proved by Szent-Györgyi to be equivalent with a potent antiscorbutic (antiscorvy) agent and was given the name ascorbic acid, currently widely known as vitamin C, which is most abundant in citrus fruits and paprika, an emblematic vegetable of Szeged. At this time, performing ongoing research in the field of biological respiration, Szent-Györgyi discovered and identified the catalysis of fumaric acid among other steps of the tricarboxylic acid cycle (also referred to as Szent-Györgyi-Krebs cycle, citric acid cycle), an essential component of cellular respiration

that provides reducing equivalents for terminal oxidation and thereby energy production from metabolic products of dietary macromolecules. “*For his discoveries in connection with the biological combustion processes, with special reference to vitamin C and the catalysis of fumaric acid,*” Albert Szent-Györgyi was awarded Nobel Prize in Physiology or Medicine in 1937. In addition to his pioneering work in muscle research—including the discovery of actin and myosin proteins and the mechanism of their joint function—as well as the discovery of vitamin P (flavanone), his subsequent research interests focused on the interactions of proteins and free radicals and their role in regulating cell division and cancer development, and he published a number of books and papers about his findings and scientific theories of bioenergetics and bioelectronics and their roles in health and disease.

Following the imaginations of our honored predecessor, this paper reviews the concepts on the role of impairments in mitochondrial respiration and subsequent excessive oxidation in degenerative central nervous system (CNS) disorders, with special attention to recent findings related to alterations in transcriptional regulation of mitochondrial biogenesis and bioenergetics, and their potential therapeutic relevance.

2. Mitochondrial Respiration: The Proper Function of a Dangerous System

Mitochondria are membrane-bound intracellular organelles evolutionary originating from the endosymbiosis of an ancient aerobic alpha-proteobacterium with an early eukaryotic host cell [1]. Harboring their own maternally inherited, double-stranded, circular genome (mtDNA), supplemented by the presence of several ancillary, structural, and regulatory proteins encoded by the nuclear DNA (nDNA), mitochondria host a number of molecular processes essential for cellular life and death. These include processes related to the production of biologically utilizable energy, adaptive thermogenesis via the uncoupling of energy production, as well as the regulation of cellular calcium homeostasis, cell-cycle, and programmed cell death.

Energy production in the mitochondria is performed through the coupled function of pyruvate dehydrogenase complex (PDC), β -oxidation (processes essential in glycolytic and ketogenic metabolism, resp.), the Szent-Györgyi–Krebs cycle, and the terminal oxidation and oxidative phosphorylation (OXPHOS). While PDC, β -oxidation, and the Szent-Györgyi–Krebs cycle take place within the mitochondrial matrix, terminal oxidation and OXPHOS are linked to the function of respiratory complexes I–V (electron transport chain, ETC) embedded in the inner mitochondrial membrane. The process of energy production has been extensively reviewed elsewhere [2, 3]. Briefly, glucose is catabolized in the cytosol to yield pyruvate through multiple enzymatic steps of the glycolysis, which is then translocated into the mitochondria and metabolized to acetyl-coenzyme A (acetyl-CoA) by PDC. On the other hand, fatty acids are oxidized during the β -oxidation to acetyl-CoA entirely within the mitochondria (or in case of longer-chain fatty acids,

initially within the peroxisomes). Mitochondrial acetyl-CoA subsequently enters the Szent-Györgyi–Krebs cycle to form reduced coenzyme NADH and succinate in multiple steps, which in turn provide electrons for respiratory complex I (NADH dehydrogenase) and complex II (succinate-ubiquinone oxidoreductase), respectively, using FMN and FAD as prosthetic groups, respectively. The electrons are then transported from both complexes via the mobile carrier coenzyme Q (ubiquinone) to complex III (ubiquinol-cytochrome *c* oxidoreductase) and flow through cytochrome *c* to reach complex IV (cytochrome *c* oxidase) to be oxidized by the final electron acceptor, oxygen. Notably, reducing equivalents produced during the glycolysis (in form of NADH) can also be translocated to the mitochondria via the malate/aspartate shuttle and the glycerol phosphate shuttle to provide NADH and FADH₂, respectively, which in turn, similarly to NADH and FADH₂ produced during β -oxidation, feed the ETC at complex I and coenzyme Q, respectively. Within the ETC, respiratory complexes are arranged in an electrochemical order, corresponding to their gradually increasing redox potential and electronegativity. The flow of electrons through the respiratory complexes provides energy used to pump out protons through complexes I, III, and IV (cytochrome *c* oxidase) to the intermembrane space. At the end of the downstream flow of electrons, molecular respiratory oxygen as the final electron acceptor is reduced by complex IV to form water molecule in a process known as terminal oxidation. The release of protons from the matrix develops a gradient of protons between the matrix and the intermembrane space also referred to as mitochondrial membrane potential (negative inside) as well as an electrochemical gradient (alkaline inside). Being impermeable to protons, the inner membrane works as a capacitor and an electric insulator. Therefore, the electrochemical drive to equalize the concentration of protons can be satisfied by the reentry of protons through respiratory complex V (H⁺-ATP synthase), the subsequent activation of which leads to the formation of ATP from ADP in a process called OXPHOS. The produced ATP represents a biologically available form of electrochemical energy, serving as the main energy-provider for eukaryotic cells (Mitchell’s chemiosmotic hypothesis) [4]. The energy stored in mitochondrial membrane potential (also known as “proton motive force”) can also be utilized to generate heat or to import calcium or proteins into the mitochondrion via uncoupling the transport of electrons from ATP production, which processes serve adaptive purposes. The proportion of dietary calories burnt within the mitochondrion and allocated to energy production is referred to as “coupling efficiency.”

In multicellular organisms, the ability to adaptively regulate and activate mitochondrial biogenesis and functions in response to a variety of conditions is essential to maintain energetic homeostasis and cellular viability. Several lines of evidence obtained in the past decade suggest that peroxisome proliferator-activated receptor-gamma (PPAR γ) coactivator 1-alpha (PGC-1 α), a nuclear-encoded coactivator of a wide range of transcriptional factors, plays a key role in the transcriptional cascade of such adaptive processes. PGC-1 α -mediated coactivation of genes such as nuclear respiratory

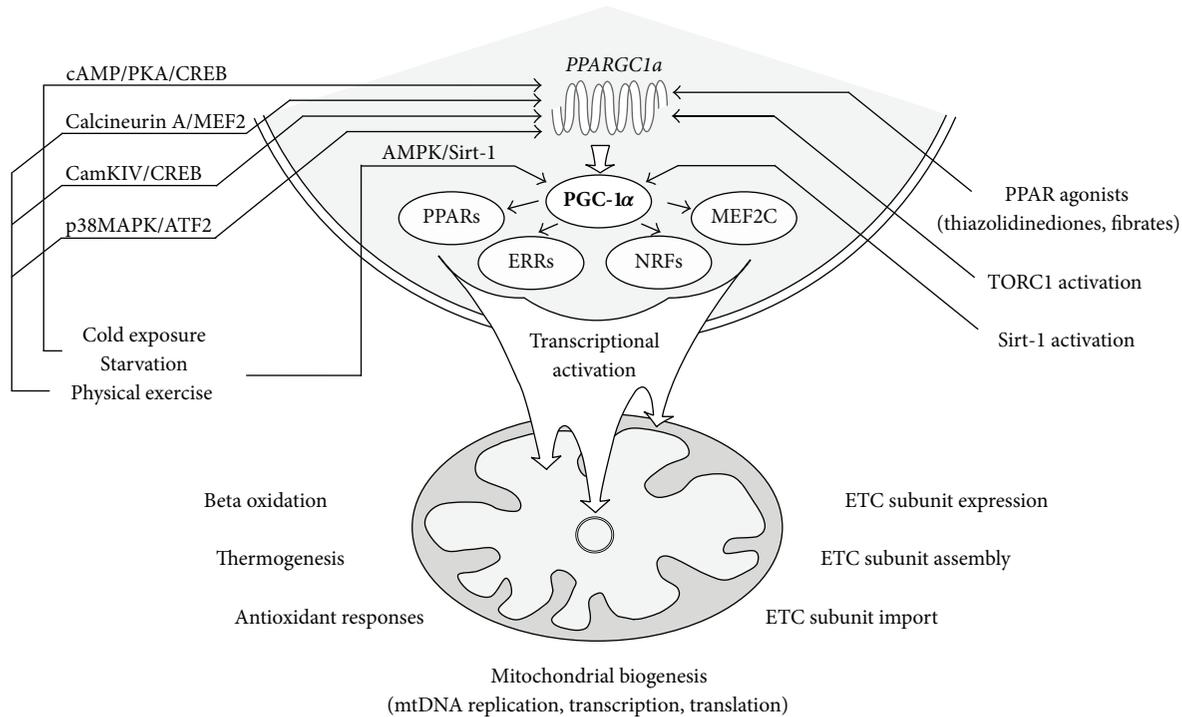


FIGURE 1: The PGC-1 α cascade. Transcriptional upregulation or posttranslational activation of PGC-1 α due to fasting, physical exercise, cold exposure, or pharmacological manipulations leads to the transcriptional activation of several nuclear-encoded proteins involved in mitochondrial functioning at multiple levels, including mitochondrial biogenesis, adaptive metabolism, antioxidant responses, and proper ETC assembly/import.

factor 1 and 2 (NRF-1, -2), PPARs, estrogen-related receptors (ERRs), and myocyte-specific enhancer factor 2C (MEF2C) leads to an increased expression of a wide range of proteins involved in mitochondrial transcription, replication, and the import and assembly of a number of nuclear-encoded respiratory complex subunits; furthermore, it boosts OXPHOS and thermoregulation in a tissue-dependent manner, enhances gluconeogenesis and fatty acid oxidation [5], and increase oxidative stress defense [6] (Figure 1). The inducing effect of *physical exercise* (mediated by calcineurin A-linked MEF2 activity, calcium/calmodulin-dependent protein kinase IV- (CaMKIV-) linked cyclic AMP (cAMP) response element-binding protein (CREB) activity, and a p38 mitogen-activated protein kinase- (MAPK-) linked activating transcription factor 2 (ATF-2) activity), *cold exposure* and *starvation* (mediated by catecholamine- and glucagon-induced cAMP elevation and a subsequent phosphorylation and activation of CREB by protein kinase A (PKA)) on PGC-1 α expression is well documented [5]. Furthermore, *energy deprivation* through a high AMP/ATP ratio leads to an increased AMP-activated protein kinase (AMPK) activity and a subsequent phosphorylation of PGC-1 α protein, priming PGC-1 α for subsequent deacetylation and thereby activation by silent information regulator 2 homolog 1 (Sirt-1) [7, 8], the expression of which is also increased in conditions with energy shortage, such as, starvation or exercise, due to a high NAD^+ / $NADH$ ratio [9]. These posttranslational modifications on PGC-1 α play pivotal roles in adaptive mitochondrial biogenesis. The roles of impaired mitochondrial function and

more recently a decreased function of the PGC-1 α cascade in the pathogenesis of degenerative CNS disorders are of extensive research interest.

3. Mitochondrial Dysfunction, Reactive Oxygen, and Nitrogen Species

Free radicals are molecules possessing unpaired electrons in their outer orbit. This renders them highly reactive towards organic macromolecules such as carbohydrates, nucleic acids, proteins, and lipids, which suffer “injury” during such a reaction. The main routes of free radical production and subsequent toxic insults are represented in a schematic depiction in Figure 2. Under physiological conditions, the efficiency of reducing oxygen during terminal oxidation is approximately 97–99%, while 1–3% undergo incomplete reduction to superoxide ($O_2^{\cdot-}$), a highly reactive free radical. $O_2^{\cdot-}$ can be transformed into hydrogen peroxide (H_2O_2) both spontaneously and through a reaction catalyzed by mitochondrial manganese superoxide dismutase (Mn-SOD) in the matrix. H_2O_2 normally undergoes degradation by glutathione peroxidase (GPX) and catalase (CAT) enzymes, yielding water. In case of an impaired function of the mitochondrial ETC, leakage of excess electrons from complexes I and III leads to a higher amount of $O_2^{\cdot-}$ and subsequent H_2O_2 production, which when exceeding the degradative capacity of the mitochondria can be transformed into the extremely toxic hydroxyl radical (HO^{\cdot}), through reaction with transition metals (Fe^{2+} and Cu^{2+} ; Fenton reaction).

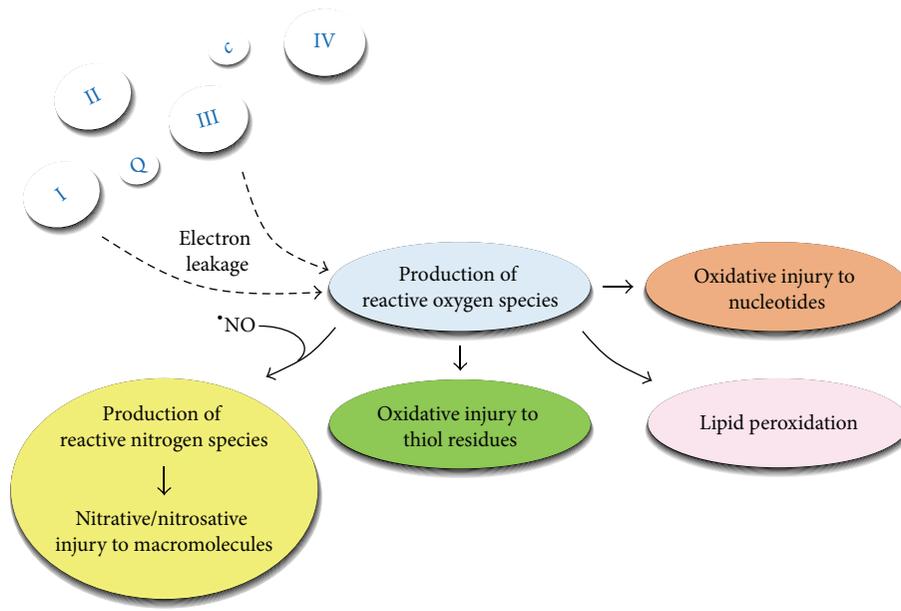


FIGURE 2: Schematic representation of the generation and the effects of free radicals within the mitochondria. The leakage of electrons from the mitochondrial ETC at complexes I and III results in the formation of superoxide anion. The high reactivity of this molecule evokes a harmful cascade mechanism including the formation of reactive oxygen and nitrogen species. The cascade mechanism deteriorates the functional groups of major components of all kinds of biomolecules (carbohydrates, lipids, proteins, and nucleic acids). In case of pronounced electron leakage or deficient antioxidant protection, a vicious circle of mitochondrial dysfunction develops.

HO^\bullet in turn can react with nucleic acids and phospholipids, yielding the formation of further toxic radicals and consequent severe functional impairments of the affected macromolecules. Furthermore, HO^\bullet can also react with thiol residues, yielding the formation of multiple reactive free radicals. In addition, $\text{O}_2^{\bullet-}$ can also react with nitric oxide (NO^\bullet) generated from L-arginine by mitochondrial nitric oxide synthase (mtNOS) enzyme [10]; however, other sources of mitochondrial NO^\bullet associated with nitrite reductase activity under hypoxic conditions have also been identified [11–13]. The reaction of NO^\bullet with $\text{O}_2^{\bullet-}$ yields the highly toxic peroxynitrite anion (ONOO^-) in a reaction that is three times as fast as the dismutation of $\text{O}_2^{\bullet-}$ by Mn-SOD. ONOO^- can evoke injury to proteins via nitration of tyrosine, tryptophan, and phenylalanine residues by nitronium ion (NO_2^+) generated through metal-peroxynitrite ($\text{ONOO}^- \text{Me}^n \text{X}$) complexes. Nitration of tyrosine can also be achieved by serial reactions of further pathways involving ONOO^- and NO^\bullet (see Figure 3 for detailed description). Nitrosylation of thiol, secondary amine, alcohol, and alkane residues are performed via their reaction with nitrosonium ion (NO^+) or indirectly with dinitrogen trioxide (N_2O_3), highly reactive radicals also derived from NO^\bullet . Furthermore, NO^\bullet can directly impair the mitochondrial ETC and OXPHOS via competing with oxygen for the oxygen-binding site of complex IV [14], which leads to a further increase in free radical production.

The toxic radicals described above are known as reactive oxygen species (ROS) and reactive nitrogen species (RNS), and their damaging effects on macromolecules are referred to as oxidative and nitratative/nitrosative stress, respectively. Figure 3 presents a detailed overview on the molecular background of toxic processes related to ROS and RNS.

With mitochondrial ETC being the main source of ROS and RNS production, macromolecular components of the mitochondria are extremely exposed to injury due to oxidative/nitratative/nitrosative stress. Of note, proteins that underwent such a damage are highly susceptible to proteolytic cleavage and degradation [15]. The injury to mitochondrial respiratory complex subunits by impaired efficacy of the ETC has two main consequences: (1) it leads to decreased energy production due to impaired OXPHOS, and (2) it decreases the efficacy of terminal oxidation, which results in increased production of ROS/RNS, generating a vicious circle.

The proximity to the main source of free radical production and the relatively high proportion of coding sequences render the mitochondrial genome particularly sensitive to ROS/RNS-mediated injury [16]. Indeed, the mutation rate of mtDNA relative to nDNA is approximately 10:1 [17]. Furthermore, as the ability to cope with oxidative/nitratative/nitrosative stress declines with aging [18], the rate of mtDNA mutations further increases in the elderly [19].

Excessive ROS and RNS accumulation can trigger the opening of mitochondrial permeability transition pores (mtPTP), which on the one hand decreases the mitochondrial membrane potential further aggravating the initial OXPHOS impairment, and, on the other hand, leads to the release of proapoptotic factors (including apoptosis-inducing factor, procaspase-9, and cytochrome c) from the intermembrane space to the cytosol. This is in severe cases followed by cellular death that can be either apoptotic or necrotic, depending on the severity of the initial insult and subsequent energy deprivation [20–22]. It should be noted, however, that being among the most ancient signals between mitochondria and their host cells, both ROS and RNS might

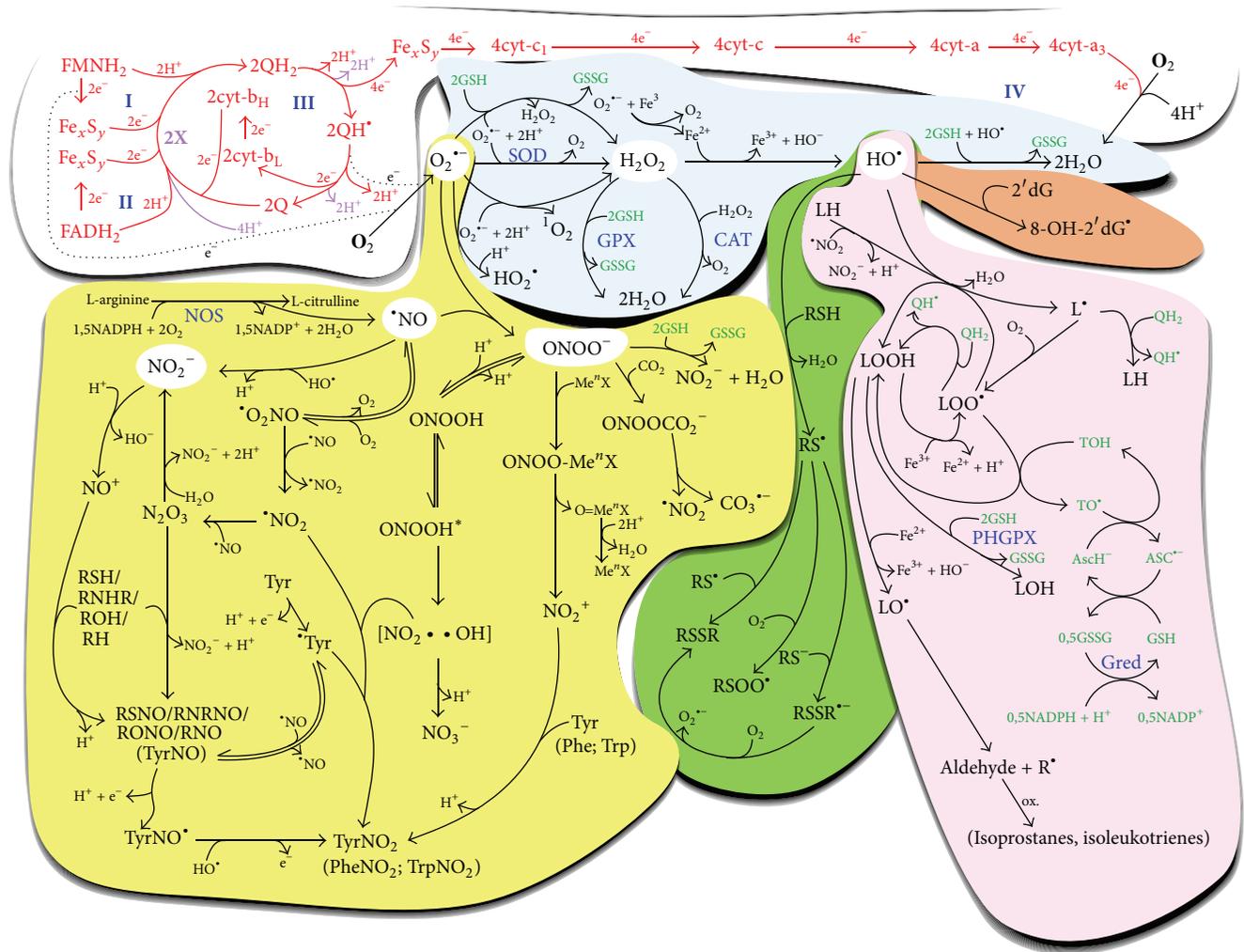


FIGURE 3: The detailed depiction of the chemistry of mitochondrial oxidative and nitrosative/nitrosative stresses. The contents of the colored bubbles correspond to the processes indicated in the bubbles of the respective color in Figure 2. Figure 3 presents the chemical processes of ETC and the terminal oxidation (white bubble; blue Roman numbers represent the site of the respective respiratory complexes) together with those involved in the generation of ROS (light blue bubble) and RNS (yellow bubble). An overview is given on the most representative molecules involved in oxidative injury to nucleic acids (brown bubble), lipids (pink bubble), and molecules with thiol residues (green bubble), as well as in nitrosylation/nitration of organic macromolecules (yellow bubble). For detailed explanation of oxidative/nitrosative/nitrosative (black) and antioxidant (green) processes as well as the function of the ETC (red), we refer to the corresponding sections within the text and the Abbreviations section.

have essential physiological functions under physiological conditions.

Defensive processes of the mitochondria to counteract excessive free radical production involve low molecular weight antioxidants (LMWAs), an enzymatic redox apparatus to clear ROS/RNS (e.g., SOD, CAT, GPX, and peroxiredoxin), and an nDNA-encoded repair machinery.

Ubiquinol and tocopherols represent the main groups of lipid-associated LMWAs. Since these molecules are transformed to semiquinone radicals upon reduction of toxic free radicals, the immediate restoration of antioxidant capacity is essential. This process depends on the standard redox potential of LMWAs. For example, reduction of the semiquinone form of lipid-associated tocopherol requires ascorbic acid (vitamin C, identified by Albert Szent-Györgyi

and the subsequent reduction of the produced ascorbic acid radical by glutathione. Therefore, at the end of the process, no free radicals are present. However, there is a need for the restoration of the reduced glutathione, which is mediated by the enzyme glutathione reductase (Gred). Reduced glutathione also participates in antioxidant functions associated with the activities of SOD and GPX (including the phospholipid-associated form (PHGPX) as well), and it is responsible for the detoxification of HO• and ONOO⁻. The proper function of this armatory requires the appropriate load of reducing equivalents (NADH + H⁺, NADPH + H⁺). The above mechanisms are depicted in Figure 3.

A number of evidence link PGC-1 α to the regulation and activation of mitochondrial antioxidant responses. In a comprehensive study of St-Pierre et al. [6], the expression

of PGC-1 α significantly increased after H₂O₂ challenge in 10T1/2 cells, which effect was recapitulated by Irrcher et al. on C₂C₁₂ muscle cells [23]. This effect is in correspondence with our recent findings of significantly increased PGC-1 α expression in the CNS of mice intoxicated with the neurotoxin 3-nitropropionic acid, an irreversible inhibitor of complex II [24]. Furthermore, RNAi against PGC-1 α reduced the baseline expression of copper/zinc (Cu/Zn)-SOD, Mn-SOD, and GPX in 10T1/2 cells, whereas the expression of Cu/Zn-SOD, Mn-SOD and peroxisomal CAT was found reduced in the heart and brain of PGC-1 α -deficient mice [6]. Similarly, overexpression of PGC-1 α in C₂C₁₂ myotubes displayed increased expression of Mn-SOD and GPX in association with a decreased amount of ROS production [25]. Moreover, PGC-1 α -deficient fibroblasts exhibited blunted response to ROS challenge and an increased sensitivity to oxidative stress, which was in correspondence with an increased sensitivity of PGC-1 α -deficient mice to intoxication with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), an irreversible inhibitor of mitochondrial respiratory complex I, as well as to that with the excitotoxin, kainate [6].

Mitochondrial repair is now widely-acknowledged as an existing phenomenon, comprising a group of processes that aim to repair deleterious alterations in mtDNA, predominantly due to oxidative injuries. These include enzymatic apparatuses for (1) the hydrolysis of oxidized deoxyribonucleotide triphosphates to prevent mismatch errors, (2) different mechanisms of single- and double-strand break repair, (3) multiple mechanisms of base excision repair, and (4) the degradation of unrepairable mtDNA. The latter is a unique mitochondrion-specific mechanism in eukaryotes, which is enabled by the redundancy of mtDNA within the organelle [26]. Certain evidence suggest that, similarly to that seen in nDNA repair, poly(ADP-ribose) polymerase-1 (PARP-1) might play central role of the epigenetic regulation of nDNA-encoded proteins involved in mtDNA repair mechanisms [27].

In case the antioxidant defense and repair systems prove insufficient to protect the organelle, severely damaged mitochondria can be sensed and degraded by a process under the regulation of PINK1 and parkin (mitophagy) [28, 29].

4. The Central Role of Mitochondrial Dysfunction in Neurodegenerative Diseases

A number of general observations and considerations explain the special susceptibility of the CNS to suffer injuries due to mitochondrial disturbances. Indeed, the CNS has an especially high energy demand as it represents merely 2% of the total body mass and accounts for some 20% of bodily oxygen consumption [30]. Besides, unlike astrocytes, neurons store low amounts of glycogen and have a poor ability to enhance glycolysis under conditions when mitochondrial respiration is impaired [31]. Therefore, neurons depend on the constant availability of oxygen and glucose to maintain their functions. Furthermore, the CNS contains high amounts of polyunsaturated lipids, which are highly susceptible to oxidative injury by means of lipid peroxidation, and the antioxidant capacity of neurons is known to be relatively poor [32, 33].

The high sensitivity of neurons as opposed to the relative resistance of astrocytes to oxygen or glucose deprivation is well known; however, recent studies suggest that oligodendrocytes are among the most sensitive cell types within the CNS to mitochondrial stress, exceeding the vulnerability of neurons [34, 35], a feature that may have implications for the pathogenesis of characteristic myelinopathies in chronic conditions with mitochondrial dysfunction, including aging, and mitochondrial encephalopathies.

Another CNS-specific mechanism leading to an increased sensitivity to mitochondrial dysfunction is excitotoxicity due to glutamate, the major excitatory neurotransmitter in the brain [36]. In an event of energy deprivation, neurons undergo partial membrane depolarization, which removes magnesium ions that block the ionophore of *N*-methyl-D-aspartate-sensitive (NMDA) glutamate receptors. This leads to a persistent activation of NMDA receptors by glutamate even if it is present in physiological levels [37]. Hyperactivation of NMDA receptors results in an influx of calcium into the cytosol. The persistent increase in intracellular calcium level leads to an increased mitochondrial sequestration of calcium, which in pathological extents evokes the opening of high-conductance mtPTPs [38], resulting in mitochondrial swelling and a decreased mitochondrial membrane potential, with subsequent OXPHOS impairment and ROS overproduction [39]. These culminate in the release of proapoptotic factors eventually triggering cell death [40] by apoptotic or necrotic mechanisms, based on the severity of the event [20, 21]. It has also been postulated, however, that the mechanism and the channel (i.e., NMDA receptor) through which calcium ions get into the cell and not the calcium overload itself may play the pivotal roles in excitotoxic cell death [41]. Indeed, NMDA receptors are functionally and spatially linked to neuronal NOS (nNOS) by postsynaptic density protein of molecular weight 95 kDa (PSD-95) that synthesize NO^{*} in a toxic amount while calcium ions enter into the cell during NMDA receptor overactivation [42]. Notably PSD-95 attaches to the NR2B subunit, which is in correspondence with the observation that glutamate excitotoxicity is predominantly mediated by NR2B subunit-containing NMDA receptors [43], which are mainly located extrasynaptically [44]. In line with these, activation of extrasynaptic NMDA receptors is regarded as neurotoxic, whereas that of the synaptic NMDA receptors appears to be neuroprotective [45, 46], indicating a role of volume transmission in NMDA receptor-mediated neurotoxicity. A central role of nNOS in excitotoxic injury was suggested by earlier studies as well [47, 48]. The role of excitotoxicity in association with mitochondrial dysfunction as well as the possible therapeutic relevance of approaches aiming to counteract glutamatergic overactivation in neurodegenerative diseases, including pharmacological manipulations with the kynurenine system, have recently been extensively reviewed [49, 50] and are not within the scope of this review.

The following subsections emphasize the relevance of mitochondrial dysfunction in the pathomechanism of degenerative CNS disorders through a detailed overview on the involvement of impaired OXPHOS and mitochondrial bioenergetics in Parkinson's disease, Huntington's disease, and

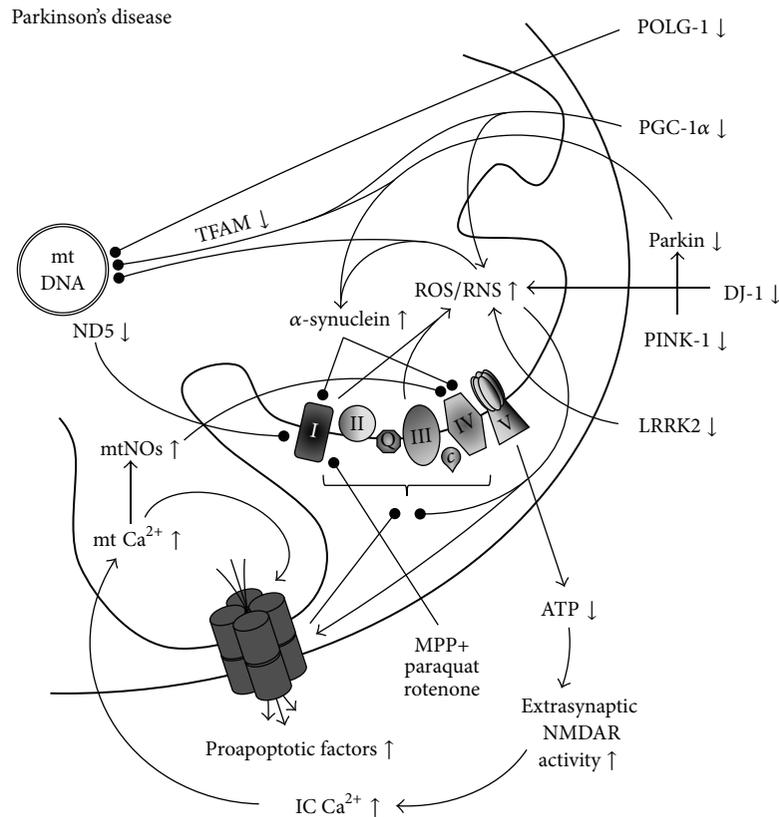


FIGURE 4: The involvement of mitochondrial dysfunction in Parkinson's disease. Complex I deficiency, the predominant electron transport disorder in sporadic PD has long been linked to the deleterious effects of α -synuclein aggregation, a pathognomonic alteration in PD, and inhibitors of complex I (such as MPTP, rotenone, and paraquat) are used in experimental modeling of the disease. Since then a number of genes have been associated with familial forms of the disease, many of them having direct implications in mitochondrial dysfunction. Disturbed OXPHOS in the affected cells can lead to the development of a vicious circle, eventually leading to cell death. Novel findings link PGC-1 α dysfunction to the pathogenesis of sporadic PD, the restoration of which may hold therapeutic value. (\uparrow = increased presence/expression/activity; \downarrow = decreased presence/expression/activity; arrow = promotion; bulb-headed arrow = inhibition/deterioration.)

mitochondrial encephalopathies, with special focus on the involvement and therapeutic relevance of PGC-1 α .

4.1. Parkinson's Disease. Parkinson's disease (PD) is a progressive, chronic neurodegenerative disorder, the pathognomonic alterations of which include loss of dopaminergic neurons, and the presence of Lewy bodies in the substantia nigra pars compacta (SNpc), with a subsequent decrease in striatal dopamine levels [51]. Leading clinical symptoms include bradykinesia, rigidity, resting tremor, and postural instability [52, 53], eventually evolving into severe akinesia, dementia, and eventually death. The development of sporadic PD is linked to a complex interplay of genetic and environmental factors, which have multiple implications for mitochondrial involvement (Figure 4). The first implication for the role of mitochondrial dysfunction in PD came from serial cases of intoxication by the side-product of a synthetic illicit drug, MPTP, which evokes parkinsonian symptoms and recapitulates the majority of PD-related pathologies [54]. Its active metabolite 1-methyl-4-phenylpyridinium (MPP⁺) selectively and irreversibly impairs the function of mitochondrial complex I in dopaminergic neurons [55, 56], and since its discovery, systemic MPTP or intraventricular MPP⁺

intoxication became the most widely applied *in vivo* toxin models of PD. Similar effects can be achieved by known environmental chemicals including the herbicide paraquat and the insecticide rotenone [57]. Corresponding with the ability of complex I inhibitors to evoke parkinsonism, a decreased activity and/or expression of respiratory complex I has been detected in the SNpc [58, 59], striatum [60] frontal cortex [61], platelets [62, 63], and skeletal muscle [64, 65] of sporadic PD patients, suggesting a systemic impairment of mitochondrial functions in this disease. Less consistent reports have been published regarding the involvement of other respiratory complexes, which indicates a predominant involvement of complex I in sporadic PD. In line with these, a decreased activity of complex I, an elevated production of ROS, an energy impairment, and an increased sensitivity to MPP⁺ intoxication can be detected in PD cybrids [66, 67]. The increased presence of oxidative damage has also been reported in post mortem SN of PD patients [68, 69].

In the past decades, genetic and, more recently, genome-wide association studies (GWAS) have identified over 20 loci in causative association with familial PD [70], many of them having direct implications in mitochondrial dysfunction. Among them, leucine-rich repeat kinase 2 (LRRK2) protein

is known to colocalize with membrane bound intracellular structures including mitochondria [71]. Its autosomal dominantly inherited mutation, G2019S, the most frequent underlying genetic alteration in both familial and sporadic PD cases, has been associated with mitochondrial dysfunction and morphological alterations in PD tissue samples [72], abnormal mitochondrial dynamics and increased ROS production in murine primary cortical neurons [73], as well as with an increased neuronal vulnerability to rotenone and paraquat in a nematode model of PD [74].

The autosomal dominantly inherited mutation of SNCA gene (A53T) leads to mitochondrial accumulation of α -synuclein, the main constituent of Lewy bodies, resulting in the inhibition of respiratory complex I [75, 76]. The protein appears to play pivotal roles in modulating oxidative stress, as its transgenic overexpression leads to enhanced sensitivity against intoxication with paraquat and MPTP [77], whereas α -synuclein-deficiency leads to resistance against intoxication with MPTP, 3-nitropropionic acid and malonate in mice [78] (the latter two are inhibitors of complex II and serve as toxin models for Huntington's disease). Accordingly, cell lines transfected with mutant α -synuclein exhibit increased levels of oxidation products, decreased glutathione levels, and a markedly increased cell death in response to toxic insults including H_2O_2 and MPP⁺ exposure [79].

Among genes associated with an autosomal recessive inheritance of familial PD, parkin, a ubiquitin E3 ligase, is responsible for the polyubiquitin tagging of toxic protein aggregates for proteasomal degradation [80]. In addition, parkin appears to be involved in antioxidant functions through regulating SOD activity and glutathione levels [81] and may play important roles in mitochondrial transcription via its association with mitochondrial transcription factor A (Tfam) [82]. Accordingly, parkin-deficient mice display decreased expression of complex I and IV subunits accompanied by a diminished antioxidant capacity and enhanced oxidative damage [83], whereas parkin-deficient flies develop abnormal mitochondria and exhibit an increased vulnerability to paraquat [84]. Among *in vitro* conditions, overexpression of wild-type parkin reduced, whereas that of the mutant allele aggravated cell death induced by different oxidative stimuli including H_2O_2 and MPP⁺ intoxication, which aggravation was accompanied by increased levels of oxidative stress markers and a decreased amount of glutathione [85]. In line with these, transfection of cell lines with mutant parkin leads to an increased presence of markers of oxidative and nitrate injuries [86]. Notably, however, the potential of wild-type parkin overexpression to protect against oxidative insults *in vitro* has been challenged [87], and another study found no increase in vulnerability to different regimens of MPTP exposure in parkin-deficient mice [88].

Parkin appears to share common pathway with phosphatase and tensin homologue- (PTEN-) induced putative kinase 1 (PINK1), another protein associated with autosomal recessive PD, with PINK1 acting upstream of parkin [89]. Indeed, both proteins are involved in the regulation mitochondrial dynamics [28, 29, 90, 91], and phenotypes associated with PINK1-deficiency have been repeatedly reported to be rescued by parkin [89, 92–94]. In

experimental models, PINK1-deficiency has been associated with impaired mitochondrial respiration (most consistently complex I deficiency) [95, 96], decreased energy production [92, 93, 97, 98], elevated ROS production [98, 99], impaired mitochondrial calcium handling [98–100], mitochondrial morphological alterations [28, 29, 89–91, 93, 98], and an increased susceptibility to mPTP [99–101]. Furthermore, PINK1-deficiency exacerbates neurodegeneration evoked by MPP⁺ *in vitro* and MPTP *in vivo* [102]. In addition to parkin, tumor necrosis factor (TNF) receptor-associated protein 1 (TRAP1), a mitochondrial molecular chaperone also known as heat shock protein 75 (Hsp75), has been postulated to be another possible downstream target of PINK1, through which PINK1 activity can prevent the release of cytochrome c and a subsequent apoptosis [103]. The functional association between TRAP1 and PINK1 has gained further support by more recent studies [104, 105], consistently suggesting that TRAP1 acts downstream of PINK1 and in parallel with parkin when mediating amelioration in mitochondrial dysfunction.

Mutations of DJ-1, an oxidative stress sensor capable of modulating glutathione metabolism and mitochondrial transcription under mitochondrial stress [106], leads to autosomal recessive familial PD. The protein is suggested to function in parallel with PINK1/parkin pathway in maintaining mitochondrial function among oxidative conditions [107]. At the experimental level, DJ-1-deficiency has been associated with increased ROS production [108–110], impaired mitochondrial respiration [109] or energy production [110], mitochondrial morphological abnormalities [109], increased opening of the mPTP [110], as well as an increased sensitivity to oxidative stressors including MPTP [111], paraquat [112], and H_2O_2 [112].

Apart from genes identified in monogenic familial PD, a number of genes have been associated with the development of sporadic PD as modifying or susceptibility factors, including genes involved in mitochondrial functions such as mtDNA polymerase gamma 1 (POLG1) [113, 114] and complex I subunit ND5 [115]. In addition to these, an increasing body of evidence suggests that PGC-1 α may add important contributions to the pathogenesis of PD. Indeed, a comprehensive genome-wide meta-analysis found a set of 425 PGC-1 α -responsive nuclear-encoded mitochondrial genes underexpressed in sporadic PD, representing pinpoint defects in glucose metabolism and mitochondrial ETC [116]. Furthermore, associations of single nucleotide polymorphisms (SNPs) of PGC-1 α have been reported with the risk of PD, the age of onset and the longevity [117]. These appear to be in correspondence with decreased expression of PGC-1 α and its target gene NRF-1 in the SN and striatum of PD patients as well as in the midbrain of conditional parkin knockout mice [118]. In line with decreased ATP production and impairments in mitochondrial OXPHOS [119] and antioxidant responses [6], PGC-1 α -deficient mice display enhanced susceptibility to MPTP toxicity [6]. Corresponding to observations that mitochondrial dysfunction can promote the aggregation of α -synuclein [120], reduced expression of PGC-1 α *in vitro* lead to enhanced α -synuclein oligomerization [121]. This effect was, however, not confirmed in PGC-1 α -deficient mice, suggesting a more complex scenario for mitochondrial

dysfunction-induced α -synuclein aggregation *in vivo* [122]. Supporting a potential therapeutic relevance in PD, overexpression of PGC-1 α demonstrated neuroprotection against α -synuclein- and rotenone-induced toxicity *in vitro* [116] and in a parkin interacting substrate (PARIS) overexpression model of PD *in vivo* [118]. In line with these, transgenic overexpression and resveratrol-induced activation of PGC-1 α (via deacetylation by Sirt-1) both rendered neuroprotection against MPTP toxicity in mice [123]. Similarly, the administration of pioglitazone, an agonist of PPAR γ that enhances the activity and expression of PGC-1 α [124], was also protective in MPTP studies [125, 126]. These altogether suggest that a deficient expression and/or function of PGC-1 α and its target genes may play important roles in the development of sporadic PD, which may be of therapeutic relevance in the future. Notably, however, contrasting results have also been published reporting that adenoviral overexpression of PGC-1 α aggravated MPTP-mediated damage in mice [127] and was ineffective against mutant α -synuclein-mediated toxicity in rats [128] and that a sustained overexpression of PGC-1 α to high levels *per se* evoked the degeneration of nigral neurons in rats [128]. These findings necessitate further investigations and draw the attention to the possibility that a sustained overactivation of mitochondrial biogenesis aiming to restore mitochondrial functions may also have deleterious consequences on the long run. This issue needs to be clarified in the future.

The search for effective neuroprotective compounds capable of modifying the disease course in PD is still extensive; as molecules targeting mitochondrial dysfunction in PD though provided promising results in experimental models of PD [129–131], they were ineffective in clinical trials [132]. In line with the data on a decreased function of PGC-1 α in PD and on the therapeutic potential of its activation, there is a hope that transcriptional activation of mitochondrial biogenesis and antioxidant responses via PGC-1 α activation may hold therapeutic value. A phase II safety and fertility clinical trial with the PPAR γ agonist pioglitazone on patients with early PD has recently been completed, and the results are about to be published in the near future (NCT01280123).

4.2. Huntington's Disease. Huntington's disease (HD) is a monogenic, progressive neurodegenerative disease of autosomal dominant inheritance. The genetic alteration is the expansion of CAG trinucleotide repeat sequence on the interesting transcript 15 (IT15) gene on chromosome 4 encoding huntingtin, with increasing number of repeat associating with earlier onset and more rapid progression [133, 134]. The disease onset is usually between 40 and 50 years of age, presenting with behavioral alterations and hyperkinesia in the early stages, subsequently associating with pyramidal symptoms, dystonia, dementia, and psychosis. The pathognomonic alteration is the preferential loss of the striatal γ -aminobutyric acid (GABA)-ergic medium-sized spiny projection neurons (MSNs) and the presence of intracytoplasmic and intranuclear protein inclusions of mutant huntingtin widely distributed in neuronal as well as extraneuronal tissues. The characteristic decreased activity of respiratory complex II, especially in the striatum, has early linked HD to

mitochondrial dysfunction [135] (Figure 5). Since then, deficiency in complex II is the most consistent and predominant alteration reported in HD; however, the involvement of other respiratory complexes has also been suggested [136, 137]. The concept of mitochondrial dysfunction mediating the pathological process induced by mutant huntingtin is consistent with an increased presence of oxidative stress [137–141], which is well-reflected by the increased amount of mtDNA mutations observed in HD patients [142]. Further alterations supporting the primary role of mitochondrial dysfunction in mediating the effects of mutant huntingtin include a transcriptional [143] and/or functional [144] repression of PGC-1 α , disturbances in mitochondrial trafficking [145], a gradually decreasing mitochondrial number [146], and an impairment of mitochondrial calcium handling [147] with an enhanced sensitivity to calcium-induced opening of mPTP and cytochrome *c*-mediated cell death [148, 149].

In line with the predominant biochemical alteration, irreversible inhibition of complex II by 3-nitropropionic acid effectively recapitulates most of the clinical and histopathological characteristics of HD, including the preferential neuronal loss of GABAergic MSNs within the striatum [150, 151]. Similar alterations can be evoked via reversible complex II blockade by malonate [152]. The relevance of complex II dysfunction in HD is highlighted by the fact that mutant huntingtin leads to decreased expression (at the protein level) of the 30 kDa iron-sulfur (Ip) subunit and the 70 kDa FAD (Fp) subunit of complex II in the striatum of HD patients [153] and *in vitro* lentiviral models [153, 154]. Rather similar pattern of alterations was found to underlie complex II deficiency in transgenic HD mice and in a lentiviral model of HD in rats [155]. Complex II dysfunction appears to be causative in HD as its overexpression demonstrated marked restorative effect in these models [153–155]. Alterations in complex II assembly were accompanied by reduced mitochondrial biogenesis in transgenic animals, prompting the authors to suggest the possible contribution of PGC-1 α repression [155]. Indeed the expression of PGC-1 α has been found to be downregulated in the striatum of HD patients [143, 144, 146, 156], in transgenic HD animals [24, 143, 144, 157–159], and in *in vitro* HD models [143, 156, 159, 160]. Correspondingly, the decreased expression of several PGC-1 α target genes has been identified in the striatum of HD patients [144, 146] and transgenic HD mice [144, 157, 158]. A possible mechanism through which mutant huntingtin can lead to the downregulation of PGC-1 α can be secondary to its effect to enhance the expression [161] and activity of NR2B subunit-containing NMDARs [162], features characteristic of transgenic HD mice [163], which in turn results in a decreased striatal CREB signaling [163], and a subsequent downregulation of PGC-1 α [164]. In addition, a decreased expression of transducer of regulated CREB-binding protein 1 (TORC1), an activator of CREB-mediated PGC-1 α expression, has been found in *post mortem* HD striatum, in transgenic HD mice, and in an *in vitro* HD model, which may contribute to the downregulation of PGC-1 α expression in HD [160], whereas others suggest that PGC-1 α repression may be secondary to the downregulation of PPAR γ in HD [159]. Supplementing the alterations in PGC-1 α expression in HD, Johri et al. reported decreased protein

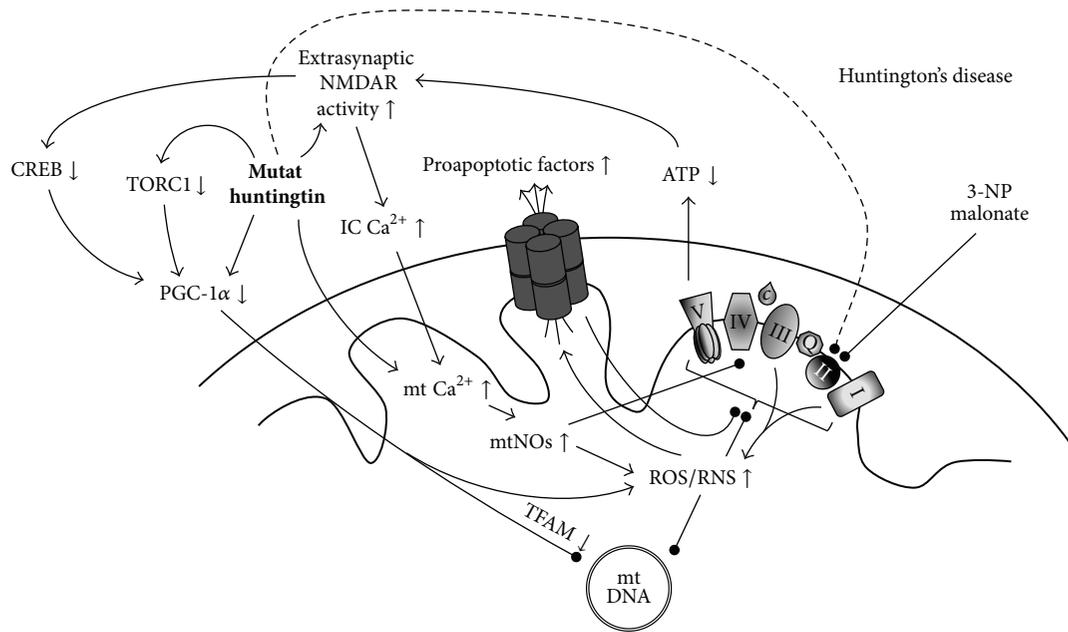


FIGURE 5: The involvement of mitochondrial dysfunction in Huntington's disease. Complex II deficiency, the predominant electron transport disorder in HD has long been linked to the deleterious effects of mutant huntingtin aggregation, a pathognomonic alteration in HD, and inhibitors of complex II (such as 3-nitropropionic acid (3-NP) and malonate) are used in experimental modeling of the disease. Disturbed OXPHOS in the affected cells can lead to the development of a vicious circle, eventually leading to cell death. Novel findings link PGC-1 α dysfunction to the pathogenesis of HD at multiple levels, the restoration of which may hold therapeutic value. (\uparrow = increased presence/expression/activity; \downarrow = decreased presence/expression/activity; arrow = promotion; bulb-headed arrow = inhibition/deterioration.)

level of the functionally active N-truncated splice variant of PGC-1 α (NT-PGC-1 α) in the striatum of low-grade HD patients and young asymptomatic transgenic N171-82Q and R6/2 HD mice, whereas its level was found to be elevated in high-grade HD patients and in older symptomatic transgenic HD mice [156]. This pattern has been recently supported by our study on transgenic N171-82Q HD mice at the mRNA level, revealing a significantly upregulated expression of NT-PGC-1 α in both the striatum and overlying cortex of older symptomatic HD mice compared to wild-type and young HD counterparts [24]. These changes were accompanied by a decreased expression of full-length PGC-1 α in the striatum and cortex of young transgenic mice, corresponding to prior observations. A main novelty of this study included a previously unidentified consistent elevation of both the full-length and the N-truncated isoforms of PGC-1 α in the cerebellum of transgenic HD mice, which may underlie the relative resistance of cerebellar neurons to degeneration in HD [24]. This study further provided evidence for a consistent striatal upregulation of both the full-length and the N-truncated isoforms of PGC-1 α following acute but not chronic injury due to 3-nitropropionic acid intoxication in mice [24]. This possibly compensatory elevation corresponds to prior findings of PGC-1 α upregulation in response to ROS challenge *in vitro* and highlights the role of PGC-1 α in concerting antioxidant responses [6, 23]. Supporting a potential therapeutic relevance, a line of evidence suggests that mechanisms associated with the upregulation of PGC-1 α can exert neuroprotection in experimental models of HD. Indeed, the administration of PPAR γ agonist

thiazolidinediones (such as rosiglitazone and pioglitazone) was proven to be protective in transgenic HD mice [158, 159, 165], in an intrastriatal quinolinic acid-induced rat toxin model of HD [166], in 3-nitropropionic acid-induced murine toxin model of HD [167], and in *in vitro* HD models [159, 165, 168]. Similarly, the pan-PPAR agonist bezafibrate exerted protection in transgenic HD mice [169]. Furthermore, TORC1 activation displayed protective and restorative effects on viability and mitochondrial functions in a striatal HD cell line model exposed to 3-nitropropionic acid [160]. The protective effect of resveratrol, a polyphenol with potent Sirt-1/PGC-1 α -activating properties, has also been demonstrated in transgenic murine and nematode models [170], in a 3-nitropropionic acid-induced murine model [171], and in an *in vitro* model of HD [170]. Notably, however, the potency of resveratrol to significantly elevate the expression of PGC-1 α and its target genes within the striatum has recently been questioned [172], which necessitates further investigations. Considering that early attempts with mitochondria-targeted molecules being neuroprotective in experimental HD models [131, 173, 174] provided little success at the clinical level [132], the transcriptional activation of mitochondrial respiration and biogenesis may hold novel therapeutic potential as a more system-based approach. A phase III clinical trial with resveratrol is just about to recruit its participants (NCT02336633).

The corresponding set of evidence implicating a potential pathogenic role of PGC-1 α repression in mitochondrial dysfunction in HD as well as early observations of striatal alterations in PGC-1 α -deficient mice [175, 176] suggested that such animals may serve as experimental models for HD;

however, findings of a recent detailed neuropathological evaluation of mice lacking the expression of full-length PGC-1 α has indicated that it might not indeed be the case and turned our attention to another group of diseases where systemic mitochondrial dysfunction is pathognomonic [122].

4.3. Mitochondrial Spongiform Leukoencephalopathies. Mitochondrial diseases are a group of multisystemic disorders where the characteristic pathologies affecting organs with high energy demand (i.e., brain, liver, heart, skeletal muscle, and kidney) are due to mitochondrial dysfunction as a consequence of a genetic alteration either in the mtDNA or in the nDNA. The deleterious loss of functions may affect several components of proper mitochondrial functioning, including genes encoding respiratory complex subunits, proteins responsible for mtDNA transcription/translation, mitochondrial tRNAs and rRNAs, and nuclear-encoded ancillary proteins of mitochondrial function [177]. The diseases are distributed to characteristic syndromes based on the clinical manifestation and the observed neuropathological alterations, including Kearns-Sayre syndrome, Leigh syndrome, mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS), myoclonic epilepsy with ragged-red fibres (MERRF), neuropathy, ataxia, retinitis pigmentosa (NARP), and mitochondrial neurogastrointestinal encephalopathy (MNGIE) [178–181]. In these diseases, impaired ATP production with various defects in respiratory complexes and excess ROS production in the affected tissues has widely been documented and has excessively been reviewed [182]. Though in somewhat different patterns, mitochondrial encephalopathies are collectively characterized by various degrees of tissue vacuolation in the white and gray matter of the CNS, accompanied by region-selective reactive astrocytosis with or without neurodegeneration.

A number of genetically modified murine strains have been developed to model diseases with mitochondrial defects, however, with variable outcomes [122]. On the one hand, many of the genetic modifications lead to embryonic or early postnatal mortality due to multisystemic insufficiency (e.g., complete knockouts of CREB [183], Tfam [184], NRF-1 [185], NRF-2 [186], ERR γ [187], POLG1 [188], synthesis of cytochrome *c* oxidase 2 (SCO2) [189], and optic atrophy 1 (OPA1) [190]). On the other hand, a remarkable proportion of viable models, surprisingly, does not have any pathological changes in the CNS (e.g., complete knockouts of adenine nucleotide translocator 1 (ANT1) [191], PPAR γ [192], ERR α [193], and SURF1 [194]; Δ mtDNA Mito-Mice [195]; and Twinkle mutant “Deletor” mice [196]). Genetic models exhibiting a neuropathology closely reminiscent of human mitochondrial leukoencephalopathies include mice deficient in Mn-SOD [197], in thymidine phosphorylase and uridine phosphorylase (TP/UP) [198], and in NADH dehydrogenase [ubiquinone] iron-sulfur protein 4 (NDUFS4) [199]. In addition to these, our recent neuropathological analysis on mice deficient in the expression of full-length PGC-1 α revealed widespread spongy vacuolation predominating in the white matter of the striatum, thalamus, cerebellum, and the brainstem, accompanied by moderate to severe

reactive astrogliosis in the pontomedullary brainstem and the cerebellar nuclei, corresponding to a pattern of alterations characteristic of the spongiform leukoencephalopathy seen in Kearns-Sayre syndrome [122]. This is especially interesting in light of the facts that experimental animals used for modeling cardiomyopathy in Kearns-Sayre syndrome are the tissue-specific knockouts of Tfam [200, 201], a gene under the regulation PGC-1 α , and the expression of which is severely downregulated in PGC-1 α -deficient mice [119, 175]. Notably, no indirect or direct signs indicative striatal neuronal degeneration and/or loss were observed in our study [122], which corresponds to the independent observations of Lucas et al. [202], both publications drawing the conclusion that PGC-1 α -deficiency *per se* is not sufficient to evoke HD-like pathology, contrasting to what had previously been suggested.

Considering the spectrum of roles of PGC-1 α in regulating and promoting mitochondrial functions and the fact that a number of genes involved in disease-causing mutations and/or that involved in modeling mitochondrial disease have direct or indirect interactions with PGC-1 α (e.g., ANT-1, POLG1, Tfam, NRF-1, NRF-2, PPARs, ERRs, Mn-SOD, and CREB), the rationale for PGC-1 α induction to provide symptomatic benefit in these currently intractable groups of diseases can be accepted [203]. Indeed, transgenic overexpression or bezafibrate-induced expression of PGC-1 α delayed the onset of symptoms in a cytochrome *c* oxidase-deficient murine model of mitochondrial myopathy [204]. Similarly, transgenic overexpression of PGC-1 α ameliorated the phenotype and increased the activity of mitochondrial respiratory complexes in POLG1 mutant “Mutator” mice [205]. Furthermore, adenoviral overexpression of PGC-1 α partially restored respiratory deficits in fibroblasts obtained from patients with mitochondrial disease of various origin (though to different efficacy) and in MELAS hybrids [206]. These altogether suggest a potential therapeutic relevance of boosting mitochondrial biogenesis via PGC-1 α -mediated approaches in diseases with genetic mitochondrial disorder.

5. Concluding Remarks

Since the revelation of the essential role electrons, originating from reducing equivalents that arise from cytosolic and/or mitochondrial metabolic processes, in cellular bioenergetics via their flow through metal-containing electron transport complexes in the mitochondrial inner membrane, an armada of evidence has accumulated linking the impaired function of this system to degenerative diseases of the CNS. While initial attempts to compensate for such alterations showed as much promise at the experimental level as deep disappointment they caused at the clinical level, novel strategies with more system-based approaches aiming to render protection via improving mitochondrial bioenergetics at a transcriptional level may open up new therapeutic perspectives and boost pharmacological research. With more and more evidence linking PGC-1 α and its target genes to the pathogenesis of neurodegenerative diseases including PD, HD, and mitochondrial disorders, pharmacological manipulations to

restore and/or activate PGC-1 α may provide valuable tools in the therapy of these currently intractable diseases.

Abbreviations

I:	First complex in the mitochondrial ETC
II:	Second complex in the mitochondrial ETC
III:	Third complex in the mitochondrial ETC
IV:	Fourth complex in the mitochondrial ETC
FMNH ₂ :	Reduced flavin mononucleotide
FADH ₂ :	Reduced flavin adenine dinucleotide
Fe _x S _y :	Iron-sulfur cluster
cyt-a:	Cytochrome a
cyt-a ₃ :	Cytochrome a ₃
cyt-b _H :	Cytochrome bH
cyt-b _L :	Cytochrome bL
cyt-c:	Cytochrome c
cyt-c ₁ :	Cytochrome c ₁
O ₂ ^{•-} :	Superoxide anion
Q:	Coenzyme Q10 (oxidized)
QH [•] :	Coenzyme Q10 (semiquinone)
QH ₂ :	Coenzyme Q10 (reduced)
GSH:	Glutathione (reduced)
GSSG:	Glutathione (oxidized)
SOD:	Superoxide dismutase
GPX:	Glutathione peroxidase
CAT:	Catalase
¹ O ₂ :	Singlet oxygen
HO ⁻ :	Hydroxide ion
HO [•] :	Hydroxyl radical
HO ₂ [•] :	Hydroperoxyl radical
NOS:	Nitrogen monoxide synthase
NADPH:	Nicotinamide adenine dinucleotide phosphate (reduced)
NADP ⁺ :	Nicotinamide adenine dinucleotide phosphate (oxidized)
NO ₂ ⁻ :	Nitrite ion
*NO:	Nitrogen monoxide
NO ⁺ :	Nitrosonium ion
*O ₂ NO:	Nitrite radical
*NO ₂ :	Nitrogen dioxide radical
N ₂ O ₃ :	Dinitrogen trioxide
ONOO ⁻ :	Peroxynitrite
ONOOH:	Peroxynitrous acid
ONOOH [*] :	Peroxynitrous acid (metastable)
NO ₃ ⁻ :	Nitrate
RSH:	Thiol (reduced)
ROH:	Alcohol
RNHR:	Secondary amine
RH:	Alkane
Tyr:	Tyrosine
*Tyr:	Tyrosyl radical
RSNO:	S-Nitrosothiol
RNRNO:	Nitrosamine
RONO:	Nitrosyl alcohol
RNO:	Nitrosoalkane
TyrNO ₂ :	3-Nitro-L-tyrosine
PheNO ₂ :	3-Nitro-L-phenylalanine

TrpNO ₂ :	6-Nitro-L-tryptophan
TyrNO [•] :	3-Nitrosotyrosine radical
TyrNO:	3-Nitrosotyrosine
Phe:	L-Phenylalanine
Trp:	L-Tryptophan
NO ₂ ⁺ :	Nitronium ion
Me ⁿ X:	Metal complexes
O=Me ⁿ X:	Oxo-metal complexes
ONOOCO ₂ ⁻ :	Nitrosoperoxycarbonate
ONOO-Me ⁿ X:	Metal-peroxynitrite complexes
RS [*] :	Thiyl radical
RSSR:	Thiol (oxidized)
RSOO [*] :	Thiol peroxy radical
RSSR ⁻ :	Disulphide radical anion
RS ⁻ :	Thiolate anion
LH:	Lipid
L [*] :	Lipid radical
LOOH:	Lipid peroxide
LOO [*] :	Lipid peroxy radical
R [*] :	Alkyl radical
LOH:	Lipid hydroperoxide
LO [*] :	Lipid alkoxy radical
Gred:	Glutathione reductase
PHGPX:	Phospholipid glutathione peroxidase
TOH:	Tocopherol (reduced)
TO [*] :	Tocopherol (semiquinone)
AscH ⁻ :	Ascorbate (reduced)
Asc ⁻ :	Ascorbate (oxidized)
2'dG:	2'-Deoxyguanosine
8-OH-2'dG [*] :	8-Hydroxy-2'-deoxyguanosine.

Conflict of Interests

The authors report no competing interests.

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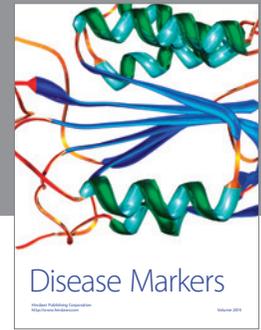
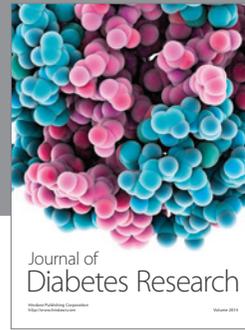
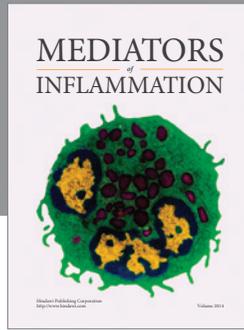
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