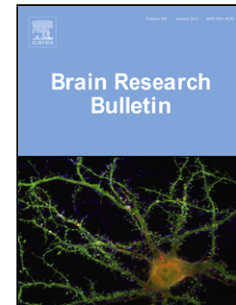


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**Metabolic Disorder Dysfunction in Parkinson's Disease: Bioenergetics, Redox
Homeostasis and Central Carbon Metabolism**

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Highlights

- Mitochondrial dysfunction in PD triggers oxidative stress and energy failure
- We provide an integrated view of bioenergetics, redox and central carbon metabolism in PD
- Clinical trials demonstrate that PD cannot be explained simply by oxidative stress and energy failure
- These findings strengthen the idea that PD is a complex metabolic disorder

Abstract

The loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and the accumulation of protein inclusions (Lewy bodies) are the pathological hallmarks of Parkinson's disease (PD). PD is triggered by genetic alterations, environmental/occupational exposures and aging. However, the exact molecular mechanisms linking these PD risk factors to neuronal dysfunction are still unclear. Alterations in redox homeostasis and bioenergetics (energy failure) are thought to be central components of neurodegeneration that contribute to the impairment of important homeostatic process in dopaminergic cells such as protein quality control mechanisms, neurotransmitter release/metabolism, axonal transport of vesicles and cell survival. Importantly, both bioenergetics and redox homeostasis are coupled to neuro-glial central carbon metabolism. We and others have recently established a link between the alterations in central carbon metabolism induced by PD risk factors, redox homeostasis and bioenergetics and their contribution to the survival/death of dopaminergic cells. In this review, we focus on the link between metabolic dysfunction, energy failure and redox imbalance in PD, making an emphasis in the contribution of central carbon (glucose) metabolism. The evidence summarized here strongly supports the consideration of PD as a disorder of cell metabolism.

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1. Introduction

Oxidative stress and energy failure associated with mitochondrial dysfunction are cardinal hallmarks of neuronal cell death associated with neurodegenerative disorders [71, 215, 257, 348]. Mitochondrial derived reactive oxygen species (ROS) contribute to neuronal cell death in neurodegeneration. However, the lack of success in the clinic of antioxidant-based therapies suggests that other contributors associated with mitochondrial dysfunction should also play an important role [1, 156, 225, 300]. Cellular bioenergetics is directly coupled with central carbon metabolism, and in the brain, glucose is the primary energy substrate. Glucose metabolism has been shown to be altered in different neurodegenerative disorders. For example, in Alzheimer's disease a disruption in glucose uptake and metabolism is found [59, 145, 341]. Hyperglycemia and amyloid β promote excitotoxicity in neuronal cells [7]. Other studies have also revealed that glucose metabolism is decreased in the cortex and basal ganglia of Huntington's disease patients [69]. Interestingly, an increase in the levels of glucose transporters was found to correlate with a decreased age of onset in Huntington's disease [327]. While cancer and diabetes/obesity are considered metabolic disorders clearly associated with a dysfunction in glucose metabolism, less is understood about the role of central carbon metabolism in neurodegeneration. Recently, we and others have revealed links between alterations in glucose metabolism and alterations in cellular bioenergetics, redox homeostasis and cell death progression induced by PD-related risk factors. In this review, we present an integrated overview of these results to evidence how alterations in central carbon metabolism have a central role in determining changes in cellular bioenergetics and redox homeostasis in PD. These findings are posed to make a significant contribution to our understanding of PD pathogenesis, and make a case for considering PD a metabolic disorder.

2. Brain Metabolism, Bioenergetics and Redox Balance

2.1. Energy Metabolism in the Brain

The brain can be considered the most complex organ in the human body. The regulation and maintenance of brain function requires high amounts of energy. The brain accounts for ~20% of total body energy consumption (25% of the glucose and 20% of the oxygen consumption), and brain energy levels are more resistant to starvation compared to other organs [279]. Glucose is considered the obligatory energy substrate in the adult brain requiring its continuous delivery across the blood brain barrier (BBB) (**Figure 1.1**); however, alternate energy sources can fuel brain function under energetic stress situations. For example, lactate transport across the BBB can provide ~8%–10% of the brain's energy requirements and has been estimated to supply ~20%–25% of energy at the expense of glucose consumption during energy demanding activities. Importantly the extracellular levels of lactate (0.5-1.5 mM) are similar to those of glucose, suggesting that an important pool of lactate is always available when required for consumption [209]. Ketone bodies derived from fatty acid metabolism in the liver can also cross the BBB [125].

All brain regions are considered to be metabolically active with heterogeneity among structures. Remarkably, metabolic activity of the brain is constant over time. Brain metabolic activity consists of the oxidation of glucose to carbon dioxide and water (oxygen consumption), which results in the production of energy in the form of ATP. Importantly both oxygen consumption and glucose metabolism do not necessarily parallel each other. Glucose is delivered to brain cells through the blood and changes in brain glucose consumption are accompanied with vascular flow modifications. An increase in blood flow of oxygen and glucose parallels an increase in brain activity. However, only glucose consumption (glycolysis) increases proportionately, while oxygen consumption (oxidative phosphorylation) does not, despite its increased supply [231, 267]. Interestingly, only 10% of glucose yields lactate. In addition to the generation of energy, glucose metabolism in the brain is also important for the synthesis of carbohydrates for

glycoproteins and glycolipids, amino acids, one-carbon donors for methylation, and neurotransmitter precursors [231].

2.2. Cellular Composition of the Brain

The brain tissue is made up of about 100 billion neurons and trillions of glia cells, and its bioenergetics and redox homeostasis is an integrated process between these different cell populations. Neurons are highly polarized cells with subcellular domains that serve different functions: the cell body (or soma), branching dendrites (signal receivers), and the axon that conducts nerve signals (**Figure 1.2 and 1.5**). Neuronal types and distribution are highly specialized across to the different brain regions. Specialization in both cytoarchitecture and neurotransmitter communication differentiates the function of neuronal populations [31, 304].

Glial cells make up 90 percent of the brain's cells and regulate a number of physiological processes required for proper neuronal survival and function. Three types of glial cells exist in the CNS: oligodendrocytes, astrocytes, and microglia (**Figure 1.3, 1.4 and 1.6**).

Oligodendrocytes are responsible for nerve fiber myelination, which provides axons with an “insulating coat” that enhances nerve impulse conduction. Oligodendrocytes have several processes and form several internodal segments of myelin on axons separated by gaps (Ranvier nodes) (**Figure 1.4**) [28, 299]. Astrocytes are small cells with processes arranged radially and a considerable molecular, structural, and functional diversity at the regional level. Astrocyte processes cover the external surface of capillaries in blood vessels (perivascular feet), the initial segment of most axons, and the bare segments of axons at the Ranvier nodes. Astrocytes processes cover a defined territory forming highly organized domains interconnected via gap junctions. They regulate neurotransmitter levels in the synaptic cleft, provide neurons with energetic and antioxidant precursors (**Figure 1.3**), play an important role in the migration of immature neurons, tissue repair, and regulate blood flow and inflammatory processes by

release of signaling mediators [301]. Microglial cells are resident macrophages distributed throughout the CNS that are embryologically unrelated to the other glial cells [44]. As innate immune cells, they are activated by infection, tissue injury (ischemia or trauma), or neurodegenerative processes. Upon activation, microglia cells retract their processes and migrate to the site of the lesion, where they proliferate and become antigen presenting cells. Microglia phagocytose degenerating cells and also act as sources of immunoregulatory and neuromodulatory factors such as cytokines, chemokines, neurotrophic factors. Microglia can be activated by cell-surface receptors for endotoxin, cytokines, chemokines, misfolded proteins, serum factors and ATP (**Figure 1.6**). While mild activation is a key adaptive immune response, continuous activation or overactivation of microglia is thought to contribute to neurodegeneration [97, 122, 123].

The BBB refers to a barrier of capillaries that restrict the exchange of solutes between the blood and the brain extracellular fluid. Endothelial cells that form BBB capillaries are connected by gap junctions and regulate the exchange of metabolites and signaling molecules while preventing the entrance of deleterious molecules or agents to the brain (**Figure 1.1**) [261, 304].

2.3. Metabolic Specialization in Brain Cells

Neurons are high energy consumers observing high rates of oxidative metabolism compared to glial cells. Neurons utilize most of their energy at the synapse to maintain and restore ionic gradients, and for the uptake and recycle of neurotransmitters (>80%). Interestingly, neurons are thought to metabolize glucose primarily via the pentose phosphate pathway (PPP) to provide reducing equivalents required to maintain antioxidant defenses via the production of nicotinamide adenine dinucleotide phosphate (NADPH) (**Figure 1.2** and **2.5**) [39]. NADPH is also required for antioxidant defense in glial cells, but it can actually mediate ROS generation by NADPH-oxidases (NOXs) (**Figure 3.1b**). NADPH is a reducing agent as well, required for the

synthesis of lipids and nucleic acids and for the metabolism of neurotransmitters and aldehydes. Other mechanisms of generating NADPH exist, which include folate metabolism, NADP-malate dehydrogenase (malic enzyme), isocitrate dehydrogenase (IDH1 and 2) (**Figure 2.6**), glutamate dehydrogenase and nicotinamide nucleotide transhydrogenase (Nnt) (**Figure 2.7**). However, their contribution to NADPH metabolism in neurons or glial cells has not been well defined [95]. In isolated brain mitochondria Nnt has been reported to be important in the removal of peroxides [202, 349].

Neurons lack 6-phosphofructose-2-kinase/fructose-2,6-bisphosphatase-3 (PFKFB3) due to its continuous degradation by the ubiquitin-proteasome (UPS) pathway [9]. PFKFB3 is involved in the biogenesis and degradation of fructose-2,6-bisphosphate (F2,6BP), a glycolytic activator (**Figure 2.2**). In astrocytes, PFKFB3 is activated by AMPK (adenosine monophosphate-activated protein kinase) and promotes glycolysis [131]. Because neurons have a limited capacity to upregulate glycolysis in response to stress, they depend on the shuttle of lactate from astrocytes and oligodendrocytes as fuel for mitochondrial OXPHOS (oxidative phosphorylation) (**Figure 1.3 and 1.4**) [32, 102, 183, 237]. Neuronal function *ex vivo* can be maintained by lactate in the absence of glucose [96]. To date, the primary neuronal energy substrate (glucose vs lactate) and the relative contributions of glycolysis and OXPHOS to neuronal bioenergetics (ATP) are still under debate [85, 142, 258, 290]. However, the fact that mice with a decreased expression of the neuron-specific glucose transporter GLUT3 do not observe alterations in glucose utilization, while astrocytes-specific GLUT1 deficiency results in a severe neurological phenotype supports the idea of the preferential consumption of glucose by astrocytes and the astrocytes-neuron lactate shuttle hypothesis (**Figure 1.1**) [308, 331].

Even though glial cells and neurons have the same oxidative capacity, glial cells are highly glycolytic and a large portion of glucose metabolism is directed to lactate production and its release to the extracellular space. Astrocyte glucose consumption does not match their energy

expenditure, which only accounts for 5-15% of the glucose consumed by the brain. Recent studies have demonstrated that the activity of pyruvate dehydrogenase (PDH), which determines the entry of pyruvate into the tricarboxylic acid (TCA or Krebs) cycle (**Figure 1.3**), is reduced by its phosphorylation in astrocytes [360]. Glucose storage within brain cells is found in astrocytes in the form of glycogen, which can also be broken down to lactate, but some evidence exist for the generation of glucose via gluconeogenesis [231]. In addition, glutamate can be used as a carbon source for the TCA cycle in both neurons and astrocytes, while acetate is preferentially used by astrocytes [32, 150, 208, 306]. The creatine / phosphocreatine / creatine kinase system has also been proposed to contribute to the regeneration of ATP in brain [30]. Ketone bodies (3- β -hydroxybutyrate [3BHM], acetoacetate, and acetone) and free fatty acids (and lactate) can be transported across the BBB during starvation and are thought to provide two thirds of the total energy required for the brain. Neurons very poorly metabolize hydrogen-rich free fatty acids (FFA) to obtain energy (**Figure 2.12**), which has been related to the high O₂ demand and resultant generation of superoxide anion (O₂^{•-}) from β -oxidation [287]. However, 20 % of total adult brain energy comes from FFA oxidation, mostly in astrocytes. Astrocytes can oxidize FFA (**Figure 1.3**) and ketone bodies, while neurons and oligodendrocytes can only use ketone bodies. β -oxidation of fatty acids by astrocytes provides ketone bodies for neurons as well [138, 287].

Astrocytes are important players in the regulation of neuronal excitability by the removal of released neurotransmitters. The excitatory amino acid glutamate (Glu) is taken up by the Na⁺-dependent excitatory amino acid transporter-1 (EAAT1 or GLAST) and EAAT2 (GLT-1) and converted to glutamine (Gln) by the astrocyte-specific enzyme glutamine synthetase (GS) (**Figure 1.3** and **2.10**). Glutamine is exported and transferred to neurons (glutamate-glutamine cycle) to regenerate glutamine via glutaminase (GLS) activity (**Figure 1.2** and **2.10**). Glutamate can also be utilized for *de novo* synthesis of the antioxidant glutathione (GSH) (**Figure 1.3, 1.5,**

2.11 and **3.4b**) [32, 288]. In general, neurons have limited defense mechanisms against ROS when compared to astrocytes (**Figure 1.2 and 1.3**). Astrocytes contain higher levels of endogenous antioxidants and antioxidant systems being more resistant to oxidative stress, which is explained by the activation of the antioxidant response via the nuclear factor erythroid-2-related factor 2 (Nrf2) transcription factor (**Figure 1.3 and 3.7**) [293]. While several reports demonstrate that Nrf2 signaling can be induced by oxidative stress in neurons [120], it has been recently suggested that neuronal Nrf2 is epigenetically silenced [33], and that induction of the Nrf2 pathway does not seem to restore their antioxidant protection (**Figure 1.5**) [152]. Astrocytes also have higher levels of NADPH and G6PD (glucose-6-phosphate dehydrogenase) [105]. Interestingly, antioxidant genes in neurons are transcriptionally regulated independent of Nrf2 by synaptic activity through the activating transcription factor 4 (ATF4) and the activator protein 1 (AP-1) (**Figure 1.5**) [29, 189]. Both neurons and astrocytes can synthesize GSH, but neurons depend on the supply of GSH precursors (**Figure 1.3 and 1.5**). GSH is released from astrocytes via the ATP-binding cassette transporters subfamily C member 1 transporter (ABCC1, or multidrug-resistance-associated protein 1 [MRP1]) [133]. Extracellular GSH is then degraded by the γ -glutamyl transpeptidase (γ GT) to produce L-cysteine-L-glycine (CysGly), which is cleaved further by the neuronal aminopeptidase N (ApN) into the amino acids glycine and cysteine that are taken up by neurons for GSH synthesis (**Figure 1.5**) [19, 32]. Thus, both the glutamate-glutamine cycle and the GSH export are also involved in the regulation of the neuronal redox environment by astrocytes.

During inflammation, changes in central carbon metabolism have been recently demonstrated to contribute to the activation and survival of astrocytes and microglia. Activation of astrocytes increases the generation of ROS, but themselves are largely resistant to these high ROS levels. Interestingly, glucose deprivation impairs GSH metabolism in astrocytes and their survival upon activation [65]. Inflammation also alters mitochondrial dynamics by favoring mitochondrial fission

over fusion in astrocytes via autophagy [238]. Upon injury, exposure to pro-inflammatory signals, or chemicals/xenobiotics microglia become polarized to a pro-inflammatory M1 phenotype triggering the production of pro-inflammatory cytokines and the upregulation of ROS production. The M1 phenotype of microglia is considered an adaptive immune response that was recently reported to be paralleled by a switch in their metabolism from oxidative phosphorylation to glycolysis that also enhances carbon flux to the PPP (**Figure 1.6**) [110, 249, 329]. An alternative activation state defined as M2 (with different subclasses) is characterized by the release of anti-inflammatory factors to re-establish cell homeostasis. Interestingly, M2 upon activation of microglia with interleukin (IL)-4/IL13, no changes in mitochondrial oxygen consumption or lactate production were evidenced by extracellular flux analysis [249]. A comparative study demonstrated that astrocytes are more resistant to oxidative damage than microglia or oligodendrocytes [135].

3. Parkinson's Disease

PD is the second most common neurodegenerative disorder affecting ~6 million people worldwide. PD is characterized by the progressive and selective loss of the dopaminergic (A9) neurons in the SNpc that conveys motor dysfunction. Although neuronal cell death is a cardinal feature of PD, the mechanisms and pathways involved remain unclear, mainly because in the majority of cases the cause of PD is unknown. The major risk factor identified for PD is aging as its prevalence and incidence increases exponentially from ages 65 to 90. A fraction of PD occurrence is also directly related to mutations in genes such as those encoding α -synuclein (*SNCA*), DJ-1 (*PARK7*), PTEN-induced putative kinase 1 (*PINK1*), leucine rich repeat kinase 2 (*LRRK2*) and Parkin (*PARK2*), while other genetic modifications only increase the risk of developing this condition.. Over 90% of PD occurs in a sporadic (idiopathic) form from which only 5% of those cases are linked to *de novo* genetic alterations (*SNCA* and *LRRK2*) [165].

Thus, PD occurs most commonly without a clearly defined genetic basis. While the etiology of PD has not been clearly established, epidemiological data suggests that exposure to environmental / occupational agents might play a key role in this disorder [112]. Thus, it is now thought that PD arises as a syndrome from the convergence of genetic susceptibility, environmental exposures, and aging. At the molecular level, PD risk factors have been shown to trigger neurodegeneration by mitochondrial dysfunction, oxidative stress, and abnormal protein accumulation [188, 347], but the exact mechanisms are still unclear.

In addition to neurons, the function of other brain cells is altered in PD, which is also reported to contribute to the degeneration of dopaminergic neurons. Since astrocytes contribute to both energy and antioxidant homeostasis in neurons it is likely that dopaminergic neurons are more susceptible to oxidative stress and energy failure due to the low number of astrocytes in the SNpc compared to other brain areas. [228]. Neurotrophic factors released by astrocytes such as the mesencephalic astrocyte-derived neurotrophic factor (MANF), the glial cell line-derived neurotrophic factor (GDNF), and the brain-derived neurotrophic factor (BDNF) regulate neuronal bioenergetics (**Figure 2.1**), and are also thought to contribute to the survival of dopaminergic neurons [213]. While astrocytes normally serve a neuroprotective role, reactive astrocytes are found in PD brains and are considered to contribute to neuroinflammatory processes [57, 330].

The density of microglial cells is higher in the SN compared to other brain regions. Increased levels of activated microglia and pro-inflammatory cytokines (IL-1 β , tumor necrosis-factor α [TNF α], IL-2 and IL-6) have been found in the SNpc of elderly individuals. Furthermore, activation of microglia in PD brains has been proposed to be triggered by aggregates / fibrils of α -synuclein, environmental toxicants, infectious events, and ATP and/or signaling proteins released from neurons (**Figure 1.6**) [163, 200, 274, 359]. PD-related genes *PARK7*, *PINK1* and *LRRK2* have also been reported to modulate mitochondrial dysfunction, oxidative stress and the

inflammatory response of glial cells [63, 234, 239, 240, 280]. Besides microglia, infiltrating cells such as T-lymphocytes, and neutrophils have been reported to contribute to inflammation in neurodegenerative disorders including PD [115, 147, 276]. For example, pathogenic T-cell populations potentiate microglial activation [41, 275]. Importantly, peripheral cells such as lymphocytes and neutrophils from PD patients observe mitochondrial dysfunction and increased oxidative stress [18, 55, 107, 263, 264, 326], but whether ROS generation from infiltrating cells contributes to PD has not been explored. A disruption in the BBB has also been linked to aging and PD, which might involve dysfunction in both endothelial and astrocytes [45, 117]. Breakdown of the BBB leads to a dysregulation in ionic transport and xenobiotic/toxin clearance, and the initiation of an inflammatory response that contributes to neuronal dysfunction and neurodegeneration [247].

3.1. Mitochondrial Dysfunction in Parkinson's Disease

3.1.1. *Genetics and Complex I Dysfunction*

Mitochondrial dysfunction is a common trait for many human disorders including neurodegeneration. The central role of mitochondrial dysfunction was recognized very early in the PD field. A decrease in the activity of the mitochondrial electron transport chain (ETC), primarily Complex I, is found in the SNpc of patients with PD (**Figure 2.9** and **3.1a**) [129, 160, 283, 285]. Mitochondrial DNA (mtDNA) mutations have also been discovered in rare families exhibiting parkinsonism. Somatic (acquired) point mutations and deletions in mtDNA also accumulate with age in the SNpc, but no specific mutations responsible for mitochondrial dysfunction in PD have been identified [70]. Mutations in polymerase gamma (POLG) are linked to mitochondrial defects in Complex I and IV acquired in PD [271]. Accordingly, a high frequency of mitochondrial Complex I mutations was found in PD patients [298]. Gene variations in the mitochondrial transcription factor A (TFAM) that controls mtDNA have also been associated with PD [10].

Mitochondrial dysfunction in PD has been linked to oxidative stress, as electron leakage from its metabolism is the primary source for ROS formation (**Figure 3.1a**). PD-associated genes have been shown to alter mitochondrial function and homeostasis leading to increased ROS formation [317]. Accumulation of α -synuclein has been suggested to trigger mitochondrial oxidative stress [83]. DJ-1, PINK1 and Parkin deficiency or mutations impair mitochondrial respiration and render cells more susceptible to oxidative stress and mitochondrial dysfunction (**Figure 2.9 and 4**) [4, 13, 149, 236, 254, 310]. Phosphorylation of the Complex I subunit NdufA10 by PINK1 is necessary for ubiquinone reduction (**Figure 2.9**) [235]. Gain-of-function of *LRRK2* mutations disturb mitochondrial bioenergetics and mitochondrial dynamics leading to increased ROS formation [246, 256]. In the mitochondria, $O_2^{\cdot-}$ is generated in the matrix by electron leakage from Complex I [118], and in both the matrix and the inner membrane space (IMS) by electron leakage from Complex III (**Figure 3.1a**) [58]. *In vitro* and *in vivo*, dopaminergic neurons are highly sensitive to Complex I inhibitors whose toxicity is ascribed, at least partially, to the generation of ROS [27, 173, 216, 278, 343]. Other environmental agents linked to PD or dopaminergic toxins have also been shown to primarily mediate dopaminergic cell death via mitochondrial dysfunction [50, 111, 278].

3.1.2. Bioenergetics

While mitochondrial dysfunction in PD is thought to mediate the increased generation of ROS and subsequent oxidative damage, another major consequence is energy failure linked to the inability of neurons to compensate their lack of capacity to generate ATP. Very few studies have aimed at understanding and distinguishing between the contribution of both oxidative stress and energy failure in dopaminergic cell death associated with mitochondrial dysfunction. A number of studies have shown that antioxidants protect dopaminergic cells from the toxicity of Complex I inhibitors [26, 159, 167, 191, 266]. However, we and others have clearly demonstrated that dopaminergic cell death induced by Complex I inhibition cannot be directly linked to the

generation of ROS or completely prevented (if at all) by antioxidants [47, 49, 100, 171, 178, 217, 241, 278, 282, 355]. This might explain the failure of antioxidants (particularly mitochondria targeted antioxidants) in PD therapy [1, 300], despite their reported success in preclinical models [108, 302]. Furthermore, some studies suggest that impaired mitochondrial bioenergetics might be the main cause for neuronal cell death induced by Complex I inhibitors rotenone and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP, or its active analog 1-methyl-4-phenylpyridinium [MPP⁺]) [27, 86, 343]. Supplementation of cells with Coenzyme Q₁₀ (ubiquinone), an electron carrier in the ETC, protects against the toxicity of Complex I inhibitors that block the electron flow from NADH dehydrogenase to Coenzyme Q [2]. Similarly, directly delivery of electrons from NADH to cytochrome c using methylene blue attenuates dopaminergic neurodegeneration induced by rotenone [345]. Importantly, because a 50% inhibition of Complex I is required to cause significant ATP depletion, and Complex I activity is only reduced by 25–30% in PD, ATP depletion might as well not be the single causative event for dopaminergic neurodegeneration [77, 284].

Dopaminergic SNpc neurons are particularly susceptible to energy failure since they consume a significant amount of energy during their pacemaking activity to maintain a basal dopamine (DA) tone in innervated regions (striatum). This level of activity and energy consumption also leads to increased levels of basal oxidative stress [121]. In addition, their extended (and probably unmyelinated) axon, and the number of striatal synapses established are characteristics expected to exert a high energy demand on the maintenance of plasma membrane potential (ionic gradients), protein/organelle (mitochondria) traffic and homeostasis [218, 253, 262]. Importantly, the intrinsic bioenergetic capacity between dopaminergic and non-dopaminergic presynaptic synaptosomes do not differ [66], suggesting that other factors besides energy dysfunction contribute to the loss of dopaminergic cells. Energy failure in dopaminergic cells would be expected to siphon energy from other important ATP-dependent homeostatic

processes in an attempt to maintain their excitability (including active uptake of neurotransmitters into vesicles) and function. These processes include: 1) protein quality control mechanisms (autophagy and the UPS) whose failure leads to the accumulation of misfolded / oxidized protein aggregates (**Figure 1.2**) [73]; 2) transport of mitochondria to pre-synaptic and post-synaptic sites (kinesin motors require ATP) (**Figure 4.6**) [68]; and 3) mitochondrial biogenesis and dynamics (fusion, fission and mitophagy) (**Figure 1.2** and **4**) [221]. In addition, energy depletion is expected to impair the ATP-dependent proton pump that drives vesicular accumulation of DA augmenting its cytosolic levels and oxidative stress as a consequence (**Figure 1.2**) [17, 203, 204]. Glutamatergic afferents in the SNpc suggest that energy impairment in astrocytes and neurons might also contribute to dopaminergic cell death due to an impaired uptake of extracellular glutamate that leads to excitotoxic cell death, but this hypothesis requires further experimental support [12, 224, 343].

While neurons have a limited capability to upregulate glycolysis, an increase in glycolysis counteracts energy failure and dopaminergic cell death induced by mitochondrial dysfunction. [54, 136, 174]. Alternative energy sources have also been demonstrated to protect against PD neurodegeneration. Under energy deprivation, ADP phosphorylation by creatine kinase (CK) to ATP requires phosphocreatine for the donation of the phosphoryl group. The phosphocreatine pool is maintained / regenerated from creatine and ATP under normal conditions by both the cytosolic and the mitochondrial forms of creatine kinase. Creatine supplementation has been shown to protect against MPTP toxicity [16, 219]. However, in clinical trials creatine supplementation does not slow down the progression of PD [161]. Conversely, the administration of ketone bodies (D-beta-hydroxybutyrate) bypasses the Complex I blockade by MPTP and reduce dopaminergic neurodegeneration by entering the mitochondrial ETC directly at Complex II. [314]. Accordingly, a ketogenic diet has been reported to exert protective effects in PD [323].

3.1.3. Mitochondrial dynamics

Mitochondrial dysfunction in PD has also been linked to the indirect alteration of mitochondrial dynamics (fusion and fission, turnover, biogenesis, and transport) that is involved in the regulation of mitochondrial health, mass and subcellular location in response to stress (**Figure 4**) [94, 322]. We will next discuss these processes in the context of how they regulate both bioenergetics and redox homeostasis in PD.

Mitochondria are dynamic organelles that undergo continuous events of biogenesis, remodeling and turnover. Fusion and fission are opposing processes working in concert to maintain the shape, size, number of mitochondria and their physiological function. Fusion enables content to be mixed between neighboring mitochondria and has been proposed to rescue “moderately” dysfunctional mitochondria. Fusion is mediated by the initial oligomerization of dynamin GTPases mitofusins 1 and 2 (Mfns) at the outer membrane to tether adjacent mitochondria together, and the subsequent fusion of the inner membranes by the optic atrophy GTPase Opa1 (**Figure 4.1**). Fission represents a quality control mechanism to transform damaged elongated mitochondria into a form suitable for engulfment by mitochondrial autophagy or mitophagy, and has also been proposed to modulate mitochondrial axonal transport. Fission requires recruitment of the GTPase Drp1 (dynamin-related protein 1) via mitochondrial surface receptors (mitochondrial fission 1 protein [Fis1], mitochondrial fission factor [Mff] and mitochondrial dynamics proteins 49 and 51 [MiD49, MiD51]) for the assembly of the fission machinery subsequently leading to membrane scission (**Figure 4.2**) [259]. Complex I inhibition promotes Drp1-mediated fission and mitophagy. Conversely, inhibition of fission protects against dopaminergic cell death induced by Complex I inhibitors [322]. Importantly, recent evidence indicates that alterations in mitochondrial dynamics by PINK1 deficiency are a result of impaired bioenergetics [325]. Mitophagy has been shown to be regulated by PINK1 and the translocation of Parkin from the cytoplasm to “defective” mitochondria (**Figure 4.3**). Fusion arrest by

polyubiquitination and proteasomal degradation of mitofusins (Mfn1 and Mfn2) by Parkin is required for mitophagy (**Figure 4.4**). On the other hand, polyubiquitination of the voltage-dependent anion channel 1 (VDAC1) by Parkin recruits the ubiquitin binding protein p62 that also interacts with the autophagosomal protein LC3/GABARAP (**Figure 4.3**). Loss of the E3-ubiquitin ligase Parkin and PINK1 has been shown to promote Drp1-dependent fission, loss of mitochondrial membrane potential, and energy failure [207]. Contradictory results exist regarding the role of Parkin on promoting proteasomal degradation of the fission promoting proteins Drp1 and Fis1, but if corroborated, they would suggest a complex scenario where Parkin can regulate both mitochondrial fusion and fission events depending on the degree of mitochondrial stress [94]. Importantly, recent reports have demonstrated that only prolonged (chronic) mitochondrial depolarization induces Parkin translocation or mitophagy in neurons (**Figure 4.2**) [180, 321]. Furthermore, mitophagy induced by dysfunction in mitochondrial respiration is independent from Parkin in dopaminergic neurons [305]. These results suggest that disruption in mitophagy is not the primary cause for PD linked to Parkin mutations. Supportive of this hypothesis is the observation that Parkin and PINK1 have also been demonstrated to mediate the formation of mitochondria-derived vesicles for the degradation of oxidized and damaged proteins via the lysosome (**Figure 4.5**) [223].

Other PD related genes also affect mitochondrial dynamics. α -synuclein has also been shown to impair mitochondrial fusion, which seems to precede mitochondrial dysfunction [242], while the A53T mutant was reported to stimulate mitophagy [67]. Loss of DJ-1 function promotes mitochondrial fission and mitophagy, but mitochondrial alterations are prevented by PINK1 and parkin [141, 313]. A pathogenic increase in the activity of LRRK2 also promotes fission [333]. Activation of AMPK by starvation promotes mitophagy, but its role in PD has not been clearly elucidated [92].

Mitochondria are actively transported into axonal and dendritic terminations due to the high energy requirements for synaptic neurotransmission (**Figure 4.6**). Notably, dopaminergic axons have reduced mitochondrial numbers compared to other synaptic terminals. Complex I inhibitors and PD-related genes impair mitochondrial transport, which leads to energy depletion in synaptic terminals and dopaminergic axons that already have reduced mitochondrial numbers compared to other terminals [162, 190]. PINK1 and Parkin also regulate mitochondrial movement via phosphorylation, ubiquitination and degradation of Miro that disrupts its interaction with the adapter protein Milton and the kinesin motor protein KIF5a. The loss of this interaction between Miro and Milton/KIF5a leads to the detachment of mitochondria from microtubules (**Figure 4.6**) [199, 332]. Finally, Parkin has also been shown to induce the proteasomal degradation of the parkin-interacting substrate (PARIS), a transcriptional repressor of the peroxisome proliferator-activated receptor gamma-co-activator 1-alpha (PGC-1 α), which stimulates mitochondrial biogenesis (**Figure 4.7**) [294].

Similar to neurons, alterations in mitochondrial function and quality control are also expected to occur in glial cells affected by PD risk factors. However, other than its involvement in the activation of inflammatory processes and increased ROS formation (mentioned in the next section), the pathological consequences that glial mitochondrial dysfunction has in PD is unclear. Astrocytes have the same oxidative capacity as neurons, but their energy requirements are met through glycolysis, and they are resistant to mitochondrial toxins. The physiological importance of mitochondrial oxidative metabolism in glial cells is still obscure. Astrocytes derived from Parkin knockout and transgenic mutant α -synuclein exhibit mitochondrial functional and morphological defects, which translate into the impairment of their neurotrophic effects in neuronal differentiation [286]. DJ-1 knockout in astrocytes alters mitochondrial function and impairs neuroprotection against Complex I inhibition [175]. There is no evidence that glial cells degenerate (or die) in PD. Interestingly, impaired astrocyte proliferation (astrogliosis) has been

reported in PD brains and this phenomenon correlates inversely with α -synuclein accumulation [315]. Accordingly, PINK1 knockout astrocytes exhibit defective proliferative signals, which were linked to alterations mitochondrial metabolism [63]. Recently, damaged mitochondria have been reported to be transferred from neuronal axons for their turnover in astrocytes [78], and conversely, astrocytes have been shown to transfer mitochondria to promote neuronal survival [127]. Thus, it is plausible that when transferred, defective mitochondria from astrocytes can have deleterious effects in neuronal function during PD.

3.2. Oxidative Stress and Alterations in Redox Metabolism

3.2.1. *Generation of Reactive Oxygen Species and Oxidative Damage*

In addition to the role of mitochondria as the primary source for $O_2^{\cdot-}$, other important alterations in redox balance contribute to dopaminergic dysfunction. Several other organelles are important sources for ROS as well, and under certain circumstances, might actually play a bigger role than mitochondria in ROS generation [42]. ROS are produced in the endoplasmic reticulum (ER) as a consequence of the activity of oxidoreductases that catalyze disulfide bond formation in nascent proteins. Protein disulfide isomerase (PDI) accepts electrons from cysteine thiol residues leading to the formation of protein disulfide bonds. ERO1 (ER oxidoreduction) transfers electrons from PDI to O_2 , which results in the production of H_2O_2 (hydrogen peroxide) [311]. ER stress and the activation of the unfolded protein response (UPR) have been reported in PD; however, its causative role in oxidative damage has not been established [230].

Another important source of $O_2^{\cdot-}$ is the NOX family of enzymes that catalyze the production of $O_2^{\cdot-}$ from O_2 and NADPH (**Figure 3.1b**) [139]. Distinct isoforms of NOX enzymes have been reported in different brain regions, but their activation appears to be primarily restricted to glial cells as a response to environmental exposures or inflammatory agents [103]. NOX-derived ROS from glial cells has been shown to contribute to oxidative damage and dopaminergic

neurodegeneration (**Figure 1.6**) [139, 309]. Nitric oxide ($\cdot\text{NO}$) is generated from L-arginine by nitric oxide synthases (NOS) which also requires reducing equivalents from NADPH [233]. When $\text{O}_2^{\cdot-}$ reacts with $\cdot\text{NO}$ it generates peroxynitrite (ONOO^{\cdot}) (**Figure 3.1a**) [82]. Inducible NOS (iNOS) is also activated by mitochondrial toxins and inflammatory events in microglia at the substantia nigra to promote neurodegeneration (**Figure 1.6**) [20, 194]. Neuronal NOS (nNOS) also contributes to dopaminergic cell death induced by MPTP [124, 265]. In addition, NOS uncoupling by the PD-related pesticide paraquat has also been recognized as an important source for $\text{O}_2^{\cdot-}$ [206, 212].

$\text{O}_2^{\cdot-}$ can be dismutated in via enzymatic (via $\text{O}_2^{\cdot-}$ dismutases [SODs]) or non-enzymatic reactions to H_2O_2 (**Figure 3.1a and 3.1b**). SOD activity was found to be increased in post-mortem PD brains [51, 281]. Metals such as iron (Fe) can also promote ROS formation via the Fenton/Haber-Weiss reaction that catalyzes the formation of hydroxyl radical ($\cdot\text{OH}$) by their reaction with H_2O_2 (**Figure 3.2**). In the brain, Fe is most abundant in SNpc dopaminergic neurons. Increased Fe deposition and increased free Fe concentrations have been found in the SNpc of PD brains, which may lead to increased generation of $\cdot\text{OH}$ [295]. In PD, Fe is deposited abundantly in the neuromelanin (NM) granules of SNpc dopaminergic neurons [295]. Fe deposition in PD might be related to alterations in Fe transport and storage systems [90, 134, 154, 177]. $\cdot\text{OH}$ formation by Fe has also been proposed to involve α -synuclein (**Figure 3.2**) [61, 214, 251, 320]. Because of their high Fe content, lysosomes are another important potential source of ROS [170], and lysosomal breakdown has also been linked to PD pathogenesis [81]. Finally, disruption of Fe-Sulfur (S) clusters by oxidative stress induced by paraquat or PINK1 mutants has also been proposed to enhance oxidative damage (**Figure 3.2**) [46, 93].

Oxidative stress in PD is also associated with the pro-oxidant properties of dopamine. Mutant α -synuclein down-regulates the vesicular monoamine transporter (VMAT2) [203, 204]. In the cytosol, dopamine is either metabolized by monoamine oxidase (MAO) to generate H_2O_2 , or

auto-oxidized in the presence of Fe generating $O_2^{\cdot-}$, H_2O_2 and dopamine-quinone species (DAQ) (**Figure 3.5**) [3]. Dopaminergic cell death induced by mitochondrial toxins has been proposed to depend on dopamine oxidation [158, 197]. DAQ byproducts from DA oxidation have been reported to react with protein cysteine thiols [126], and with glutathione (GSH) to form adducts (GS-DAQ) by the activity of GSH-S-transferases (GSTs) [75, 291]. GSTs are also involved in the detoxification of GSH adducts with byproducts of lipid peroxidation such as 4-hydroxynonenal (4-HNE) which has been shown to generate toxic protein adducts in PD (**Figure 3.4b**) [352].

3.2.2. Antioxidant Defenses

Oxidative stress is counteracted by cellular antioxidant mechanisms. A number of scavenging mechanisms exist against H_2O_2 . Catalase mediates the decomposition of H_2O_2 and is primarily localized in the peroxisomes (**Figure 3.3**). The activity of catalase was reported to be reduced in the SN and putamen of PD brains [11]. Peroxiredoxins (Prxs) are thiol peroxidases primarily seen as regulators of peroxide signaling [74]. Except for Prx6, which depends on the reducing power of GSH, thioredoxins (Trx) provide the reducing equivalents required for the peroxide scavenging activity of Prxs. The Trx redox system itself depends on thiol-disulfide exchange reactions at the active site, and Trx reductase (TrxR) transfers reducing equivalents from NADPH to reduce Trxs (**Figure 3.3**). Overexpression of Prx1, Prx2 and Prx4 protects against 6-hydroxydopamine (6-OHDA)-induced dopaminergic cell death [137, 184], whereas silencing mitochondrial Prx3 and Prx5 increases sensitivity to MPP⁺ [80]. The Trx/TrxR system also protects against MPP⁺- 6-OHDA- and paraquat-induced toxicity in dopaminergic cells [21, 23, 201, 346].

A decrease in the levels of GSH is one of the earliest biochemical alterations associated with PD as demonstrated by the observation that GSH loss occurs in incidental Lewy body disease,

which is considered an asymptomatic precursor to PD [146, 260, 296]. Accordingly, inducible depletion of GSH promotes nigrostriatal degeneration in mouse [62]. GSH peroxidases (GPx) and Prx6 use the reducing power of GSH to hydrolyze peroxides generating GSH disulfide (GSSG) as a byproduct (**Figure 3.4a**). Mice deficient in GPx1 exhibit an increased sensitivity to MPTP toxicity [166], while its overexpression protects against MPP⁺- and 6-OHDA-induced toxicity *in vitro* and *in vivo* [35, 157, 277, 312]. GSH-dependent Prx6 was recently shown to exacerbate dopaminergic neurodegeneration induced by MPTP, but this effect was linked to its calcium-independent phospholipase A2 activity and increased 4-HNE levels [354]. GSH reductase (GR), which recycles GSSG back to GSH, requires NADPH as the electron donor reductant, and the pentose phosphate pathway enzyme glucose-6-phosphate dehydrogenase (G6PD), is indispensable for the regeneration of NADPH from NADP⁺ (**Figure 2.5 and 3.4a**). Downregulation of PPP enzymes and a failure to increase the antioxidant reserve capacity are early events in the pathogenesis of sporadic PD [89]. Transgenic mice overexpressing G6PD in dopaminergic cells are resistant to MPTP-induced toxicity [227]. Impairment in the PPP leads to the depletion of NADPH and dysfunction in the GSH/Grx, Prx/Trx/TrxR and catalase systems, as well as the decrease in purine synthesis via ribose 5-phosphate [349]. We have recently demonstrated that the PD-related pesticide paraquat hijacks the NADPH from the PPP for its redox cycling, promoting oxidative stress and a toxic synergism when combined with α -synuclein overexpression [14, 186]. NOX and NO-mediated formation of ROS and reactive nitrogen species is also expected to be directly associated with NADPH levels. In contrast G6PD and IDH1 exert a protective effect against the toxicity of MPTP/MPP⁺ [227, 344]. These observations might explain why there is no generalized association between changes in G6PD activity and PD [104].

Glial cells also regulate antioxidant defenses in neuronal cells. Recently, the role of astrocytes in the protection of neurons against oxidative stress was elegantly demonstrated. Conditional

depletion of astrocytes was observed to promote neuronal injury by oxidative stress [289].

Accordingly, transcriptional regulation of antioxidant systems via the nuclear factor (erythroid-derived 2)-like 2 (Nrf-2) in astrocytes prevents dopaminergic cell death induced by MPTP [56].

3.2.3. Bioenergetics and Redox Balance

Alterations in the bioenergetics of dopaminergic cells also have an impact on antioxidant systems. Energy is required for a number of antioxidant systems to work. GSH (l- γ -glutamyl-L-cysteinyl-glycine) synthesis is initiated by generation of γ -glutamylcysteine from glutamate and cysteine via the glutamate-cysteine ligase (GCL), and the subsequent addition of glycine by the activity of GSH synthetase (GSS) (**Figure 1.3** and **3.4b**) [101, 226, 297]. Both reactions requiring ATP consumption. The transsulfuration pathway (**Figure 2.11**) contributes to the generation of cysteine, the rate limiting substrate for GSH synthesis, from one carbon metabolism of serine \rightarrow cystathionine \rightarrow cysteine. Interestingly, high levels of homocysteine, a co-substrate with serine for cystathionine formation, have been found in PD brains [36]. Both glycine and glutamate are also byproducts of central carbon metabolism (glycolysis or TCA cycle, respectively) (**Figure 2.10** and **2.11**). However, the contribution of their biosynthetic pathways to redox balance in neuro-glial cells is unclear. Efflux of GSH-adducts (including those of DA and 4-HNE) is ATP-dependent as well. Thus, GSH-dependent antioxidant systems and detoxification pathways are expected to be impaired by energy failure associated with mitochondrial dysfunction (**Figure 3.4b**) [72]. The reduction of hyperoxidized Prxs (sulfenylated, SO₂H) by sulfiredoxin (Srx) relies on the initial formation of a sulfinic phosphoryl ester (Cys-S_pO₂PO₃²⁻) between the Srx and Prx that requires ATP consumption (**Figure 3.3**) [38]. ATP is also required for the synthesis of NADP⁺ via NAD⁺ kinase (**Figure 3.8**). Transcriptional regulation of antioxidant defenses (SOD1 [CuZnSOD], SOD2 [MnSOD], the modifier and catalytic GCL subunits [GCLM and GCLC], and GSTs) via Nrf2 and conversely, the ubiquitination and degradation of the Nrf2-kefch-like ECH-associated protein 1 (Keap1) cytosolic complex also require energy (**Figure 3.7**) [155]. ATP

depletion is also anticipated to impair oxidative DNA-damage repair systems (**Figure 3.7**) [76, 119, 307, 336]. GCLM knockout was shown to increase dopaminergic neurodegeneration induced by paraquat [192] and recently, it was also reported that GSH depletion in GCLM knockout astrocytes induces a depletion in glycogen levels demonstrating a link between redox balance and bioenergetics/central carbon metabolism [176].

3.3. Alterations in Central Carbon Metabolism

3.3.1. *Glucose Metabolism and Glycolysis*

In addition to the energy failure linked to mitochondrial dysfunction, alterations in central carbon metabolism have also been reported to occur in PD. A decrease in glucose metabolism and abnormal elevated levels of lactate / pyruvate have been observed in PD patients [5, 91, 130, 255]. Disruption of glycolysis in astrocytes and oligodendrocytes triggers axon damage and neurodegeneration [182, 328]. Interestingly, glucose deprivation promotes α -synuclein aggregation (**Figure 1.2**) [34]. In contrast, lactate has been reported to exert an opposite effect on α -synuclein [151]. We and others have demonstrated that glycolysis is upregulated in response to mitochondrial dysfunction, and that ATP generation via glycolysis exerts a protective role against Complex I inhibition [14, 22, 52-54, 220, 337, 351]. As mentioned before, failure of neuronal cells to upregulate this pathway seems to make them rather sensitive to mitochondrial dysfunction [132]. Interestingly, dietary restriction and administration of 2-deoxy-d-glucose exerted protective effects against MPTP toxicity [87]. We have recently found that paraquat inhibits glucose metabolism and upregulates carbon flux via the PPP to increase its redox cycling by hijacking reducing equivalents from NADPH [186]. This effect was paralleled by an impairment of NADPH-dependent antioxidant systems leading to GSH depletion and Prx hyperoxidation [278]. Inhibition of glycolysis by paraquat, was likely associated with the

inhibition of phosphofructokinase (PFK) by citrate whose accumulation is linked to the inhibition of aconitase by PQ-derived ROS (**Figure 2.2** and **2.8**) [46, 106, 186, 243].

PD-related genes *SNCA* (α -synuclein), *PARK2* (Parkin), *PINK1* and *PARK7* (DJ-1) have been reported to indirectly regulate glycolysis by modulation of different signaling proteins including p53, the hypoxia-inducible factor 1-alpha (HIF-1 α) (**Figure 2.10**) and the adenosine monophosphate-activated protein kinase (AMPK) [272, 273, 292, 356]. Alterations in cellular energy are tightly monitored by the master regulator of metabolism AMPK [48]. We have recently demonstrated that AMPK signaling protects against paraquat-induced dopaminergic cell death and that this effect is independent from glucose metabolism and likely linked to the regulation of mitochondrial bioenergetics (**Figure 4.7**) [14]. Accordingly, a protective role for AMPK against mitochondrial dysfunction and toxicity induced by *Parkin*-*LRRK2*-mutations, α -synuclein and MPTP/MPP⁺ has also been previously reported [64, 88, 244]. In contrast, other reports have shown that AMPK mediates dopaminergic cell death induced by rotenone and 6-OHDA [164, 342]. Contradictory results have also been reported regarding the role of AMPK in α -synuclein aggregation and toxicity [88, 151]. AMPK is a central regulator of cellular metabolism via modulation of a myriad of processes. Thus, differences between the roles of AMPK in dopaminergic cell death induced by different PD-related insults might be related to distinct processes being regulated by AMPK, or to the diverse metabolic cues involved in cell death or survival.

Glycolysis has been recently demonstrated to be directly regulated by PD-genes. Glycolysis generates methylglyoxal (MGO) as a byproduct from the metabolism of glyceraldehyde 3-phosphate and dihydroxyacetone phosphate (DHAP) (**Figure 2.4**). MGO is a potent glycative agent that readily reacts with lipids, nucleic acids and protein lysines / arginines to form advanced glycation end products (AGEs). MGO also induces mitochondrial dysfunction and is

detoxified by the glyoxalase system through the sequential activity of glyoxalase-1 (GLO1) and GLO2 using GSH as a co-factor (**Figure 2.4**) [8, 79, 303]. An increase in AGEs has been reported in PD [324]. MGO is actually a precursor for 1-acetyl-6, 7- dihydroxyl-1, 2, 3, 4-tetrahydroisoquinoline (ADTIQ), a dopamine (DA)-derived tetrahydroisoquinoline (TIQ) toxin that is also found in PD brain tissue [339]. GLO1 converts the intermediary hemithioacetal (spontaneous reaction of GSH with MGO) to lactoyl-GSH, which is then metabolized to D-lactate by GLO2 that also recycles GSH (**Figure 2.4**). The activity of GLOs is higher in astrocytes than neurons [8], and is inhibited by glutathionylation (mixed disulfide bond formation between a protein cysteine and GSH) [37]. MGO formation seems to occur primarily in astrocytes as neurons have low rates of glycolysis, are very sensitive to MGO and GLO1 inhibition, and when upregulated, the glyoxylase system fails to protect them against MGO [8]. These observations actually correlate with the higher expression of DJ-1 in astrocytes when compared to neurons [25], and the discovery that DJ-1 is a cofactor-independent GLO III system (**Figure 2.4**) [179]. In addition to contributing to the detoxification of MGO, DJ-1 has been proposed to metabolize MGO and glyoxal (a byproduct from fatty acid peroxidation) to generate D-lactate and glycolate, respectively, and that these metabolites contribute to the maintenance of mitochondrial function [316]. Parkin was also recently shown to regulate glucose metabolism via ubiquitination of pyruvate kinase M1 and PKM2 that results in a decrease in their enzymatic activity (**Figure 2.3**) [198].

An increased oxidation (4-HNE adduct formation) of the glycolytic enzymes glyceraldehydes 3-phosphate dehydrogenase (GAPDH), enolase 1 and aldolase A was found in the frontal cortex from patients with PD, and dementia with Lewy bodies (DLB) [114]. These glycolytic enzymes have been reported to be metastable and thus, prone to interact with and potentially become sequestered by amyloid-like structures such as α -synuclein fibrils (**Figure 2.3**) [248, 340]. GAPDH has been shown to directly regulate α -synuclein aggregation and apoptotic neuronal

cell death, which appears to be independent from its role in glycolysis. Glucose phosphate isomerase 1 (GPI-1) was recently demonstrated to exert a protective effect against proteotoxic stress induced by α -synuclein in dopaminergic neurons and this effect was shown to be linked to glycolysis (**Figure 2.2**) [168]. We have observed that the mechanism by which α -synuclein enhances metabolic dysfunction induced by environmental toxicants is linked to an impairment of glycolysis [14]. Accordingly, other reports have reported a possible interaction between α -synuclein and glycolytic enzymes such as aldolase [153, 222]. Conversely, it has been previously reported that α -synuclein knockdown increases glycolytic stress [169].

3.3.2. Tricarboxylic Acid Cycle

A dysfunction in the tricarboxylic acid (TCA or Krebs) cycle has been reported in PD brains [5, 109]. In particular, a decrease in the activity of the 2-oxoglutarate (α -ketoglutarate) dehydrogenase (OGDH or KGDH) is found in PD brains (**Figure 2.8**) [109]. Oxidative inactivation of aconitase has been shown to be induced by Complex I inhibitors, paraquat and *PINK1* mutations [46, 93, 157, 193, 229]. It has been demonstrated that inactivation of aconitase by oxidative stress can be compensated by OGDH, which allows glutamate to fuel the TCA cycle. This likely occurs because aconitase is more sensitive to oxidative damage than OGDH [318]. In contrast, oxidative stress induced by MAO was reported to preferentially target Complex I and OGDH (**Figure 2.8**) [210].

3.3.3. Nicotinamide Adenine Dinucleotide Metabolism

Nicotinamide adenine dinucleotide (NAD^+) participates in many biological reactions involved in energy metabolism, DNA repair and transcription. NAD^+ is required for the oxidation of glyceraldehyde 3-phosphate to 1,3-bisphosphoglycerate by glyceraldehyde 3-phosphate dehydrogenase (GAPDH) in glycolysis (**Figure 2.3**). In the TCA cycle, NAD^+ is a substrate for:

1) the oxidative decarboxylation of isocitrate to oxoglutarate (α -ketoglutarate) by IDH3; 2) pyruvate / oxoglutarate decarboxylation to thiamine pyrophosphate by pyruvate / oxoglutarate dehydrogenase (PDH / OGDH) that is required for the formation of acetyl / succinyl coenzyme A (CoA); and 3) the oxidation of malate to oxalacetate (**Figure 2.8**). NAD^+ is also used to transfer reducing equivalents from NADH to NADP^+ regenerating NADPH by NNT (**Figure 2.7**). The resultant reduced NADH is reoxidized in the cytosol by either the activity of lactate dehydrogenase (LDH) (**Figure 2.3**) or glycerol 3-phosphate dehydrogenase (GPDH), and by Complex I in the mitochondria (**Figure 2.9**). NAD^+ is also consumed by poly (ADP-ribose) polymerase-1 (PARP-1) during DNA-damage repair (**Figure 2.5**). Contradictory reports exist regarding the role of PARP-1 genetic variants in PD [40, 140], but a number of studies have suggested that PARP-1 activation upon PD-related insults leads to energy depletion associated to the consumption of ATP by the NAD^+ salvage pathway, and subsequent neuronal cell loss with necrotic characteristics (Parthanatos) [143, 144, 164, 181, 185, 195, 211, 252, 338, 350]. Parthanatos might be a secondary or complementary cell death mechanism to apoptosis in PD [334]. NAD^+ siphoning by PARP-1 can also have an impact on glycolysis, but this possibility has not been explored. In contrast, it has been demonstrated that PARP-1 activity has a protective role in neuronal cell death under mild and chronic oxidative stress conditions due to its role in oxidative-DNA damage repair [84]. Accordingly, we have observed that inhibition of PARP-1 enhances dopaminergic cell death induced by paraquat, its synergism with α -synuclein, and 6-OHDA toxicity as well (*unpublished results*). Ribose 5-phosphate from the PPP is also used for ADP-ribose synthesis (**Figure 2.5**). Thus a link between carbon flux through the PPP and DNA damage repair by PARP-1 in PD-related oxidative damage is also plausible.

Acetyl-CoA, succinyl-CoA and malonyl-CoA are used as substrates for post-translational Lys acylation (acetylation, succinylation and malonylation). Sirtuins (SIRT) deacetylase proteins by transferring the acetyl group using NAD^+ as a co-substrate (**Figure 2.6 and 2.7**). Sirtuins

regulate gene transcription by histone deacetylation, but proteins other than histones are also targeted by sirtuins [250]. Deacetylation of mitochondrial proteins within the ETC, the TCA cycle, and pyruvate metabolism by SIRT3 regulates metabolic function (**Figure 2.8**) [128, 269]. SIRT3 also regulates mitochondrial dynamics and biogenesis in response to oxidative stress via the forkhead transcription factor FOXO3 [319]. Knockout of mitochondrial SIRT3 increases the acetylation of multiple Complex I components and reduces its activity and energy production [6]. Similarly, IDH2 and MnSOD activity is enhanced by deacetylation via SIRT3 [60, 353]. NAD⁺ consumption by SIRT1 is contended by PARP-1 activity demonstrating the metabolic competitiveness for NAD⁺ consumption [24]. SIRT5 has NAD⁺-dependent desuccinylation and demalonylation activity and also regulates glycolysis, mitochondrial metabolism, ATP synthesis and respiration [43, 245, 268]. SIRT3 exerts a protective effect against rotenone induced toxicity *in vitro*, but other reliable evidence regarding the role of sirtuins in PD does not currently exist [357].

NAD⁺ consumption by PARPs and sirtuins generates nicotinamide (NAM), which is recycled back to NAD⁺ by the salvage pathway. First, nicotinamide phosphoribosyltransferase (NAMPT) catalyzes the condensation of nicotinamide with 5-phosphoribosyl-1-pyrophosphate to generate nicotinamide mononucleotide (NMN). Then, nicotinamide mononucleotide adenylyltransferase (NMNAT) catalyzes the condensation of NMN or nicotinic acid mononucleotide (NaMN), the precursor of NAD⁺ *de novo* synthesis, to form NAD⁺ or nicotinic acid mononucleotide (NaAD), respectively, while consuming ATP. NaAD requires further amidation to generate NAD⁺ [116]. Nicotinamide and NMN supplementation restores ATP, mitochondrial function and protects against 6-OHDA- MPP⁺- or rotenone-induced toxicity [148, 205, 361]. We have observed that while PARP-1 activity protects against paraquat toxicity in dopaminergic cells, targeted overexpression of NAMPT to the cytosol or mitochondria fails to do so (*unpublished data*), but the effect of NAD⁺ precursors has not been evaluated yet.

NAD⁺ is also a substrate for aldehyde dehydrogenases (ALDH). Cytosolic ALDH1A1 has been reported to be specifically located in dopaminergic neurons in the SNpc and to be involved in the metabolism of 3,4-dihydroxyphenylacetaldehyde (DOPAL), a toxic oxidative by product from dopamine deamination, to 3,4-dihydroxyphenylacetic acid (DOPAC) (**Figure 3.5**). ALDH1A1 and the mitochondrial ALDH2 are also involved in the metabolism of 4-HNE (**Figure 3.6**) [358]. Lipid peroxidation byproducts and mitochondrial / environmental toxins inhibit ALDH activity [98, 99, 187, 270]. Importantly, the inhibition of ALDH activity by rotenone is directly associated with decreased NAD⁺ availability [113, 187, 232]. ALDH1A1 is downregulated in PD brains and ALDH1A1 deficiency is linked to an increase in α -synuclein induced toxicity [196]. Interestingly, inhibition or downregulation of ALDH activity potentiates the toxicity of rotenone but not MPP⁺ [172, 196]. Age-dependent loss of dopaminergic neurons in the substantia nigra is observed in mouse lacking both ALDH1A1 and ALDH2, but not ALDH1A1 alone [15, 335].

4. Conclusions and Perspectives

Mitochondrial dysfunction has been well recognized and established as a causative mediator of PD pathogenesis. Mitochondrial dysfunction has also been highlighted as the main reason behind energy failure and oxidative stress in dopaminergic cells leading to their progressive degeneration. However, up till now, therapeutic approaches aimed at either preventing (mitochondrial) ROS formation and oxidative damage, or supplementing energy “fuel” to the brain have for the most part, failed to stop or ameliorate PD progression. We and others have demonstrated that dopaminergic cell death associated with PD-risk factors (genes and environmental exposures) is mediated by a dysfunction in both bioenergetics and redox homeostasis coupled to alterations in central carbon metabolism. In this review, we have aimed to provide an integrated view between bioenergetics, redox homeostasis, and central carbon metabolism and their potential role in dopaminergic degeneration (and glial dysfunction) in PD.

Taken together these findings strengthen the idea that PD is a complex metabolic disorder that cannot be simplistically and independently explained by either oxidative stress or energy failure.

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Figure Legends

Figure 1. Redox homeostasis and metabolic coupling between neurons and glia. Redox and metabolic homeostasis is carried out by a complex interaction between neurons, glia and the extracellular microenvironment. **1.1.** Glucose and lactate from blood circulation cross the blood brain barrier (BBB) through the GLUT1 (glucose transporter 1) and MCT1 (monocarboxylate transporter 1) transporters. Lactate is mainly taken up by neurons, while glucose is thought to be preferentially consumed by glial cells. **1.2** Neuronal ATP generation is dependent on oxidative phosphorylation, while glucose metabolism is primarily directed towards the PPP to generate NADPH required for antioxidant defense. Energy failure in PD is expected to impair a number of ATP-dependent processes that include: a) protein quality control mechanisms, including protein folding and protein aggregate (α -synuclein) degradation via the UPS and autophagy; b) transport of mitochondria across the axon and dendritic terminals (See **1.5**); c) dopamine and glutamate capture into vesicles; and d) maintenance of ionic gradients and plasma membrane potential during synaptic transmission. **1.3.** Glycolysis in astrocytes exceeds energy demands and thus lactate is shuttled as an energy substrate to neurons, which have a limited ability to upregulate glycolysis in response to mitochondrial dysfunction as it occurs in PD. Glucose flux to the TCA cycle is reduced in astrocytes due to phosphorylation of PDH. Astrocytes are able to store glucose in the form of glycogen. Glutamate (Glu) uptake from the inter-synaptic space via EAATs prevents excitotoxicity and facilitates neurotransmitter recycling via the synthesis of glutamine (Gln) that is also shuttled to neurons. In addition, Glu exchange for Cystine (that is reduced to Cysteine [Cys] inside the cell) via xCT (or Xc-), maintains Cys supply for *de novo* GSH synthesis. Furthermore, Nrf2 activation in response to oxidative stress promotes GSH synthesis, which is also released to provide precursors for its *de novo* synthesis in neurons (See **1.5**). Astrocytes also have the capacity to use oxidize FFA to fuel mitochondria but its functional relevance is unclear. **1.4.** Oligodendrocytes also shuttle

lactate as energy fuel to myelinated axons. **1.5.** In neurons, Nrf2 is repressed by methylation. Nevertheless, upregulation of antioxidant defenses is dependent on neuronal activity and the activation of ATF4 and AP-1 transcription factors. **1.6.** Environmental toxicants, α -synuclein oligomers, and cytokines activate microglia and induce oxidative stress. Importantly the pro-inflammatory M1 phenotype of activated microglia has been reported to be associated to a switch in their metabolism from oxidative phosphorylation to glycolysis that also enhances carbon flux to the PPP.

Figure 2. Interaction of Parkinson disease-related genes and risk factors with bioenergetics and central carbon metabolism. **2.1.** BDNF released by glial cells (and activation of the tropomyosin receptor kinase B [TrkB]) has protective effects in dopaminergic cells that can potentially be associated with the regulation of neuronal bioenergetics. **2.2** In astrocytes, energy can be stored as glycogen or it can be metabolized via glycolysis to meet energy demands. Glucose metabolism is also directed to lactate production that can be shuttled to neurons. In neurons PFKFB3 is constantly degraded and thus, they depend primarily in oxidative phosphorylation to meet their energy demands. GPI has been demonstrated to exert a protective effect against α -synuclein toxicity via glycolysis. **2.3.** Downstream the glycolytic pathway a number of enzymes have been shown to be altered / regulated in PD and by PD-related risk factors. Aldolase (ALDO), GAPDH and enolase (ENO) are found aggregated and oxidized in PD. Amyloid-like α -synuclein fibrils are expected to interact with and likely inhibit metastable glycolytic enzymes such as ALDO. Other groups have reported on the role of Parkin inhibiting PKM activity by ubiquitination. **2.4.** Spontaneous generation of methylglyoxal is thought to account for 0.1-0.4% of glycolytic flux. Accumulation of AGEs and dopamine-related methylglyoxal derivatives is linked to PD. DJ-1 is a cofactor-independent GLO III system that detoxifies methylglyoxal while also generating D-lactate that can contribute to the maintenance of mitochondrial function. DJ-1 is a redox-sensitive protein whose protective effects against PD-

related insults can be impaired by oxidative stress. **2.5** In neurons, glucose is primarily metabolized via the PPP to generate NADPH that provides reducing equivalents for antioxidant defense. Astrocytes have higher levels of NADPH and G6PD, and in glial cells, NADPH also has a pro-oxidant role by providing reducing equivalents for the generation of ROS by NOX and NOS. In addition, the ribose-5-P from the PPP is used for the generation ADP-ribose that is used during DNA-damage repair as a substrate for PARP-1 mediated ADP-ribosylation. NADPH is also regenerated by IDH1 in cytosol (**2.6**) and in the mitochondria by Nnt (**2.7**), and both systems have been reported to protect against PD-related insults MPP⁺ and paraquat. **2.8.** Alterations in the TCA cycle have also been found associated with PD. In the mitochondria, pyruvate decarboxylation by PDH is a necessary step for the generation of acetyl-CoA and Mn (manganese), a PD-risk factor has been reported to inhibit its activity. Aconitase (ACO) inactivation by oxidative stress is a biomarker of oxidative damage induced by PD-related insults or PINK1 mutants, while a decrease in OGDH is found in PD. **2.9.** A decrease in Complex I activity is found in PD. In addition Complex I has been reported to be targeted by environmental toxicants acting as Complex I inhibitors or inducing oxidative stress. PD-related genes DJ-1 and PINK1 regulate Complex I activity via direct interaction or phosphorylation of its subunits. **2.10.** The mitochondrial shuttles enable electrons and precursors transport across the inner membrane. Glutamate is metabolized to glutamine by GS an enzyme exclusively present in the astrocytes. Glutamine is shuttled from astrocytes to neurons where it is metabolized back to glutamate by GLS. A number of metabolites act as substrates for the activity of signaling proteins (highlighted in green circles). Prolyl hydroxylase (PDH)-dependent hydroxylation of HIF-1 α requires 2-oxoglutarate. **2.11.** One-carbon metabolism of serine to glycine and cysteine (via the transsulfuration pathway) contribute to the formation of GSH. **2.12.** Neurons very poorly metabolize FFA to obtain energy due the high O₂ demand and resultant generation of superoxide anion (O₂⁻) from β -oxidation. However, 20% of total adult brain energy comes from FFA oxidation, mostly in astrocytes, but its functional relevance is unclear. Enzymes highlighted

in blue circles are those within central carbon metabolism found to be modulated by oxidative stress and PD-related risk factors. PD-related genes are highlighted in red circles. Abbreviations and enzyme commission (EC) numbers for enzymes involved in central carbon metabolism: ACC, Acetyl-CoA carboxylase [EC: 6.4.1.2]; ACLY, ATP-citrate synthase [EC:2.3.3.8]; ACO, Aconitase [EC:4.2.1.3]; ALDO (A/B), Fructose-bisphosphate aldolase [EC:4.1.2.13]; cAspAT, Aspartate aminotransferase, cytoplasmic [EC:2.6.1.1 2.6.1.3]; mAspAT, Aspartate aminotransferase, mitochondrial [EC:2.6.1.1 2.6.1.7]; AR, aldose reductase [1.1.1.21]; CBS, Cystathionine beta-synthase [EC: 4.2.1.22]; CPT1, carnitine O-palmitoyltransferase 1 (CPT1 or 2 (CPT2) [EC: 2.3.1.21]; CS, Citrate synthase [EC:2.3.3.1]; CTH, Cystathionine gamma-lyase [EC: 4.4.1.1]; ENO, Enolase [EC:4.2.1.11]; FBP, fructose-1,6-bisphosphatase I [EC:3.1.3.11]; FUM, Fumarate hydratase [EC:4.2.1.2]; G3PP; Glucose-3-phosphate permease [EC:]; G6PD, Glucose-6-phosphate 1-dehydrogenase [EC:1.1.1.49]; GAPDH, Glyceraldehyde 3-phosphate dehydrogenase [EC:1.2.1.12]; GCL, Glutamate cysteine ligase [EC: 6.3.2.2]; GDH, Glutamate dehydrogenase, [EC: 1.4.1.3]; GLO1, Glyoxalase 1 or Lactoylglutathione lyase [EC:4.4.1.5]; GLO2, Glyoxalase 2 or Hydroxyacylglutathione hydrolase [EC 3.1.2.6]; GLS, Glutaminase [EC: 3.5.1.2]; GPI, Glucose-6-phosphate isomerase [EC:5.3.1.9]; GS, Glutamine synthetase [EC:6.3.1.2]; GSS, glutathione synthetase [EC: 6.3.2.3]; HK, hexokinase [EC:2.7.1.1]; IDH1, Isocitrate dehydrogenase 1 (NADP⁺), soluble [EC:1.1.1.42]; IDH3, isocitrate dehydrogenase 3 (NAD⁺); LDH, L-lactate dehydrogenase [EC:1.1.1.27]; MDH, Malate dehydrogenase [EC:1.1.1.37]; OGDH, 2-Oxoglutarate dehydrogenase, [EC:1.2.4.2]; SCS, Succinyl-CoA synthetase [EC:6.2.1.4 6.2.1.5]; PC, Pyruvate carboxylase [EC:6.4.1.1]; PGD, 6-phosphogluconate dehydrogenase [EC:1.1.1.44]; PDH, Pyruvate dehydrogenase [EC:1.2.4.1]; PGK, phosphoglycerate kinase [EC:2.7.2.3]; PGM, Phosphoglucomutase [EC:5.4.2.2]; PFK, 6-phosphofructokinase 1 [EC:2.7.1.11]; PFKFB3, 6-phosphofucto-2-kinase/fructose-2,6-biphosphatase 3 [EC:3.1.3.46]; PKM, Pyruvate Kinase [EC:2.7.1.40]; RPI, Ribose 5-phosphate

isomerase A [EC:5.3.1.6]; SDH, Succinate dehydrogenase [EC:1.3.5.1]; SHMT, Serine hydroxymethyltransferase [EC 2.1.2.1]; TPI, triose-phosphate isomerase [EC:5.3.1.1].

Figure 3. Bioenergetic requirements of antioxidant systems. Energy failure and ROS are the main consequences associated with mitochondrial dysfunction in PD. **3.1a.** Electron leakage from the mitochondria leads to one electron reduction of O_2 to $O_2^{\bullet-}$ that can be dismutated by SODs to H_2O_2 . $\bullet NO$ can outcompete SODs reacting with $O_2^{\bullet-}$ to generate $\bullet ONOO$. **3.1b.** In the plasma membrane $O_2^{\bullet-}$ can be generated by NOXs. **3.2.** In the presence of metals such as Fe, H_2O_2 and $O_2^{\bullet-}$ generate $\bullet OH$ through the Fenton/Haber-Weiss reaction. In PD, α -synuclein, neuromelanin and Fe-S clusters are important pools of Fe. **3.3.** Catalase and Prxs catalyze H_2O_2 degradation. The Trx/TrxR system supplies reducing equivalents for most Prxs. Prx hyperoxidation is reversed by Srx. **3.4a.** Gpxs detoxifies peroxides using GSH which is reduced back from GSSG by GR using NADPH. **3.4b.** GSH also detoxifies electrophiles (DAQ and 4-HNE) via the action of GSTs, and these adducts can be transported outside of the cell to become eliminated by the activity of MRP proteins. **3.5.** In the cytosol, dopamine (DA) becomes auto-oxidized in the presence of Fe generating DAQs and ROS. DA metabolism by MAO also generates ROS and DOPAL, which is further metabolized by ALDHs. **3.6.** ALDHs also detoxify 4-HNE into 4-hydroxy-2-nonenic acid (HNA) that is metabolized by cytochrome P450 enzymes (P450). **3.7.** Oxidative stress triggers antioxidant response elements (AREs)-regulated gene transcription by Nrf2, which promotes GCLC/GCLM, CuZnSOD and MnSOD transcription. **3.8.** A number of antioxidant systems and ROS generating enzymes utilize reducing equivalents from NADPH (in blue letters) that is regenerated by enzymes such as G6PD, and synthesized *de novo* via the phosphorylation of NAD^+ by NAD-kinase (NADK). Thus, antioxidant systems are tightly coupled to NAD^+ and central carbon metabolism. In addition, many antioxidant enzymes and stress responses (DNA-damage repair and the transcription of antioxidant enzymes by

Nrf2) require energy consumption (ATP, highlighted in dark red) demonstrating that redox homeostasis is tightly coupled to bioenergetics and cell metabolism.

Figure 4. Mitochondrial dynamics and biogenesis are coupled to oxidative stress and energy failure. **4.1.** Mitochondrial fusion rescues “moderately” dysfunctional mitochondria by enabling their “damaged” content to be mixed between neighboring mitochondria. Fusion is impaired by the ubiquitination of Mfns by PINK1 and Parkin (See **4.4**). **4.2.** Fission, transforms damaged mitochondria into a form suitable for engulfment by mitophagy, and it has been suggested to facilitate transport of mitochondria into terminals (See **4.6**). **4.3.** Parkin translocates to the mitochondria and interacts with PINK1 in response to a loss in membrane potential ($\Delta\Psi_m$) induced by energy failure or oxidative damage. VDAC1 is polyubiquitinated and recruits p62, which in turn interacts with LC3 at the autophagosomal membrane. Finally, engulfed damaged mitochondria are degraded after the autophagosome fuses with the lysosome and lysosomal hydrolases are released within the fused autolysosome. **4.5.** It has also been proposed that Parkin and PINK1 induce the formation of mitochondrial derived vesicles that translocate damaged mitochondrial proteins into lysosomes. **4.6.** Transportation of mitochondria to axonal and dendritic terminations is essential to meet energy demands associated with synaptic transmission. PINK1 and Parkin mediate phosphorylation, ubiquitination and degradation of Miro leading to the detachment of mitochondria from microtubules. **4.7.** Oxidative stress and energy failure activate PGC-1 α to stimulate mitochondrial biogenesis. Energy failure in PD is expected to impair transport of mitochondria into terminals, and the mitochondrial quality control mechanisms mitophagy and UPS. **4.4.** The proteasome has also been proposed to translocate to the mitochondria and mediate the degradation of damaged proteins. (ATP consumption is highlighted in red).

