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Research report

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

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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 processes 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.

1. Introduction

Oxidative stress and energy failure associated with mitochondrial dysfunction are cardinal hallmarks of neuronal cell death associated with neurodegenerative disorders (Cobb and Cole, 2015; Martin, 2012; Pathak et al., 2013; Yin et al., 2014). 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 also play an important role (Parkinson Study Group, 1993; Johri and Beal, 2012; Mecocci and Polidori, 2012; Snow et al., 2010). 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 (Chen and Zhong, 2013; Jagust et al., 1991; Xu et al., 2016). Hyperglycemia and amyloid β promote excitotoxicity in neuronal cells (Akhtar et al., 2016). Other studies have also revealed that glucose metabolism is decreased in the cortex and basal ganglia of Huntington's disease patients (Ciarmiello et al., 2006). Interestingly, an increase in the levels of glucose transporters was found to correlate inversely with the age of onset in Huntington's disease (Vittori et al., 2014). 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 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

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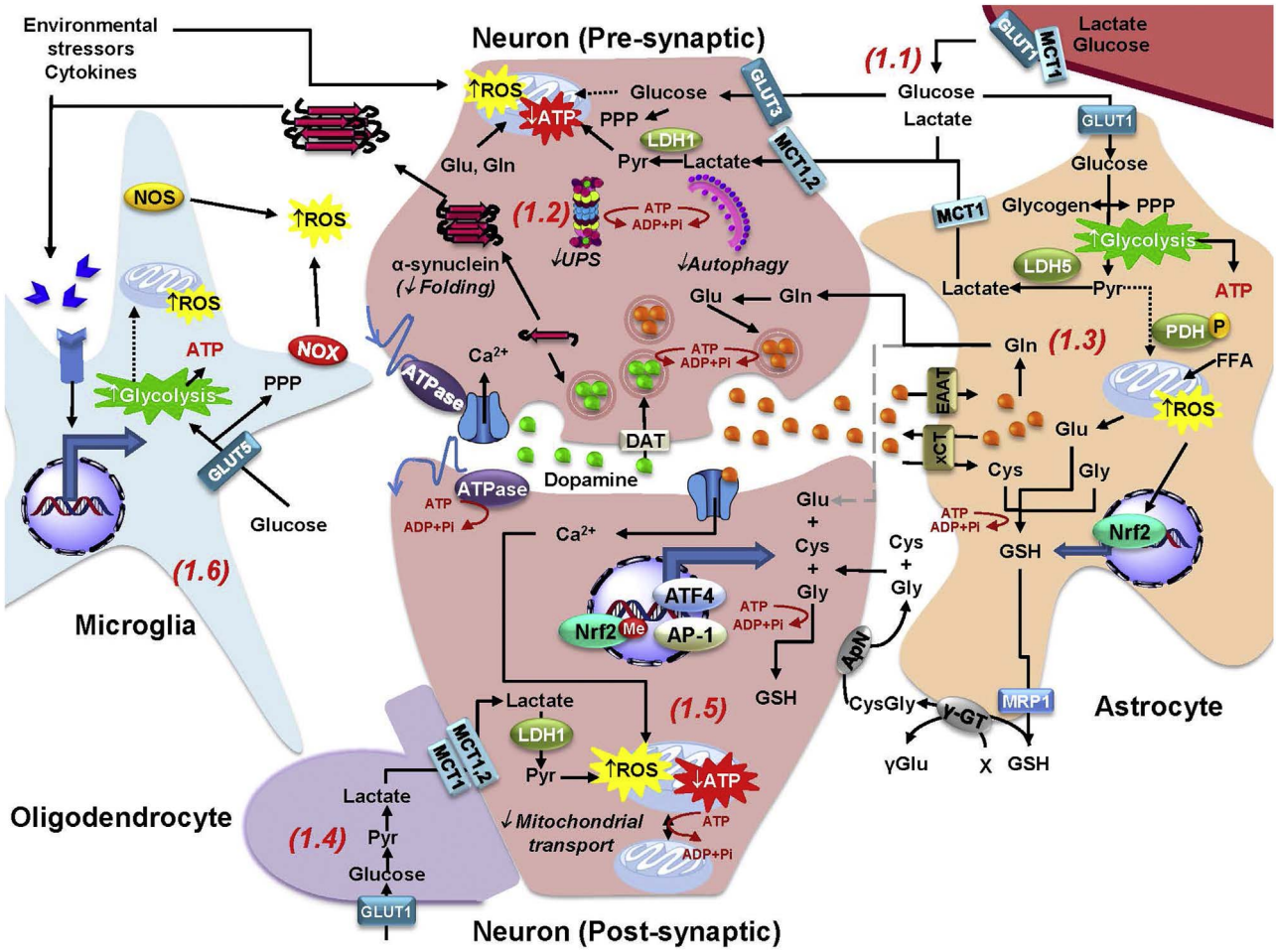

Fig. 1. Redox homeostasis and metabolic coupling between neurons and glia. Redox and metabolic homeostasis is carried out by a complex interaction between neurons, glia and the extracellular microenvironment. 1.1. Glucose and lactate cross the blood brain barrier (BBB) through the GLUT1 (glucose transporter 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 Glu 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. Glu uptake from the inter-synaptic space via EAATs prevents excytotoxicity and facilitates neurotransmitter recycling via the synthesis of Gln that is also shuttled to neurons. In addition, Glu exchange for Cystine (that is reduced to 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 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 has been suggested to be 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 with a switch in their metabolism from oxidative phosphorylation to glycolysis that also enhances carbon flux to the PPP.

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 consumes ~20% of total body energy (25% of the glucose and 20% of the oxygen consumption), and it is more resistant to energy starvation compared to other organs (Rolfe and Brown, 1997). Glucose is considered the obligatory energy substrate in the adult brain requiring its continuous delivery across the blood brain barrier (BBB) (Fig. 1(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 (Magistretti and Allaman, 2015). Ketone bodies derived from fatty acid metabolism in the liver can also cross the BBB (Hasselbalch et al., 1995).

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.

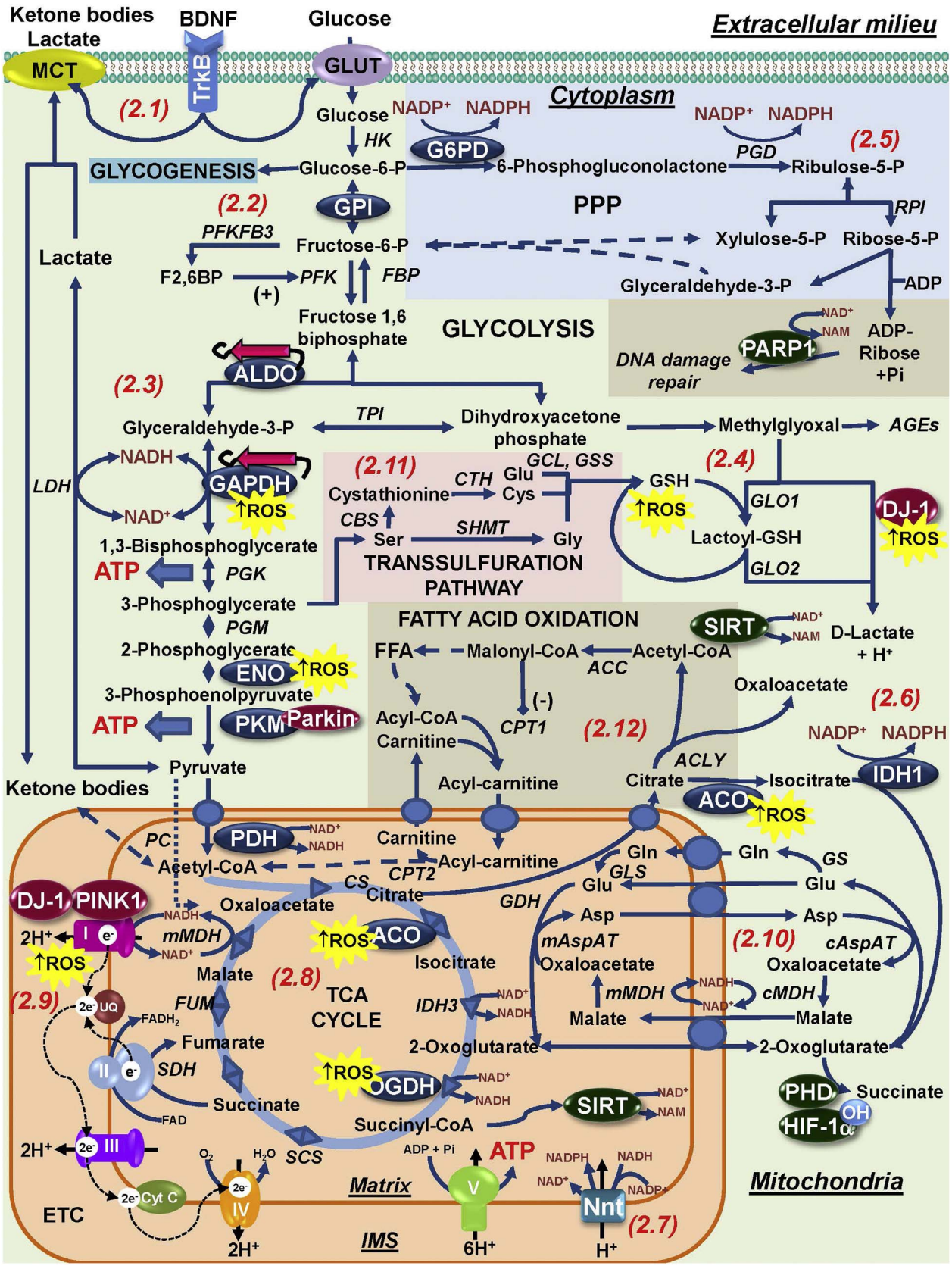

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Fig. 2. Interaction of Parkinson disease-related genes and risk factors with bioenergetics and central carbon metabolism. 2.1. BDNF released from glial cells (and the activation of the tropomyosin receptor kinase B [TrkB]) has protective effects in 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 than neurons, 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 the cytosol (2.6) and by Nnt in the mitochondria (2.7), and both NADPH recycling 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 also 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. Glu is metabolized to Gln by GS an enzyme exclusively present in the astrocytes. Gln is shuttled from astrocytes to neurons where it is metabolized back to Glu by GLS. A number of metabolites act as substrates for the activity of signaling proteins (highlighted in green circles). Prolyl hydroxylase (PHD)-dependent hydroxylation of HIF-1α requires 2-oxoglutarate. 2.11. One-carbon metabolism of Ser to Gly and Cys (via the transsulfuration pathway) contribute to the formation of GSH. 2.12. Neurons very poorly metabolize FFA to obtain energy due the high O_2 demand and resultant generation of superoxide anion ($O_2\cdot^-$) 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-phosphofructo-kinase 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].

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 the 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 (Mergenthaler et al., 2013; Raichle and Gusnard, 2002). 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 (Mergenthaler et al., 2013).

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 (Fig. 1(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 (Becker et al., 2000; Squire, 2008).

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 (Fig. 1(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) (Fig. 1(1.4)) (Baumann and Pham-Dinh, 2001; Snell, 2010). 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 (Fig. 1(1.3)), play an important role in the migration of immature neurons, tissue repair, and regulate blood flow and inflammatory processes by the release of signaling mediators (Sofroniew and Vinters, 2010). Microglial cells are resident macrophages distributed throughout the CNS that are embryologically unrelated to the other glial cells (Byrne and Roberts, 2009). 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 phagocyte 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 (Fig. 1(1.6)). While mild activation is a key adaptive immune response, continuous activation or overactivation of microglia is thought to contribute to neurodegeneration (Finsen and Owens, 2011; Hanisch, 2013; Hanisch and Kettenmann, 2007).

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

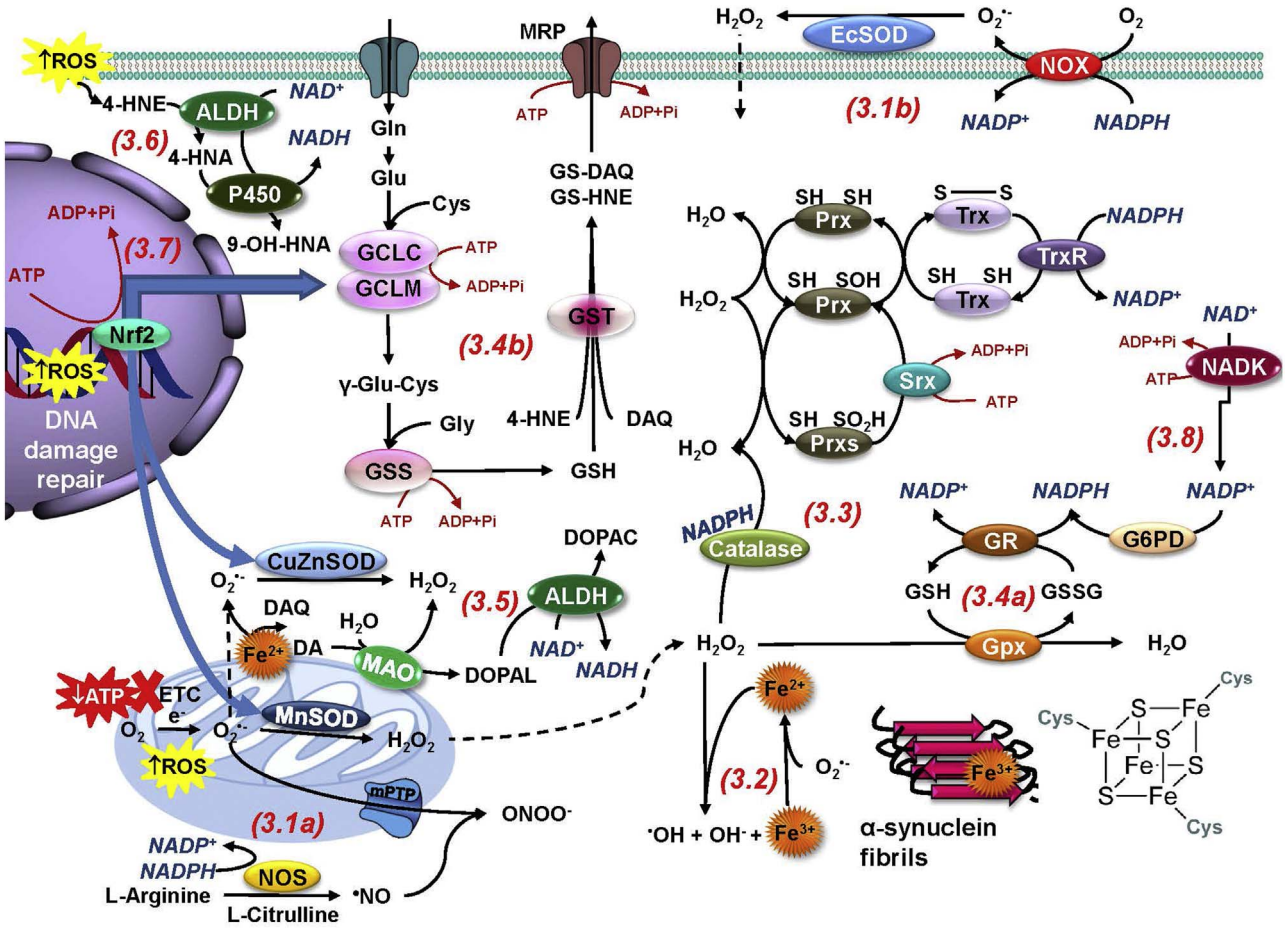

Fig. 3. Bioenergetic requirements of antioxidant systems. Energy failure and ROS are the main consequences associated with mitochondrial dysfunction in PD. 3.1a. Electron leakage from the mitochondria leads to one electron reduction of O_2 to $O_2\cdot^-$ that can be dismutated by SODs to H2O2. ·NO can outcompete SODs reacting with $O_2\cdot^-$ to generate $^-$ONOO. 3.1b. In the plasma membrane $O_2\cdot^-$ can be generated by NOXs. 3.2. In the presence of metals such as Fe, H2O2 and $O_2\cdot^-$ generate ·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 H2O2 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, 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-nonenoic 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.

(Fig. 1(1.1)) (Peters et al., 1991; Squire, 2008).

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) (Figs. 1(1.2) and 2(2.5)) (Brekke et al., 2012). NADPH is also required for antioxidant defense in glial cells, but it can actually mediate ROS generation by NADPH-oxidases (NOXs) (Fig. 3(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) (Fig. 2(2.6)), glutamate (Glu) dehydrogenase and nicotinamide nucleotide transhydrogenase (Nnt) (Fig. 2(2.7)). However, their contribution to NAPDH metabolism in neurons or glial cells has not been well defined (Fan et al., 2014). In isolated brain mitochondria Nnt has been reported to be important in the removal of peroxides (Lopert and Patel, 2014; Ying, 2008).

Neurons lack 6-phosphofructose-2-kinase/fructose-2,6-bisphosphatase-3 (PFKFB3) due to its continuous degradation by the ubiquitin-proteasome (UPS) pathway (Almeida et al., 2004). PFKFB3 is involved in the biogenesis and degradation of fructose-2,6-bisphosphate (F2,6BP), a glycolytic activator (Fig. 2(2.2)). In astrocytes, PFKFB3 is activated by AMPK (adenosine monophosphate-activated protein kinase) and promotes glycolysis (Herrero-Mendez et al., 2009a). 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) (Fig. 1(1.3) and (1.4)) (Belanger et al., 2011; Funfschilling et al., 2012; Lee et al., 2012c; Morrison et al., 2013). Neuronal function *ex vivo* can be maintained by lactate in the absence of glucose (Fernandez-Fernandez et al., 2012). 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 (Dienel, 2012; Ivanov et al., 2014; Pellerin and Magistretti, 2012; Schurr, 2014). 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 (Fig. 1(1.1)) (Stuart et al., 2011; Wang et al., 2006).

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 (Fig. 1(1.3)), is reduced by its phosphorylation in astrocytes (Zhang et al., 2014). 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 glucogenesis (Mergenthaler et al., 2013). In addition, Glu can be used as a carbon source for the TCA cycle in both neurons and astrocytes, while acetate is preferentially used by astrocytes (Belanger et al., 2011; Jiang et al., 2013a; Magistretti, 2009; Stobart and Anderson, 2013). The creatine/phosphocreatine/creatine kinase system has also been proposed to contribute to the regeneration of ATP in brain (Beard and Braissant, 2010). 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 (Fig. 2(2.12)), which has been related to the high O_2 demand and resultant generation of superoxide anion ($O_2^{\cdot -}$) from β-oxidation (Schonfeld and Reiser, 2013). However, 20% of total adult brain energy comes from FFA oxidation, mostly in astrocytes. Astrocytes can oxidize FFA (Fig. 1(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 (Iglesias et al., 2016; Schonfeld and Reiser, 2013).

Astrocytes are important players in the regulation of neuronal excitability by the removal of released neurotransmitters. The excitatory amino acid 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 Gln synthetase (GS) (Figs. 1(1.3) and 2(2.10)). Gln is exported and transferred to neurons (Glu-Gln cycle) to regenerate Glu via glutaminase (GLS) activity (Figs. 1(1.2) and 2(2.10)). Glu can also be utilized for *de novo* synthesis of the antioxidant glutathione (GSH) (Figs. 1(1.3), (1.5), 2(2.11) and 3(3.4b)) (Belanger et al., 2011; Schousboe et al., 2010). In general, neurons have limited defense mechanisms against ROS when compared to astrocytes (Fig. 1(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 (Figs. 1(1.3) and 3(3.7)) (Shih et al., 2003). While several reports demonstrate that Nrf2 signaling can be induced by oxidative stress in neurons (Guzman-Beltran et al., 2008), it has been recently suggested that neuronal Nrf2 is epigenetically silenced (Bell et al., 2015), and that induction of the Nrf2 pathway does not seem to restore their antioxidant protection (Fig. 1(1.5)) (Jimenez-Blasco et al., 2015). Astrocytes also have higher levels of NADPH and G6PD (glucose-6-phosphate dehydrogenase) (Garcia-Nogales et al., 2003). Interestingly, antioxidant genes in neurons are transcriptionally regulated by synaptic activity independent of Nrf2 through the activating transcription factor 4 (ATF4) and the activator protein 1 (AP-1) (Fig. 1(1.5)) (Baxter and Hardingham, 2016; Lewerenz and Maher, 2009). Both neurons and astrocytes can synthesize GSH, but neurons depend on the supply of GSH precursors (Fig. 1(1.3) and (1.5)). GSH is released from astrocytes via the ATP-binding cassette transporters subfamily C member 1 transporter (ABC-C1, or multidrug-resistance-associated protein 1 [MRP1]) (Hirrlinger and Dringen, 2005). Extracellular GSH is then degraded by the γ-glutamyl transpeptidase (γGT) to produce l-cysteine-L-glycine (CysGly), which is cleaved further by the neuronal aminopeptidase N (ApN) into the amino acids Gly and Cys that are taken up by neurons for GSH synthesis (Fig. 1(1.5)) (Aoyama et al., 2008; Belanger et al., 2011). Thus, both the Glu-Gln 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 (Choi et al., 2004). Inflammation also alters mitochondrial dynamics by favoring mitochondrial fission over fusion in astrocytes via autophagy (Motori et al., 2013). 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 (Fig. 1(1.6)) (Gimeno-Bayon et al., 2014; Orihuela et al., 2016; Volobouéva et al., 2013). 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, upon M2 activation of microglia with interleukin (IL)-4/IL13, no changes in mitochondrial oxygen consumption or lactate production were evidenced by extracellular flux analysis (Orihuela et al., 2016). A comparative study demonstrated that astrocytes are more resistant to oxidative damage than microglia or oligodendrocytes (Hollensworth et al., 2000).

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*) (Klein and Westenberger, 2012). 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 (Goldman, 2014). 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 (Levy et al., 2009; Yao and Wood, 2009), but the exact mechanisms are still unclear.

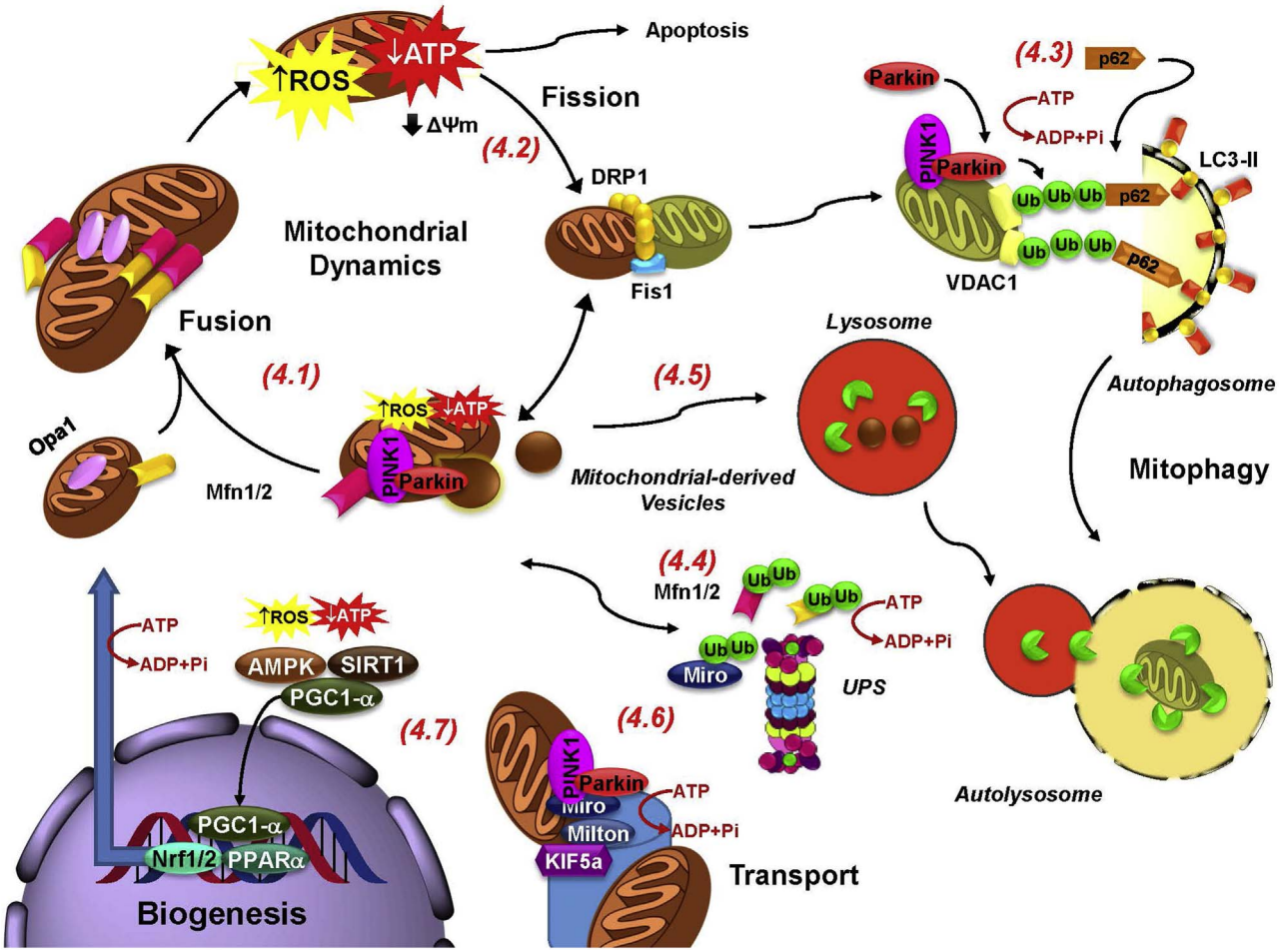

Fig. 4. Mitochondrial dynamics and biogenesis are coupled to oxidative stress and energy failure. 4.1. Mitochondrial fusion rescues 'moderately' dysfunctional mitochondria by enabling their "damaged" content to be mixed between neighboring mitochondria. Fusion is impaired by the ubiquitination of Mfns 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 (Δψm) 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 matrix of the newly formed 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-1α 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).

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. (Mena and Garcia de Yebenes, 2008). 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 (Fig. 2(2.1)), and are also thought to contribute to the survival of dopaminergic neurons (Marosi and Mattson, 2014). While astrocytes normally serve a neuroprotective role, reactive astrocytes are found in PD brains and are considered to contribute to neuroinflammatory processes (Chen et al., 2006; Voutilainen et al., 2009).

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-1β, tumor necrosis-factor α [TNFα], 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 (Fig. 1(1.6)) (Kim et al., 2013a; Long-Smith et al., 2009; Reynolds et al., 2008; Zhang et al., 2005). PD-related genes *PARK7, PINK1* and *LRRK2* have also been reported to modulate mitochondrial dysfunction, oxidative stress and the inflammatory response of glial cells (Choi et al., 2013; Moehle et al., 2012; Mullett and Hinkle, 2009; Mullett and Hinkle, 2011; Russo et al., 2015). Besides microglia, infiltrating cells such as T-lymphocytes, and neutrophiles have been reported to contribute to inflammation in neurodegenerative disorders including PD (Gonzalez and Pacheco, 2014; Ji et al., 2008; Rezai-Zadeh et al., 2009). For example, pathogenic T-cell populations potentiate microglial activation (Brochard et al., 2009; Reynolds et al., 2010). Importantly, peripheral cells such as lymphocytes and neutrophiles from PD patients observe mitochondrial dysfunction and increased oxidative stress (Annesley et al., 2016; Chen et al., 2009a; Gatto et al., 1996; Prigione et al., 2006; Prigione et al., 2009; Vitte et al., 2004), 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 cells and astrocytes (Cabezas et al., 2014; Gray and Woulfe, 2015). 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 (Obermeier et al., 2013).

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 (Figs. 2 (2.9) and 3 (3.1a)) (Henchcliffe and Beal, 2008; Keeney et al., 2006; Schapira, 2008; Schapira et al., 1989). 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 (Clark et al., 2011). Mutations in polymerase gamma (POLG) are linked to mitochondrial defects in Complex I and IV acquired in PD (Reeve et al., 2013). Accordingly, a high frequency of mitochondrial Complex I mutations was found in PD patients (Smigrodzki et al., 2004). Gene variations in the mitochondrial transcription factor A (TFAM) that controls mtDNA have also been associated with PD (Alvarez et al., 2008).

Mitochondrial dysfunction in PD has been linked to oxidative stress, as electron leakage from its metabolism is the primary source for ROS formation (Fig. 3(3.1a)). PD-associated genetic alterations alter mitochondrial function and homeostasis leading to increased ROS formation (Trancikova et al., 2012). Accumulation of α-synuclein has been suggested to trigger mitochondrial oxidative stress (Devi et al., 2008). DJ-1, PINK1 and Parkin deficiency or mutations impair mitochondrial respiration and render cells more susceptible to oxidative stress and mitochondrial dysfunction (Figs. 2(2.9) and 4) (Abramov et al., 2011; Amo et al., 2014; Jiang et al., 2004; Morais et al., 2009; Palacino et al., 2004; Taira et al., 2004). Phosphorylation of the Complex I subunit NdufA10 by PINK1 is necessary for ubiquinone reduction (Fig. 2(2.9)) (Morais et al., 2014). Gain-of-function of *LRRK2* mutations disturb mitochondrial bioenergetics and mitochondrial dynamics leading to increased ROS formation (Niu et al., 2012; Papkovskaia et al., 2012). In the mitochondria, $O_2 \cdot^-$ is generated in the matrix by electron leakage from Complex I (Grivennikova and Vinogradov, 2006), and in both the matrix and the inner membrane space (IMS) by electron leakage from Complex III (Fig. 3(3.1a)) (Chen et al., 2003). Dopaminergic neurons are highly sensitive to Complex I inhibitors whose toxicity is ascribed, at least partially, to the generation of ROS (Bates et al., 1994; Langston et al., 1983; Martinez and Greenamyre, 2012; Rodriguez-Rocha et al., 2013; Yadava and Nicholls, 2007). Other dopaminergic toxins or environmental agents linked to PD have also been shown to primarily mediate dopaminergic cell death via mitochondrial dysfunction (Castello et al., 2007; Glinka et al., 1998; Rodriguez-Rocha et al., 2013).

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 (Barkats et al., 2006; Kaul et al., 2003; Klivenyi et al., 1998; Liang et al., 2007b; Przedborski et al., 1992). 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 (Cappelletti et al., 2005; Cartelli et al., 2010; Fonck and Baudry, 2001; Kweon et al., 2004; Lee et al., 2000; Maruoka et al., 2007; Nakamura et al., 2000; Rodriguez-Rocha et al., 2013; Sanchez-Ramos et al., 1997; Zeevalk and Bernard, 2005). This might explain the failure of antioxidants (particularly mitochondria targeted antioxidants) in PD therapy (Parkinson Study Group, 1993; Snow et al., 2010), despite their reported success in preclinical models (Ghosh et al., 2010; Solesio et al., 2013). Furthermore, some studies suggest that impaired mitochondrial bioenergetics might be the main cause for neuronal cell death induced by the Complex I inhibitors rotenone and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP, or its active analog 1-methyl-4-phenylpyridinium [MPP^+]) (Bates et al., 1994; Dranka et al., 2012; Yadava and Nicholls, 2007). Supplementation of cells with Coenzyme Q_{10} (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 (Abdin and Hamouda, 2008). Similarly, directly delivery of electrons from NADH to cytochrome c using methylene blue attenuates dopaminergic neurodegeneration induced by rotenone (Yang et al., 2015). 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 (Davey and Clark, 1996; Schapira et al., 1990).

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 (Guzman et al., 2010). 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 (Matsuda et al., 2009; Pacelli et al., 2015; Pissadaki and Bolam, 2013). Importantly, the intrinsic bioenergetic capacity between dopaminergic and non-dopaminergic presynaptic synaptosomes does not differ (Choi et al., 2011), 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 (Fig. 1(1.2)) (Cook et al., 2012); 2) transport of mitochondria to pre-synaptic and post-synaptic sites (kinesin motors require ATP) (Fig. 4(4.6)) (Chu et al., 2012); and 3) mitochondrial biogenesis and dynamics (fusion, fission and mitophagy) (Figs. 1(1.2) and 4)(McCoy and Cookson, 2012). 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 (Fig. 1(1.2)) (Anne and Gasnier, 2014; Lotharius et al., 2002; Lotharius and Brundin, 2002). 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 Glu that leads to excitotoxic cell death, but this hypothesis requires further experimental support (Ambrosi et al., 2014; McNaught and Jenner, 2000; Yadava and Nicholls, 2007).

While neurons have a limited capability to upregulate glycolysis, an increase in glycolysis counteracts energy failure and dopaminergic cell death induced by mitochondrial dysfunction (Chaudhuri et al., 2015; Hong et al., 2016; Lannuzel et al., 2003). 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 (Andres et al., 2005; Matthews et al., 1999). However, in clinical trials creatine supplementation does not slow down the progression of PD (Kieburtz et al., 2015). 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. (Tieu et al., 2003). Accordingly, a ketogenic diet has been reported to exert protective effects in PD (Vanitallie et al., 2005).

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 (Fig. 4) (Exner et al., 2012; Van Laar and Berman, 2013). 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 (Fig. 4(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 (Fig. 4(4.2)) (Perier and Vila, 2012). Complex I inhibition promotes Drp1-mediated fission and mitophagy. Conversely, inhibition of fission protects against dopaminergic cell death induced by Complex I inhibitors (Van Laar and Berman, 2013). Importantly, recent evidence indicates that alterations in mitochondrial dynamics by PINK1 deficiency are a result of impaired bioenergetics (Vilain et al., 2012). Mitophagy has been shown to be regulated by PINK1 and the translocation of Parkin from the cytoplasm to “defective” mitochondria (Fig. 4(4.3)). Fusion arrest by polyubiquitination and proteasomal degradation of mitofusins (Mfn1 and Mfn2) by Parkin is required for mitophagy (Fig. 4(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 (Fig. 4(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 (Lutz et al., 2009). 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 (Exner et al., 2012). Importantly, recent reports have demonstrated that only prolonged (chronic) mitochondrial depolarization induces Parkin translocation or mitophagy in neurons (Fig. 4(4.2)) (Lee et al., 2015; Van Laar et al., 2011). Furthermore, mitophagy induced by dysfunction in mitochondrial respiration is independent from Parkin in dopaminergic neurons (Sterky et al., 2011). 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 (Fig. 4(4.5)) (McLelland et al., 2014).

Other PD related genes also affect mitochondrial dynamics. α-synuclein has been shown to impair mitochondrial fusion, which seems to precede mitochondrial dysfunction (Nakamura et al., 2011), while the A53T mutant was reported to stimulate mitophagy (Choubey et al., 2011). Loss of DJ-1 function promotes mitochondrial fission and mitophagy, but mitochondrial alterations are prevented by PINK1 and parkin (Irrcher et al., 2010; Thomas et al., 2011). A pathogenic increase in the activity of LRRK2 also promotes fission (Wang et al., 2012). Activation of AMPK by starvation promotes mitophagy, but its role in PD has not been clearly elucidated (Egan et al., 2011).

Mitochondria are actively transported into axonal and dedritic terminations due to the high energy requirements for synaptic neurotransmission (Fig. 4(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 (Kim-Han et al., 2011; Liang et al., 2007a). 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 (Fig. 4(4.6)) (Liu et al., 2012; Wang et al., 2011). 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-1α), which stimulates mitochondrial biogenesis (Fig. 4(4.7)) (Shin et al., 2011).

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 (Schmidt et al., 2011). DJ-1 knockout in astrocytes alters mitochondrial function and impairs neuroprotection against Complex I inhibition (Larsen et al., 2011). 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 (Tong et al., 2015). Accordingly, PINK1 knockout astrocytes exhibit defective proliferative signals, which were linked to alterations mitochondrial metabolism (Choi et al., 2013). Recently, damaged mitochondria have been reported to be transferred from neuronal axons for their turnover in astrocytes (Davis et al., 2014), and conversely, astrocytes have been shown to transfer mitochondria to neurons to promote survival (Hayakawa et al., 2016). 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 (Brown and Borutaite, 2012). 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 Cys 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) (Tavender and Bulleid, 2010). 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 (Mercado et al., 2013).

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 (Fig. 3(3.1b)) (Infanger et al., 2006). 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 (Gao et al., 2011). NOX-derived ROS from glial cells contributes to oxidative damage and dopaminergic neurodegeneration (Fig. 1(1.6)) (Infanger et al., 2006; Taetzsch and Block, 2013). Nitric oxide (·NO) is generated from L-arginine by nitric oxide synthases (NOS) which also requires reducing equivalents from NADPH (Miersch et al., 2008). When $O_2\cdot^-$ reacts with ·NO it generates peroxynitrite ($ONOO^-$) (Fig. 3(3.1a)) (Denicola et al., 1998). Inducible NOS (iNOS) is also activated by mitochondrial toxins and inflammatory events in microglia at the SN to promote neurodegeneration (Fig. 1(1.6)) (Arimoto and Bing, 2003; Liberatore et al., 1999). Neuronal NOS (nNOS) also contributes to dopaminergic cell death induced by MPTP (Hantraye et al., 1996; Przedborski et al., 1996). In addition, NOS uncoupling by the PD-related pesticide paraquat has also been recognized as an important source for $O_2\cdot^-$ (Luo et al., 2014; Margolis et al., 2000).

$O_2\cdot^-$ can be dismutated via enzymatic (via $O_2\cdot^-$ dismutases [SODs]) or non-enzymatic reactions to H_2O_2 (Fig. 3(3.1a) and (3.1b)). SOD activity was found to be increased in post-mortem PD brains (Ceballos et al., 1990; Saggu et al., 1989). Metals such as iron (Fe) can also promote ROS formation via the Fenton/Haber-Weiss reaction that catalyzes the formation of hydroxyl radical (·OH) by their reaction with H_2O_2 (Fig. 3(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 ·OH (Sian-Hulsmann et al., 2011). In PD, Fe is deposited abundantly in the neuromelanin (NM) granules of SNpc dopaminergic neurons (Sian-Hulsmann et al., 2011). Fe deposition in PD might be related to alterations in Fe transport and storage systems (Dusek et al., 2012; Hochstrasser et al., 2005; Jin et al., 2011; Lee and Andersen, 2010). ·OH formation by Fe has also been proposed to involve α-synuclein (Fig. 3(3.2)) (Chew et al., 2011; Martin et al., 2003; Ostrerova-Golts et al., 2000; Turnbull et al., 2001). Because of their high Fe content, lysosomes are another important potential source of ROS (Kurz et al., 2010), and lysosomal breakdown has also been linked to PD pathogenesis (Dehay et al., 2013). Finally, disruption of Fe-Sulfur (S) clusters by oxidative stress induced by paraquat or PINK1 mutants has also been proposed to enhance oxidative damage (Fig. 3(3.2)) (Cantu et al., 2009; Esposito et al., 2013).

Oxidative stress in PD is also associated with the pro-oxidant properties of DA. Mutant α-synuclein down-regulates the vesicular monoamine transporter (VMAT2) (Lotharius et al., 2002; Lotharius and Brundin, 2002). In the cytosol, DA 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) (Fig. 3(3.5)) (Abou-Sleiman et al., 2006). Dopaminergic cell death induced by mitochondrial toxins has been proposed to depend on DA oxidation (Kang et al., 2009; Liu et al., 2005). DAQ byproducts from DA oxidation have been reported to react with protein Cys thiols (Hastings et al., 1996), and with GSH to form adducts (GS-DAQ) by the activity of GSH-S-transferases (GSTs) (Dagnino-Subiabre et al., 2000; Segura-Aguilar et al., 1997). 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 (Fig. 3(3.4b)) (Yoritaka et al., 1996).

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 (Fig. 3(3.3)).The activity of catalase was reported to be reduced in the SN and putamen of PD brains (Ambani et al., 1975). Peroxiredoxins (Prxs) are thiol peroxidases primarily seen as regulators of peroxide signaling (Cox et al., 2010). 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 (Fig. 3(3.3)). Overexpression of Prx1, Prx2 and Prx4 protects against 6-hydroxydopamine (6-OHDA)-induced dopaminergic cell death (Hu et al., 2011; Lee et al., 2008), whereas silencing mitochondrial Prx3 and Prx5 increases sensitivity to MPP^+ (De Simoni et al., 2008). The Trx/TrxR system also protects against MPP^+- 6-OHDA- and paraquat-induced toxicity in dopaminergic cells (Arodin et al., 2014; Bai et al., 2002; Lopert et al., 2012; Yang et al., 2009).

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 (Jenner, 1993; Perry and Yong, 1986; Sian et al., 1994). Accordingly, inducible depletion of GSH promotes nigrostriatal degeneration in mouse (Chinta et al., 2007). GSH peroxidases (GPx) and Prx6 use the reducing power of GSH to hydrolyze peroxides generating GSH disulfide (GSSG) as a byproduct (Fig. 3(3.4a)). Mice deficient in GPx1 exhibit an increased sensitivity to MPTP toxicity (Klivenyi et al., 2000), while its overexpression protects against MPP^+- and 6-OHDA-induced toxicity *in vitro* and *in vivo* (Bensadoun et al., 1998; Kalivendi et al., 2003; Ridet et al., 2006; Thiruchelvam et al., 2005). 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 (Yun et al., 2015).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 $NADP^+$ (Figs. 2(2.5) and 3(3.4a)). Downregulation of PPP enzymes and a failure to increase the the antioxidant reserve capacity are early events in the pathogenesis of sporadic PD (Dunn et al., 2014). Transgenic mice overexpressing G6PD in dopaminergic cells are resistant to MPTP-induced toxicity (Mejias et al., 2006). Impairment of 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-phoshate (Ying, 2008). 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 (Anandhan et al., 2016; Lei et al., 2014). 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 protectives effect against the toxicity of MPTP/

MPP^+ (Mejias et al., 2006; Yang and Park, 2011). These observations might explain why there is no generalized association between changes in G6PD activity and PD (Gao et al., 2008).

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 (Schreiner et al., 2015). 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 (Chen et al., 2009b).

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 Glu and Cys via the glutamate-cysteine ligase (GCL), and the subsequent addition of Gly by the activity of GSH synthetase (GSS) (Figs. 1(1.3) and 3(3.4b)) (Franco and Cidlowski, 2012; Meister, 1995; Sies, 1999). Both reactions requiring ATP consumption. The transsulfuration pathway (Fig. 2(2.11)) contributes to the generation of Cys, the rate limiting substrate for GSH synthesis, from one carbon metabolism of serine (Ser) → cystathionine → Cys. Interestingly, high levels of homocysteine, a co-substrate with Ser for cystathionine formation, have been found in PD brains (Bhattacharjee and Borah, 2016). Both Gly and Glu are also byproducts of central carbon metabolism (glycolysis or TCA cycle, respectively) (Fig. 2(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 (Fig. 3(3.4b)) (Cole, 2014). The reduction of hyperoxidized Prxs (sulfenylated, SO_2H) by sulfiredoxin (Srx) relies on the initial formation of a sulfinic phosphoryl ester ($Cys\text{-}S_PO_2PO_3^{2-}$) between the Srx and Prx that requires ATP consumption (Fig. 3(3.3)) (Biteau et al., 2003). ATP is also required for the synthesis of $NADP^+$ via NAD^+ (nicotinamide adenine dinucleotide) kinase (Fig. 3(3.8)). Transcriptional regulation of antioxidant defenses (SOD1 [CuZnSOD], SOD2 [MnSOD], the modifier and catalycic GCL subunits [GCLM and GCLC], and GSTs) via Nrf2 and conversely, the ubiquitination and degradation of the Nrf2-kelch-like ECH-associated protein 1 (Keap1) cytosolic complex also require energy (Fig. 3(3.7)) (Johnson and Johnson, 2015). ATP depletion is also anticipated to impair oxidative DNA-damage repair systems (Fig. 3(3.7)) (Dahan-Grobgeld et al., 1998; Guzder et al., 1997; Storr et al., 2013; Wright et al., 2016). GCLM knockout was shown to increase dopaminergic neurodegeneration induced by paraquat (Liang et al., 2013). 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 (Lavoie et al., 2011).

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 abnormally elevated levels of lactate/pyruvate have been observed in PD patients (Ahmed et al., 2009; Eberling et al., 1994; Henchcliffe et al., 2008; Palombo et al., 1990). Disruption of glycolysis in astrocytes and oligodendrocytes triggers axon damage and neurodegeneration (Lee et al., 2012b; Volkenhoff et al., 2017). Interestingly, glucose deprivation promotes α-synuclein aggregation (Fig. 1(1.2)) (Bellucci et al., 2008). In contrast, lactate has been reported to exert an opposite effect on α-synuclein aggregation (Jiang et al., 2013b). 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 (Anandhan et al., 2016; Badisa et al., 2010; Chalmers-Redman et al., 1999; Chan et al., 1993; Chaudhuri et al., 2015; Mazzio and Soliman, 2003; Wu et al., 1992; Yoon and Oh, 2015), As mentioned before, failure of neuronal cells to upregulate this pathway seems to make them rather sensitive to mitochondrial dysfunction (Herrero-Mendez et al., 2009b). Interestingly, dietary restriction and administration of 2-deoxy-D-glucose exerted protective effects against MPTP toxicity (Duan and Mattson, 1999). 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 (Lei et al., 2014). This effect was paralleled by an impairment of NADPH-dependent antioxidant systems leading to GSH depletion and Prx hyperoxidation (Rodriguez-Rocha et al., 2013). 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 (Fig. 2(2.2) and (2.8)) (Cantu et al., 2009; Gardner and Fridovich, 1991; Lei et al., 2014; Newsholme et al., 1977).

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-1α) (Fig. 2(2.10)) and the AMPK (Requejo-Aguilar et al., 2014; Requejo-Aguilar et al., 2015; Shi et al., 2015; Zhang et al., 2011). Alterations in cellular energy are tightly monitored by the master regulator of metabolism AMPK (Cardaci et al., 2012). 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 (Fig. 4(2.7)) (Anandhan et al., 2016). 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 (Choi et al., 2010; Dulovic et al., 2014; Ng et al., 2012). In contrast, other reports have shown that AMPK mediates dopaminergic cell death induced by rotenone and 6-OHDA (Kim et al., 2013b; Xu et al., 2014). Contradictory results have also been reported regarding the role of AMPK in α-synuclein aggregation and toxicity (Dulovic et al., 2014; Jiang et al., 2013b). 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) (Fig. 2(2.4)). MGO is a potent glycative agent that readily reacts with lipids, nucleic acids and protein lysines (Lys)/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 (Fig. 2(2.4)) (Allaman et al., 2015; de Arriba et al., 2007; Sousa Silva et al., 2013). An increase in AGEs has been reported in PD (Vicente Miranda et al., 2016). MGO is actually a precursor for 1-acetyl-6, 7- dihydroxyl-1, 2, 3, 4-tetrahydroisoquinoline (ADTIQ), a DA-derived tetrahydroisoquinoline (TIQ) toxin that is also found in PD brain tissue (Xie et al., 2015). 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 (Fig. 2(2.4)). The activity of GLOs is higher in astrocytes than neurons (Allaman et al., 2015), and is inhibited by glutathionylation (mixed disulfide bond formation be-

tween a protein Cys and GSH) (Birkenmeier et al., 2010). 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 (Allaman et al., 2015). These observations actually correlate with the higher expression of DJ-1 in astrocytes when compared to neurons (Bandopadhyay et al., 2004), and the discovery that DJ-1 is a cofactor-independent GLO III system (Fig. 2(2.4)) (Lee et al., 2012a). 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 (Toyoda et al., 2014). 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 (Fig. 2(2.3)) (Liu et al., 2016).

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) (Gomez and Ferrer, 2009). 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 (Fig. 2(2.3)) (Olzscha et al., 2011; Xu et al., 2013). 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 (Fig. 2(2.2)) (Knight et al., 2014). We have observed that the mechanism by which α-synuclein enhances metabolic dysfunction induced by environmental toxicants is linked to an impairment of glycolysis (Anandhan et al., 2016). Accordingly, other reports have reported a possible interaction between α-synuclein and glycolytic enzymes such as aldolase (Jin et al., 2007; McFarland et al., 2008). Conversely, it has been previously reported that α-synuclein knockdown increases glycative stress (Kurz et al., 2011).

3.3.2. Tricarboxylic acid cycle

A dysfunction in the tricarboxylic acid (TCA or Krebs) cycle has been reported in PD brains (Ahmed et al., 2009; Gibson et al., 2003). In particular, a decrease in the activity of the 2-oxoglutarate (α-ketoglutarate) dehydrogenase (OGDH or KGDH) is found in PD brains (Fig. 2(2.8)) (Gibson et al., 2003). Oxidative inactivation of aconitase has been shown to be induced by Complex I inhibitors, paraquat and *PINK1* mutations (Cantu et al., 2009; Esposito et al., 2013; Kalivendi et al., 2003; Liang and Patel, 2004; Mena et al., 2011). It has been demonstrated that inactivation of aconitase by oxidative stress can be compensated by OGDH, which allows Glu to fuel the TCA cycle. This likely occurs because aconitase is more sensitive to oxidative damage than OGDH (Tretter and Adam-Vizi, 2000). In contrast, oxidative stress induced by MAO was reported to preferentially target Complex I and OGDH (Fig. 2(2.8)) (Mallajosyula et al., 2009).

3.3.3. Nicotinamide adenine dinucleotide metabolism

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-biphosphoglycerate by GAPDH in glycolysis (Fig. 2(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 decarboxilation to thiamine phyrophosphate 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 (Fig. 2(2.8)). NAD^+ is also used to transfer reducing equivalents from NADH to $NADP^+$ regenerating NADPH by Nnt (Fig. 2.**7**). The resultant reduced NADH is reoxidized in the cytosol by either the activity of lactate dehydrogenase (LDH) (Fig. 2(2.3)) or glycerol 3-phosphate dehydrogenase (GPDH), and by Complex I in the mitochondria (Fig. 2(2.9)). NAD^+ is also consumed by poly (ADP-ribose) polymerase-1 (PARP-1) during DNA-damage repair (Fig. 2(2.5)). Contradictory reports exist regarding the role of PARP-1 genetic variants in PD (Brighina et al., 2011; Infante et al., 2007), 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) (Iwashita et al., 2004a; Iwashita et al., 2004b; Kim et al., 2013b; Lee et al., 2013; Lehmann et al., 2016; Linsenbardt et al., 2012; Mandir et al., 1999; Outeiro et al., 2007; Wu et al., 2014; Yokoyama et al., 2010). Parthanatos might be a secondary or complementary cell death mechanism to apoptosis in PD (Wani et al., 2014). 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 (Diaz-Hernandez et al., 2007). 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 (Fig. 2(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 (Fig. 2(2.6) and (2.7)). Sirtuins regulate gene transcription by histone deacetylation, but proteins other than histones are also targeted by sirtuins (Osborne et al., 2016). Deacetylation of mitochondrial proteins within the ETC, the TCA cycle, and pyruvate metabolism by SIRT3 regulates metabolic function (Fig. 2(2.8)) (Hebert et al., 2013; Rardin et al., 2013b). SIRT3 also regulates mitochondrial dynamics and biogenesis in response to oxidative stress via the forkhead transcription factor FOXO3 (Tseng et al., 2013). Knockout of mitochondrial SIRT3 increases the acetylation of multiple Complex I components and reduces its activity and energy production (Ahn et al., 2008). Similarly, IDH2 and MnSOD activity is enhanced by deacetylation via SIRT3 (Cheng et al., 2016; Yu et al., 2012). NAD^+ consumption by SIRT1 is contended by PARP-1 activity demonstrating the metabolic competitiveness for NAD^+ consumption (Bai et al., 2011). SIRT5 has NAD^+-dependent desuccinylation and demalonylation activity and also regulates glycolysis, mitochondrial metabolism, ATP synthesis and respiration (Buler et al., 2014; Nishida et al., 2015; Rardin et al., 2013a). 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 (Zhang et al., 2016).

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^+ (Gossmann et al., 2012). Nicotinamide and NMN supplementation restores ATP, mitochondrial function and protects against 6-OHDA- MPP^+- or rotenone-induced toxicity (Jia et al., 2008; Lu et al., 2014; Zou et al., 2016). We have observed that while PARP-1 activity protects against paraquat toxicity in dopaminergic cells, targeted overexpression of NAMPT to the cytosol or mitochon-

dria 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) (Fig. 3(3.5)). ALDH1A1 and the mitochondrial ALDH2 are also involved in the metabolism of 4-HNE (Fig. 3(2.6)) (Zhang et al., 2010). Lipid peroxidation byproducts and mitochondrial/environmental toxins inhibit ALDH activity (Fitzmaurice et al., 2013; Florang et al., 2007; Leiphon and Picklo, 2007; Rees et al., 2007). Importantly, the inhibition of ALDH activity by rotenone is directly associated with decreased NAD^+ availability (Goldstein et al., 2015; Leiphon and Picklo, 2007; Meyer et al., 2004). ALDH1A1 is downregulated in PD brains and ALDH1A1 deficiency is linked to an increase in α-synuclein induced toxicity (Liu et al., 2014). Interestingly, inihibition or downregulation of ALDH activity potentiates the toxicity of rotenone but not MPP^+ (Lamensdorf et al., 2000; Liu et al., 2014). Age-dependent loss of dopaminergic neurons in the SN is observed in mouse lacking both ALDH1A1 and ALDH2, but not ALDH1A1 alone (Anderson et al., 2011; Wey et al., 2012).

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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