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Mitochondria in Neuronal Health: From Energy Metabolism to Parkinson's Disease

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Mitochondria are the main suppliers of neuronal adenosine triphosphate and play a critical role in brain energy metabolism. Mitochondria also serve as Ca^{2+} sinks and anabolic factories and are therefore essential for neuronal function and survival. Dysregulation of neuronal bioenergetics is increasingly implicated in neurodegenerative disorders, particularly Parkinson's disease. This review describes the role of mitochondria in energy metabolism under resting conditions and during synaptic transmission, and presents evidence for the contribution of neuronal mitochondrial dysfunction to Parkinson's disease.

1. Introduction

Information processing in our brains consumes staggering amounts of energy. It has been estimated that a single resting cortical neuron consumes over 4.7×10^9 adenosine triphosphate (ATP) molecules per second,[1] and this number rises significantly upon action potential firing. The release and recycling of synaptic vesicles during neurotransmission[2] and the re-equilibration of ion influx all along the neuron by the Na^+/K^+ ATPase[3] are highly energy consuming events. Other processes, such as the transport of molecules over the large distances spanned by axons and dendrites, as well as the synthesis of proteins upon stimulation, add to the neuronal energy usage. In this review, we discuss how this enormous amount of ATP is supplied by the different routes of ATP generation and is altered in disease states.

Energy metabolism is mediated by the interplay of cytosolic glycolysis with mitochondrial oxidative phosphorylation (OXPHOS). Glucose is the main energy source for the brain and is first imported into the cytoplasm of neurons or astrocytes and converted to pyruvate via glycolysis. Pyruvate is then transported across the mitochondrial membranes and decarboxylated to form acetyl-CoenzymeA (acetyl-CoA). Acetyl-CoA is also the final product of fatty acid β-oxidation, which can occur in mitochondria or peroxisomes alike. Another source of acetyl-CoA is ketone bodies derived from fatty acid oxidation in the liver and secreted into the bloodstream for uptake by extrahepatic tissues. Acetyl-CoA from various sources can then enter the tricarboxylic acid (TCA) cycle to produce the reducing equivalents NADH and FADH, which will finally be fed into the respiratory chain to produce ATP.

Although mitochondria are essential for OXPHOS, they are more than just the "powerhouse of the cell," as they also regulate several catabolic processes, such as amino acid or steroid synthesis, influence Ca^{2+} and redox equivalent concentrations in the cytosol, and are crucial hubs in the execution of cell death (**Figure 1**). Thus, it is impossible to review mitochondrial energy metabolism in health and disease without discussing other mitochondrial functions. Therefore, we will briefly describe our current knowledge of mitochondrial function in other catabolic and homeostatic processes. Further, we discuss the cellular responses to mitochondrial dysfunction and how these pathways enhance or deteriorate the pathogenesis of Parkinson's (PD), a neurodegenerative disease that is deeply linked to mitochondrial dysfunction.

2. ATP Sources in Neurons

Unlike most metabolically demanding tissues such as muscle, neurons do not have significant energy stores in the form of glycogen, lipids, or creatine phosphate.[4] As a result, neuronal energy metabolism is tightly regulated, and even acute interruptions in fuel supply rapidly suppress cognitive function. Below, we discuss some of the important sources of ATP in neurons and their contribution to energetic homeostasis and neuronal survival.

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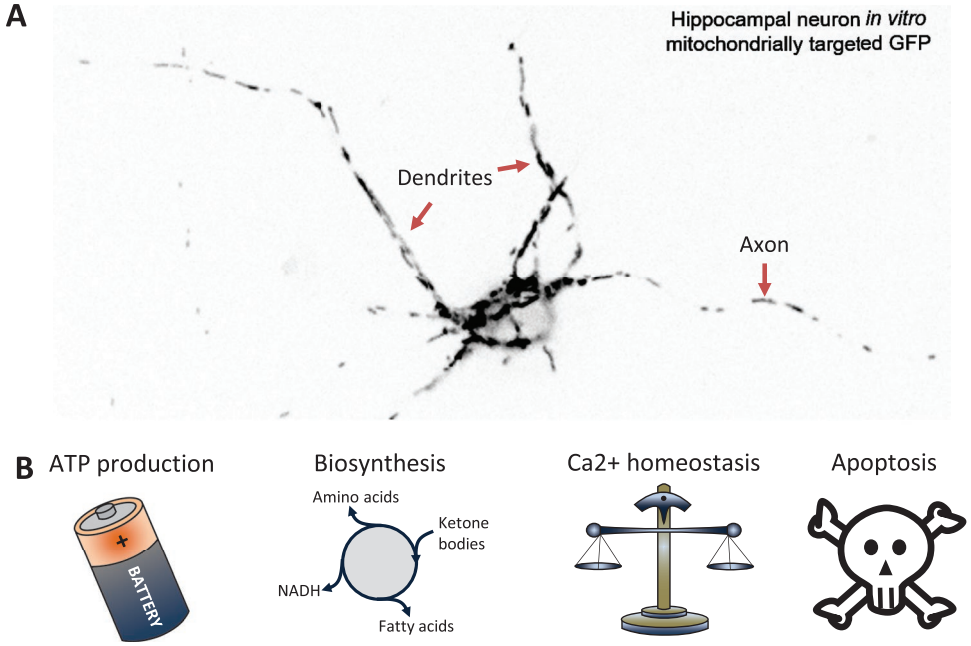

Figure 1. Mitochondrial functions in neurons. A) Microscopic image of a hippocampal rat neuron grown in culture and transfected with mitochondrially targeted GFP. Note the different density and shapes of mitochondria in axons and dendrites. B) Mitochondria are crucial for neuronal ATP synthesis, but also are involved in various biosynthetic and homeostatic processes including Ca^{2+} regulation and programmed cell death (apoptosis).

2.1. Glucose Metabolism in the Brain

Glucose is the primary fuel available to the brain for energy production. This 6-carbon molecule crosses the blood-brain barrier with the help of glucose transporter (GLUT)-1 expressed in endothelial cells and subsequently reaches neurons through GLUT3 and GLUT4.[5,6] The most prominent pathway of glucose metabolism is glycolysis which generates two 3-carbon molecules of pyruvate, per molecule of glucose. In the presence of oxygen, pyruvate is directed to mitochondria for OXPHOS to generate additional ATP molecules. Under certain conditions, such as in anaerobic environments, cancerous cells, or cell lacking mitochondria, pyruvate is converted to lactate and extruded from the cell to maintain the NAD^+ concentrations required for glycolysis. Both neurons and astrocytes are reported to generate lactate from glucose, although to different extents.[7,8] The astrocyte-neurons-lactate-shuttle (ANLS) model suggests that neurons preferentially utilize lactate released from astrocytes during synaptic activity (**Figure 2**).[9] There are various reported findings in support of the ANLS model: 1) higher NADH levels in astrocytes than neurons,[10] 2) lower expression level of a key glycolytic enzyme that catalyzes the formation of fructose-2,6-bisphosphate(6-phosphofructose-2-kinase/fructose-2,6-bisphosphatase-3) in neurons versus astrocytes,[11] and 3) active neurons absorbing higher amounts of lactate than glucose.[12] On the other hand, there are also several lines of evidence that are inconsistent with the ANLS model: 1) recruitment of the glucose transporter GLUT4 to firing synapses,[13] 2) no observed change in neuronal cytosolic NADH levels when lactate uptake is inhibited,[14] and 3) continuous glucose uptake and consumption in neurons imaged through cranial windows in awake mice.[15] Overall, the existence and metabolic relevance of the ANLS may depend on specific cell types, brain regions, and/or types of neuronal activity.[9]

2.1.1. Glycolysis

Glycolysis plays a privileged role in supporting synaptic activity in nerve terminals. During electrical activity, nerve terminals orchestrate what is known as a "glycolytic metabolon," which is the reorganization of glycolytic enzymes at the synapse, to provide ATP for sustainable synaptic transmission under energy stress.[16] Indeed, glycolysis is closely associated with the movement of synaptic vesicles within neuronal axons through the localization of glycolytic enzymes on vesicles and local provision of ATP to fuel molecular motors.[17] Furthermore, both glycolysis and the glucose transporter GLUT4 are essential for synaptic vesicle recycling in hippocampal neurons.[5] Positron emission tomography of stimulated brain regions not only shows an increase in cerebral blood flow but also an immediate uptake of glucose and O_2 (indicating OXPHOS), with the increase in glucose consumption being larger than O_2,[18] signifying a causative dependency on sustained glycolysis for neurotransmission. Glycolysis is a more rapid but less efficient ATP-producing process therefore it is ideally suited to support the acute energy demands immediately after neuronal stimulation while subsequently activating the slower but more efficient aerobic respiration for sustained energy expenditure.[19] Glucose hypometabolism is consistently observed in various neurodegenerative diseases, including PD[20,21] as will be discussed below.

2.1.2. Tricarboxylic Acid Cycle

Upon import into mitochondria through the mitochondrial pyruvate carrier (MPC), pyruvate is irreversibly decarboxylated by the pyruvate decarboxylase complex (PDC) to form acetyl-CoA, a major component of the TCA cycle.[22] The

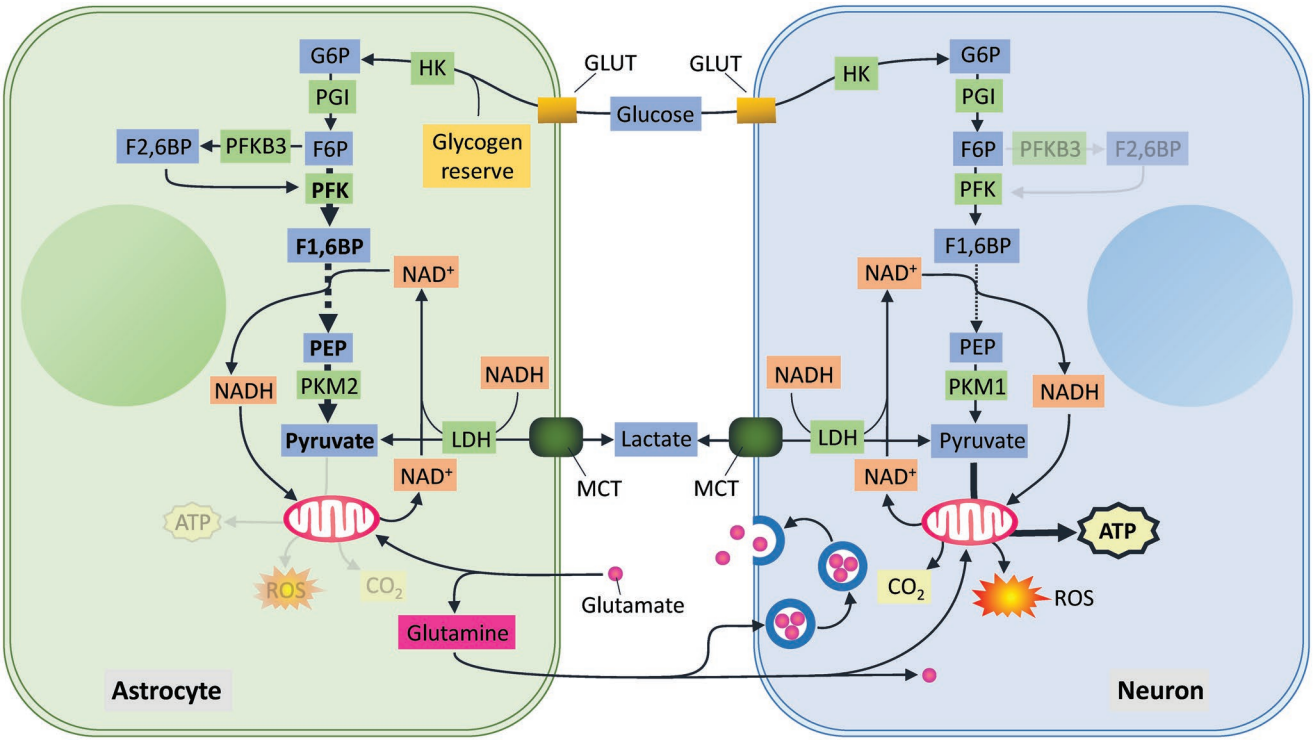

Figure 2. Distribution of bioenergetic pathways between neurons and astrocytes. Neuron and astrocytes can take up glucose and metabolize it via glycolysis and OXPHOS. Additionally, astrocytes can support neuronal OXPHOS by transferring lactate via the astrocyte-neuron-lactate shuttle (ANLS). Additional bioenergetics coupling happens in glutamatergic neurons, in which the neurotransmitter glutamate is taken up by astrocytes surrounding the synapse. This glutamate can either be catabolized in astrocytic mitochondria or resupplied to neurons as the nonexcitable amino acid glutamine.

activity of PDC is inhibited by phosphorylation (PDH kinase) and enhanced by dephosphorylation (PDH phosphatase) of its subunit pyruvate dehydrogenase (PDH).[23] Once acetyl-CoA is generated inside mitochondria, it enters the TCA cycle, where the remaining two carbons of the original glucose molecule are added to oxaloacetate to form citrate and subsequently decarboxylated to yield the final reaction products, CO_2 and H_2O. Simultaneously, one GTP is generated, and electrons are transferred to form three NADH and one $FADH_2$ molecules.

Several TCA intermediates can be used as building blocks for amino acid synthesis, while conversely, amino acids can be catabolized for ATP generation via the TCA cycle. For example, glutamate, an excitatory neurotransmitter, can enter the TCA cycle at the level of α-ketoglutarate. Upon glutamate release, it is taken up primarily by astrocytes surrounding the synapse, where it is either consumed in the TCA cycle or converted to the nonexcitatory amino acid, glutamine, for its return to neurons (Figure 2).[24] Moreover, since the major inhibitory neurotransmitter, γ-aminobutyric acid (GABA), is also derived from glutamine metabolism, neurons need to constantly replenish their glutamate levels in order to keep up with neurotransmission. This task is compartmentalized between neurons and astrocytes as neurons do not express pyruvate carboxylase (PCx), the main enzyme for anaplerosis of oxaloacetate from pyruvate,[25] which is then turned to glutamine and supplied to neurons as precursor for glutamate/GABA synthesis. TCA intermediates are also instrumental in regulating nonmetabolic functions such as, post-translational modifications (lysine acetylation or succinylation), oxygen homeostasis (prolyl hydroxylases), immune, and stem cell functions (reviewed in ref. [26]).

Nicotinamide adenine dinucleotide (NAD^+) and its reduced form NADH are cofactors in mitochondrial metabolic reactions, including the TCA cycle. By transferring its electrons to the ETC, NADH helps to establish the mitochondrial membrane potential, thereby providing the ATP synthase's driving force to produce ATP. NAD^+ also plays a signaling role as a substrate for mitochondrial sirtuins (SIRT3, 4, and 5) that regulate mitochondrial function through post-translational protein modifications.[27] Additionally, NAD^+ is an important cofactor in the mitochondrial one-carbon metabolism which is involved in nucleotide synthesis.[28]

In the cytosol, NAD^+ is also an essential electron acceptor for glycolytic ATP production. Although the mitochondrial and cytosolic NAD^+/NADH pools are separate, they are connected through multiple exchange routes, such as via the mitochondrial protein SLC25A51, a recently identified NAD^+ transporter,[29,30] and two shuttle systems in the mitochondrial inner membrane (the malate-aspartate shuttle and the glycerol-3-phosphate shuttle) that replenish NAD^+ in the cytosol and transfer NADH to the mitochondrial matrix.[31] However, it is still unknown whether other NAD^+ precursors can be transported through the mitochondrial membrane to fuel its

synthesis.[32] Interestingly, cytosolic Ca^{2+} has been shown to upregulate the activity of these shuttles in neurons, and this may represent a mechanism through which neuronal activity modulates mitochondrial redox state and metabolic output.[33,34] Apart from energy metabolism, NAD^+ also activates the poly ADP-ribose polymerases (PARPs) which is a sensor of DNA damage.[35,36] Altogether, the TCA cycle and its intermediates hold a multifaceted role in contributing to neuronal energy and homeostatic maintenance.

2.1.3. OXPHOS

The brain uses about 20% of the oxygen we breathe, despite accounting for only 2% of our body mass.[3] This oxygen is used by mitochondria during OXPHOS to supply most of the neuronal energy demands.[37] OXPHOS is the final step of the aerobic consumption of glucose, which results in the generation of 32 ATP molecules. A major component of OXPHOS is the electron transport chain (ETC), which consists of five protein complexes embedded in the inner mitochondrial membrane (IMM). Briefly, NADH and $FADH_2$ reduce CI (Complex I; NADH:ubiquinone oxidoreductase) and CII (Complex II; succinate dehydrogenase), respectively. The transferred electrons further travels through CIII (Complex III; coenzyme-Q:cytochrome-c reductase) and subsequently reaches CIV (cytochrome-c oxidase) with the help of co-Q (coenzyme-Q) and cyt-c (cytochrome-c), respectively, ultimately generating water after being accepted by oxygen.[38–41] Throughout these subsequent reduction-oxidation reactions, electrons travel from a higher to a lower energy level, and CI, III, and IV, utilize this energy to pump protons to the IMS (intermembrane space), thus creating an electrochemical gradient (concentration imbalance). Due to the impermeability of the lipid bilayer, the protons return to the matrix through CV (F_1/F_0 ATP synthase), converting ADP to ATP with the help of the F_1 motor. The mitochondrial respiratory complexes that orchestrate OXPHOS are thought to (co)exist as unified assemblies, called supercomplexes (reviewed in refs. [42, 43]). Supercomplexes lower the necessary mobile electron carrier pools (co-Q and Cyt-c), thus regulating the electron flux during OXPHOS,[44,45] and enhancing its efficiency.

To achieve optimal activity of the respiratory chain, proton pumping needs to be maximally coupled with the reduction of molecular oxygen and ATP production. Any slips in this well-oiled machine could potentiate reactive oxygen species (ROS) generation. While low levels of ROS can serve signaling functions, high levels lead to increased oxidative damage of mitochondrial proteins and mtDNA, exacerbating mitochondrial dysfunction.[46] Under conditions of abundant substrate supply, the respiratory chain is limited by its ability to channel protons through CV, which slows electron transfer in CIII and CI and therefore favors reverse electron flow and the partial reduction of oxygen to superoxide. Uncoupling proteins (UCPs) overcomes this limit by allowing the flow of protons through the IMM uncoupled from the ATP synthase, which leads to a reduction in ROS production and decreases membrane potential and its associated Ca^{2+} and metabolite influx (reviewed in ref. [47]).

2.2. Other Sources of ATP

2.2.1. Ketone Body Metabolism

Neuronal access to fuels is not constant and varies with feeding or fasting state and circuit activity, as evidenced in dynamic magnetic resonance imaging studies of the brain.[48] Glucose availability is also altered in neurological disorders broadly classified as metabolic encephalopathies with systemic abnormalities resulting from diabetes, liver, or renal failure. In many of these disorders, including diabetic ketoacidosis, ketone bodies such as acetoacetate and β-hydroxybutyrate, which are byproducts of fatty acid oxidation in the liver, are released into the bloodstream and utilized by the brain as an alternative fuel. Ketogenic diets, in which carbohydrate consumption is severely limited, are also clinically used as a treatment for intractable childhood epilepsies.[49] Despite its profound effects on the nervous system, the mechanisms of ketone oxidation and its impacts on neuronal function are still poorly understood. In the substantia nigra pars reticulata, acute treatment with ketone bodies has been shown to dampen spontaneous firing rates of neurons by reducing excitability.[50] This is attributed to the inability of ketones to undergo glycolytic ATP production, thus reducing cytosolic ATP levels that inactivate ATP-sensitive K_{ATP} channels. By removing this inhibition, ketones trigger the opening of K_{ATP} channels and neuronal hyperpolarization. In addition to this metabolic effect, ketones are also thought to directly inhibit glutamate loading into synaptic vesicles and thus reduce neuronal excitability.[51]

2.2.2. β-Oxidation

Although glucose has long been considered as the main fuel source for the brain, recent studies suggest that fatty acids can supply up to 20% of the total brain energy needs.[52] Fatty acids are broken down to produce ATP in the mitochondrial matrix (as well as the peroxisome) through the process of β-oxidation which involves the conversion of long acyl chains to acetyl-CoA that then enters the Krebs cycle for further oxidation.[53] The majority of β-oxidation is thought to occur in astrocytes as neurons express low levels of the mitochondrial enzymes and transporters required for this process.[54,55] Why did neurons fail to evolve the capacity for β-oxidation? There are several reasons that lipids may not be suitable fuels for neurons.[54] First, the rate of ATP production from lipids is slower than that from blood glucose. Second, β-oxidation requires more oxygen than glucose and may expose neurons to hypoxia or the damaging effects of superoxides. By limiting β-oxidation to astrocytes, the nervous system can take advantage of energy-rich lipid resources without jeopardizing neuronal function or survival.

3. Nonmetabolic Functions of Mitochondrial

Mitochondria are essential suppliers of neuronal ATP yet also play important roles in Ca^{2+} ion homeostasis and in the execution of programmed cell death.

3.1. Calcium Homeostasis

It has long been known that mitochondria can take up Ca^{2+} from the cytosol.[56] The voltage-dependent anion channel (VDAC) makes the OMM predominantly permeable to ions like Ca^{2+}.[57] However, the IMM presents a permeability barrier that requires Ca^2 to pass through a specialized channel, the mitochondrial Ca^{2+} uniporter (MCU).[58,59] Ca^{2+} can leave mitochondria through the Na^+/Ca^{2+} exchanger (NCLX),[60] and also other mitochondrial ion exchangers may directly or indirectly alter Ca^{2+} levels, including the putative $2H^+/Ca^{2+}$ exchanger LETM1.[61] In neurons, as in other nonexcitable cells, MCU is the primary pathway for rapid Ca^{2+} uptake into the mitochondrial matrix.[62] The Ca^{2+} affinity of MCU is relatively low (hundreds of nM), thus requiring microdomains of elevated Ca^{2+} in its vicinity to open.[63] These transient microdomains only occur at sites of mitochondrial juxtaposition with Ryanodine or IP3 receptors on the endoplasmic reticulum, which directly release Ca^{2+} to MCU.[64] In neurons, physical tethering of the ER with mitochondria is shown to be critical for synaptically evoked mitochondrial Ca^{2+} uptake in dendritic but not axon mitochondria.[65,66]

In addition to regulating OXPHOS, mitochondrial Ca^{2+} also stimulates ROS through direct activation of ROS-generating enzymes like glycerol phosphate and α-ketoglutarate dehydrogenase.[67] Indirectly, mitochondrial Ca^{2+} uptake mildly dissipates the mitochondrial membrane potential, thereby triggering ROS generation.[68] Ca^{2+} is also a potent regulator of apoptosis as mitochondrial Ca^{2+} overload triggers the opening of the mitochondrial permeability transition pore (mPTP), which leads to mitochondrial swelling, loss of membrane potential, and disruption of ATP synthesis.[68] Ultimately, these events activate a feed-forward cycle that results in the induction of apoptosis, as discussed below.[69]

Consistent with its central regulatory role, alterations in neuronal mitochondrial Ca^{2+} handling are implicated in several genetic models of PD neurodegeneration.[70,71] We speculate that perturbation of mitochondrial Ca^{2+} is a fundamental feature of many forms of neurological disorders that ultimately impairs neuronal metabolism and survival.

3.2. Apoptosis

When the time comes, cells open the door to a series of sequential steps that lead to programmed cell death, also known as apoptosis.[72] The two main apoptotic pathways are the extrinsic and the intrinsic pathways. The latter is also called the mitochondrial pathway due to the critical role of mitochondria in integrating pro- and antiapoptotic signals to launch a cell death program.[73,74] The mitochondrial pathway is mediated by the B cell lymphoma 2 (BCL-2) family of proteins. Once apoptosis is initiated, macropores form on the OMM that lead to the release of cyt-c and activation of caspases that execute cell destruction (see ref. [75] for more detail). In neurons, the apoptotic machinery also plays a role in axonal degeneration, which occurs in response withdrawal of neurotrophic support, excitotoxicity, or in neurodegenerative diseases, including PD.[76–78]

Mitochondria can undergo permeabilization and swelling during a process termed mitochondrial permeability transition. Interestingly, the ATP synthase has also been implicated in mitochondrial permeability transition as it is suggested to be the actual pore-forming complex of the permeability transition pore (PTP) (reviewed in ref. [79]). Indeed, overexpression of an inhibitory subunit of the ATP synthase partially protects neurons from quinolone–induced excitotoxicity and associated gliosis.[80] Inhibition of the ATPase function of the ATP synthase can be beneficial under hypoxic conditions since it prevents the depletion of cytosolic ATP, opening of the PTP, and consequently cell death. High mitochondrial Ca^{2+} influx is known to activate the PTP,[81] thereby coupling activation of the PTP to pathologically elevated Ca^{2+} levels.

4. Mitochondrial Biogenesis and Transport in Neurons

Due to the large size of neurons, the upkeep of the mitochondrial proteome requires mitochondrial transport and local mitochondrial biogenesis in distal neurites (reviewed in ref. [82]). Indeed, the local translation and import of mitochondrial proteins in neurites has been observed.[83,84] The upkeep of the local mitochondrial proteome plays a vital role in sustaining functional organelles to support neuronal viability and synaptic function. Conversely, failure to correctly position mitochondria by the means discussed below leads to a reduction in axonal and dendritic complexity.[85,86]

4.1. Mitochondrial Biogenesis

Mitochondria are endosymbiotic organelles whose proteins are derived from two genomes: a few core subunits of the respiratory chain are encoded within mitochondria on the mitochondrial DNA (mtDNA). All other mitochondrial proteins (≈1500 or 2000 in yeast or mammals respectively) are encoded by nuclear genes and therefore must be imported into the organelle to allow for their proper functionality.[87,88] This task is achieved by the concerted action of translocases present in the inner and outer mitochondrial membranes. The translocase of the outer mitochondrial membrane (TOM) serves as the general entry gate into the organelle, whereas two translocases of the inner mitochondrial membrane (TIM22 and TIM23) are dedicated to the insertion of proteins into the inner membrane or complete translocation into the matrix (for full review see ref. [89]). Two types of energy sources power this sorting process: ATP, which is hydrolyzed by chaperones like HSP70 interacting with mitochondrial precursors both on the cytosolic and the matrix side, and the electrochemical gradient across the inner mitochondrial membrane (IMM).[90,91]

4.2. Mitochondrial Dynamics and Their Influence on Mitochondrial Functions

Mitochondrial dynamics are crucial for proper distribution of organelles throughout the neuron.[92] The textbook view

of mitochondria as individual bean-shaped entities has long been overhauled by the visualization of mitochondria forming a tubular network that is readily remodeled by mitochondrial fusion and fission.[93] In neurons, this network is present in the cell body and to some extent in dendrites, yet axons display a very unique mitochondrial morphology with mitochondria as relatively uniform and dispersed single entities of approximately 1 μm long (compare Figure 1).[93] Interestingly, although mitochondria appear more interconnected in dendrites, photoconversion experiments in cultured rat hippocampal neurons have shown that those mitochondria still form separate compartments that are spatially stable over time.[94]

The proteins driving mitochondrial fusion and fission belong to a family of large GTPases: dynamin-related protein 1 (DRP1) for fission,[95] and dominant optic atrophy 1 (OPA1) and Mitofusin 1/2 for inner and outer membrane fusion, respectively.[96] Multiple signaling pathways converge on these proteins to alter mitochondrial shape to fit the needs of the cell (reviewed in ref. [97]).

Mitochondrial fusion creates elongated mitochondria that may be more efficient in respiration due to enhanced shuttling of metabolites. Indeed, overexpression of OPA1 has been shown to enhance assembly and stability of respiratory chain supercomplexes.[98] However, OPA1 is also involved in the formation of mitochondrial cristae and the maintenance of the mitochondrial genome,[99,100] and its overexpression or deletion has pleiotropic effects on the respiratory chain. Therefore, it remains a question whether a simple change in mitochondrial shape is conducive to metabolite flow. A recent study describes a "mitochondrial safeguard" mechanism that prevents complete hyperfusion of the mitochondrial network in DRP1 KO cells,[101] leading to a bioenergetic deficit. It may be too simplistic to assume that "form follows function," and therefore, mitochondria in dendrites would be more bioenergetically efficient than their shorter counterparts in axons. Initial measures using membrane potential-sensitive dyes suggest that dendritic mitochondria are more energized than axonal mitochondria.[102] However, the correlation between a higher membrane potential and ATP output is not simply linear.[103] Interestingly, mitochondrial membrane potential can differ between cristae even within one mitochondrion,[104] adding even more complexity to this system.

4.3. Mitochondrial Positioning

Mitochondria associate with the microtubule network in order to be transported from the cell body to the synapse (anterograde) and back (retrograde) by the molecular motor proteins kinesin and dynein, respectively.[105,106] Kinesin and dynein interact with the mitochondrial motor adapter complex consisting of the mitochondrial outer membrane protein Miro (RHOT1/2) and the adaptor protein Milton (TRAK1/2).[107–109] Mitochondrial transport requires energy, as each 8 nm step of a single kinesin motor is powered by the hydrolysis of 1 molecule of ATP.[110] Mitochondrial motility is higher in cultured neurons and the main axonal shaft as compared to terminal branches, and motility decreases with neuronal maturity and synapse density.[111] About 50% of synapses are occupied by a resident mitochondrion, which allows those synapses to finely tune their Ca^{2+} homeostasis,[112] and access ample ATP supply for synaptic processes. Presynaptic boutons with resident mitochondria contain more docked synaptic vesicles, thereby sustaining synaptic activity and long-term potentiation (LTP).[113] Likewise, mitochondria at the postsynaptic densities are essential to power local protein synthesis needed for synaptic plasticity.[94] A study in retinal ganglion cells found that dendritic mitochondria in mature neurons are largely stationary and remain anchored at postsynaptic densities and dendritic branch points.[114]

4.3.1. The Role of Mitochondrial Fission in Mitochondrial Positioning

Mitochondrial fission is required for mitochondrial movement into axons and dendrites.[115–117] This has been used experimentally to alter mitochondrial density in animal models, including *Drosophila* and mice. Loss of mitochondrial dynamics consistently reduces axonal and dendritic complexity, synapse development, and synaptic transmission.[118] As mitochondria also perform multiple functions, addition of ATP only partially restored synaptic vesicle cycling defects observed in *Drosophila* mutants of the mitochondrial fission protein DRP1.[115]

DRP1-induced mitochondrial fission also plays an essential role in mitochondrial quality control and apoptosis (reviewed in ref. [119]) and is required for LTP in response to Ca^{2+} influx.[120] Therefore, in the absence of DRP1, dysfunctional mitochondria accumulate and are unable to respond to the incoming Ca^{2+} flux in order to supply the increased amount of ATP required for structural plasticity in the hippocampus.

4.3.2. Mitochondrial Anchoring

Regulation of mitochondrial transport and their placement inside the axon is another area of active research. Mitochondria stop transiently in response to Ca^{2+} influx, high glucose concentrations, and ADP,[121–123] and their association with synapses is regulated by the liver kinase B1 (LKB1),[112] and Myosin VI/Syntaphilin.[124] Syntaphilin serves as a protein anchor that stops axonal mitochondria through its ability to bind microtubules,[125] and may help to switch mitochondria from microtubule-dependent transport to actin-mediated tethering.[124] Loss of Syntaphilin increases mitochondrial motility, facilitates short-term plasticity at synapses, probably due to decreased Ca^{2+} buffer capacity,[125] and facilitates axonal growth.[126] Therefore, Syntaphilin could be exploited in disease states with reduced mitochondrial trafficking, like in toxin- or mutation-induced demyelinated axons, a model system for multiple sclerosis (MS).[127,128]

In conclusion, mitochondria are essential for neuronal health, and defects in mitochondrial biogenesis, distribution, and anchoring will invariably lead to neurological defects. Mitochondria are more than just "the powerhouse of the cell" and perform many different cellular functions, such as Ca^{2+} buffering, that are closely interconnected with their bioenergetic role.

5. Synaptic Transmission

Synaptic transmission is the process of neural communication in which synaptic vesicles containing neurotransmitters are released into the trans-synaptic space. Synaptic vesicle release is evoked by the opening of voltage-gated Ca^{2+} channels in nerve terminals in response to membrane depolarization and action potential propagation. The binding of neurotransmitters to postsynaptic receptors triggers ionic currents that constitute the inputs received by the postsynaptic neuron. The intricate cascade of events that occur during neurotransmission relies on substantial and highly dynamic energetic support. It has been estimated that the majority of this energy is consumed in postsynaptic compartments to reverse ionic fluxes through neurotransmitter receptors.[2] In response to synaptic input, dendritic spines, the postsynaptic specializations of excitatory synapses, undergo significant structural remodeling involving energy-consuming events, such as AMPA receptor trafficking, protein synthesis, and rearrangement of the actin cytoskeleton.[129] This structural plasticity, which is the molecular basis of learning and memory in the brain, is highly ATP-consuming and is preferentially supported by mitochondrial OXPHOS.[94] In cellular models of synaptic plasticity, LTP, which involves the persistent strengthening of synaptic responses in response to recent activity, requires postsynaptic mitochondrial Ca^{2+} uptake and fission[120] and is less efficient in presynaptic terminals that lack mitochondria.[113]

5.1. Energy Use in Synaptic Transmission

In presynaptic terminals, recycling of synaptic vesicles and restoration of ionic balance after action potential propagation are both highly energy-consuming, although the relative consumption of each is still debated.[2,130] Specifically, ATP is consumed by four types of membrane ATPases to maintain ionic balance: the Na^+ pump and N^+/K^+-ATPase, which reverse the gradients created by action potentials, the Ca^{2+}-ATPase, which extrudes cytosolic Ca^{2+} that enter through voltage-gated Ca^{2+} channels, and the vacuolar H^+-ATPase which powers neurotransmitter uptake into synaptic vesicles (**Figure 3**).[2] Although membrane docking of synaptic vesicles prior to release is not sensitive to ATP levels,[131] multiple steps during the vesicle retrieval process are energetically costly, including the dynamin-driven pinching of nascent vesicles, uncoating of clathrin-coated vesicles, and re-establishment of vesicular proton gradient by the vacuolar H^+-ATPase (Figure 3). It is important to note that dynamin is a GTPase and thus utilizes ATP indirectly through the activity of nucleoside diphosphate kinases (NDPKs) which convert ATP to GTP. While NDPKs have been found to colocalize with dynamin and are essential for clathrin-dependent endocytosis in HeLa cells,[132] their role in the endocytosis of synaptic vesicles remains unexplored. Although several studies suggest that either glycolysis or mitochondrial OXPHOS can sustain the energetics of synaptic vesicle retrieval during mild levels of activity,[66,133,134] OXPHOS is essential for recovery from vesicle depletion induced by prolonged stimulation.[115,133,135]

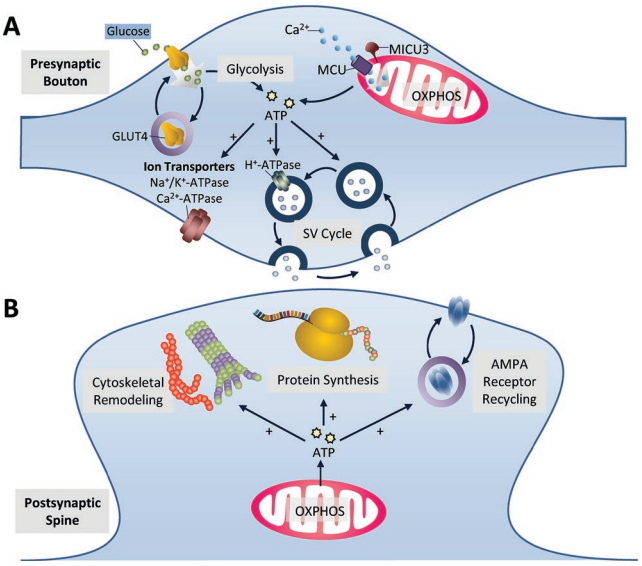

Figure 3. Energetic support of neurotransmission. A) In presynaptic terminals, glycolysis and mitochondrial OXPHOS provide ATP to power the recycling synaptic vesicle (SV), and maintenance of ionic balance by membrane ATPases. During electrical activity, presynaptic glycolysis is upregulated through recruitment of GLUT4, while OXPHOS is stimulated through Ca^{2+} uptake by the MCU complex. B) In postsynaptic compartments, mitochondria power synaptic plasticity through energetic support of cytoskeletal remodeling, protein synthesis, and AMPA receptor cycling.

5.2. Mitochondrial Bioenergetics in Active Synapses

In contrast to dendrites, mitochondria Ca^{2+} uptake in axons is ER-independent, and the affinity of MCU for Ca^{2+} uptake is substantially higher in axonal mitochondria.[66] This is due to a unique structural adaptation of the MCU complex, which is composed of channel-forming and regulatory subunits with tissue-specific expression patterns.[136] Unlike most nonexcitable cells that express the MCU regulatory proteins, MICU1 and MICU2,[63] axonal mitochondria express a distinct MICU homolog, called MICU3, that enhances mitochondrial Ca^{2+} uptake.[66,137] As a result, cytosolic Ca^{2+} entry during synaptic activity is sufficient to trigger MCU opening and mitochondrial Ca^{2+} uptake, even when axonal ER is pharmacologically depleted of Ca^{2+}.[66] Thus, axonal mitochondria are primed for Ca^{2+} uptake, and this specialization enables metabolic adaptation to the energy demands of neurotransmission as elevated Ca^{2+} levels in the mitochondrial matrix stimulates oxidative ATP synthesis.[66] Specifically, several TCA cycle dehydrogenases in the matrix, NAD/NADH shuttle systems, and the F_1F_O ATP synthase, among others, are activated by mitochondrial Ca^{2+}.[138]

5.3. Mitochondrial Dynamics in Active Synapses

Mitochondria not only respond bioenergetically to the influx of Ca^{2+} but their shape and subcellular distribution are regulated by cytosolic Ca^{2+} changes in synaptic signaling. The mitochondrial motor adaptor Miro contains two Ca^{2+} binding EF-hand domains, and mitochondrial motility stops upon Ca^{2+}binding.[121,139] Furthermore, Syntaphilin may be involved in mitochondrial motility

Table 1. Genes affected in PD discussed in this review.

Parkinson's related gene	Pathogenic protein/mutation	Effect on bioenergetics	Effect on mitochondrial dynamics or mitostasis
Sporadic	Unknown, α-synuclein aggregations	Calcium dysregulation impacts bioenergetics[138]	Calcium dysregulation impacts mitochondrial motility and shape[121,139,140,226]
PARK1/4	α-Synuclein GOF/duplication		Disrupted mitochondrial transport[174]
PARK2	Parkin LOF mutation	Loss of PARIS inhibition leads to reduced expression of PGC1-α[187,188]	Loss of mitochondrial quarantine in response to mitochondrial dysfunction (Mfn2, Miro degradation)[170,176]
PARK6	PINK1 LOF mutation	Decreased glucose import[153]	Loss of mitochondrial quarantine in response to mitochondrial dysfunction (Mfn2, Miro degradation)[170,176]
		Loss of NdufA10 phosphorylation[154]	
		Loss of stimulation of OXPHOS local translation[156]	
		Loss of PARIS inhibition leads to reduced expression of PGC1-α[187,188]	
PARK7	DJ-1 LOF	Impaired ATP synthase function[150]	Altered dynamics[151]
PARK8	LRRK2 GOF		Decreased interaction and degradation of Miro[171]

arrest in response to Ca^{2+}.[140] Several models have been proposed to explain the exact mechanism for Ca^{2+}-mediated mitochondrial arrest (reviewed in ref. [118]). In addition to Ca^{2+}, energy deficits due to synaptic signaling activate AMPK to anchor mitochondria at nerve terminals through the action of Syntaphilin and Myosin VI.[124] Activation of AMPK also inhibits retrograde transport of mitochondria during local nutrient deprivation,[141] which may occur through similar mechanisms. Likewise, measures that induce the formation and strengthening of synapses, like the application of BDNF (Brain-derived neurotrophic factor), stimulate the docking of mitochondria at synapses.[142]

Besides, mitochondrial shape responds to cytosolic Ca^{2+}. Smaller mitochondria may be more easily transported and have been suggested to be better suited to handle the influx of Ca^{2+} during synaptic activity.[120] Synaptic activity activates Ca^{2+}-dependent CamKs (calmodulin-dependent Kinases), which in turn phosphorylate and activate DRP1 and induce mitochondrial fission.[143,144] This may be prioritized during synaptic signaling as long as the potential drop in ATP supply associated with mitochondrial fission is balanced by the increased activity of Ca^{2+}-regulated mitochondrial dehydrogenases or increased utilization of glycolytic ATP.

6. Metabolic Changes in Parkinson's Disease

The incidence of neurodegenerative diseases rises exponentially with aging. One popular theory builds on the fact that with age, mitochondria become less efficient producing less ATP, while their toxic ROS production increases, which ultimately hampers ATP-dependent repair mechanisms. The "free radical theory of aging" proposes that the increased production of ROS causes oxidation of mtDNA and thereby exacerbates mitochondrial dysfunction, thus accelerating the point of no return.[46] Indeed, mitochondrial dysfunction is frequently observed in many neurodegenerative diseases, and the presence of protein aggregates like α-synuclein in PD often directly impact mitochondrial functionality (reviewed in ref. [145]).

In this review, we summarize evidence of brain mitochondrial dysfunction in Parkinson's disease, mostly using evidence derived from hereditary forms of PD (**Table 1**). We discuss how mitostatic and adaptive mechanisms might fail to rescue mitochondrial health in the disease. We conclude this review by a discussion on differential cell type susceptibilities to PD mutations and the role of metabolism versus other mitochondrial functions in the etiology of PD.

6.1. Genetics of Parkinson's Disease

Parkinson's disease is a multifactorial neurodegenerative disease, presenting as a progressive movement disorder mainly due to the loss of dopaminergic neurons in substantia nigra of midbrain that may result from the accumulation of fibrillar cytoplasmic aggregates of α-synuclein. More evidence that mitostasis is affected in PD comes from genome whole associated studies (GWAS) which revealed mutations in multiple genes, in addition to α-synuclein, that contribute to PD development.[146] Table 1 gives an overview of the genes we discuss below, but does not provide an exhaustive list as the number of genes implicated in PD is continuously growing. In addition to genetic factors, environmental conditions such as exposure to toxins like herbicide paraquat and the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) cause PD-like symptoms and are used frequently to model PD in animals.[147,148]

6.2. Respiratory Changes in PD

Loss of the PD-associated protein DJ-1 (PARK7) leads to mitochondrial dysfunction and accumulation of ROS through its various roles as a chaperone and antioxidant protein (reviewed in ref. [149]). Additionally, DJ-1 has been reported to regulate the function of the ATP synthase.[150] DJ-1 mutant cells show impaired ATP production and increased leakage of protons across the IMM (**Figure 4**), which is required for maintaining the stoichiometry of the ATP synthase complex.[150] DJ-1 mutants also display altered mitochondrial dynamics,[151] and DJ-1 has been recently implicated in mitochondrial Ca^{2+} uptake at mitochondria-ER contact

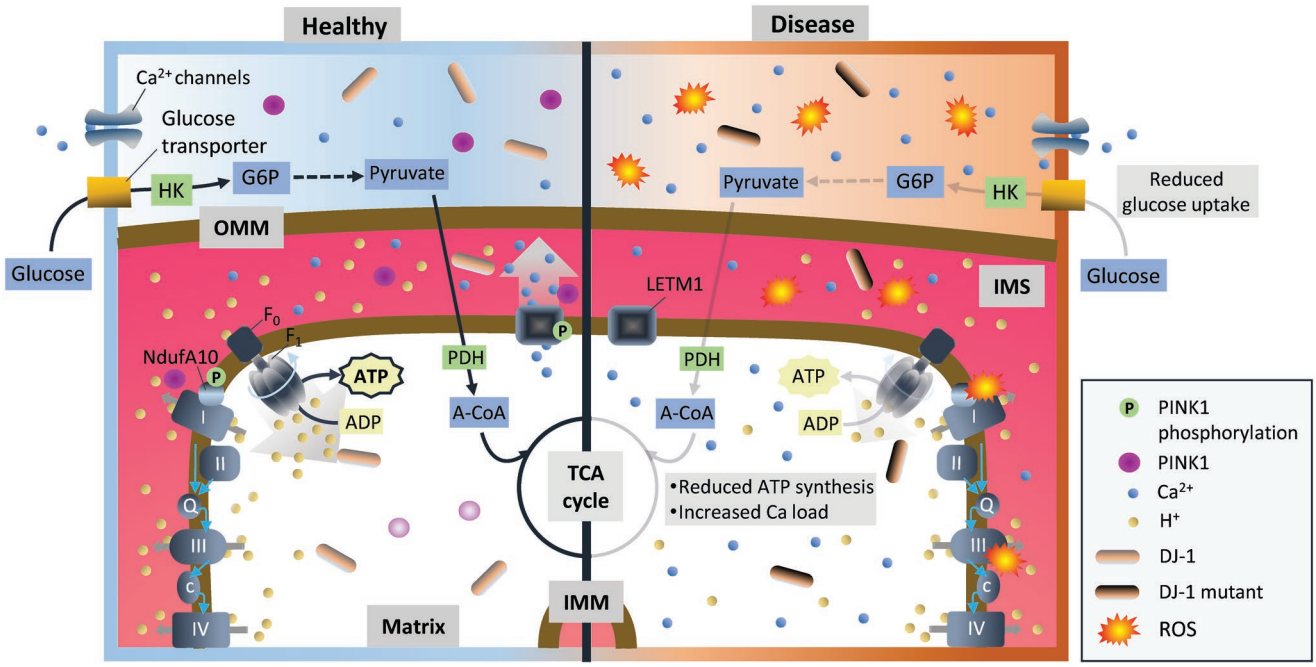

Figure 4. Metabolic changes in hereditary forms of PD. Absence of DJ-1 protein and/or presence of DJ-1 mutants affect the neuronal respiratory status and mitochondrial dynamics by increasing proton leakage across IMM, ROS production, and calcium uptake, and reducing ATP synthase activity (right panel). Moreover, PINK1 phosphorylation sites are identified on complex I subunit, NdufA10, and the Ca^{2+} exporter, LETM1 (left panel) implying that either loss of or mutations in PINK1 would majorly contribute to the increased mitochondrial Ca^{2+} load observed in Parkinson's disease.

sites,[152] suggesting that DJ-1 mutants disturb more than just the bioenergetic properties of mitochondria.

Two other PD-associated proteins, PTEN-induced kinase 1 (PINK1, PARK6) and Parkin (PARK2) work together to drive the removal of damaged mitochondria through mitophagy (see below). Interestingly, PINK1 activity also impacts mitochondrial functions independent of mitophagy. PINK1 knock out (KO) neurons show decreased glucose uptake (Figure 4), mediated by an unknown mechanism involving mitochondrial Ca^{2+} and ROS.[153] Furthermore, despite its short half-life in healthy mitochondria, several PINK1-dependent phosphorylation sites have been identified in IMM proteins, including phosphorylation of the complex I subunit NdufA10[154] and the Ca^{2+} exporter LETM1.[155] This suggests that PINK1 can upregulate respiration and may boost mitochondrial Ca^{2+} efflux (Figure 4). OMM targeted PINK1 has been reported to enhance bioenergetics independent of mitophagy by activating the translation of several subunits of the respiratory chain,[156] which be a replacement strategy aimed to repair mitochondrial defects without inducing mitophagy. All of these functions require PINK1 kinase activity, which is frequently disturbed by disease-causing mutations in PINK1.[157]

6.3. Defects in Mitophagy

Mitochondria use fission to shed damaged proteins and mtDNA. This can occur through selective autophagy, termed mitophagy (reviewed in ref. [158]), or through the budding of mitochondrial-derived vesicles (MDV) (reviewed in ref. [159]). It has been proposed that mild chronic mitochondrial stress will lead to MDV shedding, whereas acute stress may rely more on PINK1/Parkin mediated mitophagy.[160] PINK1 is a mitochondrial protein kinase whose N-terminal mitochondrial targeting sequence directs its import toward the TOM and TIM23 translocases.[157] Upon import into the IMM, PINK1 is cleaved by the rhomboid protease PARL,[161] which destabilizes the protein and leads to its retro-translocation via the import complexes and its degradation by the proteasome (**Figure 5**).[162,163]

Upon mitochondrial damage, PINK1 import is arrested at the TOM complex,[164] where it is stabilized and phosphorylates several outer membrane and cytosolic proteins, among them ubiquitin,[165,166] and the E3 ubiquitin ligase Parkin.[167] This increases Parkin recruitment and its activity which then leads to the formation of phospho-ubiquitin chains on damaged mitochondria that can be recognized by autophagy receptors like Optineurin and NDP52 (nuclear dot protein 52) (Figure 5).[168] Upon engulfment into an autophagosome, fusion with lysosomes causes the degradation of the dysfunctional organelle and protects the cell from further damage.

The signals that lead to the arrest of PINK1 import and mitophagy are an active area of research. Loss of the mitochondrial membrane potential is the best known trigger of PINK1 arrest, but other mitochondrial stressors like accumulation of misfolded proteins can also cause PINK1 stabilization.[169]

6.4. Defects in Mitochondrial Transport

Prior to degradation, damaged mitochondria become quarantined from the mitochondrial network due to PINK1-dependent phosphorylation of the transport adapter Miro, which leads to its proteasomal degradation and mitochondrial arrest

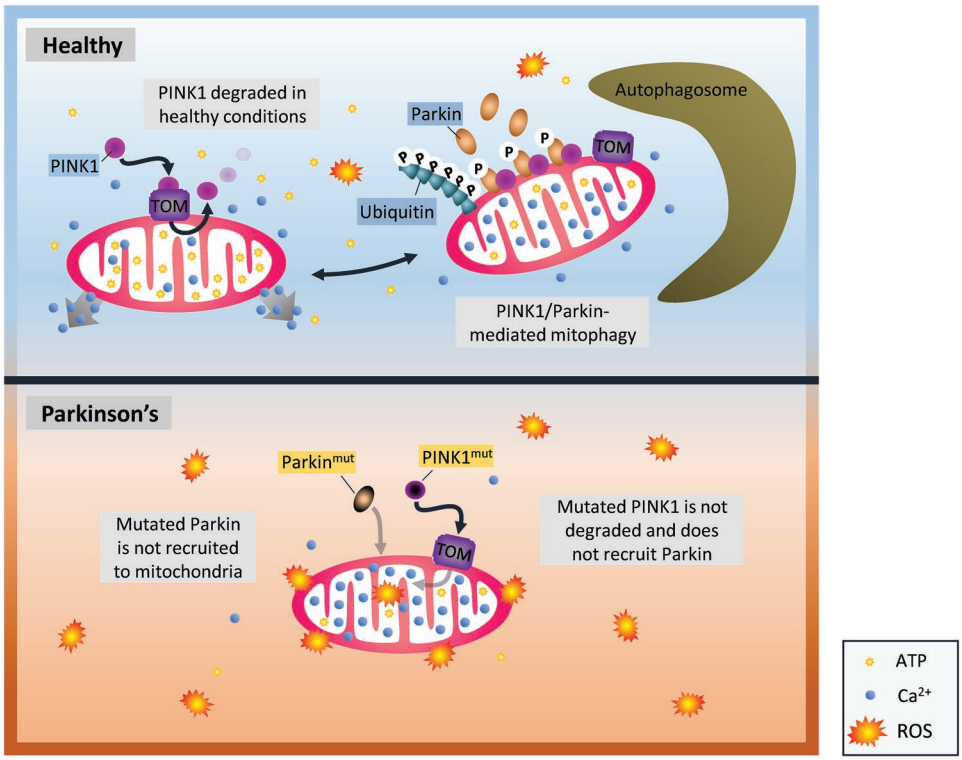

Figure 5. Mitophagy in health and disease. Removal of damaged mitochondria happens through an organelle-specific autophagy, called mitophagy. PINK1, which is otherwise degraded upon import within healthy mitochondria, stabilizes on the surface of damaged mitochondria and phosphorylates among other substrates Ubiquitin and Parkin. The subsequent accumulation and formation of chains of phosphorylated Ubiquitin further are recognized by autophagy receptors (above panel). However, mutations in PINK and/or Parkin impair the mitophagic process in Parkinson's (below panel).

(**Figure 6**).[170] Mitochondrial degradation is therefore a joint effort between the two major proteostatic mechanisms in the cell, the proteasome and autophagy. Defects in mitochondrial clearance, be it due to mutations in mitophagic players or failure in autophagosome formation or lysosomal dysfunction, ultimately lead to the accumulation of dysfunctional mitochondria.

Interestingly, Miro degradation is impaired in induced pluripotent stem cell (iPSC)-derived neurons of both familial as well as sporadic forms of PD,[171] thereby preventing arrest of damaged mitochondria and their uptake into mitophagosomes. A parallel pathway also exists for degradation of Miro that depends on its interaction with LRRK2 (leucine-rich repeat kinase 2, PARK8), which is mutated in familial forms of PD and is a risk factor for sporadic PD.[172] Genetic or pharmacological depletion of Miro can therefore be used therapeutically to decrease the number of damaged yet moving mitochondria, greatly facilitating their removal by mitophagy and neuronal health.[173]

Finally, accumulation of α-synuclein (PARK2/4 and sporadic forms) has been reported to inhibit mitochondrial transport by acting on the subcellular distribution of Miro and Syntaphilin (Figure 6).[174] Activation of AMPK increases mitochondrial anchoring via Syntaphilin as described above,[124] thereby allowing mitochondria to respond to increased energetic demands. Application of BDNF (brain-derived neurotrophic factor), a potent inducer of synaptic plasticity and AMPK signaling, accordingly enhances mitochondrial arrest at synapses[142] and may be a potential therapeutic agent in neurodegenerative diseases.[175]

6.5. Defects in Mitochondrial Fusion and Fission

Mitochondrial dysfunction is coupled to increased mitochondrial fission through several mechanisms. PINK1 and Parkin activation leads to the ubiquitination and degradation of Mitofusin, thereby inhibiting fusion of damaged mitochondria.[176] Loss of the mitochondrial membrane potential also activates the IMM protease OMA1, which cleaves OPA1 and antagonizes fusion (**Figure 7**).[177] Furthermore, increased cytosolic Ca^{2+} during mitochondrial dysfunction activates the Ca^{2+}-dependent phosphatase calcineurin, which removes inhibitory phosphates from DRP1 (Figure 7).[178] Multiple kinases phosphorylate DRP1 to induce mitochondrial fission, including GSK3- β[179] and p38 MAPK.[180] The activity of these pathways is increased in several neurodegenerative diseases including PD, leading to fission of the mitochondrial network.[180–184] Likewise, Mitofusin2 is a target for the stress-induced kinase JNK (Jun N-terminal kinase), which triggers its proteasomal degradation and hence favors mitochondrial fission and apoptotic cell death (Figure 7).[185]

6.6. Defects in Mitochondrial Biogenesis

Transcriptional control of mitochondrial genes is driven by peroxisome proliferator-activated receptor-γ coactivator (PGC)-1 α (reviewed in ref. [186]). Mitochondrial dysfunction and the associated activation of PINK1/Parkin mediated mitophagy

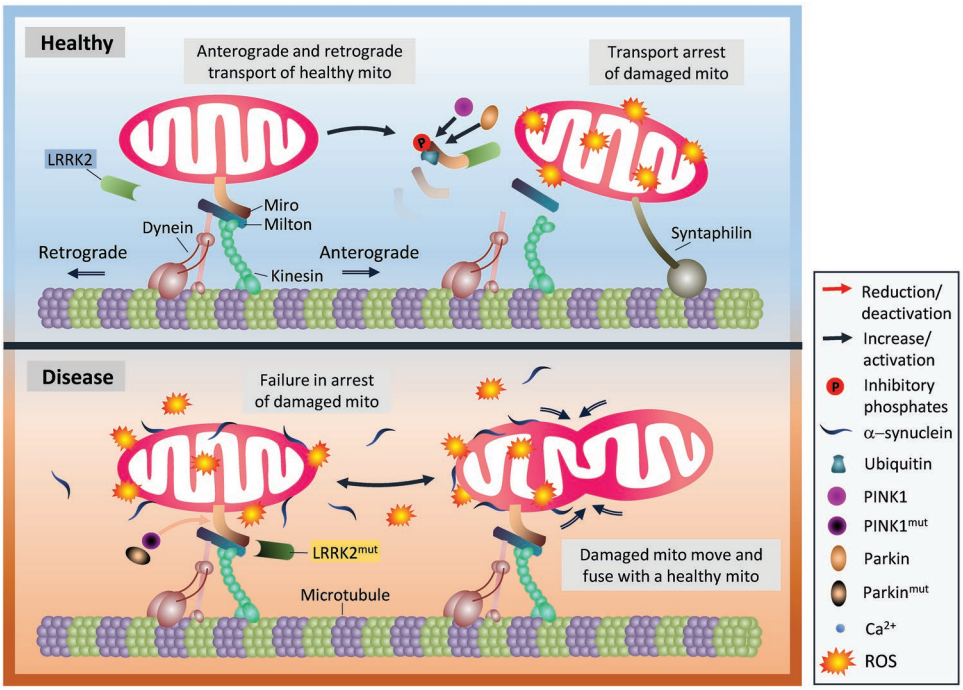

Figure 6. Mitochondrial transport in health and disease. In order to meet the energy demands at distal parts of the neuron, mitochondria are constantly transported anterograde (kinesin complex) and retrograde (dynein complex) along the microtubule with the help of the OM protein, Miro, and the adaptor protein, Milton. Anchoring of mitochondria is mediated by syntaphilin-mediated attachment to microtubules. To facilitate the degradation of damaged mitochondria, transport is arrested by the degradation of Miro by PINK1/Parkin, and through a parallel pathway via an interaction between Miro and LRRK2 (above panel). Mutations in PINK1, Parkin, or LRRK2, as well as accumulation of α-synuclein that affect the distribution of Miro and syntaphilin, impair the arrest of damaged mitochondria and subsequently their degradation in Parkinson's (below panel).

induces PGC1-α by destabilization of PARIS (Parkin-interacting-substrate, or ZNF746), which transcriptionally represses the PGC1-α promoter (Figure 7).[187,188] Therefore, loss of mitochondrial biogenesis may be part of the pathogenic mechanism in PINK1/Parkin-associated PD, as recently confirmed in *Drosophila* models.[189]

In concert with transcription factors such as PPARγ and NRF1/2, expression of PGC1-α activates the transcription of

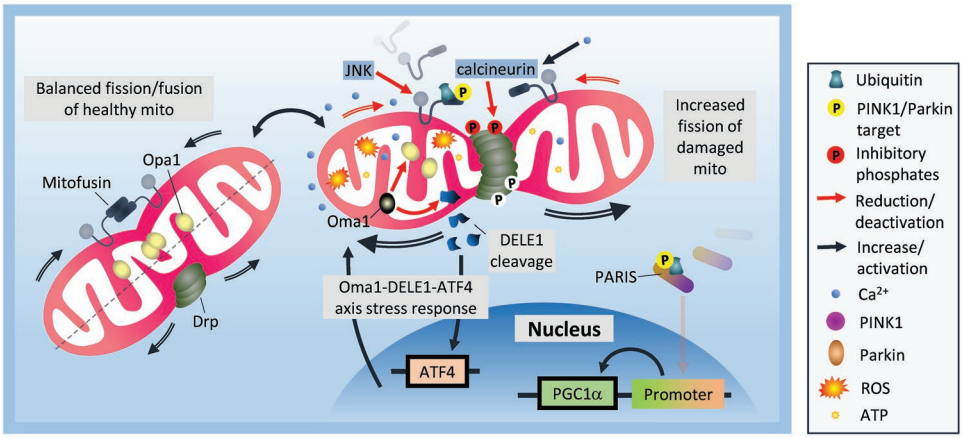

Figure 7. Mitochondrial biogenesis in health and disease. A balance between fission and fusion of mitochondria is maintained based on the regional energy needs of the neuron. Fusion is mediated by the outer membrane GTPase Mitofusin and the inner membrane GTPase OPA1, whereas DRP1 mediates fission from the cytosolic side. Fission is often induced in pathological conditions. This may occur through external signaling cues (JNK, Ca^{2+}-inducible calnineurin), or internal loss of membrane potential triggering activation of the PINK1/Parkin pathway and degradation of Mitofusin and/or the degradation of OPA1 by the protease OMA1. OMA1 was is also recently found to be involved in a bidirectional communication between damaged mitochondria and the nucleus (through ATF4) in mounting the integrated stress response, which includes a metabolic shift toward glycolysis and one carbon metabolism. Nuclear control of mitochondrial biogenesis occurs via the expression of PGC1-α. One pathway by which expression of PGC1-α is regulated occurs via its molecular repressor, PARIS, a PINK1/Parkin substrate. PGC1-α is not only involved in activating the transcription of various mitochondrial genes but also in compensatory processes such as alternate substrate use and antioxidant responses.

nuclear-encoded mitochondrial genes. Among these are not only the nuclear-encoded OXPHOS subunits but also proteins involved in the expression of their mitochondrial counterparts,[190] cofactor synthesis,[191] and mitochondrial protein import.[192] In addition, PGC1-α has been reported to coactivate transcription of genes involved in glucose transport,[193] and fatty acid oxidation to allow for increased glucose influx and the use of alternative substrates during times of energy deficit.[194] PGC1-α also mounts an antioxidant response, thus protecting neurons from ROS-generating agents like the complex I inhibitor MPTP.[195] PGC1-α induces the expression of UCPs, and exogenous overexpression of UCP2 has been shown to be neuroprotective under several pathological conditions, including PD.[196]

6.7. Defects in Mitochondrial Stress Response

Several perturbations within mitochondria can signal retrogradely to the nucleus, including the accumulation of damaged proteins or increased ROS. Distinct molecular signaling pathways for mitochondrial-nuclear communication have been described in yeast and *Caenorhabditis elegans* (reviewed in ref. [197]), but the mammalian pathway of the mitochondrial unfolded protein response (UPR^{mt}) still remains less defined. Interestingly, it was shown recently that the integrated stress response (ISR) protein ATF4 is also activated by mitochondrial stress through activation of OMA1 and cleavage of the DELE-1, providing a link between loss of mitochondrial membrane potential, mitochondrial fission and induction of a compensatory stress response (Figure 7).[198,199] Activation of ISR by ER stress or glucose deprivation has also been reported to enhance respiratory chain supercomplex formation due to enhanced expression of supercomplex assembly factor 1 (SCAF1),[200] thereby increasing bioenergetics output without the need for increased mitochondrial biogenesis. UPR^{mt} induction is triggered in a *C. elegans* model of α-synuclein, and loss of UPR^{mt} potentiates the observed neurotoxicity.[201] More general measures that reduce protein synthesis, such as inhibition of mTOR by rapamycin, can rescue mitochondrial defects such as complex I mutations.[202] In this study, rapamycin conferred neuronal protection without rescuing mitochondrial respiration by inducing a metabolic shift toward amino acid catabolism as an alternative energy source. As complex I inhibitors like MPTP and rotenone induce PD-like symptoms in animal models it will interesting to study the role of the ISR and translation in metabolic adaption in these models.

7. Mitochondria in PD—More Than Lack of ATP?

In this review, we have summarized the role of mitochondria in neuronal energy metabolism with a focus on the molecular disturbances occurring in PD. However, mitochondria perform multiple functions that are not limited to ATP production, including buffering Ca^{2+} and supplying intermediates to the anabolic reactions of amino acid or nucleotide synthesis. Furthermore, their roles in cellular redox reactions as suppliers of NAD^+/NADH and as gatekeepers of apoptosis contribute to the long-term survival of neurons. Mitochondrial functions decline during normal aging as well as in many forms of neurodegenerative disorders. The question remains as to whether neuronal hypometabolism is a causative factor in neurodegeneration or a byproduct of declining neuronal health.

7.1. The Tangled net of ATP, Ca^{2+}, and NAD^+

As mentioned above, mitochondria also perform other functions for the cell that are as important for neuronal survival as ATP generation. Few studies have tried to untangle the relative contributions of mitochondrial functions to disease, particularly since their interdependence greatly hampers our understanding of cause and consequences. As an example, PINK1 KO neurons have been reported to display mitochondrial Ca^{2+} overload and to maintain their mitochondrial membrane potential mainly by reverse action of the ATP synthase, implying a metabolic shift toward glycolysis.[153] Paradoxically, glucose uptake is also reduced in PINK1 KO neurons which stands in contrast to their dependence on glycolytic ATP.[153] The bioenergetics crisis in PINK1 KO cells may be a downstream consequence of dysregulated Ca^{2+} dynamics, but even in this single PD model many unknowns such as the origins of Ca^{2+} overload and its interplay with glycolytic ATP production remain.

Further evidence for additional non-bioenergetic causes of neurodegeneration comes from the beneficial effect of uncoupling proteins. The PD model of MPTP-induced loss of complex I function can be rescued by the addition of glucose to cultured neurons through reverse action of the ATP synthase.[203] Similarly, neurodegeneration in mice treated with MPTP can be reduced through caloric restriction or application of the hunger-inducing hormone ghrelin.[204] This hormone shifts cellular metabolism via activation of AMPK and expression of UCP2,[205] indicating that the bioenergetic failure induced by MPTP can be rescued by mild uncoupling. This would limit ROS generation while still supporting mitochondrial Ca^{2+} uptake and continued generation of NAD^+. This again exemplifies the surprising metabolic flexibility of neurons and suggests that neurodegeneration in PD may not be purely driven by the lack of ATP.

Modulation of NAD^+ metabolism has received much attention due to its potential to slow aging (reviewed in ref. [32]). Complex I dysfunction not only leads to reduced respiration but also has implications for mitochondrial one-carbon metabolism.[206] Expression of a bacterially derived water-forming NADH oxidase targeted to mitochondria is able to increase the cellular NAD^+/NADH ratio[207] and was recently shown to rescue mitochondrial complex I deficits.[208] As complex I deficits are linked to PD, this may also be a strategy also to ameliorate disease progression in PD. Overexpression of the mitochondrial one-carbon NAD-dependent metabolic enzymes indeed rescues dopaminergic neurodegeneration in PINK1, and Parkin mutant flies.[209] Therefore, it is conceivable that PD is not only caused by the loss of mitochondrial ATP production due to defects in mitophagy or disturbed mitochondrial dynamics but also the dysregulation of anabolism due to complex I dysfunction and altered NAD^+ availability. Administration of folic acid and thus enhancement of one-carbon metabolism

protected PINK1 mutant flies from mitochondrial dysfunction and neurodegeneration,[210] indicating that other non-bioenergetic mitochondrial functions may be involved in the decline of neuronal health in PD.

Similarly, PGC1-α also integrates the redox state of the cell, as it is regulated by acetylation and deacetylation in response to changes in NAD^+/NADH ratio. The nuclear NAD^+-dependent deacetylase Sirtuin 1 (SIRT1) directly interacts with and deacetylates PGC1-α,[211] and overexpression of SIRT1 increases mitochondrial density in neurons.[212] Both pathways are interconnected as AMPK also modulates NAD^+ metabolism and SIRT1 activity.[213] PGC1-α also stimulates the expression of the mitochondrial NAD^+-dependent deacetylase Sirt3,[214] which increases OXPHOS capacity through deacetylation of several mitochondrial proteins and upregulates PDC activity.[215]

Finally, NAD^+ metabolism plays an important role in axon degeneration since injury activates the activity of SARM1 (sterile alpha and TIR motif 1),[216] an enzyme that degrades NAD^+.[217] This may be important in neurodegenerative diseases, as mitochondrial dysfunction or neuroinflammation also lead to SARM1 activation.[218,219] The recent identification of the mitochondrial NAD^+ transporter now provides experimental access to dissect the molecular mechanisms influencing mitochondrial NAD^+ import and its role in axonal degeneration in neurodegenerative disease.[29,30]

Taken together, loss of ATP generation may not be the only reason why mitochondrial dysfunction is often associated with neurodegenerative diseases, especially as neurons are remarkably flexible in their metabolism. Production of NAD^+ as well as the buffering of Ca^{2+} are also major contributors to mitochondrial health in neurons.

7.2. Cell-Type Specificity

Another conundrum in the field is the selective vulnerability of individual neuron types to specific mitochondrial or mitostatic defects.[220] At the onset of degeneration, neurons have the ability to reprogram their metabolic pathways to maintain basic function. Therefore, it may only be the very long and branched or highly active neurons that over time fail to respond to mitostatic challenges. The process of maintaining a healthy mitochondrial proteome becomes increasingly more challenging with large and more complex morphology.[92] Hence, reduced ATP levels in distal nerve terminals has been proposed to cause the dying back of distal neurites in highly branched dopaminergic neurons in PD.[221] The short half-life of the mitophagy inducer PINK1 requires continuous translation and abundant cytosolic ATP to maintain sensitivity for detection of mitochondrial damage,[222] implying that this pathway of mitophagy energetically relies on healthy mitochondria nearby or on glycolytic ATP. Axonal mitochondria, despite their relative sparseness, still undergo PINK1-dependent mitophagy.[223] The selective vulnerability of dopaminergic neurons to mutations in PINK1 and Parkin can be potentially explained by a shortage of ATP supply in the vast axonal arbors of these neurons which ultimately impairs mitochondrial quality control.[224] It remains to be determined how cell type specific differences in expression of individual proteins in the tangled net of mitochondrial bioenergetics, calcium buffering, and NAD^+ redox-metabolism contribute to the specific vulnerabilities observed in PD and other neurodegenerative diseases. We anticipate that future efforts will focus on therapeutic targeting of the pathways by which neurons sense and respond to mitochondrial damage through pharmacology or diet and exercise (reviewed in ref. [225]).

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Conflict of Interest

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glycolysis, neurodegeneration, OXPHOS, synaptic transmission

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