Chapter

Lifestyle Factors, Mitochondrial Dynamics, and Neuroprotection

Katheryn Broman, Abigail U. Davis, Jordan May and Han-A Park

Abstract

The brain requires vast amounts of energy to carry out neurotransmission; indeed, it is responsible for approximately one-fifth of the body's energy consumption. Therefore, in order to understand functions of brain cells under both normal and pathological conditions, it is critical to elucidate dynamics of intracellular energy. The mitochondrion is the key intercellular organelle that controls neuronal energy and survival. Numerous studies have reported a correlation between altered mitochondrial function and brain-associated diseases; thus mitochondria may serve as a promising target for treating these conditions. In this chapter, we will discuss the mechanisms of mitochondrial production, movement, and degradation in order to understand accessibility of energy during physiological and pathological conditions of the brain. While research targeting molecular dynamics is promising, translation into clinical relevance based on bench research is challenging. For these reasons, we will also summarize lifestyle factors, including interventions and chronic comorbidities that disrupt mitochondrial dynamics. By determining lifestyle factors that are readily accessible, we can propose a new viewpoint for a synergistic and translational approach for neuroprotection.

Keywords: mitochondria, neuroprotection, Bcl-2, exercise, diet

1. Introduction

Frequently referred to as the "the powerhouse of the cell," the mitochondrion is the key organelle that contributes to neuronal energy and viability through the production of adenosine triphosphate (ATP) via oxidative phosphorylation. During oxidative phosphorylation, electrons from $FADH_2$ or NADH travel across the electron transport chain (ETC) creating an electrical gradient along the inner mitochondrial membrane allowing protons to diffuse through the ATP synthase. This allows the ATP synthase to bind a phosphate group to adenosine diphosphate (ADP) creating ATP. Compared to other metabolic pathways such as fermentation and anaerobic respiration, oxidative phosphorylation is the most efficient process to generate ATP. Energy in the brain is used for overall maintenance of cellular processes, neuronal growth, and axonal branching [1]. However, a majority of the ATP produced is utilized to support one of the neuron's most essential functions, synaptic transmission [2]. For example, the Na^+, K^+ -ATPase or the Na^+, K^+-pump is responsible for approximately half of the energy consumed by the brain, through its use of active transport to pump out sodium ions while taking in potassium ions [3].

This pump is essential in neurotransmission through its regulation of membrane potential, cell volume, and intracellular Ca^{2+} homeostasis [4, 5]. Likewise, exocytosis requires sufficient energy to release neurotransmitters from presynaptic to postsynaptic vesicles [5].

Beyond the mitochondria's role in energy production, it is also a key regulator of apoptotic cell death [6]. Various proteins, such as cytochrome c, reside in the mitochondria and participate in apoptotic pathways. In normal physiological conditions, cytochrome c plays a role as an electron carrier in the ETC. However, during neurotoxic conditions, permeabilization of the mitochondrial membrane occurs, and cytochrome c is released into the cytoplasm. Upon release, cytochrome c binds to apoptotic protease activating factor 1 (Apaf-1) which, in turn, activates caspase-9, forming the apoptosome that then activates downstream caspases leading to cell death [7]. Second mitochondria-derived activator of caspase (Smac)/direct IAP-binding protein with low PI (DIABLO) is also a mitochondrial protein released during apoptosis. The N-terminus of Smac/DIABLO directly interacts with inhibitor of apoptosis proteins (IAPs), a family of proteins that inhibit caspase 3, 7, and 9 activities; thus Smac/ DIABLO exhibits pro-apoptotic roles [8].

It has been well studied that Bcl-2 family of proteins controls neuronal survival or death via regulating apoptotic pathways, i.e., pro-apoptotic proteins versus anti-apoptotic proteins [9]. The presence of at least one of the four Bcl-2 homology (BH) domains influences a Bcl-2 family member's role in apoptosis. Pro-apoptotic Bcl-2 family members include the multidomain homology proteins such as Bax and Bak as well as the BH3-only homology proteins such as Bid, Bim, Bad, PUMA, and NOXA. These pro-apoptotic Bcl-2 proteins enhance mitochondrial membrane permeabilization resulting in subsequent release of cytochrome c [10–14].

Anti-apoptotic proteins of the Bcl-2 family include Bcl-2, Bcl-xL, Bcl-w, Mcl-1, and Bfl-1. These proteins contain the BH4 homology, which is essential for anti-apoptotic functionality. Both Bcl-2 and Bcl-xL antagonize pro-apoptotic members to prevent apoptosis [15, 16]; for instance, Bcl-xL targets Bak, preventing its oligomerization and inhibiting it from damaging the mitochondrial outer membrane [17]. Similarly, the C-terminal of Bcl-xL binds to the BH3 domain of Bax, resulting in retro-translocation-activated Bax. [18]. Protein-protein binding is further demonstrated with additional members of Bcl-2 family. These observations suggest that the Bcl-2 family's role in mediating apoptosis and mitochondrial permeabilization is largely influenced by dynamic protein-protein interactions with each other [19–21].

The mitochondrion is also responsible for the production of reactive oxygen species (ROS), namely, superoxide and hydrogen peroxide, at Complex I and III of the ETC [22]. This occurs as a result of electron leakage from the complexes, which then allows oxygen to react [23]. Due to the high energy demands required by neuronal mitochondria, this results in increased ROS generation. Increased ROS activity contributes to lipid peroxidation, causing disruption of the hydrophobic interaction between cytochrome c and cardiolipin, thus releasing cytochrome c [24]. Furthermore, the brain is particularly susceptible to oxidative damage due to its composition of high lipid content. Indeed, ROS play a significant role in the regulation of cell death; however, ROS have recently been reported to induce DNA demethylation via 8-oxoguanine DNA glycosylase-1 (OGG1) [25]. As a result, DNA demethylation induces activation of the reelin gene [26], which has been implicated in enhancing synaptic plasticity by inducing long-term potentiation (LTP) [27], thus indicating that normal levels of ROS may play a role in supporting LTP. Additionally, elimination of ROS negatively impacted neural stem cell proliferation in hippocampal cells indicating that homeostatic levels of ROS may possibly be involved in cell proliferation during growth and development [28]; however additional information is needed in order to elucidate the mechanism behind this.

2. Mitochondrial dynamics

Mitochondria were previously thought of as static organelles. Due to advances in molecular biotechnologies, it has been revealed that mitochondria are indeed very dynamic; mitochondria undergo fission and fusion, can vary in morphology, and achieve intracellular movement. Precise execution of these processes is especially vital for proper ATP production, apoptosis, and ROS homeostasis in neurons to properly execute neurotransmission.

2.1 Fission and fusion

Fission and fusion are integral processes of cellular homeostasis that maintain proper mitochondrial morphology and turnover. Both are mediated by GTPases in the dynamin family, with rates of occurrence depending on changes in metabolic demands. Undoubtedly, fission is essential for dividing cells in order to maintain an adequate number of mitochondria; however, even in nonproliferating neurons, fission is necessary for cell survival [29]. Dynamin-related protein 1 (Drp1) is the primary GTPase that mediates fission, with its activity controlled by phosphorylation via kinases, primarily on two serine residues. Specifically, phosphorylation at Ser616 promotes fission, while phosphorylation at Ser637 inhibits fission, so balance of Drp1 phosphorylation is crucial for proper fission functionality [30]. Impairment in Drp1 leads to alterations in mitochondrial distribution, with mitochondria accumulation occurring at the soma and reduced density in the dendrites. Conversely, Drp1 overexpression yields an increase in dendritic mitochondria [31]. Hippocampal neurons lacking Drp1 display compromised function of axonal mitochondria due to the inability to maintain ATP levels, recycling at synapses [32]. Prominent regulators of fusion include mitofusion 1 and 2 (Mfn1 and Mfn2, respectively) and optic protein atrophy 1 (Opa1). Mitofusion proteins mediate the outer membrane, while Opa1 regulates the inner membrane; however, both work in coordination in a two-step process to carry out fusion [33, 34].

Both fission and fusion are enhanced by Bcl-xL, with fission being induced in a Drp1-dependent manner [35]. This is conclusive with a previous study demonstrating the direct interaction of Bcl-xL with Drp1, initiating Drp1-dependent synapse formation in hippocampal cells [36]. When investigated further, this Bcl-xL-Drp1 complex was found to be necessary for presynaptic plasticity by regulating endocytic vesicles [37].

2.2 Mitochondrial trafficking

Trafficking, mobility, and docking are intertwining processes that are vital to ensure neurons are equipped with the proper distribution and recycling of mitochondria at axons and synapses throughout the cell's life span. **Figure 1** demonstrates how mitochondria are motile and change morphology in primary hippocampal cells. Mitochondrial trafficking is mediated by intracellular signaling, physiological events, and alterations in metabolic demands. Approximately 70% of mitochondria are stationary, with the remaining 30% motile [38]. Furthermore, five distinct mitochondria motility patterns have been described by Sun's research group: stationary outside of synapses, docking at synapses, passing though synapses, pausing at synapses for a short amount of time, and pausing for a longer time [39].

Mechanisms of mitochondrial movement and transport are overall influenced by the polarity of axons, with the positive end directed toward the soma and the negative at the tips. Utilizing this consistent axonal polarity is how microtubule

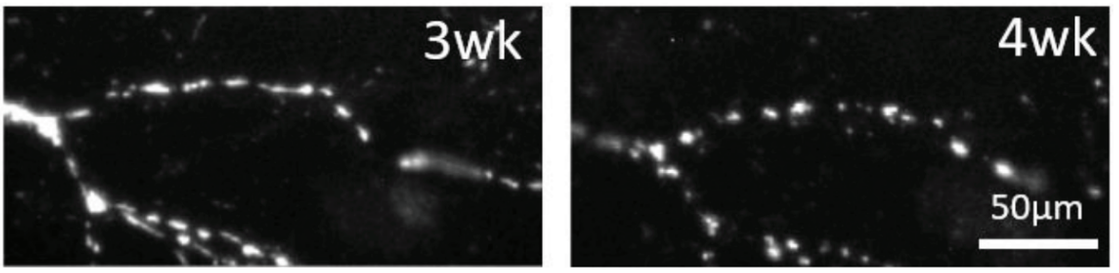

Figure 1.
Mitochondrial movement in primary hippocampal neurons. Primary hippocampal neurons were labeled with mitoRFP, a red fluorescent tag that labels mitochondria. Micrographs were taken at 3 and 4 weeks after seeding. Morphology and location of mitochondria change over time.

motors drive transport in two directions. Movement away from the soma or anterograde movement is conducted by the ATPase family of kinesins, with kinesin-1 being responsible for mitochondrial transport, specifically in neurons [38, 40]. Kinesin-1 consists of heavy chains (KHC) and light chains, with the heavy chains being the driving force that allows kinesin-1 to function as a motor protein [41]. Retrograde movement or movement toward the soma is driven by dynein. However, it is likely that these movements are coordinated rather than competitive toward each other, as it has been demonstrated that inhibiting kinesin-1 in *Drosophila* reduces retrograde movement [42].

Mitochondrial Rho-GTPase, or Miro, is an outer membrane receptor, Ca^{2+} sensor, and another pertinent regulator of mitochondrial motility due to its ability to anchor kinesin and dynein to the mitochondrial outer membrane [43]. Miro's anchoring role has been extensively studied in anterograde movement in the motor/adaptor complex formed between KHC and Miro, connected by the protein adaptor milton [44, 45].

Another important component of mitochondria trafficking is stationary docking. Mitochondrial docking is largely mediated by the axonal outer membrane protein syntaphilin (SNPH) and its interaction with microtubules in the cytoskeleton. This is demonstrated in rodent models in which deletion of the SNPH gene results in an increase in mitochondria motility and reduced density, while overexpression of endogenous or exogenous SNPH abolished mobility [46]. Along with decreasing the percentage of immobile mitochondria, loss of SNPH decreases axonal branching in cortical neurons [47]. This effect is comparable to neurons lacking LKB-1 and NUAK1, which is necessary for axonal specification [48]. The removal of either of these kinases leads to a decrease in the number of stationary mitochondria along with decreased branching. However, overexpression of SNPH in the LKB-1 and NUAK1-null neurons rescued these effects. Collectively, this implies that docking of mitochondria is required for axonal branching and growth [47]. Since Bcl-xL is required for neurite outgrowth [49], it is possible that Bcl-xL exerts this effect by interacting with docking proteins such as syntaphilin. However, the exact role of Bcl-xL in docking mechanisms must be further elucidated.

3. Alteration of mitochondrial function in brain-associated diseases

While various brain-associated diseases have different pathophysiologies, there is an underlying similarity that consistently occurs: mitochondrial dysfunction. Throughout these conditions, neurodegeneration is correlated with an energy deficit caused by inefficient operation of the ETC, activation of mitochondria-dependent apoptosis, and accumulation of ROS. In addition, excitotoxicity, which commonly

occurs during cerebral ischemia and traumatic brain injury, impairs homeostasis of excitatory neurotransmitter glutamate [50–53]. Overstimulation of glutamate receptors further leads to Ca^{2+} release; because mitochondria are one of the key regulators of Ca^{2+}, excessive influx can consequently lead to mitochondrial dysfunction, altered membrane permeabilization, and subsequent cell death [50, 54–56]. Pathways such as these have been extensively explored in neurological conditions. However, research in the past decade has begun to determine the relationship between brain-associated conditions and mitochondrial dynamics.

3.1 Parkinson's disease

Parkinson's disease (PD) is a common neurodegenerative disease that has detrimental clinical effects including tremors, impaired gait, and stiffness of limbs [57]. These symptoms are often due to PD's hallmark characterization of degeneration of the dopaminergic neurons in the substantia nigra. Individuals with PD are vulnerable to increased ROS production due to reduced complex 1 activity, increased lipid oxidation, and altered antioxidant systems [58].

As several PD-specific proteins impact mitochondrial dynamics, it is possible that the neurodegeneration that occurs with PD is linked to alterations in fission and fusion [59, 60]. Dopaminergic neurons depleted of Drp1 demonstrated decreased mitochondrial mass, impaired motility, and overall neuron loss. Neurons depleted with Drp1 had less mitochondria in the soma and were almost completely depleted from the axons; by not having mitochondria at axons, this can lead to the neurodegeneration due to energy deficits, as synaptic transmission requires a high demand of ATP [61].

The PINK1/Parkin pathway has been traditionally studied with its roles in mitophagy. Under normal physiological conditions, PINK1 accumulates on the surface of dysfunctional mitochondria to signal Parkin translocation to initiate ubiquitination [62]. However, mutations in PINK1 and Parkin, which have been linked to early onset familial forms of PD, lead to loss of mitochondrial membrane potential, leading to impairment of Parkin's translocation and thus accumulation of dysfunctional mitochondria [63]. Research in recent years has begun to uncover the role of the PINK1/Parkin pathway in mitochondrial transport. Overexpression of PINK1 phosphorylates Miro, targeting it for ubiquitination and subsequent degradation. This results in the dismantling of the motor/adaptor complex, releasing kinesin and milton from the mitochondrial surface, and leads to halting of mitochondrial motility [64]. It is possible that this system may promote neuroprotection by preventing anterograde transport of mitochondria and allowing PINK1 to accumulate on damaged mitochondria to initiate mitophagy [65]. Furthermore, PINK1 may exert neuroprotection due to its interaction with Bcl-xL [66]. It has been shown that PINK1 phosphorylates Bcl-xL at its Ser62; as a result, this prevents N-terminal cleavage of Bcl-xL or formation of ΔN-Bcl-xL, which has been associated with neuronal death [67–69]. However, if altered PINK1 expression occurs as a result of genetic mutation, this may lead to dysregulated mitochondrial transport and promotion of apoptosis.

The presynaptic protein α-synuclein is a major constituent of Lewy bodies, with mutations in its encoding gene, SNCA, being linked to familial PD [70]. Some amount of α-synuclein can localize to the mitochondria, inducing mitochondrial fragmentation, dysfunction, and downregulation of complex 1 activity, potentially contributing to ROS production [71]. Overexpression of α-synuclein results in cytotoxicity due to decreased Bcl-xL expression and increased Bax expression [72]. Shaltouki's research group recently investigated the role of α-synuclein on

mitochondrial dynamics by using multiple PD models. In the postmortem brains of humans with PD, it was observed that protein levels of α-synuclein and Miro were highly upregulated compared to the control brains, while KHC, VDAC, and Mfn2 remained unchanged. Additionally, the β-subunit of ATP synthase was upregulated in the PD brains. When this was further explored in human cell lines and in *Drosophila* bearing SNCA mutations, neurodegeneration and locomotion defects occurred as a result of the upregulated α-synuclein and subsequent upregulation of Miro. These effects were rescued with a partial reduction of Miro. Interestingly, upregulation of Miro led to delayed mitophagy implying that α-synuclein's impact on Miro is probably independent of the PINK1/Parkin pathways [73].

Recently, it was shown that the β-subunit of ATP synthase binds to DJ-1 suggesting that DJ-1 plays a role in increasing ATP efficiency [74]. Mutations in DJ-1 also demonstrate inefficient ATP production, alterations in mitochondrial morphology, and enhanced membrane permeability [74–76]. Although its functions are not completely understood, DJ-1 has been noted to prevent the aggregation of α-synuclein [77]. As Lewy bodies in PD are primarily a result of α-synuclein aggregation, inhibiting this aggregation may consequently delay Lewy body formation. Thus, therapies targeting DJ-1 may serve as a multi-faceted mechanism for PD treatment.

3.2 Alzheimer's disease

Alzheimer's disease (AD) is the most common neurodegenerative disease and the leading cause of dementia worldwide [78]. Two hallmark characteristics of AD are the presence of amyloid-beta peptide (Aβ) plaques and tau protein tangles. The formation of Aβ occurs as a consequence of cleavage of amyloid precursor protein (APP), where Aβ peptides can then aggregate into oligomers or fibrils [79]. In the brain, the typical role of tau proteins is to stabilize microtubules; however, in AD, it is suspected that hyperphosphorylation of tau leads to the formation of neurofibril tangles [80]. Both Aβ and tau tangles can cause impairments or interruptions in pathways essential for neuronal survival.

Reduced transport of axonal mitochondria has been documented in subjects with AD, but there may be multiple mechanisms to cause this disruption [81]. The presence of Aβ reduces bidirectional axonal mitochondrial motility but has a more significant impact on anterograde movement versus retrograde [82, 83]. This may be because Aβ activates GSK-3β, which is a negative regulator of kinesin-1. Phosphorylation of kinesin-1 by GSK-3β can lead to a reduction in mitochondria density [84]. Furthermore, mutations in presenilin-1 (PS1), which is linked to familial AD, promote GSK-3β-mediated kinesin-1 phosphorylation and reductions of anterograde mitochondria transport [84]. Overexpression of tau also has the ability to redirect mitochondrial transport; kinesin-1 encounters tau and is detracted from microtubule tracks, slowing down anterograde movement and increasing the favorability of dynein-mediated retrograde movement [85, 86]. Abnormal fission mechanics have also been observed in AD as a result of alteration in Drp1 function. Neurotoxicity via tau interrupts fission, causing elongated mitochondria and mislocalization of Drp1. This occurs because hyperphosphorylation of tau causes disruptions in actin, preventing actin-based translocation of Drp1 to the mitochondria [87].

3.3 Stroke

Cerebral ischemia, or more commonly stroke, is characterized by the decrease or cessation of blood flow to the brain. Consequently, the loss of oxygen and nutrients to neurons causes ATP deficits, apoptosis, and Ca^{2+} influx. It is not surprising then that mitochondrial dynamics are influenced after ischemic events. This is

demonstrated by Zou's research group as they sought to elucidate how mechanisms of fission and mitophagy are impacted after ischemia [88]. Using a model of middle cerebral artery occlusion (MCAO), Drp1 initially increased but then decreased, implying that ischemia induced fission, but the process was disrupted due to abnormalities in translocation of Drp1 caused by MCAO. Mitophagy is also selectively induced by mild ischemia in a Drp1-dependent manner; this is evident by increased expressions of LC3B and Beclin-1 and decreased p62. Moreover, inhibition of Drp1 led to early onset of apoptotic pathways [88]. This may be supported by transient ischemia models, in which p-Drp1 is upregulated [89, 90]. Interestingly, evidence shows that p-Drp1 at Ser616 may be regulated by PINK1, establishing a link between fission and mitophagy [90]. Like fission, mechanisms of fusion are also impacted by ischemic insult. Mfn2 expression is decreased after MCAO and leads to apoptosis, but when overexpressed, Mfn2 shows an anti-apoptotic effect by modulating Bcl-2 and Bax [91]; these results are conclusive with a similar study, showing that Mfn2 expression is decreased after excitotoxic insult with a subsequent increase in Bax translocation to the mitochondria [92].

Excitotoxicity via overactivation of glutamate receptors, namely, N-methyl-D-aspartate (NMDA) receptors (NMDARs), is a key player of neuronal death after cerebral ischemia [93]. Thus, uncovering mechanisms effecting NMDARs is an attractive idea for therapeutic agents. While mechanisms of mitochondrial motility are less investigated in models of cerebral ischemia, a recent study has elucidated a novel role of kinesin-1 transport. The heavy chain of kinesin-1 has been shown to bind directly to NMDARs, mediating their transport. By either disassociating this bond or suppressing kinesin-1 expression, this can improve Ca^{2+} influx and NMDA excitotoxicity resulting from ischemia [94].

3.4 Traumatic brain injury (TBI)

Reducing excessive fission that occurs post-TBI is a potential target of neuroprotection to prevent neuronal impairments and death. In rodent models, TBI causes an increase in translocation of Drp1 to the mitochondria, increasing rates of fission. Consequently, this led to neuronal apoptosis, decreased neurogenesis, impaired cognition, and memory defects. When administered with Mdivi-1, a pharmacological inhibitor of Drp1, these negative effects were attenuated, confirming the role of increased Drp1 activity [95, 96]. Interestingly, Pietro's research group suggest that many molecular responses after severe TBI are opposite from that of mild TBI. Rodents with severe TBI presented with activation of fission as shown by overexpression of Drp1 and FIS1, a protein that binds to Drp1 for anchoring to the mitochondrial outer membrane. Furthermore, expressions of Mfn1 and Mfn2 were downregulated, and there were no changes in Opa1 gene and protein expressions, demonstrating an inhibition of fusion as a result of severe TBI. Additionally, the increase of dysfunctional mitochondria led to a subsequent overexpression of PINK1 and PARK2, triggering mitophagy. Conversely, mild TBI demonstrated activation of fusion with inhibition of fission; together, this did not change PINK1 or PARK2 gene expressions, thus showing no difference in mitophagy [97].

4. The effect of lifestyle factors on mitochondria function and dynamics

4.1 Exercise and mitochondria

Traditionally observed at a large, systemic level, research in recent years has begun to investigate the effect of exercise on mitochondrial function and dynamic

processes. Furthermore, encouraging results have been observed by analyzing these effects in physiological processes in the brain and pathological conditions such as Alzheimer's disease and Parkinson's disease [98–101]. After old and young mice were subjected to 6 weeks of treadmill exercise, old mice were found to respond positively, showing attenuated activity of coupled complexes I–III of the ETC [99].

Exercise regulates mitochondrial fission and fusion proteins such as Opa1, Mfn2, and Drp1 and enhances mitochondrial biogenesis via upregulation of mitochondrial DNA. This suggests a role for exercise in maintaining a healthy population of mitochondria [98, 101]. In addition, rodents that undergo physical exercise demonstrate improved cognitive and exploratory behaviors along with improved mitochondrial redox homeostasis and mitochondria-mediated brain energy metabolism [102–104].

Exercise has been shown to regulate apoptosis through the regulation of the Bcl-2 family in various models and tissues. As previously discussed, age can have a significant role in mitochondrial dysfunction. A study conducted by Kim et al. investigated how hippocampal neurogenesis and apoptosis were affected by treadmill exercise in young and old-aged rats [105]. Expressions of caspase-3, Bax, Bid, and Bcl-2 were all increased in old mice. After being subjected to treadmill exercise for 30 minutes, once per day for 6 weeks, old rats exhibited further enhancement of Bcl-2 expression, along with decreased expressions of caspase-3, Bax, and Bid. Interestingly, exercise did not impact expressions of Bcl-2, Bax, or caspase-3 in young mice. These results implicate that aerobic exercise may be especially important during aging to exert neuroprotective properties. Aboutaleb et al. examined the effect exercise had on the ratio of Bax/Bcl-2 proteins in hippocampal CA3 cells after ischemia. Ischemic insult led to an increase in caspase-3 and decrease in Bcl-2, thus an increase in Bax/Bcl-2 ratio. However, rats pre-subjected to exercise showed reduced levels of caspase-3 and attenuation of Bax/Bcl-2 ratio [106]. Similar results have been seen in a rodent TBI model, in which treadmill exercise lowered the Bax/Bcl-2 ratio and decreased the levels of active caspase-3 [107]. Likewise, endurance exercise exerted neuroprotection in PD models by modulation of Mcl-1, Bcl-2, and apoptosis-inducing factor [108]. Although Bcl-2 has primarily been investigated in rodent exercise models, exercise results in a negative regulatory effect on caspase-3 [105–107] which may reduce post-translational cleavage of Bcl-xL supporting neuronal survival [67, 69].

Since the Bcl-2 family proteins are present in the mitochondria throughout all tissue types, it is plausible that protective effects observed in non-neuronal mitochondria are indeed simultaneously occurring in neuronal mitochondria. For example, due to the correlation between diabetes and cardiovascular disease, Cheng et al. examined the relationship between apoptosis, cardiomyocytes, and aerobic exercise in streptozotocin (STZ)-induced diabetic rats. The STZ rats had significantly lower amounts of Bcl-2, Bcl-xL, and p-Bad and higher levels of caspase-3 than controls. However, these levels were all rescued when subjected to aerobic exercise [109]. These results implicate the ability of aerobic exercise to regulate apoptosis and exert cellular protection, even during chronic conditions.

4.2 Non-neurological conditions and mitochondrial consequences

As chronic diseases such as diabetes and obesity become more prevalent worldwide, research is uncovering the relationship between traditional non-neurological and brain-associated diseases. However, many interventions in studies concerning chronic diseases observe outcomes on a macrolevel and may not consider molecular effects. For these reasons, it is important to uncover how these non-neurological chronic conditions are impacting the mitochondria. By elucidating these

mechanisms, this can serve as an additional, albeit perhaps overlooked, means of prevention against brain pathology.

Besides disrupting the uptake of glucose, diabetes can also damage the function, population, and morphology of mitochondria in neurons, potentially contributing to impaired cognition later in life [110–113]. Metabolic pathways that can lead to energy failure in mitochondria as well as prevent antioxidant interception are affected by diabetes. In the diabetic brain, mitochondrial perturbation can result in a lack of neuronal energy that will alter synaptic function and eventually cause the neurons to degenerate [114]. The effect of energy impairments is demonstrated in a cross-sectional study in which adolescents with type 2 diabetes had slower conversion rates of ADP to ATP than obese and lean controls. The explanation for this effect was suspected to be due to decreased blood flow, thus causing alterations in oxygen delivery [115]. Studies have shown that diabetes can modify fission mechanisms in rodent models. Although amounts of Mfn1 and Opa1 remain unchanged during diabetes, Drp1 mRNA is increased. Furthermore, there is an increase of translocation of Drp1 to the mitochondria in diabetes [110, 113]. This increase in translocation is due to GSK3β-mediated phosphorylation at Ser616 of Drp1. The combination of unchanged Mfn1 and Opa1 with increased Drp1 proposes that the disproportion between fission and fusion proteins contributes to mitochondrial dysfunction in rats with diabetes. This was further evident by altered mitochondrial morphology and density. Elevated levels of Drp1 can lead to mitochondrial fragmentation that is conducive to damage in the synapses of neurons, contributing to impairments in learning and memory [116]. Beyond alterations in fission and fusion, decreased ATP production and activity of complex I were observed in the diabetic hippocampus. Moreover, glutathione and ascorbate levels were decreased, suggesting that diabetes impairs mitochondrial antioxidant systems [110]. These results are supported by a study that found decreased coenzyme Q9 and ATPase activity in the mitochondria of diabetic rats [117].

Obesity is known to increase the risk of developing diabetes, cardiovascular disease, and neurological conditions. Indeed, obese animal models are often utilized to study insulin resistance. A characteristic of obesity is chronic inflammation and oxidative stress, so it is not surprising that mitochondrial dysfunction occurs throughout the body, including the brain [114]. Specifically, brain mitochondria of obese rats induced via a high-fat diet have repeatedly demonstrated a shift to pro-apoptotic pathways, as shown by elevated Bax expressions, lowered Bcl-2, and a higher Bax/Bcl-2 ratio [118, 119]. The detrimental effects of obesity continue to be demonstrated in the brain by upregulating production of ROS and alteration of mitochondrial membrane potential [120–122].

4.3 Diet and mitochondria

Diet, including intake of specific nutrients and overall encompassing dietary patterns, is a driver of maintaining cellular processes throughout the body. Treatment of diseases via diet is appealing due to the ability of nutrients to cross the blood brain barriers and ease of accessibility. Specifically, it is important to consider how an individual's overall dietary pattern impacts cellular processes. Dietary patterns, including composition of macronutrients and caloric provision, have been studied regarding efficacy in neuroprotection [123–125].

Caloric restriction has been implicated in the protection against several pathological brain conditions in various animal models such as AD and PD and under conditions of excitotoxicity [126–130]. Caloric restriction has been shown to confer protection from neurodegeneration by improving mitochondrial redox status

by reducing ROS production localized to complex I of the ETC [131]. Recent evidence suggests that caloric restriction may prevent formation of ROS via upregulation of antioxidants such as mitochondrial superoxide dismutase 2 (SOD2) and glutathione [132]. Caloric restriction has also been reported to upregulate antioxidants localized to the plasma membrane such as coenzyme Q10 and α-tocopherol via an increase in redox enzymes that are capable of reducing these molecules back to their antioxidant form [133]. Due to coenzyme Q10's pivotal role as an electron carrier in the ETC, we speculate that caloric restriction may be beneficial to maintain redox balance in the mitochondrial membrane. Additionally, mRNA expressions of Bcl-2 and Bcl-xL were also reported to be upregulated in the ipsilateral cortex region of mice placed on caloric restriction against TBI [134], indicating that caloric restriction may prevent TBI-induced neuronal loss. Furthermore, caloric restriction improves mitochondrial function by enhancing ATP levels in aging mice [135]. Mice placed on caloric restriction for 6 months had increased mitochondrial biogenesis and increased levels of cytochrome c oxidase and citrate synthase activity, enhancing mitochondrial respiration [136]. Caloric restriction may enhance mitochondrial metabolism by also upregulating the activity of complexes I, III, and IV [128]. Interestingly, recent evidence shows that caloric restriction enhances expression of brain-derived neurotrophic factor (BDNF) [137, 138], which has been reported to regulate mitochondrial mobility and enhance presynaptic docking [139]. However, the mechanisms of how caloric restriction mediates BDNF expression are still unclear. Clinical trials in which older adults are placed on caloric restriction consistently yield positive results, such as improved memory and enhanced gray matter [140, 141]. Additionally, caloric restriction attenuated behavioral dysfunction in a model of PD in adult rhesus monkeys [130]. Taken together, these studies point *toward* caloric restriction mediating biological markers of chronic disease such as oxidative stress and supporting mitochondrial function by enhancing ATP metabolism and possibly lessening clinical symptoms associated with neurodegeneration.

The ketogenic diet, popular for its high-fat and very low carbohydrate pattern, has recently been implicated in protection of the brain through apoptotic pathways. Various mammalian animals placed on the ketogenic diet show decreased rates of apoptotic stimuli in neuronal cells via downregulation of mitochondrial cytochrome c release and active caspase-3 both in seizures [142, 143] and TBI models [144], respectively. The decrease in translocation of cytochrome c from the mitochondria to the cytosol may be through the regulation of Bcl-2. One study found that both a high carbohydrate and a high ketogenic diet upregulate Bcl-2 in cortical neurons after focal cerebral ischemia; however, the ketogenic diet displayed higher upregulation [145], indicating that the ketogenic diet may be more efficient in regulating apoptosis than a high carbohydrate diet. The ketogenic diet may play an additional role in cell death and survival pathways, as it has been noted to protect hippocampal cells from death by preventing the interaction between Bad and Bcl-xL [146]. The ketogenic diet further supports neuronal energy metabolism by maintaining mitochondrial morphology, enhancing biogenesis of mitochondria, and improving mitochondrial respiration [147–151]. After neurotoxic insult, the ketogenic diet enhanced complex I-driven oxygen consumption and prevented loss of complex II–III function, implicating the ketogenic diet's ability to improve the activity of the ETC [147, 149]. Likewise, the ketogenic diet attenuates mitochondrial oxidative stress levels in both in vitro and in vivo model, which prevents energy deficit associated with brain cell damage [147, 149, 151]. Interestingly, the ketogenic diet has also been shown to upregulate Beclin-1 [142] and Drp1 [148], suggesting that the ketogenic diet may be able to control mitochondrial population by regulating autophagy and mitochondrial fission, respectively.

5. Conclusions

Mitochondria are well established in their role with ATP production, apoptosis, ROS homeostasis, and intracellular ion signaling. Research in recent years has recognized that proper execution of these processes is reliant on the mitochondria's dynamic capabilities. In this chapter we have discussed mechanisms of mitochondrial morphology, degradation, and trafficking, as well as the relationship between these processes and pathological brain conditions. Utilizing lifestyle factors, such as exercise and diet, can serve as a neuroprotective strategy by targeting neuronal mitochondrial dynamics. Implementing lifestyle changes serves as an accessible treatment that is easily translated from bench to bedside.

Acknowledgements

This research was funded by Summer Research Support by the College of Human Environmental Sciences, the University of Alabama.

Conflict of interest

The authors declare no conflict of interest.

Author details

Katheryn Broman, Abigail U. Davis, Jordan May and Han-A Park*
Department of Human Nutrition and Hospitality Management, College of Human Environmental Sciences, The University of Alabama, Tuscaloosa, AL, USA

*Address all correspondence to: hpark36@ches.ua.edu

References

[1] Smith GM, Gallo G. The role of mitochondria in axon development and regeneration. Developmental Neurobiology. 2018;**78**(3):221-237

[2] Harris JJ, Jolivet R, Attwell D. Synaptic energy use and supply. Neuron. 2012;**75**(5):762-777

[3] Skou JC. The identification of the sodium pump. Bioscience Reports. 2004;**24**(4-5):436-451

[4] Pivovarov AS, Calahorro F, Walker RJ. Na(+)/K(+)-pump and neurotransmitter membrane receptors. Invertebrate Neuroscience. 2018;**19**(1):1

[5] Pathak D, Shields LY, Mendelsohn BA, Haddad D, Lin W, et al. The role of mitochondrially derived ATP in synaptic vesicle recycling. The Journal of Biological Chemistry. 2015;**290**(37):22325-22336

[6] Kroemer G, Dallaporta B, Resche-Rigon M. The mitochondrial death/life regulator in apoptosis and necrosis. Annual Review of Physiology. 1998;**60**:619-642

[7] Zou H, Li Y, Liu X, Wang X. An APAF-1.cytochrome c multimeric complex is a functional apoptosome that activates procaspase-9. The Journal of Biological Chemistry. 1999;**274**(17):11549-11556

[8] Wu G, Chai J, Suber TL, Wu JW, Du C, et al. Structural basis of IAP recognition by Smac/DIABLO. Nature. 2000;**408**(6815):1008-1012

[9] Czabotar PE, Lessene G, Strasser A, Adams JM. Control of apoptosis by the BCL-2 protein family: Implications for physiology and therapy. Nature Reviews. Molecular Cell Biology. 2014;**15**(1):49-63

[10] Ren D, Tu HC, Kim H, Wang GX, Bean GR, et al. BID, BIM, and PUMA are essential for activation of the BAX- and BAK-dependent cell death program. Science. 2010;**330**(6009):1390-1393

[11] Desagher S, Osen-Sand A, Nichols A, Eskes R, Montessuit S, et al. Bid-induced conformational change of Bax is responsible for mitochondrial cytochrome c release during apoptosis. The Journal of Cell Biology. 1999;**144**(5):891-901

[12] Jurgensmeier JM, Xie Z, Deveraux Q, Ellerby L, Bredesen D, et al. Bax directly induces release of cytochrome c from isolated mitochondria. Proceedings of the National Academy of Sciences of the United States of America. 1998;**95**(9):4997-5002

[13] Kirkland RA, Franklin JL. Bax, reactive oxygen, and cytochrome c release in neuronal apoptosis. Antioxidants and Redox Signaling. 2003;**5**(5):589-596

[14] Wei MC, Lindsten T, Mootha VK, Weiler S, Gross A, et al. tBID, a membrane-targeted death ligand, oligomerizes BAK to release cytochrome c. Genes and Development. 2000;**14**(16):2060-2071

[15] Huang DC, Adams JM, Cory S. The conserved N-terminal BH4 domain of Bcl-2 homologues is essential for inhibition of apoptosis and interaction with CED-4. The EMBO Journal. 1998;**17**(4):1029-1039

[16] Cheng EH, Wei MC, Weiler S, Flavell RA, Mak TW, et al. BCL-2, BCL-X(L) sequester BH3 domain-only molecules preventing BAX- and BAK-mediated mitochondrial apoptosis. Molecular Cell. 2001;**8**(3):705-711

[17] Lee EF, Grabow S, Chappaz S, Dewson G, Hockings C, et al. Physiological restraint of Bak by Bcl-xL

is essential for cell survival. Genes and Development. 2016;**30**(10):1240-1250

[18] Todt F, Cakir Z, Reichenbach F, Youle RJ, Edlich F. The C-terminal helix of Bcl-x(L) mediates Bax retrotranslocation from the mitochondria. Cell Death and Differentiation. 2013;**20**(2):333-342

[19] Ku B, Liang C, Jung JU, Oh BH. Evidence that inhibition of BAX activation by BCL-2 involves its tight and preferential interaction with the BH3 domain of BAX. Cell Research. 2011;**21**(4):627-641

[20] Clohessy JG, Zhuang J, de Boer J, Gil-Gomez G, Brady HJ. Mcl-1 interacts with truncated bid and inhibits its induction of cytochrome c release and its role in receptor-mediated apoptosis. The Journal of Biological Chemistry. 2006;**281**(9):5750-5759

[21] Chen L, Willis SN, Wei A, Smith BJ, Fletcher JI, et al. Differential targeting of prosurvival Bcl-2 proteins by their BH3-only ligands allows complementary apoptotic function. Molecular Cell. 2005;**17**(3):393-403

[22] Murphy MP. How mitochondria produce reactive oxygen species. The Biochemical Journal. 2009;**417**(1):1-13

[23] Liu Y, Fiskum G, Schubert D. Generation of reactive oxygen species by the mitochondrial electron transport chain. Journal of Neurochemistry. 2002;**80**(5):780-787

[24] Ott M, Robertson JD, Gogvadze V, Zhivotovsky B, Orrenius S. Cytochrome c release from mitochondria proceeds by a two-step process. Proceedings of the National Academy of Sciences of the United States of America. 2002;**99**(3):1259-1263

[25] Zhou X, Zhuang Z, Wang W, He L, Wu H, et al. OGG1 is essential in oxidative stress induced DNA demethylation. Cellular Signalling. 2016;**28**(9):1163-1171

[26] Miller CA, Sweatt JD. Covalent modification of DNA regulates memory formation. Neuron. 2007;**53**(6):857-869

[27] Weeber EJ, Beffert U, Jones C, Christian JM, Forster E, et al. Reelin and ApoE receptors cooperate to enhance hippocampal synaptic plasticity and learning. The Journal of Biological Chemistry. 2002;**277**(42):39944-39952

[28] Yoneyama M, Kawada K, Gotoh Y, Shiba T, Ogita K. Endogenous reactive oxygen species are essential for proliferation of neural stem/progenitor cells. Neurochemistry International. 2010;**56**(6-7):740-746

[29] Youle RJ, van der Bliek AM. Mitochondrial fission, fusion, and stress. Science. 2012;**337**(6098):1062-1065

[30] Mishra P, Chan DC. Metabolic regulation of mitochondrial dynamics. The Journal of Cell Biology. 2016;**212**(4):379-387

[31] Li Z, Okamoto K, Hayashi Y, Sheng M. The importance of dendritic mitochondria in the morphogenesis and plasticity of spines and synapses. Cell. 2004;**119**(6):873-887

[32] Shields LY, Kim H, Zhu L, Haddad D, Berthet A, et al. Dynamin-related protein 1 is required for normal mitochondrial bioenergetic and synaptic function in CA1 hippocampal neurons. Cell Death and Disease. 2015;**6**:e1725

[33] Ranieri M, Brajkovic S, Riboldi G, Ronchi D, Rizzo F, et al. Mitochondrial fusion proteins and human diseases. Neurology Research International. 2013;**2013**:293893

[34] van der Bliek AM, Shen Q, Kawajiri S. Mechanisms of mitochondrial fission and fusion. Cold

Spring Harbor Perspectives in Biology. 2013;**5**(6):a011702

[35] Berman SB, Chen YB, Qi B, McCaffery JM, Rucker EB 3rd, et al. Bcl-x L increases mitochondrial fission, fusion, and biomass in neurons. The Journal of Cell Biology. 2009;**184**(5):707-719

[36] Li H, Chen Y, Jones AF, Sanger RH, Collis LP, et al. Bcl-xL induces Drp1-dependent synapse formation in cultured hippocampal neurons. Proceedings of the National Academy of Sciences of the United States of America. 2008;**105**(6):2169-2174

[37] Li H, Alavian KN, Lazrove E, Mehta N, Jones A, et al. A Bcl-xL-Drp1 complex regulates synaptic vesicle membrane dynamics during endocytosis. Nature Cell Biology. 2013;**15**(7):773-785

[38] Sheng ZH. Mitochondrial trafficking and anchoring in neurons: New insight and implications. The Journal of Cell Biology. 2014;**204**(7):1087-1098

[39] Sun T, Qiao H, Pan PY, Chen Y, Sheng ZH. Motile axonal mitochondria contribute to the variability of presynaptic strength. Cell Reports. 2013;**4**(3):413-419

[40] Saxton WM, Hollenbeck PJ. The axonal transport of mitochondria. Journal of Cell Science. 2012;**125** (Pt 9):2095-2104

[41] Jolly AL, Kim H, Srinivasan D, Lakonishok M, Larson AG, et al. Kinesin-1 heavy chain mediates microtubule sliding to drive changes in cell shape. Proceedings of the National Academy of Sciences of the United States of America. 2010;**107**(27):12151-12156

[42] Ligon LA, Tokito M, Finklestein JM, Grossman FE, Holzbaur EL. A direct interaction between cytoplasmic dynein and kinesin I may coordinate motor activity. The Journal of Biological Chemistry. 2004;**279**(18):19201-19208

[43] Tang BL. Miro-working beyond mitochondria and microtubules. Cell. 2018;**7**(3):18

[44] Schwarz TL. Mitochondrial trafficking in neurons. Cold Spring Harbor Perspectives in Biology. 2013;**5**(6):a011304

[45] Stowers RS, Megeath LJ, Gorska-Andrzejak J, Meinertzhagen IA, Schwarz TL. Axonal transport of mitochondria to synapses depends on Milton, a novel drosophila protein. Neuron. 2002;**36**(6):1063-1077

[46] Kang JS, Tian JH, Pan PY, Zald P, Li C, et al. Docking of axonal mitochondria by syntaphilin controls their mobility and affects short-term facilitation. Cell. 2008;**132**(1):137-148

[47] Courchet J, Lewis TL Jr, Lee S, Courchet V, Liou DY, et al. Terminal axon branching is regulated by the LKB1-NUAK1 kinase pathway via presynaptic mitochondrial capture. Cell. 2013;**153**(7):1510-1525

[48] Barnes AP, Lilley BN, Pan YA, Plummer LJ, Powell AW, et al. LKB1 and SAD kinases define a pathway required for the polarization of cortical neurons. Cell. 2007;**129**(3):549-563

[49] Park HA, Licznerski P, Alavian KN, Shanabrough M, Jonas EA. Bcl-xL is necessary for neurite outgrowth in hippocampal neurons. Antioxidants and Redox Signaling. 2015;**22**(2):93-108

[50] Wang R, Reddy PH. Role of glutamate and NMDA receptors in Alzheimer's disease. Journal of Alzheimer's Disease. 2017;**57**(4):1041-1048

[51] Johnson KA, Conn PJ, Niswender CM. Glutamate receptors

as therapeutic targets for Parkinson's disease. CNS and Neurological Disorders Drug Targets. 2009;**8**(6):475-491

[52] Lai TW, Zhang S, Wang YT. Excitotoxicity and stroke: Identifying novel targets for neuroprotection. Progress in Neurobiology. 2014;**115**:157-188

[53] Guerriero RM, Giza CC, Rotenberg A. Glutamate and GABA imbalance following traumatic brain injury. Current Neurology and Neuroscience Reports. 2015;**15**(5):27

[54] Onyango IG, Dennis J, Khan SM. Mitochondrial dysfunction in Alzheimer's disease and the rationale for bioenergetics based therapies. Aging and Disease. 2016;**7**(2):201-214

[55] Hiebert JB, Shen Q, Thimmesch AR, Pierce JD. Traumatic brain injury and mitochondrial dysfunction. The American Journal of the Medical Sciences. 2015;**350**(2):132-138

[56] Pivovarova NB, Andrews SB. Calcium-dependent mitochondrial function and dysfunction in neurons. The FEBS Journal. 2010;**277**(18):3622-3636

[57] DeMaagd G, Philip A. Parkinson's disease and its management: Part 1: Disease entity, risk factors, pathophysiology, clinical presentation, and diagnosis. Pharmacy and Therapeutics. 2015;**40**(8):504-532

[58] Hwang O. Role of oxidative stress in Parkinson's disease. Experimental Neurobiology. 2013;**22**(1):11-17

[59] Pozo Devoto VM, Falzone TL. Mitochondrial dynamics in Parkinson's disease: A role for alpha-synuclein? Disease Models and Mechanisms. 2017;**10**(9):1075-1087

[60] Santos D, Esteves AR, Silva DF, Januario C, Cardoso SM. The impact of mitochondrial fusion and fission modulation in sporadic Parkinson's disease. Molecular Neurobiology. 2015;**52**(1):573-586

[61] Berthet A, Margolis EB, Zhang J, Hsieh I, Zhang J, et al. Loss of mitochondrial fission depletes axonal mitochondria in midbrain dopamine neurons. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience. 2014;**34**(43):14304-14317

[62] Pickrell AM, Youle RJ. The roles of PINK1, parkin, and mitochondrial fidelity in Parkinson's disease. Neuron. 2015;**85**(2):257-273

[63] Geisler S, Holmstrom KM, Treis A, Skujat D, Weber SS, et al. The PINK1/Parkin-mediated mitophagy is compromised by PD-associated mutations. Autophagy. 2010;**6**(7): 871-878

[64] Wang X, Winter D, Ashrafi G, Schlehe J, Wong YL, et al. PINK1 and Parkin target Miro for phosphorylation and degradation to arrest mitochondrial motility. Cell. 2011;**147**(4):893-906

[65] Liu S, Sawada T, Lee S, Yu W, Silverio G, et al. Parkinson's disease-associated kinase PINK1 regulates Miro protein level and axonal transport of mitochondria. PLoS Genetics. 2012;**8**(3):e1002537

[66] Arena G, Gelmetti V, Torosantucci L, Vignone D, Lamorte G, et al. PINK1 protects against cell death induced by mitochondrial depolarization, by phosphorylating Bcl-xL and impairing its pro-apoptotic cleavage. Cell Death and Differentiation. 2013;**20**(7):920-930

[67] Ofengeim D, Chen YB, Miyawaki T, Li H, Sacchetti S, et al. N-terminally cleaved Bcl-xL mediates ischemia-induced neuronal death. Nature Neuroscience. 2012;**15**(4):574-580

[68] Park HA, Jonas EA. DeltaN-Bcl-xL, a therapeutic target for neuroprotection. Neural Regeneration Research. 2017;**12**(11):1791-1794

[69] Park HA, Licznerski P, Mnatsakanyan N, Niu Y, Sacchetti S, et al. Inhibition of Bcl-xL prevents pro-death actions of DeltaN-Bcl-xL at the mitochondrial inner membrane during glutamate excitotoxicity. Cell Death and Differentiation. 2017;**24**(11):1963-1974

[70] Moon HE, Paek SH. Mitochondrial dysfunction in Parkinson's disease. Experimental Neurobiology. 2015;**24**(2):103-116

[71] Stefanis L. Alpha-synuclein in Parkinson's disease. Cold Spring Harbor Perspectives in Medicine. 2012;**2**(2):a009399

[72] Seo JH, Rah JC, Choi SH, Shin JK, Min K, et al. Alpha-synuclein regulates neuronal survival via Bcl-2 family expression and PI3/Akt kinase pathway. The FASEB Journal. 2002;**16**(13):1826-1828

[73] Shaltouki A, Hsieh CH, Kim MJ, Wang X. Alpha-synuclein delays mitophagy and targeting Miro rescues neuron loss in Parkinson's models. Acta Neuropathologica. 2018;**136**(4):607-620

[74] Chen R, Park HA, Mnatsakanyan N, Niu Y, Licznerski P, et al. Parkinson's disease protein DJ-1 regulates ATP synthase protein components to increase neuronal process outgrowth. Cell Death and Disease. 2019;**10**(6):469

[75] Hao LY, Giasson BI, Bonini NM. DJ-1 is critical for mitochondrial function and rescues PINK1 loss of function. Proceedings of the National Academy of Sciences of the United States of America. 2010;**107**(21):9747-9752

[76] Strobbe D, Robinson AA, Harvey K, Rossi L, Ferraina C, et al. Distinct mechanisms of pathogenic DJ-1 mutations in mitochondrial quality control. Frontiers in Molecular Neuroscience. 2018;**11**:68

[77] Shendelman S, Jonason A, Martinat C, Leete T, Abeliovich A. DJ-1 is a redox-dependent molecular chaperone that inhibits alpha-synuclein aggregate formation. PLoS Biology. 2004;**2**(11):e362

[78] Alzheimer's Association, editor. Alzheimer's Disease Facts and Figures. United States: Elsevier Science B.V. Amsterdam; 2018

[79] Hamley IW. The amyloid beta peptide: A chemist's perspective. Role in Alzheimer's and fibrillization. Chemical Reviews. 2012;**112**(10):5147-5192

[80] Kolarova M, Garcia-Sierra F, Bartos A, Ricny J, Ripova D. Structure and pathology of tau protein in Alzheimer disease. International Journal of Alzheimer's Disease. 2012;**2012**:731526

[81] Stokin GB, Goldstein LS. Axonal transport and Alzheimer's disease. Annual Review of Biochemistry. 2006;**75**:607-627

[82] Calkins MJ, Manczak M, Mao P, Shirendeb U, Reddy PH. Impaired mitochondrial biogenesis, defective axonal transport of mitochondria, abnormal mitochondrial dynamics and synaptic degeneration in a mouse model of Alzheimer's disease. Human Molecular Genetics. 2011;**20**(23):4515-4529

[83] Calkins MJ, Reddy PH. Amyloid beta impairs mitochondrial anterograde transport and degenerates synapses in Alzheimer's disease neurons. Biochimica et Biophysica Acta (BBA)—Molecular Basis of Disease. 2011;**1812**(4):507-513

[84] Rui Y, Tiwari P, Xie Z, Zheng JQ. Acute impairment of mitochondrial trafficking by beta-amyloid peptides in hippocampal neurons. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience. 2006;**26**(41):10480-10487

[85] Chaudhary AR, Berger F, Berger CL, Hendricks AG. Tau directs intracellular trafficking by regulating the forces exerted by kinesin and dynein teams. Traffic. 2018;**19**(2):111-121

[86] Dixit R, Ross JL, Goldman YE, Holzbaur EL. Differential regulation of dynein and kinesin motor proteins by tau. Science. 2008;**319**(5866):1086-1089

[87] DuBoff B, Gotz J, Feany MB. Tau promotes neurodegeneration via DRP1 mislocalization in vivo. Neuron. 2012;**75**(4):618-632

[88] Zuo W, Zhang S, Xia CY, Guo XF, He WB, et al. Mitochondria autophagy is induced after hypoxic/ischemic stress in a Drp1 dependent manner: The role of inhibition of Drp1 in ischemic brain damage. Neuropharmacology. 2014;**86**:103-115

[89] Liu W, Tian F, Kurata T, Morimoto N, Abe K. Dynamic changes of mitochondrial fusion and fission proteins after transient cerebral ischemia in mice. Journal of Neuroscience Research. 2012;**90**(6):1183-1189

[90] Chen SD, Lin TK, Yang DI, Lee SY, Shaw FZ, et al. Roles of PTEN-induced putative kinase 1 and dynamin-related protein 1 in transient global ischemia-induced hippocampal neuronal injury. Biochemical and Biophysical Research Communications. 2015;**460**(2):397-403

[91] Peng C, Rao W, Zhang L, Wang K, Hui H, et al. Mitofusin 2 ameliorates hypoxia-induced apoptosis via mitochondrial function and signaling pathways. The International Journal of Biochemistry and Cell Biology. 2015;**69**:29-40

[92] Martorell-Riera A, Segarra-Mondejar M, Munoz JP, Ginet V, Olloquequi J, et al. Mfn2 downregulation in excitotoxicity causes mitochondrial dysfunction and delayed neuronal death. The EMBO Journal. 2014;**33**(20):2388-2407

[93] Wu QJ, Tymianski M. Targeting NMDA receptors in stroke: New hope in neuroprotection. Molecular Brain. 2018;**11**(1):15

[94] Lin R, Duan Z, Sun H, Fung ML, Chen H, et al. Kinesin-1 regulates extrasynaptic targeting of NMDARs and neuronal vulnerability toward excitotoxicity. iScience. 2019;**13**:82-97

[95] Song Y, Li T, Liu Z, Xu Z, Zhang Z, et al. Inhibition of Drp1 after traumatic brain injury provides brain protection and improves behavioral performance in rats. Chemico-Biological Interactions. 2019;**304**:173-185

[96] Fischer TD, Hylin MJ, Zhao J, Moore AN, Waxham MN, et al. Altered mitochondrial dynamics and TBI pathophysiology. Frontiers in Systems Neuroscience. 2016;**10**:29

[97] Di Pietro V, Lazzarino G, Amorini AM, Signoretti S, Hill LJ, et al. Fusion or fission: The destiny of mitochondria in traumatic brain injury of different severities. Scientific Reports. 2017;**7**(1):9189

[98] Chuang CS, Chang JC, Cheng FC, Liu KH, Su HL, et al. Modulation of mitochondrial dynamics by treadmill training to improve gait and mitochondrial deficiency in a rat model of Parkinson's disease. Life Sciences. 2017;**191**:236-244

[99] Gusdon AM, Callio J, Distefano G, O'Doherty RM, Goodpaster BH, et al.

Exercise increases mitochondrial complex I activity and DRP1 expression in the brains of aged mice. Experimental Gerontology. 2017;**90**:1-13

[100] E L BJM, Swerdlow RH. Effect of high-intensity exercise on aged mouse brain mitochondria, neurogenesis, and inflammation. Neurobiology of Aging. 2014;**35**(11):2574-2583

[101] Steiner JL, Murphy EA, McClellan JL, Carmichael MD, Davis JM. Exercise training increases mitochondrial biogenesis in the brain. Journal of Applied Physiology (Bethesda, MD: 1985). 2011;**111**(4):1066-1071

[102] Leem YH, Lim HJ, Shim SB, Cho JY, Kim BS, et al. Repression of tau hyperphosphorylation by chronic endurance exercise in aged transgenic mouse model of tauopathies. Journal of Neuroscience Research. 2009;**87**(11):2561-2570

[103] Garcia-Mesa Y, Gimenez-Llort L, Lopez LC, Venegas C, Cristofol R, et al. Melatonin plus physical exercise are highly neuroprotective in the 3xTg-AD mouse. Neurobiology of Aging. 2012;**33**(6):1124 e13-1124 e29

[104] Bo H, Kang W, Jiang N, Wang X, Zhang Y, et al. Exercise-induced neuroprotection of hippocampus in APP/PS1 transgenic mice via upregulation of mitochondrial 8-oxoguanine DNA glycosylase. Oxidative Medicine and Cellular Longevity. 2014;**2014**:834502

[105] Kim SE, Ko IG, Kim BK, Shin MS, Cho S, et al. Treadmill exercise prevents aging-induced failure of memory through an increase in neurogenesis and suppression of apoptosis in rat hippocampus. Experimental Gerontology. 2010;**45**(5):357-365

[106] Aboutaleb N, Shamsaei N, Khaksari M, Erfani S, Rajabi H, et al. Pre-ischemic exercise reduces apoptosis in hippocampal CA3 cells after cerebral ischemia by modulation of the Bax/Bcl-2 proteins ratio and prevention of caspase-3 activation. The Journal of Physiological Sciences. 2015;**65**(5):435-443

[107] Kim DH, Ko IG, Kim BK, Kim TW, Kim SE, et al. Treadmill exercise inhibits traumatic brain injury-induced hippocampal apoptosis. Physiology and Behavior. 2010;**101**(5):660-665

[108] Jang Y, Kwon I, Song W, Cosio-Lima LM, Taylor S, et al. Modulation of mitochondrial phenotypes by endurance exercise contributes to neuroprotection against a MPTP-induced animal model of PD. Life Sciences. 2018;**209**:455-465

[109] Cheng SM, Ho TJ, Yang AL, Chen IJ, Kao CL, et al. Exercise training enhances cardiac IGFI-R/PI3K/Akt and Bcl-2 family associated pro-survival pathways in streptozotocin-induced diabetic rats. International Journal of Cardiology. 2013;**167**(2):478-485

[110] Zhou Y, Lian S, Zhang J, Lin D, Huang C, et al. Mitochondrial perturbation contributing to cognitive decline in Streptozotocin-induced type 1 diabetic rats. Cellular Physiology and Biochemistry. 2018;**46**(4):1668-1682

[111] Moreira PI, Santos MS, Moreno AM, Seica R, Oliveira CR. Increased vulnerability of brain mitochondria in diabetic (Goto-Kakizaki) rats with aging and amyloid-beta exposure. Diabetes. 2003;**52**(6):1449-1456

[112] Moreira PI, Santos MS, Moreno AM, Proenca T, Seica R, et al. Effect of streptozotocin-induced diabetes on rat brain mitochondria. Journal of Neuroendocrinology. 2004;**16**(1):32-38

[113] Huang S, Wang Y, Gan X, Fang D, Zhong C, et al. Drp1-mediated

mitochondrial abnormalities link to synaptic injury in diabetes model. Diabetes. 2015;**64**(5):1728-1742

[114] Sripetchwandee J, Chattipakorn N, Chattipakorn SC. Links between obesity-induced brain insulin resistance, brain mitochondrial dysfunction, and dementia. Frontiers in Endocrinology (Lausanne). 2018;**9**:496

[115] Cree-Green M, Gupta A, Coe GV, Baumgartner AD, Pyle L, et al. Insulin resistance in type 2 diabetes youth relates to serum free fatty acids and muscle mitochondrial dysfunction. Journal of Diabetes and Its Complications. 2017;**31**(1):141-148

[116] Vantaggiato C, Castelli M, Giovarelli M, Orso G, Bassi MT, et al. The fine tuning of Drp1-dependent mitochondrial remodeling and autophagy controls neuronal differentiation. Frontiers in Cellular Neuroscience. 2019;**13**:120

[117] Moreira PI, Santos MS, Sena C, Seica R, Oliveira CR. Insulin protects against amyloid beta-peptide toxicity in brain mitochondria of diabetic rats. Neurobiology of Disease. 2005;**18**(3):628-637

[118] Sa-Nguanmoo P, Tanajak P, Kerdphoo S, Jaiwongkam T, Pratchayasakul W, et al. SGLT2-inhibitor and DPP-4 inhibitor improve brain function via attenuating mitochondrial dysfunction, insulin resistance, inflammation, and apoptosis in HFD-induced obese rats. Toxicology and Applied Pharmacology. 2017;**333**:43-50

[119] Sa-Nguanmoo P, Tanajak P, Kerdphoo S, Satjaritanun P, Wang X, et al. FGF21 improves cognition by restored synaptic plasticity, dendritic spine density, brain mitochondrial function and cell apoptosis in obese-insulin resistant male rats. Hormones and Behavior. 2016;**85**:86-95

[120] Pintana H, Sripetchwandee J, Supakul L, Apaijai N, Chattipakorn N, et al. Garlic extract attenuates brain mitochondrial dysfunction and cognitive deficit in obese-insulin resistant rats. Applied Physiology, Nutrition, and Metabolism. 2014;**39**(12):1373-1379

[121] Pratchayasakul W, Sa-Nguanmoo P, Sivasinprasasn S, Pintana H, Tawinvisan R, et al. Obesity accelerates cognitive decline by aggravating mitochondrial dysfunction, insulin resistance and synaptic dysfunction under estrogen-deprived conditions. Hormones and Behavior. 2015;**72**:68-77

[122] Wang D, Yan J, Chen J, Wu W, Zhu X, et al. Naringin improves neuronal insulin signaling, brain mitochondrial function, and cognitive function in high-fat diet-induced obese mice. Cellular and Molecular Neurobiology. 2015;**35**(7):1061-1071

[123] Wlodarek D. Role of ketogenic diets in neurodegenerative diseases (Alzheimer's disease and Parkinson's disease). Nutrients. 2019;**11**(1):169

[124] Agarwal P, Wang Y, Buchman AS, Holland TM, Bennett DA, et al. MIND diet associated with reduced incidence and delayed progression of Parkinsonism in old age. The Journal of Nutrition, Health and Aging. 2018;**22**(10):1211-1215

[125] Morris MC, Tangney CC, Wang Y, Sacks FM, Barnes LL, et al. MIND diet slows cognitive decline with aging. Alzheimer's and Dementia. 2015;**11**(9):1015-1022

[126] Duan W, Mattson MP. Dietary restriction and 2-deoxyglucose administration improve behavioral outcome and reduce degeneration of dopaminergic neurons in models of Parkinson's disease.

Journal of Neuroscience Research. 1999;**57**(2):195-206

[127] Anson RM, Guo Z, de Cabo R, Iyun T, Rios M, et al. Intermittent fasting dissociates beneficial effects of dietary restriction on glucose metabolism and neuronal resistance to injury from calorie intake. Proceedings of the National Academy of Sciences of the United States of America. 2003;**100**(10):6216-6220

[128] Amigo I, Menezes-Filho SL, Luevano-Martinez LA, Chausse B, Kowaltowski AJ. Caloric restriction increases brain mitochondrial calcium retention capacity and protects against excitotoxicity. Aging Cell. 2017;**16**(1):73-81

[129] Halagappa VK, Guo Z, Pearson M, Matsuoka Y, Cutler RG, et al. Intermittent fasting and caloric restriction ameliorate age-related behavioral deficits in the triple-transgenic mouse model of Alzheimer's disease. Neurobiology of Disease. 2007;**26**(1):212-220

[130] Maswood N, Young J, Tilmont E, Zhang Z, Gash DM, et al. Caloric restriction increases neurotrophic factor levels and attenuates neurochemical and behavioral deficits in a primate model of Parkinson's disease. Proceedings of the National Academy of Sciences of the United States of America. 2004;**101**(52):18171-18176

[131] Sanz A, Caro P, Ibanez J, Gomez J, Gredilla R, et al. Dietary restriction at old age lowers mitochondrial oxygen radical production and leak at complex I and oxidative DNA damage in rat brain. Journal of Bioenergetics and Biomembranes. 2005;**37**(2):83-90

[132] Hu Y, Zhang M, Chen Y, Yang Y, Zhang JJ. Postoperative intermittent fasting prevents hippocampal oxidative stress and memory deficits in a rat model of chronic cerebral hypoperfusion. European Journal of Nutrition. 2019;**58**(1):423-432

[133] Hyun DH, Emerson SS, Jo DG, Mattson MP, de Cabo R. Calorie restriction up-regulates the plasma membrane redox system in brain cells and suppresses oxidative stress during aging. Proceedings of the National Academy of Sciences of the United States of America. 2006;**103**(52):19908-19912

[134] Loncarevic-Vasiljkovic N, Milanovic D, Pesic V, Tesic V, Brkic M, et al. Dietary restriction suppresses apoptotic cell death, promotes Bcl-2 and Bcl-xl mRNA expression and increases the Bcl-2/Bax protein ratio in the rat cortex after cortical injury. Neurochemistry International. 2016;**96**:69-76

[135] Lin AL, Coman D, Jiang L, Rothman DL, Hyder F. Caloric restriction impedes age-related decline of mitochondrial function and neuronal activity. Journal of Cerebral Blood Flow and Metabolism. 2014;**34**(9):1440-1443

[136] Cerqueira FM, Cunha FM, Laurindo FR, Kowaltowski AJ. Calorie restriction increases cerebral mitochondrial respiratory capacity in a NO*-mediated mechanism: Impact on neuronal survival. Free Radical Biology and Medicine. 2012;**52**(7):1236-1241

[137] Duan W, Lee J, Guo Z, Mattson MP. Dietary restriction stimulates BDNF production in the brain and thereby protects neurons against excitotoxic injury. Journal of Molecular Neuroscience. 2001;**16**(1):1-12

[138] Stranahan AM, Lee K, Martin B, Maudsley S, Golden E, et al. Voluntary exercise and caloric restriction enhance hippocampal dendritic spine density and BDNF levels in diabetic mice. Hippocampus. 2009;**19**(10):951-961

[139] Su B, Ji YS, Sun XL, Liu XH, Chen ZY. Brain-derived neurotrophic factor (BDNF)-induced mitochondrial motility arrest and presynaptic docking contribute to BDNF-enhanced synaptic transmission. The Journal of Biological Chemistry. 2014;**289**(3):1213-1226

[140] Witte AV, Fobker M, Gellner R, Knecht S, Floel A. Caloric restriction improves memory in elderly humans. Proceedings of the National Academy of Sciences of the United States of America. 2009;**106**(4):1255-1260

[141] Prehn K, Jumpertz von Schwartzenberg R, Mai K, Zeitz U, Witte AV, et al. Caloric restriction in older adults-differential effects of weight loss and reduced weight on brain structure and function. Cerebral Cortex. 2017;**27**(3):1765-1778

[142] Wang BH, Hou Q, Lu YQ, Jia MM, Qiu T, et al. Ketogenic diet attenuates neuronal injury via autophagy and mitochondrial pathways in pentylenetetrazol-kindled seizures. Brain Research. 2018;**1678**:106-115

[143] Luan G, Zhao Y, Zhai F, Chen Y, Li T. Ketogenic diet reduces Smac/Diablo and cytochrome c release and attenuates neuronal death in a mouse model of limbic epilepsy. Brain Research Bulletin. 2012;**89**(3-4):79-85

[144] Hu ZG, Wang HD, Jin W, Yin HX. Ketogenic diet reduces cytochrome c release and cellular apoptosis following traumatic brain injury in juvenile rats. Annals of Clinical and Laboratory Science. 2009;**39**(1):76-83

[145] Puchowicz MA, Zechel JL, Valerio J, Emancipator DS, Xu K, et al. Neuroprotection in diet-induced ketotic rat brain after focal ischemia. Journal of Cerebral Blood Flow and Metabolism. 2008;**28**(12):1907-1916

[146] Noh HS, Kim YS, Kim YH, Han JY, Park CH, et al. Ketogenic diet protects the hippocampus from kainic acid toxicity by inhibiting the dissociation of bad from 14-3-3. Journal of Neuroscience Research. 2006;**84**(8):1829-1836

[147] Greco T, Glenn TC, Hovda DA, Prins ML. Ketogenic diet decreases oxidative stress and improves mitochondrial respiratory complex activity. Journal of Cerebral Blood Flow and Metabolism. 2016;**36**(9):1603-1613

[148] Hasan-Olive MM, Lauritzen KH, Ali M, Rasmussen LJ, Storm-Mathisen J, et al. A ketogenic diet improves mitochondrial biogenesis and bioenergetics via the PGC1alpha-SIRT3-UCP2 axis. Neurochemical Research. 2019;**44**(1):22-37

[149] Maalouf M, Sullivan PG, Davis L, Kim DY, Rho JM. Ketones inhibit mitochondrial production of reactive oxygen species production following glutamate excitotoxicity by increasing NADH oxidation. Neuroscience. 2007;**145**(1):256-264

[150] Nylen K, Velazquez JL, Sayed V, Gibson KM, Burnham WM, et al. The effects of a ketogenic diet on ATP concentrations and the number of hippocampal mitochondria in Aldh5a1(−/−) mice. Biochimica et Biophysica Acta. 2009;**1790**(3):208-212

[151] Yao J, Chen S, Mao Z, Cadenas E, Brinton RD. 2-Deoxy-D-glucose treatment induces ketogenesis, sustains mitochondrial function, and reduces pathology in female mouse model of Alzheimer's disease. PLoS One. 2011;**6**(7):e21788