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Regulation of Neuron Mitochondrial Biogenesis and Relevance to Brain Health

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Abstract

Mitochondrial dysfunction has severe cellular consequences, and is linked to aging and neurological disorders in humans. Impaired energy supply or Ca^{2+} buffering, increased ROS production, or control of apoptosis by mitochondria may contribute to the progressive decline of long-lived postmitotic cells. Mitochondrial biogenesis refers to the process via which cells increase their individual mitochondrial mass. Mitochondrial biogenesis may represent an attempt by cells to increase their aerobic set point, or an attempt to maintain a pre-existing aerobic set point in the face of declining mitochondrial function. Neuronal mitochondrial biogenesis itself has been poorly studied, but investigations from other tissues and model systems suggest a series of transcription factors, transcription co-activators, and signal transduction proteins should function to regulate mitochondrial number and mass within neurons. We review data pertinent to the mitochondrial biogenesis field, and discuss implications for brain aging and neurodegenerative disease research efforts.

Introduction

Mitochondria are the only organelles in animal cells, besides the nucleus, that contain their own separate DNA. The human mitochondrial DNA (mtDNA) is a 16 569 bp circular, double-stranded molecule encoding 13 respiratory chain protein subunits, and 24 RNA components (22 tRNAs and two rRNAs) necessary for mitochondrial protein synthesis [1]. The majority of the ~1500 different mitochondrial proteins are encoded by nuclear DNA (nDNA), translated in the cytoplasm and transported into mitochondria [1]. The biogenesis of the respiratory chain is therefore dependent on an intricate and still poorly understood cross talk between mitochondrial and nuclear genomes.

Mammalian cells each have ~ 1000–10 000 copies of the mitochondrial genome. This high copy number of mtDNA ensures that mutations affecting a single copy do not impact overall mitochondrial function but does not prevent expansion of de novo mutations arising in a single mtDNA molecule. Mitochondrial number and morphology are controlled by an equilibrium of mitochondrial fusion and fission [2] that is vital for mitochondrial metabolism, energy production, Ca²⁺ signaling, reactive oxygen species (ROS) production, apoptosis, and senescence [3-5]. Fusion allows the exchange of mitochondrial components including mtDNA between different mitochondria. Severe damage of mitochondria impairs fusion resulting in fragmentation of mitochondria that are then selectively removed by an autophagic process called mitophagy [6]. Mitophagy prevents the release of pro-apoptotic proteins from damaged mitochondria. Consistent with a cytoprotective function of autophagy, apoptosis is suppressed upon induction but induced upon inhibition of autophagy [7]. This effectively maintains the integrity and homogeneity of the mitochondria population throughout the cell [8-10]. This is vital for neuronal homeostasis including synaptic function and imbalances in mitochondrial fission and fusion is implicated in neurodegenerative diseases such as Charcot-Marie-Tooth neuropathy type 2A (CMT-2A) [11, 12],

dominant optic atrophy [13, 14], Parkinson's, Alzheimer's, and Huntington's diseases [15, 16, 17, 18, 19].

The first pathogenic mtDNA mutations in human patients were reported in 1988 [20, 21] with affected patients being either homoplasmic, i.e. having only mutated mtDNA [20], or heteroplasmic, i.e. having a mixture of wild-type and mutated mtDNA [21]. Heteroplasmic mtDNA mutations segregate during cell division as there is no mechanism to ensure that every mtDNA molecule is replicated once and only once during each cell cycle [22]. A minimal threshold level of a pathogenic mtDNA mutation is required to induce respiratory chain dysfunction. This has been reported to range from 90% for some tRNA mutations to 60% for mtDNA deletions [1], but research into threshold phenomena have used to a large extent models that are insensitive to aerobic perturbations and may thereby overestimate the amount of mtDNA mutation needed to have a functional consequence.

Mitochondria in the aging brain and neurodegenerative diseases

The brain is a highly metabolic tissue, and neurons in the central nervous system have an intense demand for mitochondria [17]. Mitochondria provide most of the ATP for cellular reactions. ATP production in mitochondria is coupled to an electron transport system in which the passage of electrons down the various electron carriers is associated with the transport of protons from the matrix into the intermembrane space. The majority of these protons reenter the mitochondrial matrix by the ATP synthase, thereby generating ATP. However, approximately 20% of mitochondrial oxygen consumption is not coupled to ATP production, and protons enter the matrix through the phospholipid bilayer and through uncoupling proteins, generating heat [23].

Mitochondrial metabolism is also responsible for the majority of the ROS production in cells [24]. The formation of ROS occurs when unpaired electrons escape the electron transport chain and react with molecular oxygen, generating superoxide. Superoxide can react with DNA, proteins, and lipids; plays an important role in intracellular signaling; and is associated with both neurodegenerative diseases and aging [24]. ROS can also react with NO, generating reactive nitrogen species (RNS) [25]. The maintenance of physiologic ROS levels is critical to normal cell functions, and thus prolonged increases in mitochondrial activity can increase ROS levels and alter intracellular physiologic set points.

Studies of aging brain mitochondria consistently report reductions of complex I activity, complex IV activity, and increased ROS production [26]. Other age-related mitochondrial changes include reduced membrane potential and increased size. mtDNA mutations may contribute to age-related mitochondrial decline. mtDNA deletions accumulate with age in many tissues, especially brain [27]. It is easier to find low abundance, heteroplasmic point mutations (microheteroplasmy) in the brains of elderly individuals than in the brains of young individuals [28, 29]. The number of microheteroplasmic mtDNA CO1 gene mutations inversely correlates with cytochrome oxidase activity [29]. Mice with impaired mtDNA polymerase γ (mtPOLG) proofreading show accelerated mutation accumulation, an age-dependent progressive reduction of electron transport chain (ETC) enzyme activities, and accelerated aging despite the fact that oxidative stress markers are not increased [30-32].

Mitochondria are altered in brains of persons with certain neurodegenerative diseases [33, 34]. There are activity reductions of complex I in Parkinson's disease (PD), cytochrome oxidase in Alzheimer's disease (AD), and multiple electron transport chain (ETC) enzymes in Huntington's disease (HD). Mitochondrial dysfunction occurs in amyotrophic lateral sclerosis and progressive supranuclear palsy. Leber's hereditary optic neuropathy (LHON), a focal degeneration of the optic

nerves, arises from mutations in mtDNA-encoded complex I genes and is associated with complex I dysfunction.

Falling oxidative phosphorylation capacity in aging human brain associates with increased amounts of mtDNA [35, 36]. This mtDNA increase occurs in conjunction with a steady state decrease in mRNA levels and presumably is compensatory. The status of mitochondrial biogenesis in AD is unclear. In AD brain increased mtDNA, ETC protein, and ETC gene expression are reported [35, 37]. Upregulated expression of ETC genes occurs in mutant APP transgenic mice and low levels of beta amyloid ($A\beta$) induce mitochondrial biogenesis [37, 38]. Other studies alternatively report reduced AD brain mtDNA and ETC gene expression [39-42]. Perhaps neurons in different stages of disease show different patterns of mitochondrial biogenesis.

Data pertinent to mitochondrial mass regulation in a neurodegenerative disease state are also inferred from transgenic mouse models of HD. The R6/2 HD mouse shows reduction of the peroxisome proliferator-activated receptor γ coactivator 1 α (PGC1 α), a transcriptional coactivator critical to mitochondrial biogenesis [43]. This suggests polyglutamine-expanded huntingtin interference with mitochondrial biogenesis. Beyond HD and AD, though, little is known about mitochondrial biogenesis pathway activation or deactivation in late-life neurodegenerative diseases but relevant precedents do exist. For example, some mitochondrial encephalomyopathies such as the myoclonic epilepsy and ragged red fiber (MERRF) syndrome, which does exhibit neurodegeneration, shows profound muscle cell mitochondrial proliferation [44].

Manipulation of mitochondrial biogenesis

A variety of interventions appear able to influence cell aerobic setpoints in general and mitochondrial biogenesis specifically. Some of these interventions are discussed below.

Caloric restriction

Caloric restriction (CR) induces endothelial NO synthetase (eNOS) expression which increases nitric oxide (NO) production and ultimately mitochondrial biogenesis [45]. This process involves PGC1 α [45, 46]. This leads to increased autophagy, recycling damaged components and producing newer, more efficient organelles. This process is modulated, in part, by mammalian target of rapamycin (mTOR) and forkhead box-containing protein O (FOXO) transcriptional factors [47, 48]. The arising mitochondria have a reduced membrane potential, produce less ROS, consume increased levels of oxygen and exhibit an improved ATP/ROS ratio – leading to decreased energy expenditure [46].

Anti-oxidants

CR induces a switch to mitochondrial respiration and increased ROS, which in turn, activates mitochondrial biogenesis. Subjecting neurons to adverse stimuli in order to mitigate damage induced by subsequent stressors has provided insight into the hormesis-mediating role of ROS [49]. ROS and reactive nitrogen species (RNS) may mediate the protective influence of preconditioning on various cell populations and may actually operate as signal transduction elements. The stress associated with the fasting state may inflict modest damage upon metabolically active neuron mitochondria, which prompts the neurons to increase mitochondrial mass and maintain mitochondrial integrity via mechanisms that encompass mitophagy, mitochondrial fusion, upregulated antioxidant defenses, and enhanced mtDNA repair i.e. “mitohormesis” [50, 51]. In this context ROS primarily appear to serve as drivers of hormetic phenomena as opposed to drivers of cell damage. It is nevertheless necessary to note mitochondria that are damaged due to mutated mtDNA or to deleterious protein alterations may not

be able to withstand stressors tolerated by intact mitochondria, and activate quality-control proteins such as the putative mitochondrial membrane potential sensor, DAPK [52].

Recently the hormesis theory has been extended to the ROS-generating effects of exercise [53, 54]. ROS increase in skeletal muscle during exercise and there is some evidence that such small, physiological increases in ROS are required for normal increases in mitochondrial biogenesis following exercise [55]. Indeed, markers of mitochondrial biogenesis do not increase during exercise-training if rats are treated with vitamin C as a non-specific antioxidant [55]. PGC-1 α has been shown to switch on the anti-oxidant system when free radicals begin to accumulate. This protective system may be what fails in some neurodegenerative diseases. PGC-1 α both drives the mitochondria to make energy and establishes the maximum level of free radicals the cell will accept as a consequence of increased aerobic activity. As excess free radicals build up, the cell enters a state of "oxidative stress," which prompts the cell to produce more PGC-1 α , which in turn spurs the anti-oxidant defenses into action [56]. The administration of antioxidants may actually serve to disrupt this delicate and certainly physiologic feed-back loop.

Resveratrol

The polyphenol resveratrol is a natural polyphenolic compound mainly found in the skin of grapes and is well known for its phytoestrogenic and antioxidant properties [57]. It has been shown to induce mitochondrial biogenesis by significantly increasing SIRT1 activity through an allosteric interaction, resulting in the increase of SIRT1 affinity for both NAD⁺ and its acetylated substrates [58]. These findings are consistent with the fact that in various species, resveratrol treatment mimics Sir2-dependent lifespan extension during CR [58-60].

Exercise

Exercise is a powerful inducer of mitochondrial biogenesis in skeletal muscle [61, 62]. It increases muscle AMP/ATP ratios and activates AMP-activated protein kinase (AMPK), which proliferates mitochondria [63]. Drugs that activate AMPK also induce mitochondrial biogenesis.

Thiazolidinediones

Thiazolidinedione drugs activate peroxisome proliferator-activated receptor γ (PPARG) and are used to reduce insulin resistance in type II diabetes [64-66]. These agents affect mitochondria and the consequences of acute versus chronic exposure differ [67, 68]. Thiazolidinediones increase ETC uncoupling [69-72]. Although uncoupling should reduce ROS, acute exposure of hepatocytes to a thiazolidinedione increases oxidative stress. Chronic exposure induces mitochondrial biogenesis in human subcutaneous adipose tissue, human neuronal NT2 cells, and mouse brain [67, 73, 74]. The clinically available thiazolidinediones, pioglitazone and rosiglitazone, poorly cross the blood brain barrier but have been considered for treating AD [75-78]. Rationales are that thiazolidinedione anti-inflammatory effects or insulin system modulation confers putative benefits [78, 79]. More recently, it was proposed thiazolidinedione induced mitochondrial effects are worth considering [80].

Pyruvate

Increasing concentrations of pyruvate have been shown to increase mitochondrial biogenesis in myoblasts [81]. Acetyl-CoA generated from pyruvate entering into the mitochondria is converted into acetyl-carnitine. Acetyl-carnitine in addition to liberating mitochondrial CoA, can pass out of the mitochondria and cell, providing an overflow mechanism for excess energy supply when the cell is energy depleted. Supplementing diets with acetyl-carnitine has been shown to help maintain or improve mitochondrial function in rats [82, 83]. Excess pyruvate results in the production of lactate with the concomitant oxidation of NADH to NAD⁺. The NAD⁺-dependent

histone deacetylase SIRT1 interacts with PGC1 α [84] and regulates PGC1 α -dependent gene expression in a nutrient-sensitive manner in hepatocytes [85].

Proteins and pathways implicated in mitochondrial biogenesis

PGC1 α

While the mechanisms that underlie mitochondrial biogenesis vary between tissues PGC1 α often serves as a master regulator, modulating ~20% of the genes that are regulated during CR, including acute phase response (APR) genes [86]. PGC1 α co-activates numerous metabolically relevant nuclear and non-nuclear receptor transcription factors [87-89]. It is highly expressed in brown adipose tissue, skeletal muscle, and brain. Nuclear respiratory factor 1 (NRF1) and nuclear respiratory factor 2 (NRF2) are PGC1 α co-activated transcription factors. Their activation coordinates expression of genes encoding mitochondrial proteins [90]. Part of this coordination includes expression of mitochondrial transcription factor A (TFAM), which increases levels and expression of mtDNA [91, 92]. In some tissues PGC1 α increases expression of transcription factors it subsequently co-activates, creating positive feedback loops. For example, the estrogen-related factor α (ERR α) promoter contains cis-elements that bind NRF2 and ERR α itself. PGC1 α increases NRF2 and ERR α expression, and subsequently co-activates them to produce even more ERR α . ERR α then binds PGC1 α to drive NRF1 expression [93, 94]. PGC1 α also co-activates antioxidant enzyme expression [95] and expression of mammalian homolog of tribble 3 (TRB-3), an Akt pathway inhibitor [96].

PGC1 α is influenced by post-translational modification, including acetylation (usually suppresses activity), p38 MAP kinase-mediated phosphorylation (enhances activity by reducing binding of the p160MBP repressor protein, as well as by increasing the PGC1 α half-life), and

arginine methylation [89, 97-100]. PGC1 α levels are also controlled by the cAMP response element binding protein (CREB) and FOXO transcription factors. CREB activates the PGC1 α promoter and drives PGC1 α expression [101, 102]. In this function CREB acts in conjunction with a family of calcium and cAMP-sensitive co-activators, the transducer of regulated CREB binding protein family (NB: TORC; not to be confused with mTORC). Of the three TORC proteins, under basal conditions TORC1 and TORC2 are in the cytoplasm, and move to the nucleus when calcium and cAMP levels rise. TORC1 is especially prominent in the brain. Like CREB, forkhead in rhabdomyosarcoma (FKHR; FoxO1) activates the PGC1 α promoter by binding internally located insulin response sequences [103]. It is activated by oxidative stress, which favors nuclear over cytoplasmic localization, and by SIRT1-mediated deacetylation [104, 105]. Akt prevents FKHR transcription, since phosphorylation causes cytoplasmic retention. Akt phosphorylation of FoxO3 also prevents its nuclear localization. FoxO3-mediated transcription is associated with longevity [106].

Some mitochondria-targeted, nuclear-encoded protein gene expression is mediated by signal protein 1 (Sp1) or myocyte-enhancing factor-2 (MEF2) rather than the NRFs. Other nuclear receptors not discussed (PPAR α , PPARG, thyroid hormone receptors, retinoid receptors, glucocorticoid receptors) contribute to mitochondrial biogenesis through effects on PGC1 α expression, PGC1 α interactions, or both [107]. Along with PGC1 α two other related transcription factors, PGC-1-related coactivator (PRC) and PGC-1-related estrogen receptor coactivator (PERC), comprise the PGC-1 “family” of coactivators. There is functional overlap within the family, although its members vary in promotional emphasis. PRC may play a particularly important role in regulating mitochondrial content in cultured fibroblasts, which do not express PGC1 α [108].

SIRT1

SIRT1 is activated by a rising NAD⁺/NADH ratio [99, 109]. SIRT1 is a member of the sirtuin family of NAD⁺-dependent class III histone deacetylases (HDAC) [110-113]. SIRT1, deacetylates and thereby activates the nuclear PGC1 α , which in turn induces mitochondrial biogenesis [114]. Although SIRT1 is largely nuclear where it deacetylates histones H3 and H4 as well as transcription factors such as NF- κ B, p53, FOXO, Ku70, and PGC1 α [115, 116], it has however been shown to shuttle between the nucleus and cytosol in response to oxidative stress [115, 117, 118]. Since it requires NAD⁺ for its activation and as substrate for deacetylase reactions, changes in the cellular NAD⁺/NADH ratio, i.e., the redox state, influence its activity. Increased NAD⁺ biosynthesis and SIRT1 activation have been shown to protect axons against degeneration [119]. However, since HDAC inhibitors, including nicotinamide, confer neuroprotective effects in models of neurodegenerative diseases [120, 121], the role of HDAC in neuronal survival becomes complicated. Since both SIRT1 and PARP-1 utilize NAD⁺ for their activity, depletion of cellular NAD⁺ due to PARP-1 activation may influence SIRT1 activity [122, 123]. SIRT1's requirement of NAD⁺ has the potential to consume cellular energy and render neurons vulnerable to stress.

AMPK

PGC1 α function is also modulated by AMPK [124]. AMPK therefore appears to be critical in the mitochondrial bioenergetic process, especially during exercise [125]. In muscle, PGC1 α is activated by AMPK, a heterotrimer affected by cell AMP/ATP ratios [126]. AMPK favors catabolism, and serves as a counterweight to the anabolism-oriented Akt pathway. Anabolic cell processes increase the AMP/ATP ratio, prompting AMPK to increase cell catabolic processes. ADP phosphorylation, glycolysis, mitochondrial biogenesis, and glucose uptake are stimulated, while anabolic processes are concurrently inhibited. AMPK is stimulated by events that reduce

ATP production (hypoxia, glucose deprivation, metabolic inhibitors) or that increase ATP consumption. Rising cytoplasmic calcium levels typically increase ATP consumption and activate AMPK. A calcium/calmodulin-dependent protein kinase kinase (CaMKK) appears to mediate this, especially in neural tissue [127, 128]. Resveratrol activates AMPK in HepG2 cells and in *C. elegans* liver [129, 130]. In cultured myocytes, fibroblasts, and hepatocytes very short duration (under 3 hour) thiazolidinedione exposure increased AMP/ATP ratios and increased AMPK activity [131, 132]. Chronic thiazolidinedione administration also increased AMPK activity in rat liver and adipose tissue [133, 134]. Metformin, a diabetes drug, activates AMPK [135]. AMPK may also modulate the function of FOXO, implying coordination of resistance to oxidative stress and energy metabolism [136].

mTOR

mTOR regulates cell growth in response to nutrient status and regulates PGC1 α levels and oxidative phosphorylation capacity [126, 137]. It mediates both pro-survival and proliferative functions. Its inhibition with rapamycin lowers mitochondrial membrane potential, oxygen consumption, and ATP synthetic capacity [138]. Its activity is modulated by p53 and AMPK [139] and it impacts mitochondrial function as part of a complex with PGC1 α and the transcription factor yin-yang 1 (YY1) [140]. The mTOR pathway can also self inhibit via the S6 kinase [141]. Insulin may therefore promote mitochondrial biogenesis as part of a general proliferative function, while stressors promote it as a mechanism to ensure increased resistance to stress.

HIF1 α/β

The HIF-1 α/β (hypoxia induction factor 1 α and β) transcription factor heterodimer favors glycolysis over oxidative phosphorylation. The HIF-1 α component is degraded under normal oxygen concentrations and accumulates under hypoxic conditions. HIF-1 suppresses

mitochondrial biogenesis [142]. This is at least partly mediated through negative regulation of AMPK. Brief hypoxic exposure, on the other hand, induces mitochondrial biogenesis through nitric oxide-dependent physiology [143]. The fact that hypoxia is associated with mitochondrial biogenesis while HIF-1, which is hypoxia-induced, suppresses it is conceptually complex. Experimental details relating to the cell type or hypoxia stimulus duration may influence outcomes.

TFAM and Mitochondrial Transcription Factor B

Mitochondrial biogenesis induced by CR, resveratrol, exercise, or pyruvate is regulated by crosstalk between nuclear and mitochondrial genomes and is coordinated by nuclear coactivators such as PGC1 α and the nuclear respiratory factors (NRF-1 and NRF-2), which transactivates genes for oxidative phosphorylation and protein importation [144-146]. These transcription factors also mediate mtDNA transcription and replication through two nuclear genes: mitochondrial transcription factor A (TFAM) and its cofactor, mitochondrial transcription factor B [144, 145]. Activation of these molecular regulators of biogenesis during adaptation to oxidative stress enhances cell and organ survival [144, 147, 148].

Could mitochondrial biogenesis induction benefit the brain?

The aging brain exhibits mitochondrial biogenesis although aging muscle apparently does not [26, 35, 149, 150]. Mitochondrial biogenesis may represent an attempt by cells to increase their aerobic set point, or an attempt to maintain a pre-existing aerobic set point in the face of declining mitochondrial function. In the case of brain aging, it is reasonable to consider that increased brain mitochondrial mass might represent a compensatory response to longitudinal declines in brain mitochondrial function. In AD, though, data suggest the mitochondrial biogenesis picture may be mixed. There are certainly fewer normal mitochondria and more abnormal mitochondria in AD neurons. Mitochondrial removal via lysosomes is increased [35]. Expression

of oxidative phosphorylation subunit genes also appears mixed, with some studies showing decreased expression and others showing increased expression (at least up through intermediate stages of the disease) [35, 41, 151, 152]. This raises the possibility that switching from an enhanced state of mitochondrial biogenesis to a diminished state of mitochondrial biogenesis could represent a key transition between normal brain aging and AD. If so, then inducing mitochondrial biogenesis should represent a viable pharmacologic target for the treatment of AD and other NDDs.

While enhancing mitochondrial biogenesis of abnormal brain mitochondria might prove therapeutically useful for AD as well as other neurodegenerative diseases associated with decreased oxidative phosphorylation enzyme activities, safety issues require consideration. For example, in one mouse study PGC1 α cardiac overexpression caused cardiomyopathy [153].

Mitochondrial therapeutics of neurodegenerative diseases

Since many neurodegenerative diseases cause mitochondria to malfunction, it may be important to focus on developing methods to repair and restore mitochondria. Already a few strategies are being developed that open up ways for manipulating mitochondrial functions and may allow for the selective protection or eradication of neurons in the treatment of neurodegenerative diseases.

Recombinant-human mitochondrial transcription factor A (rhTFAM)

A recent study shows that the human mitochondrial genome can be manipulated from outside the cell to change expression and increase mitochondrial energy production. Mitochondrial transcription factor A (TFAM), a naturally occurring protein, can be engineered to rapidly pass through cell membranes and target mitochondria. It has been shown that rhTFAM acts on cultured cells carrying a mitochondrial DNA disease as well as lab mice. rhTFAM enters and energizes the

DNA of the mice's mitochondria, enabling these mice to run two times longer on their rotating rods than a control group cohort [154, 155].

Dimebon

Dimebon (or Dimebolin hydrochloride) is an antihistamine drug that may inhibit mitochondrial permeability transition pore and protect neuronal mitochondria from mutant proteins such as amyloid beta ($A\beta$), mutant Huntingtin and other mitochondrial toxic insults [156]. It clinically reduced cognitive deficits in AD patients in a phase II clinical trial and may enhance cognition in healthy individuals [19, 157].

Mitochondria targeting antioxidants

Because mitochondria are the primary producers of cell ROS, oxidative damage of mitochondrial proteins or DNA is likely to contribute to the mitochondrial dysfunction that is characteristic of many neurodegenerative diseases [158]. Developing antioxidants that target mitochondria such as MitoQ, MitoVitE, MitoPBN, MitoPeroxidase, SS-tetra peptides, choline esters of glutathione and N-acetyl-L-cysteine maybe useful in protecting neurons from excessive ROS. Initial studies of aging and amyotrophic lateral sclerosis (ALS)-transgenic mice found that these antioxidants enter the mitochondria several hundred fold compared to naturally occurring antioxidants, neutralize free radicals rapidly and decrease mitochondrial toxicity. Therefore, such mitochondrially targeted antioxidants might be promising candidates to treat elderly persons and neurodegenerative disease patients [159].

Conclusions

In the brain, mitochondrial function declines with age and this functional decline associates with increased mitochondrial biogenesis. In various neurodegenerative disease states brain

mitochondrial function declines even further, perhaps to the point that mitochondrial biogenesis can no longer compensate for functional declines. It is worth considering that at some point neurons with impaired mitochondria may reach a point where mitochondrial biogenesis pathways deactivate. Neuron mitochondrial biogenesis has not been studied extensively, although it is reasonable to expect that proteins and pathways implicated in mitochondrial biogenesis in other tissues are also relevant in neuron mitochondrial biogenesis. A complete and integrated picture of mitochondrial biogenesis mechanisms is worth pursuing, as pharmacologic manipulations of brain mitochondrial biogenesis could prove therapeutically useful.

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