



Mitochondria, energy, and metabolism in neuronal health and disease

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Mitochondria are associated with various cellular activities critical to homeostasis, particularly in the nervous system. The plastic architecture of the mitochondrial network and its dynamic structure play crucial roles in ensuring that varying energetic demands are rapidly met to maintain neuronal and axonal energy homeostasis. Recent evidence associates aging and neurodegeneration with anomalous neuronal metabolism as age-dependent alterations of neuronal metabolism are now believed to occur prior to neurodegeneration. The brain has a high energy demand, which makes it particularly sensitive to mitochondrial dysfunction. Distinct cellular events causing oxidative stress or disruption of metabolism and mitochondrial homeostasis can trigger a neuropathology. This review explores the bioenergetic hypothesis for the neurodegenerative pathomechanisms, discussing factors leading to age-related brain hypometabolism and its contribution to cognitive decline. Recent research on the mitochondrial network in healthy nervous system cells, its response to stress, and how it is affected by pathology, as well as current contributions to novel therapeutic approaches will be highlighted.

Keywords: ageing; Alzheimer; axon; Huntington; mitochondria; mitophagy; neurodegeneration; neuron; Parkinson; ROS

Mitochondria are ubiquitous organelles forming large tubular structures that spread throughout the cytoplasm. They are closely opposed to other organelles, such as the nucleus, the endoplasmic reticulum (ER), the Golgi apparatus, or structures such as the cytoskeleton. In addition to their well-known role in energy metabolism as the major cellular ATP producers, mitochondria regulate cellular events, including Ca^{2+} homeostasis, reactive oxygen species (ROS) signaling, ion channel regulation, and exocytosis. Mitochondria control cellular homeostasis by acting together with the ER

to regulate intracellular calcium levels [1] or by activating the Unfolded Protein Response (UPR) in response to stress. This control is mainly carried out *via* ROS signaling and modulating immune responses *via* signaling molecules and metabolic reprogramming [2].

Metabolic changes influence all cellular activities and can also contribute to the onset and progression of many neurodegenerative disorders, which become more prevalent with aging [3]. In fact, glucose availability, uptake, and mitochondrial function in brain cells decrease with aging and are exacerbated in

Abbreviations

AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; BDNF, brain-derived neurotrophic factor; CMR, cerebral metabolic rate; CNS, central nervous system; ER, endoplasmic reticulum; ETC, electron transport chain; GLUT, glucose transporters; HD, Huntington's disease; HIF, hypoxia-inducible factor; PD, Parkinson's disease; ROS, reactive oxygen species; UPR, unfolded protein response.

neurodegenerative pathologies [4] (Fig. 1). Consistently, bioenergetic deficits largely contribute to the cognitive decline observed during aging and in neurodegenerative disorders. The human brain constitutes only 2% of body weight, but requires 20% of the metabolic output [5], using up to 25% of the body's total glucose (most of it undergoing glycolysis and oxidative phosphorylation) to assist in synaptic transmission [4]. Neurons consume 70%–80% of that energy, the remainder of which is used by glial cells, such as astrocytes, oligodendrocytes, and microglia [6].

Metabolic adaptations in the brain are important to support the expansion and complexity of the cerebral cortex. Hormesis, a novel brain ability to respond to certain types of stress, allowing it to obtain beneficial effects from theoretically harmful conditions, has recently been described [7]. Bioenergetic challenges, such as fasting, physical exercise, and intellectual tasks, are examples of situations that force the brain to adapt to and effectively respond to unfavorable situations [8].

The present review characterizes mitochondrial homeostasis in the nervous system, the role of brain metabolic changes in aggravating aging and neurodegeneration, and explores the bioenergetic hypothesis, which states that aging-associated cognitive decline and neurodegeneration are a consequence of brain metabolic changes.

Fundamental characteristics of mitochondria

Mitochondria produce most of the cellular ATP *via* the oxidative phosphorylation system. This process involves electron transfer between the respiratory chain complexes I through IV, associated with transport of protons across the mitochondrial membrane, thus driving the synthesis of ATP by the ATP synthase complex [9]. A byproduct of oxidative phosphorylation is mitochondrial ROS results from electron leakage along the electron transport chain (ETC) during normal respiration. These electrons, originating from NADH or FADH₂, are transferred to O₂, forming superoxide (O₂^{•−}), which is subsequently dismutated to H₂O₂. [10]. Regulated by several factors and enzymes, these two species play important physiological signaling roles, mediating important cellular processes [11]. O₂^{•−} and H₂O₂ are normally maintained at low cellular concentrations (from 10^{−11} to 10^{−8} M) [12,13], but when these overcome physiological levels, signaling specificity is lost, leading to macromolecule oxidative damage. Eventually, this results in cell death (“oxidative distress”) [14]. Being the initial target for oxidative damage, mitochondria are, thus, tightly associated with oxidative stress homeostasis [15]. Dysfunctional mitochondria contribute to aging, perturbed apoptotic signaling, and

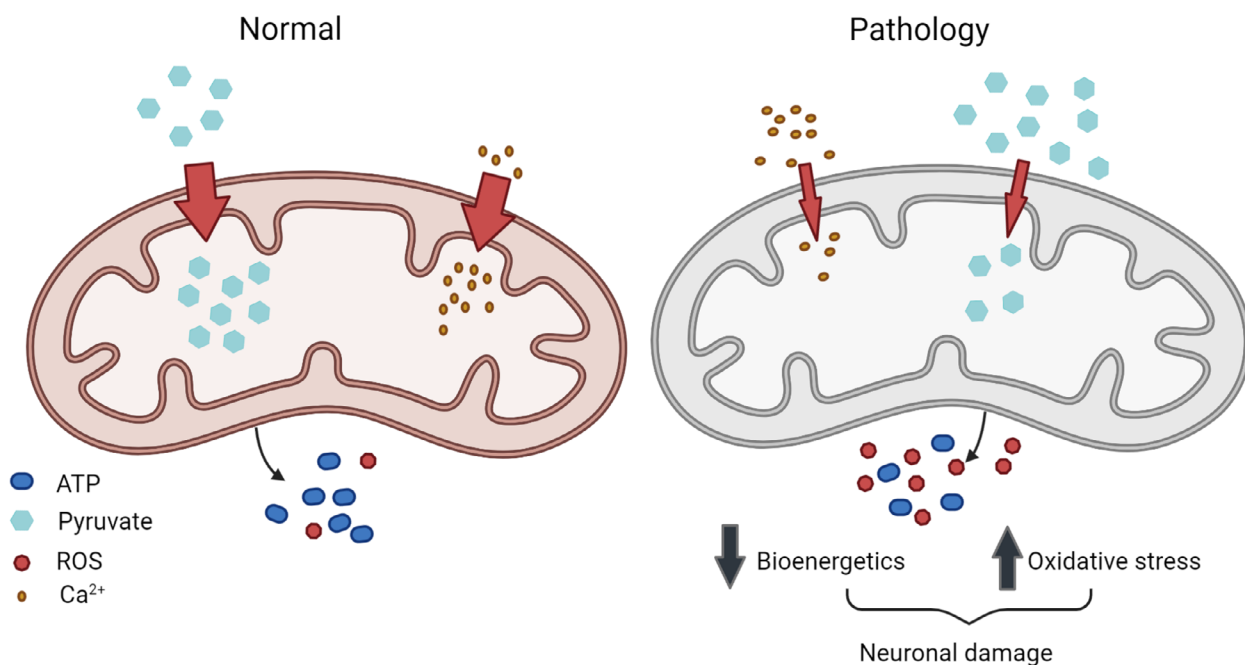


Fig. 1. Metabolic pathways in mitochondria in health and disease. Pathways altered in mitochondrial dysfunction, which are associated with neuronal metabolic alterations and neuron damage in pathological conditions. Neuronal damage results from reduced bioenergetics and increased oxidative stress. Thick red arrows indicate normal metabolite transport; thin red arrows illustrate reduced metabolite transport.

trigger inflammatory responses [16]. In turn, oxidative stress (also caused by ischemia and hypoxia) disrupts metabolism [15,17]; neurons cope with oxygen deprivation by adjusting metabolic and energetic demands through various pathways, including the hypoxia-inducible factor (HIF) family of transcription factors [18], a signaling pathway also involved in mitochondrial dynamics. The neuronal-specific HIF 1- α (HIF-1 α) regulates oxygen consumption by mitochondria [19], and the HIF-1 α -induced HUMMR mediates mitochondrial transport [20,21]. Additionally, HIF-1 α -mediated promotion of oxidative phosphorylation and mitochondria recruitment in the growing cone of regenerating axons has been described by a member of our group [22]. This research established the hypoxia signaling pathway as essential for allowing the mitochondrial network to respond to energetic or metabolic demands or stressors and insults (such as ROS or Ca²⁺ dysregulation), thus permitting optimization of mitochondria shape and distribution [23,24].

Mitochondrial homeostasis (mitostasis) is maintained *via* a series of processes such as fission, fusion, active transport, degradation, and biogenesis. The collectively termed mitochondrial dynamics regulates mitochondrial DNA (mtDNA) stability, organelle turnover, its proper distribution, and cell death mechanisms [24]. Disruption of mitochondrial network dynamics is obviously not only detrimental to neuronal survival but also to other cellular functions. Although a causal relation has not yet been unequivocally established; such anomalies have been strongly implicated in the pathogenesis of neurodegenerative diseases such as Parkinson's

disease (PD) [25], Alzheimer's disease (AD) [26], or Huntington's disease (HD) [27] (Fig. 1, Table 1). Tightly related to mitostasis and signaling, mitophagy is the autophagic selective removal of mitochondria. Mitophagy relies on pathways independent of autophagy [28], and even though it is facilitated by mitochondria fission and fragmentation [29], it is initially induced by mitochondrial dysfunction [30].

Mitochondria biogenesis was classically believed to occur entirely in the cell bodies due to the proximity to the nuclear machinery [31]. However, this model did not appear to consider the morphology of long, branched axons in neuronal cells, which would need replacing of older and damaged mitochondria at very distal locations. Indeed, biogenesis occurs extensively in the axon [32], where it is apparently upregulated in situations of increased energetic needs, such as axonal elongation [33] and early disease response mechanisms [34]. This complex process requires mtDNA replication, coordinated gene expression, protein synthesis, membrane formation, and mitochondrial division [35]. Mitochondrial biogenesis occurs when existing mitochondria grow and divide into daughter organelles in a process synchronized with the cell cycle (but not exclusively) [36]. Biogenesis is crucial for mitochondria maintenance and cellular health; consequently, anomalous mitochondrial biogenesis is linked to neurodegenerative pathogenesis [37]. However, in post mitotic cells, such as neurons, regulation of this process is poorly understood. A recent study has described replication of mitochondrial DNA along the axon, distal to the somatic cell, upregulated in

Table 1. Association between neurodegenerative diseases and metabolism. Main neurodegenerative diseases; alterations to: metabolism and oxidative stress, mitochondria dynamics, biogenesis, transport, and mitophagy are indicated. PD, Parkinson's Disease; HD, Huntington's Disease; AD, Alzheimer's Disease; ALS, Amyotrophic Lateral Sclerosis.

	Metabolism	Oxidative stress	Dynamics	Biogenesis	Transport	Mitophagy
PD	Impaired [37,181], risk factor [182]	Increased [138,182]	Disrupted [25,181]	Disrupted [153,181]	Disrupted [181,183]	Disrupted [148,181,184,185]
HD	Impaired [37,186]	Possibly increased [135,187]	Altered [27,188]	Disruption associated with transcriptional dysregulation [186,189,190]	Impaired [186,191]	Impaired [150]
AD	Impaired [37,192,193]	Increased [136], associated with mitochondria dysfunction, possibly protein aggregation [194]	Disrupted [26,195]	Possibly disrupted [37]	Impaired [26,156,196]	Impaired [149,197]
ALS	Impaired [37,57,198]	Increased, worsened by disrupted SOD response [137]	Disrupted [198,199]	Disrupted [199,200]	Disrupted [198]	Possibly impaired [201,202]

response to neurodegeneration-relevant stresses [34], but this process is not yet fully characterized.

Detailed knowledge of the coupling between mitochondrial structure, motility, and function is essential for understanding the interdependence of mitochondrial and neuronal function in health and disease. The plasticity and transient characteristics of the mitochondrial network has promoted some discussion as to how to characterize these organelles; the focus can be on individual mitochondrial tubules at the nanometer scale [38] or on all of the mitochondria in a cell, at a micron scale [39]. The plastic architecture of the mitochondrial network can fluctuate in extension by three orders of magnitude and transition from fragmented to fully connected [40,41]. This organization is tightly associated with metabolic demands, and for the reasons already described, neurons are extremely sensitive to network alterations.

The mitochondrial network can be characterized by four distinct components: size, shape, dynamics, and position and by how these features change with time. These distinct features do not exist independently; rather, they are all interlinked [42]. Significant plasticity is at play. Of these, size is the simpler feature and refers to the mitochondrial tubules and their length, which determine cellular mitochondria volume. Mitochondria length can vary from sub- to tens of micrometers [43] and is directly associated with mitochondria shape, but it is also related to their recruitment and distribution [44]. The textbook mitochondrial shape is tubular, with a constant diameter, but other shapes are routinely found in the network, in both physiological and pathological situations, including tube swelling, inconsistent diameter, and spheroid shapes [42]. As already mentioned, mitochondrial features are interlinked, and tubules also contribute to mitochondrial size and shape. Tubulation is achieved due to mitochondrial internal organization, including the association between membranes, cristae orientation, and interaction with other organelles [45,46]. Shape has been found to be an important determinant of mitochondrial function, both in terms of calcium homeostasis [47] and energy production [48]. It is also related to ROS generation as most of the cellular ROS are produced by leakage of electrons at complexes I and III of the ETC [49]. On the other hand, defects in the respiratory chain can result in mitochondria fragmentation [50].

Dynamics refers to the fission and fusion events that mitochondria are constantly undergoing, remodeling and adapting the network to cellular needs and to insults and stress. Fission divides a mitochondria tubule, while fusion can connect separate tubules.

These processes are in a constant dynamic equilibrium reflected in the network shape. Nevertheless, it should be kept in mind that these are not independent organelles but transiently disconnected portions of the same network. Mitochondria dynamics are important for cell division in proliferative cells, such as glia, ensuring an appropriate mitochondria pool [51]. In post-mitotic cells, such as neurons, dynamics are associated with organelle quality control, namely, the rescuing or removing of damaged mitochondria (reviewed by Ni *et al.* [52]). Elevated levels of aerobic respiration are correlated with elaborate mitochondria networks, while lower respiratory activity warrant simpler networks [53] in a dynamic equilibrium adjusted in response to energetic or metabolic demands in a bidirectional relationship [23,24]. The network also reacts to stressors of insults, such as ROS [54,55] or dysregulated Ca^{2+} [56], allowing for optimization of mitochondria shape and distribution along the axon. Should this optimization fail, cellular homeostasis would be seriously compromised, and several neuronal disorders are linked to faulty mitochondria dynamics, among them amyotrophic lateral sclerosis (ALS) [57], AD [58,59], or PD [60] (Table 1).

Mitochondrial morphology is partially determined by dynamics. Modulation of mitochondrial dynamics is observed in situations requiring increased mitochondrial proliferation [61], regulated by hypoxia signaling [22], and, as already mentioned, tightly associated with ROS. In fact, excessive oxidative stress can result in network fragmentation [62], and increased ROS production can be dependent on mitochondria network modification [63]. Metabolically and energetically active cells warrant elaborate mitochondrial networks, where each mitochondrion in the network maintains a certain degree of functional independence [64,65]. This feature ensures that the network properties do not occur at the expense of quick mitochondria response to homeostatic changes.

Finally, but not least important, the position of mitochondria in a cell is mainly determined by their transport along cytoskeletal tracks, and this characteristic is particularly relevant for neurons as axonal length requires correct mitochondria distribution to satisfy local metabolic requirements [66]. In pathological conditions, this is even more so as proper mitochondrial transport and distribution (increased following axonal injury [67]) are required, for instance, during axonal regeneration [68]. Should this mechanism fail, axonal health and function are severely impaired, as in the axonal form of Charcot-Marie-Tooth disease, where mitochondrial transport is impaired due to mutations of the mitofusin2 gene [69].

Metabolism in the nervous system

Neurons are particularly susceptible to mitochondrial malfunction due to their intrinsic characteristics. Unlike other highly energetically demanding cells, these cells rely strictly on aerobic metabolism, meaning that their main source of energy comes from glucose metabolism [70]. Axonal mitochondria metabolising glucose provide the ATP essential for impulse conduction [71], but ATP might not be uniformly available along the axoplasm due to axonal length, and axonal energy homeostasis depends on mitochondria distribution [72]. Axonal mitochondria are transported *via* microtubules and neurofilaments [73] through different mechanisms depending on the direction of movement [66]. Dynein motors are involved during retrograde [74] and kinesin motors during anterograde transport [75]. Even though the regulation mechanism of these motor proteins is not yet clear, the MIRO protein family is associated with mitochondrial axonal stopping [76]. This mechanism is particularly interesting, considering that MIRO acts by interacting with the hypoxia mediator HUMMR, a neuronal protein upregulated in mitochondria *via* HIF-1 α , which promotes anterograde transport [21]. Additionally, ischemia affects axonal excitability [77], and since axonal transport is ATP-dependent [78], transport will be affected by energetic deficits, furthering said deficits.

Axonal excitability involves the activation of ion channels and energy-dependent pumps that generate the action potential along the axon. However, for the axon to repeat and maintain impulse conduction, the local environment must be restored. Maintaining the resting membrane potential is indispensable for normal neuronal function. This is achieved through a specific ionic distribution by energy-consuming pumps such as the sodium and potassium adenosine triphosphatase (sodium pump) [71]. This enzyme couples the energy generated from ATP hydrolysis with ionic translocation across the membrane, which means that metabolic reduction severely impairs the basic unit of information. In physiologic situations, mitochondria accumulate in certain neuronal subcellular locations [79], speculated to be caused by a checkpoint mechanism or an active recruitment of mitochondria due to increased metabolic needs [80], possibly due to activity of the sodium pump restoring axonal homeostasis following signal conduction [81]. Neuronal mitochondria homeostasis is, thus, vital for signal conduction.

In the nervous system, not only are neurons essential, but astrocytes are also fundamental as they play important regulatory roles in the central nervous system (CNS) homeostasis. Here too, mitochondria have

an essential role, given their unique metabolic characteristics. Energy production in astrocytes does not rely so much on oxidative phosphorylation as in neurons, but more so on anaerobic glycolysis [70]. Astrocytic mitochondria distribution is very characteristic due to this cell's structure, in which most of the cytoplasm volume takes the shape of thin branches. These peri-synaptic structures feature an elevated mitochondria population [82], functionally different from those of the cell body [83]. Lacking electrical properties, neurotransmitter signaling in astrocytes is regulated by Ca²⁺ concentration; calcium buffering is under mitochondrial responsibility, as is the production of energy requirements for neurotransmitter release [1]. As such, one of the proposed roles of astrocytic peri-synaptic mitochondria is the regulation of astrocyte neurotransmission. Additionally, the theoretical "horizontal transfer" of mitochondria between cells, *via* astrocytic microvesicles [84], has recently been hypothesized and proposed to rescue neurons undergoing energetic deficits [85]. Similarly, horizontal gene transfer is widely described in prokaryotes and has been identified in the last decade to also occur in eukaryotes [86]. Consequently, mtDNA genomic transfer is a possibility being investigated [87,88], but its occurrence in the nervous system is not yet clear [89]. Finally, astrocytic mitochondria are also responsible for production of ATP to be used extracellularly as a signaling molecule [90,91] in neuron–glia communication [92–94], adenosine metabolites are important neurotransmitters [95] and modulators [96], with important roles in health and disease [97]. As such, astrocytic mitochondria are currently being explored as potential therapeutic targets for various pathologies.

Age-dependent changes in neuronal glucose metabolism

Establishing and maintaining bioenergetic homeostasis is crucial for normal cell function; thus, it is essential to understand this process to unravel the cellular mechanisms underlying cell regulation. Neurons in the adult brain depend on a continuous flow of blood glucose as an energy source, and this is regulated by the blood–brain barrier-located glucose transporters (GLUT) [6,98]. However, in some circumstances, neurons are able to use other substrates, such as ketone bodies (during fasting) or lactate (during vigorous physical exercise) [99]. In addition to ATP production, glucose is used to generate metabolic intermediates for the synthesis of fatty acids and other lipids necessary for the synthesis of myelin; amino acids for protein synthesis and production of neurotransmitters; sugars

for nucleotide synthesis; and astrocytic glycogen. This highlights the different, complementary metabolic profiles of glia cells (predominantly glycolytic) and neurons (mostly oxidative) [6,99].

The most significant metabolic pathways are the cytosolic glycolytic pathway, the mitochondrial Krebs cycle and oxidative phosphorylation, the latter two are responsible for producing most of ATP used by neurons [4,6,99]. Pyruvate, the final metabolite of glycolysis, undergoes the action of the mitochondrial pyruvate dehydrogenase complex, resulting in acetyl-CoA production, which will be metabolized in the Krebs cycle. NADH molecules, generated in the Krebs cycle, flow through the ETC to produce ATP. This process is closely dependent on the correct activity of enzyme complexes present in the inner membrane of the mitochondria (Complex I, II, III, and IV) [4,99]. Deficits in the mitochondrial catalytic machinery contribute to a state of hypometabolism and oxidative stress [100]. Alterations to glucose metabolism promote a neuronal glucose metabolic deficit, a state of glucose hypometabolism (Figs 1 and 2). Considering the need for a continuous energy supply in the brain, metabolic deviations will, thus, have consequences for the brain's normal function, particularly for neurons [4,6].

Many factors contribute to glucose hypometabolism in aged brains, at a cellular and molecular level,

affecting every step of glucose metabolism. Glucose entry into the brain relies on continuous blood flow, accompanied by the activity of GLUT. Several studies point to a negative correlation between age and blood flow in different areas of the brain and consequently impaired glucose availability, compromising brain function [101–103]. Indeed, imaging studies on the murine aging hippocampus demonstrated significant age-dependent decline in the glucose brain uptake [104] and decrease in GLUT3 [105]. This is an interesting model due to the role of the hippocampus in memory processing and recovering, which correlates with age-associated decline of the episodic and work memory and learning ability [6,105]. The generalized decrease of GLUT3 expression has also been observed throughout the aged mouse brain [106]. In fact, expression of glycolytic enzymes, such as hexokinase enzyme and the pyruvate dehydrogenase complex, was also found to decrease with aging in mouse models [104]. These findings are consistent with those of prior studies showing age-dependent enzymatic changes both in mouse [107] and in autopsies of aged human brain [108].

Mitochondrial function depends on the enzymatic complexes of the ETC, and any alteration to its activity will impair energy production and increase oxidative stress and neuron damage. Studies on primates [109] and rodents [110] have shown a reduction in

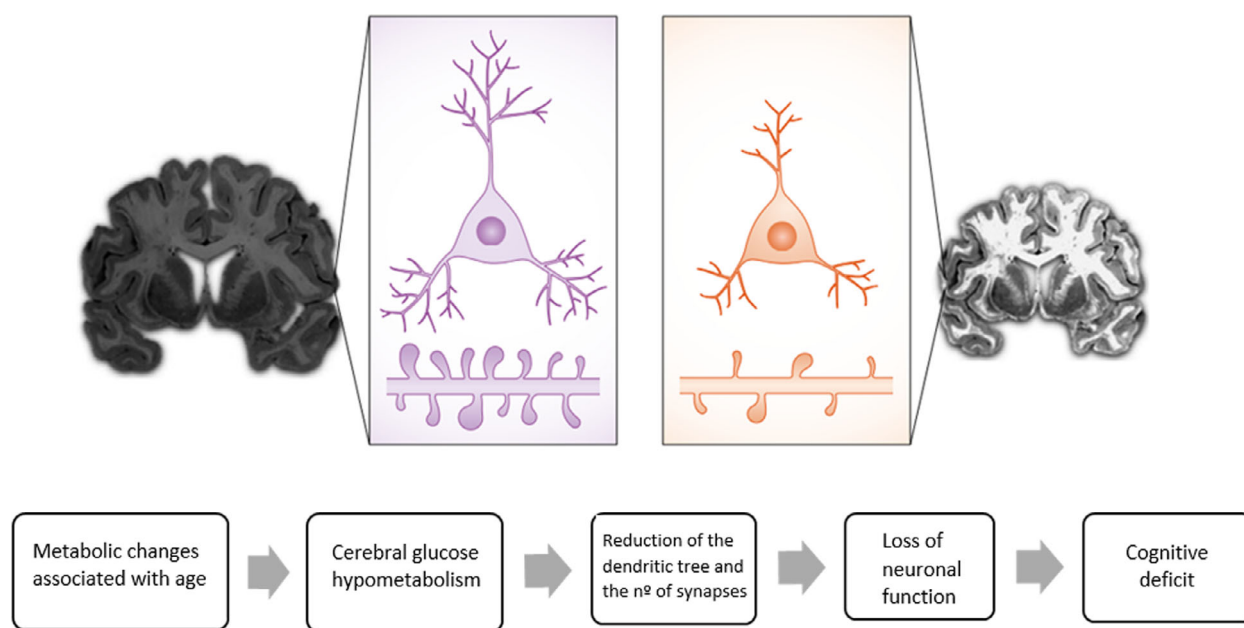


Fig. 2. Schematic representation of neuroanatomical changes in aging brain and neurons. Metabolic changes associated with age result in a reduction in the dendritic tree and synaptic number, alterations that culminate in a cognitive deficit. Young neuron (left), aged neuron (right). Adapted from Ref. [6].

activity of all mitochondrial ETC complexes in aged brains, with a particularly significant reduction in the activity of complexes I and IV in the cerebral cortex of primates [109]. Conversion of NAD into its reduced (NADH) and oxidized (NAD⁺) forms is crucial for the energy production process: NADH results from glycolysis, pyruvate decarboxylation, and Krebs Cycle, while NAD⁺ is a product of oxidative phosphorylation in the ETC of the mitochondria [111]. A significant decrease in the NAD⁺/NADH relation has been demonstrated during physiological aging, supporting a decline of the ETC enzyme activity and loss of mitochondrial function with age [111]. The decline of NAD⁺ levels and changes in NAD⁺/NADH ratio are strongly associated with many age-dependent pathologies, and this pathway has been heralded a promising new therapeutic strategy [112].

PET studies have analyzed whether glucose metabolism is altered in the elderly brain, aiming to relate alterations with cognitive deficit and dementia associated with aging and neurodegenerative diseases, but results are discordant regarding the evaluation of the cerebral metabolic rate of glucose (CMR glucose) in healthy elderly. While some failed to observe a significant age-associated CMR glucose decrease [113–118], others reported the opposite [119,120]. Although the latter argue that the decrease in CMR glucose is justified by cerebral atrophy of old brains, a more recent study [113] describes a decrease in glucose metabolism with patterns and expression distinct from those of cerebral atrophy, suggested to be due to molecular changes. These discrepancies can be explained by variations in methodology, namely, subject selection criteria, sample sizing [113,121], age ranges [121], or analysis techniques (e.g. the classic region of interest analysis [122,123] versus the modern Statistical Parametric Mapping [116,117]). Although recent studies support the existence of an aging-associated generalized decline of CMR glucose, it does not appear to be homogenous, with some brain regions being more susceptible [4,6].

Nonetheless, it is now widely accepted that physiological aging is strongly associated with a metabolic decline in brain areas such as the lateral and medial frontal cortex, the basal forebrain, and the anterior cingulate cortex [118,124–126]. Some studies identify age-related metabolic reductions in temporal lobe regions [124,127,128], but results vary significantly between subjects [124,127], and evidence suggests that the anterior regions of the brain are the most vulnerable, particularly the frontal lobe [125,127,129]. In AD, this decline follows a regional pattern in the parieto-temporal cortex and posterior cingulate cortex (PCC)

[118,125], and PET studies describe a regional decline of CMR glucose in the presence of mild cognitive impairment concordant with the AD pattern, with parietal and posterior cingulate hypometabolism [118]. Even though these results suggest that the process of AD differs from physiological aging [124,125], they do not consider molecular changes contributing to brain hypometabolism, regional hypometabolism, typical of normal aging, correlates with age-associated cognitive decline, and attention and mood dysregulation, consistent with metabolism decline observed in the ACC and basal forebrain [118].

Taken together, these findings support the bioenergetic hypothesis by demonstrating that changes in glucose metabolism and mitochondria dysfunction with aging lead to a bioenergetic deficit in the aged brain. With less energy available, neuronal function is compromised, a major factor in the physiological cognitive decline typical of aging [4,6]. Thus, an aggravation of these age-dependent mitochondria metabolic changes will contribute to neurodegeneration.

Ageing, mitostasis dysfunction, and neuropathology

Cerebral glucose hypometabolism, typical of neurodegenerative diseases [4], was classically seen as a clinical consequence of pathology, namely, due to structural changes within patient's brains, resulting from the accumulation of disease-specific protein aggregates [130]. These aggregates are deemed responsible for neuronal and synaptic dysfunctions culminating in clinical symptoms, such as dementia [3]. However, recent evidence, here reviewed, supports the alternative bioenergetic hypothesis. This theory proposes that it is the aging-associated metabolic changes within the brain that lead to neuroanatomic changes and, consequently, to the physiologic cognitive decline and to neurodegeneration, in case of exacerbation of these alterations (Fig. 2).

Aging and lifespan are regulated by various metabolism-related mechanisms, including diet and caloric intake, ROS production, or mitochondria activity [110,131]. However, mitochondrial dysfunction is itself a consequence of aging [132]; as cells and organisms age, respiratory chain efficiency decreases, with electron leakage and reduced ATP generation, increasing ROS levels and eventually exacerbating age-associated damage [130]. Oxidative stress-driven metabolism disruption affects proteins and nucleic acids [133,134] and can contribute to pathogenesis of HD [135], AD [136], ALS [137], PD [138], and TTR amyloidosis (FAP) [139] (Table 1). Dysfunctional

mitochondria can contribute to aging *via* increased permeabilization in response to stress, affecting apoptotic signaling and triggering inflammatory reactions, as already mentioned above. Additionally, endogenous and exogenous stressors cause protein misfolding and unfolding. In healthy organisms, quality control cellular processes restore proteostasis [140], but these deteriorate with aging [130], with a deleterious effect on longevity [141]. Furthermore, the cumulative oxidative stress, experienced by aged cells, increases transcriptional and translational errors and impairs protein degradation [142], and protein oxidation hinders their degradation. The resulting increased debris and damaged proteins can overflow the cellular response, resulting in accumulation of damaged mitochondria as a result of imperfect autophagy [143].

Mitophagy and autophagy are essential for healthy aging and lifespan, declining with aging [144] (Fig. 1). Lifespan is decreased by hindering mitophagy [145] and extended by promoting autophagy [146]. The exact mechanisms behind these relationships are not yet clear, but it has been theorized that efficient mitophagy reduces mitochondria-associated oxidative stress and removes dysfunctional mitochondria featuring mutated mtDNA [147]. Given the nervous system's energy demands, it is especially susceptible to mitochondria dysfunction; dysfunctional mitophagy is also related with neuropathologies, featuring in some familial forms of PD [148], AD [149], and HD [150] and is being explored as a potential therapeutic target. In addition to its obvious role in energy homeostasis, mitostasis disruption also affects calcium homeostasis, with dire consequences in neuropathologies: in AD, defective Ca^{2+} handling contributes to glutamate-induced excitotoxicity, intracellular calcium accumulation, and neuron loss [151]; in PD, upregulated calcium uptake by mitochondria leads to calcium overload [152]; in ALS, an elevated calcium flux, paired with impaired transfer from ER to mitochondria, contribute calcium overload [83].

Mitochondrial biogenesis has been proposed to be the link between neurodegeneration in PD and dysregulation of mitochondrial homeostasis. The underlying nature of the degenerative process of this pathology appears to be initiated in long, poorly myelinated, highly branched axons with high ATP requirements [153], in which mitochondrial biogenesis would be critical. Indeed, neurodegeneration is associated with mutations in PINK1 and parkin, mitochondrial biogenesis regulators [154], whose upregulation prevents neurodegeneration in α -synuclein gene overexpression [34,155]. Mitochondria are also implicated in synapse degeneration in AD as mitochondrial function and

transport are impaired by the AD-related proteins Amyloid beta and tau [156] and mitochondrial dysfunction are an early pathophysiological event of ALS and HD [157,158]. In cerebral ischemia, decreased expression of GLUT 1 and 3 and decreased glycolytic enzymatic activity are examples of age-dependent changes. Longitudinal studies using PET have shown a decline in glucose CMR in old healthy subjects, several years before the appearance of symptoms associated to a cognitive decline [124,159], supporting the importance of upstream metabolic changes in the development of these symptoms. In addition, the extension of CMR glucose decline is related to symptom severity, with glucose cerebral hypometabolism aggravating when symptoms first appear [124,159]. Nevertheless, the exact mechanisms by which a healthy old brain turns into a pathological state with specific structural characteristics of each disease are yet to be discovered, and further studies are required.

Targeting mitochondria homeostasis as a future therapeutic approach

As neurons require steady amounts of energy to trigger action potentials, age-related metabolic decline contributes to cognitive deterioration [160] (Fig. 2). Brain aging is accompanied by metabolic, morphological, and neurophysiological changes leading to synaptic loss, which affects cognition, learning, and memory [161].

Such observations have been reported in several neurodegenerative diseases, the onset and progression of which are influenced by energetic changes that occur when neurons fail to respond in an adaptive way to this progressive metabolic decline [160]. Moreover, unfavorable changes in cerebral vasculature and in neuronal energy availability contribute to increased brain vulnerability to cognitive impairment and dementia [3].

The brain is organized in such an optimized way that processing of complex cognitive information occurs efficiently and economically due to metabolic costs. This suggests a fundamental link between brain bioenergetics and function consistent with results, indicating that network dysfunctions develop during cognitive ageing, in parallel with metabolic disorders [162]. Aged neurons are characterized by significant reduction in dendritic tree and changes in size, shape, density, and turnover of the dendritic spines (Fig. 2). These structural changes disturb neuronal function, memory, and learning and are responsible for the cognitive decline associated with brain aging and neurodegenerative disorders [4].

The bioenergetic hypothesis is supported by empirical evidence indicating that fasting, exercise, and intellectual challenges – bioenergetic challenges – increase synaptic plasticity and cognitive performance [163]. In the neuronal context, hormesis is defined as the ability of low doses of a potentially harmful stimulus to promote beneficial changes in synaptic plasticity [7,8]. When neurons are submitted to mild metabolic challenges, brain function is, indeed, improved, and resistance to dysfunction and degeneration is increased [164].

Thoroughly associated with mitochondria function [164], the relevance of brain-derived neurotrophic factor (BDNF) has extensively been demonstrated in synaptic plasticity, neuronal survival, and differentiation [8,165], and BDNF signaling plays an important role in cognitive effects in situations of exercise and fasting [164]. In these situations, BDNF is upregulated, mediating glucose and ketone body uptake [165]: the former by increasing GLUT3 expression [164], the latter by acting *via* the FOXO3 transcription factor [166]. Neuron-released BDNF stimulates mitochondrial biogenesis and acts *via* the tropomyosin kinase B (TrkB) receptor, activating transcription factors involved in synaptic plasticity, cognition, and memory [167]. Different BDNF-centred approaches have been identified for prevention and treatment of metabolic and neurological disorders [8,168]. A clinical trial evaluated the effects of physical exercise on neurotrophic factors in multiple sclerosis and concluded that exercise stimulates the production and secretion of BDNF, thus being recommended as an adjuvant therapy [169].

Recent evidence suggests that raising BDNF levels through bioenergetic challenges is beneficial for brain resistance, resilience, and adaption to unfavorable situations. However, some questions remain unanswered; in fact, the specific contributions of BDNF to the effects of exercise and fasting in the brain are not yet clear, and it has not been plainly demonstrated to be a therapeutic option for neurodegenerative diseases. Although, low levels of BDNF have been observed in the brains of AD patients, suggesting that raising its production could become an effective alternative to delay disease onset [170]. Similar results were obtained with animal models of PD [171], but evidence showing that bioenergetic challenges are effective in treating neurological diseases is still extremely limited. In summary, these bioenergetic challenges should be considered as tools for early intervention in neurodegenerative conditions. As such, further studies are necessary to investigate not only the role of mitochondria in this process but also

the clinical effectiveness of these challenges as a neurological therapeutic strategy in human beings.

In line with these novel therapeutic strategies, mitochondria transplantation (mitotherapy) is being investigated with varying degrees of success [172]. In a rat model of schizophrenia, where mitochondria dysfunction is prevalent, injection of active mitochondria prevents mitochondrial dysfunction and ameliorates attention deficits [173]. A similar approach has been tried in a PD model, where mitochondria injection delayed PD progression [174]. Mitochondria transplantation also increased bioenergetics-associated neuroprotection in response to spinal cord [175] and nerve injury [176].

In closing, it appears that mitochondria will present novel therapeutic opportunities. Following up on the observation that “horizontal transfer” of mitochondria is possible *in vitro* [177], transfer of mitochondria between cells was performed *in vivo* as an experimental therapy for acute lung injury [178]. Considering the rich vesicle-mediated intercellular crosstalk in the nervous system, it was hypothesized that this mechanism could also occur in the brain. Evidence first revealed that cultured astrocytes have the capacity to release mitochondria containing microvesicles [84], which was expanded into the notion that neurons can themselves shed damaged mitochondria for degradation by neighboring glial cells *in vivo* [179]. It was eventually demonstrated that astrocytes can in turn transfer functional, healthy mitochondria to neurons in a neuroprotective effort following stroke [85]. In 2019, mitochondria trafficking between neurons and astrocytes was observed in the demyelinating leukodystrophy Alexander disease [180], thus strengthening this mechanism as a target and therapeutic approach in various neuropathologies.

Conclusion

The nervous system is particularly affected by aging, and disruption of neuronal mitochondrial function and homeostasis takes a high toll on the nervous system, being linked to several age-related neuropathologies. Mitochondrial dysfunction is being explored as a possible therapeutic target, but the potential beneficial effects of modulating mitochondrial status to ameliorate aging-associated dysfunction have not yet been clearly characterized. However, in the span of a decade, mitochondrial transfer for neuroprotection and neuroregeneration is rapidly transitioning from being a theoretical concept to a translational or even a clinical approach. It is expected that further ground-

breaking contributions will help bring this transition to completion in the next decade.

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