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# Mitochondrial Dysfunction as a Key Event during Aging: From Synaptic Failure to Memory Loss

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## Abstract

Mitochondria are important cellular organelles with key regulatory functions in energy production, oxidative balance, and calcium homeostasis. This is especially important in the brain, since neurons require a large number of functional mitochondria to supply their high energy requirement, mainly for synaptic processes. A decrease in the activity and quality of mitochondria in the brain, particularly in the hippocampus, is associated with normal aging and a large number of neurodegenerative diseases compromising memory function. Although synaptic and cognitive dysfunction is multifactorial, growing evidence demonstrates that mitochondria play a key role in these processes and suggests that maintaining mitochondrial function could prevent these age-dependent alterations. In this chapter, we will discuss the hippocampal mitochondrial dysfunction present in aging and how these defects promote age-associated synaptic damage and cognitive impairment. We will summarize evidence that shows how neurodegeneration can be accelerated or attenuated during aging by modulating mitochondrial function.

**Keywords:** aging, mitochondria, oxidative stress, synapses, memory

## 1. Introduction

Aging is an extensively studied process, identifying a growing interest in how and why cognitive processes are affected from a neurobiological approach [1]. Aging is a multifactorial biological process, characterized by deterioration of physiological and cellular functions including brain function [2], where age is the main risk factor for the development of pathologies such as cancer, diabetes, cardiovascular disorders, and neurodegenerative diseases [3]. Cognitive deterioration occurs during aging, where reasoning, attention, and memory, among other processes, decrease gradually with the age [4]. Cellular senescence and alterations to mitochondria and in proteolytic systems are considered hallmarks of aging [3], where one of the most studied is the mitochondria [5]. In fact, mitochondrial dysfunction has been directly associated with the aging phenotype and the majority of diseases that lead to cognitive damage.

Over the last decades, a great interest has arisen regarding mitochondrial structure and function due to its relation with the aging brain [5]. Mitochondria are organelles essential for energy production, whose size is usually 0.5–1  $\mu\text{m}$ , composed

by two membranes, forming the intermembranous space and the mitochondrial matrix [6]. The outer membrane contains many copies of the transport protein porin (or voltage-dependent anion-selective channels (VDAC)), which allows the passage of molecules with a maximum weight of 5 KDalton (KDa), and the inner membrane forms numerous invaginations, tubular structures, called cristae [6]. Mitochondria are capable of remodeling their architecture through fission and fusion processes, allowing morphological adaptation to different situations [6]. Fission is essential for mitochondrial duplication and is necessary for mitophagy, allowing dysfunctional mitochondrial sections to be recycled. Fusion allows mitochondria to interconnect, allowing damaged mitochondria to maintain their function. However, fission-fusion processes are interrupted during aging, generating damaged mitochondria [7].

Mitochondria have a small circular genome called mtDNA, which encodes 22 tRNAs, 2 mitochondrial rRNAs, and 13 subunits of the electron transport chain (ETC) [8]. mtDNA can be damaged by exposure to reactive oxygen species (ROS), chemical carcinogens, and ionizing radiation affecting the mitochondrial function; changes are also observed during aging [9]. The internal mitochondrial membrane contains the ETC, responsible for generating ATP. ETC is formed by five protein complexes; complex I (NADH dehydrogenase) receives electrons of NADH which pass through the ETC via oxidation-reduction reactions forming an electrochemical gradient that allows the formation of ATP. In addition, FADH<sub>2</sub> donates its electrons to complex II (succinate dehydrogenase) performing the same action for ATP generation but at lower production levels [10]. As a secondary product, the ETC forms ROS, specifically by complexes I and III, but its production is controlled by antioxidant enzymes [11]. Therefore, in normal conditions ROS production is moderate, providing certain physiological roles [11]; however, during aging ROS accumulation causes biological damage known as “oxidative stress” [12].

In the past, mitochondria have always been highlighted for its role in ATP production; however, another key function is to maintain intracellular calcium homeostasis [13]. The outer mitochondrial membrane is permeable to ions and ~5 KDa metabolites because its lipid bilayer has transmembrane proteins that form the mitochondrial permeability transition pore (mPTP). mPTP opening and closing dynamics regulates the concentration of calcium [13]. However, in conditions of high calcium concentrations, permanent mPTP opening generates massive transport of ions and small molecules <1.5 KDa through the membrane, causing increased ROS production, inhibition of the ETC, and mitochondrial swelling, which finally results in the release of pro-apoptotic factors and cell death [14].

In this chapter we will discuss the mitochondrial alterations observed in the brain during aging, focusing on mitochondrial functions including redox balance, bioenergetics, and calcium homeostasis, and its implications in the aging process. In addition, we will discuss the contribution of mitochondrial dysfunction to synaptic failure and cognitive impairment. Finally, we will summarize potential treatments that have been proposed to prevent or attenuate the loss of mitochondrial function that could be used as potential antiaging treatment.

## **2. Oxidative stress: the main characteristic of normal aging**

Aging is a complex process that involves both intrinsic and extrinsic factors [3]. Several researches showed that the reduction of synaptic function during aging could be related to increased oxidative stress and mitochondrial dysfunction [15, 16]. The latter involves decreased production of energy and redox balance, activation of nitric oxide synthase, and an abundant generation of free radicals; meanwhile increased ROS production impairs neuronal function at advanced ages [17].

Mitochondria have a pivotal role in ROS production; they are the main organelle producer of species such as hydrogen peroxide ( $\text{H}_2\text{O}_2$ ), superoxide anion ( $\text{O}^{2-}$ ), and hydroxyl radicals ( $\text{OH}^\cdot$ ) [18]. ROS comprise all molecules derived from oxygen, can exist independently, and contain one or more unpaired electrons in their orbitals [19]. Normally, mitochondria generate ROS as a result of adequate function of the ETC by complexes I and III in OXPHOS to produce ATP. Likewise, electrons that escape mitochondrial ETC can reduce oxygen to form  $\text{O}^{2-}$  [20]. Additionally,  $\text{H}_2\text{O}_2$  is more stable than  $\text{O}^{2-}$  and can diffuse freely through the membranes to the cytosol or nucleus, causing oxidative damage to many cellular compartments [21].

The mitochondrial ROS produced in normal conditions have important physiological roles in maintaining cell homeostasis, participate as signaling molecules, and are also related to the regulation of cell survival [22]. In contrast, excessive ROS production promotes cellular damage [23]. For example, recent evidence suggests that higher mitochondrion-derived ROS result in enhanced formation of A $\beta$ , an effect that is prevented with the use of antioxidants that rescue mitochondrial function in cellular and animal models of Alzheimer's disease (AD) [24]. This suggests that higher ROS generation mediated by mitochondria is involved in early stages of age-associated diseases and during aging [25].

Cells maintain a balance between free radicals by the action of antioxidant molecules, which neutralize or remove them [22]. Cells are equipped with a variety of defense mechanisms to remove ROS, including antioxidant enzymes that facilitate antioxidant reactions and decompose ROS [26]. Among the antioxidant enzymes are glutathione reductase (GR), glutathione peroxidase (GPx), and catalase (CAT). In addition, superoxide dismutases (SODs), such as copper-zinc-superoxide dismutase (CuZnSOD) and manganese superoxide dismutase (MnSOD), help the dismutation of superoxide radicals to generate  $\text{H}_2\text{O}_2$ , which is further removed by CAT and GPx enzymes [26]. Altogether, these antioxidant defenses regulate the amount of ROS, preventing accumulation and oxidative stress [27].

Oxidative stress occurs when the antioxidant defense mechanisms are unable to neutralize free radicals in the cell. This imbalance between the production of oxidative molecules and the antioxidant defense leads to an accumulation of ROS, which oxidize and produce damage to lipids, proteins, and DNA molecules. Similarly, ROS could alter many cell compartments, for example, promoting peroxidation of lipid membranes and inactivation of enzymes by oxidation [28].

In oxidative stress conditions, the concentration of ROS increases transiently or chronically, altering the cellular metabolism and its regulation [23]. Interestingly, these elements are implicated in the aging process, the mitochondrial free radical theory of aging (MFRTA) being the most accepted theory to explain the age-associated degeneration [29]. This theory exposed by Harman proposes that mitochondria play a central role in aging and indicates that aging is the product of accumulated damage caused by mitochondrial ROS in the cells and tissues of organisms [30, 31]. Nevertheless, this theory has also been questioned, since aging is a multifactorial biological process and not just the consequence of a unique factor [32]. Thus, the mitochondrial theory of aging is relevant since these organelles are energy sources for cells and coordinate important processes such as apoptosis. During aging, accumulation of mtDNA mutations is increased, the mitochondrial genes related to energy production become progressively less active, and the mitochondria are observed as fragmented, producing less energy [33]. The brain is particularly susceptible to oxidative damage being the most aerobically active organ in the body due to its high metabolism [34]. The brain is generally in a redox balance; however, the high production and accumulation of ROS accompanied by a reduction in the antioxidant defense system plays a key role in aging, causing damaging effects due to the large number of potential harmful intermediates that cause neuronal



dysfunction [3, 35]. In turn, increased oxygen radical-induced oxidative damage during aging leads to significant changes in brain mitochondrial function [29]. Therefore, oxidative stress is implicated in aging and a wide range of age-related pathologies, such as AD and Parkinson's disease (PD), among others [3, 16, 36].

In the aged brain, a reduction in normal antioxidant defense machineries is observed, which increases the brain's susceptibility to the harmful effects of oxidative molecules [27, 37]. In addition to this, mitochondrial dysfunction contributes to ROS overproduction. It is important to emphasize that a decrease in the activity of oxidative enzymes accompanied by excessive production of oxidant molecules during aging is the main toxic mechanism that explains the neurodegeneration observed at an advanced age [27, 37]. Since mitochondria are the main source of ROS production, they are in turn more exposed to oxidative damage at a faster and stronger rate than other organelles and cell compartments [16]. Moreover, the mitochondrial antioxidant system is less active than the antioxidant systems of other organelles, a feature that increases with age [5]. These mitochondrial "defects" can greatly affect several cellular processes that contribute to the aging phenotype [38]. Therefore, age is an important risk factor that increases the susceptibility of mitochondria, making them more vulnerable to oxidative stress, resulting in a vicious cycle of mitochondrial dysfunction and more oxidative damage [5, 33]. Mitochondria should be considered as a key factor in the development of age-related neurodegeneration, and therefore therapeutic strategies such as mitochondrial protectors or antioxidants that improve mitochondrial function could be used to prevent or delay aging.

### **3. Bioenergetic failure during aging**

One of the main functions of mitochondria is energy production in the form of ATP through OXPHOS [39]. The main substrate of neurons is glucose. Through the glycolytic pathway, the cell generates only two ATP molecules per glucose molecule; however in this pathway two pyruvate molecules are produced. These molecules then enter the mitochondria to be oxidized in the tricarboxylic acid (TCA) cycle producing NADH and FADH<sub>2</sub>, which in turn enter the ETC to produce high amounts of ATP by OXPHOS [40]. Electrons from NADH and FADH<sub>2</sub> are transferred through four complexes to molecular oxygen, pumping protons to the intermembrane space, which form a proton gradient that generates the mitochondrial membrane potential ( $\Delta\psi_m$ ). This  $\Delta\psi_m$  is fundamental for adequate mitochondrial function, mainly for ATP synthesis by the ATPase complex [39].

Due to the importance of mitochondrial energy production, failures in mitochondrial bioenergetics are related to several neurological diseases such as amyotrophic lateral sclerosis (ALS) [41] and several age-associated neurodegenerative disorders such as AD [42]. A mitochondrial failure can be caused by either a dysfunction in the OXPHOS complexes or by mutations in the mtDNA, which encodes for 13 proteins that makes the different subunits of the ETC complexes. Interestingly, mtDNA mutations produce a group of pathologies known as primary mitochondrial disorders, characterized by neurological alterations. Thus, neurodegeneration is often related to mitochondrial dysfunction as a primary or secondary target, mediating the pathogenic events [43]. Since the main energy source in brain cells is glucose oxidation, the energy obtained from the mitochondrial OXPHOS system is vital to fulfilling their high basal energy requirement, including maintenance of the membrane potential for the propagation of electric signals, reestablishment of the ion balance after the action potential (Na<sup>+</sup>/K<sup>+</sup> ATPase activity), vesicle recycling, and neurotransmitter release [44].

Therefore, a deficit in ATP production can lead to neuronal damage and finally cell death, producing diverse defects in brain functions as occurs during normal aging, considered an important risk to the development of neurodegenerative disease [45]. An example of this is the glutamate-glutamine cycle, an essential process for the release of glutamate from the presynaptic terminal. Glutamate uptake occurs in astrocytes, where it is converted to glutamine and then transferred back to glutamatergic neurons. For these processes to occur, the neuron requires ATP [46], as well as for the accumulation of glutamate in synaptic vesicles [47]. Therefore lower ATP levels will result in reduced glutamate release leading to decreased excitatory synapsis and consequently decreased synaptic plasticity as a result of altered long-term potentiation (LTP) and long-term depression (LTD) [48].

In addition, AD is a neurodegenerative pathology where mitochondrial deficiency is observed in oxidative phosphorylation, with defective OXPHOS enzymes [49]. Several studies showed decreased cytochrome c oxidase activity but an increase in mitochondrial mRNA for complex IV, which may be a compensatory response for the reduced cytochrome c oxidase activity [50, 51]. Also, there is a decrease in NADH dehydrogenase expression and an increase in complex III mRNA in AD patients [51]. These defects in the OXPHOS complex impede correct ATP production and increase ROS production [52], which could generate damage to mitochondrial proteins, activate the mPTP, and mutagenize the mtDNA, leading to defective OXPHOS. All these mitochondrial defects can ultimately contribute to the characteristic synapse loss in the neocortex and hippocampus of AD patients [53], which correlates with cognitive impairment and memory loss. Similarly, critical mitochondrial dysfunction has been associated with PD. Several mutations in proteins that can directly or indirectly regulate mitochondrial activity and morphology have been described. Examples of this are PTEN-induced kinase 1 (PINK1) which induced mitochondrial autophagy during stress [54] and protein deglycase (DJ-1) which is a multifunctional protein that reacts against anti-oxidative stress [55]. These two proteins are localized in the mitochondria, while parkin, another protein that degrades dysfunctional mitochondria, translocates to damaged mitochondria [54]. The first evidence that mitochondria could be related to PD was published by Langston et al. in 1983 where they showed that the mitochondrial complex I inhibitor, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) can cause acute and irreversible parkinsonian symptoms in humans [56]. Later, other mitochondrial toxins such as rotenone, which induces similar symptoms to MPTP, were described, leading to the development of a rotenone rodent model of Parkinson's disease [57]. Other studies of postmortem tissue from PD patients showed defects in complex I, NADH dehydrogenase in the substantia nigra [58].

Interestingly, similar bioenergetic deficits present in neurodegenerative disease are also seen in normal aging. In this natural process, it is well known that a large number of mutations accumulate in the mtDNA in different tissues, such as the brain and the muscle, the tissues with most accumulation of mutations, possibly due to the higher energetic demand [59]. For example, in a study performed with humans between 49 and 92 years old, they showed an increase by 25% in the muscle fibers that exhibit abnormalities in mitochondrial ETC in 92-year-old individuals compared to 49 year olds [60]. Another study showed that a mouse with a deficiency for mitochondrial DNA polymerase  $\gamma$  (POLG) had an impaired proof-reading ability, accumulated mtDNA mutations, and presented a premature-aged phenotype (hair loss, graying, kyphosis, reduced survival percentage, loss of bone mass, etc.) at the age of 9 months [61]. These mutations can lead to mitochondrial dysfunction associated with a deficient respiratory chain and a decrease in ATP production [62]. There is evidence that the brain of aged mice (26 months old) contains mutations in protein-coding regions that result in significant changes

in the complex I subunit ND5 and complex III subunit CytB [62]. These mutations may limit correct assembly of these complexes, which correlates with their decreased activity during aging [62]. Other studies also showed downregulation of several genes coding for mitochondrial proteins in heart tissue, which correlated with a significant decrease in the respiratory capacity of mitochondria to oxidize substrates [63]. In liver tissue, there is a decrease in the respiratory control ratio and in ADP/oxygen (an index of ATP synthesis efficiency) in senescence-accelerated mice (SAMP8) mitochondria [64], suggesting that at 18 months of age, there is insufficient ATP for normal cell metabolism, which may be due to a dysfunctional energy transfer mechanism.

In the brain, it is widely known that with aging there is a decrease in the electron transfer activity accompanied by a decrease mainly in complexes I and IV [65, 66]. Several studies showed that complex IV activity is decreased in substantia nigra, hippocampal dentate gyrus, frontal cortex, and cerebellum during aging [67, 68]. A study performed with aged CD1 Swiss mice showed that NADH-cytochrome c reductase (complexes I and III) activity is the most affected during aging, decreasing by 48% in old mice (18 months), while succinate-cytochrome c reductase activity (complexes II and III) remain unmodified with age, indicating selective impairment of NADH dehydrogenase activity (complex I) during normal aging [69]. Likewise, cytochrome oxidase (complex IV) activity is decreased by 13% in old animals [69]. Additionally, there is evidence of increased expression of mitochondrial genes for complexes I, III, IV, and V in 18-month-old mice in the hippocampus, medial prefrontal cortex, and striatum [70], suggesting a compensatory mechanism that could induce overproduction of ETC proteins. However, this increased mRNA expression is not sustained over time, since 24-month-old mice have decreased expression of ETC complexes [70].

Another parameter that is altered during aging is the  $\Delta\psi_m$  due to increased  $H^+$  permeability of the inner mitochondrial membrane and a consequent failure in maintaining the  $H^+$  electrochemical gradient [71]. There is evidence that there is a decrease in the membrane potential in the cortical and striatal mitochondria of 33-month-old rats [72]. In the same way, a study in primary cultures of glial cells from the brain of young (4–6 months) and old (26–29 months) mice shows a decay in the  $\Delta\psi_m$  in astrocytes [73].

Thus, mitochondrial bioenergetic failure is a hallmark of different diseases including neurodegenerative disorders. Interestingly, these same patterns of decreased ATP production, OXPHOS failure, and depolarization of the mitochondrial membrane are seen during aging, a natural process of everybody's life. This makes the mitochondria an important player in all neurological degeneration related with aging, such as synaptic failure and cognitive impairment.

#### 4. Age-associated calcium dysregulation

Calcium ( $Ca^{+2}$ ) is an ion that participates in a wide variety of functions in the cells of organisms, being an intracellular regulator of many physiological processes [74]. Intracellular calcium signals participate in the regulation of a large number of processes, which include gene expression, cell cycle stages, control of muscle contraction, autophagy, and cell death, among other functions, being a second intracellular messenger [74, 75].

In the central nervous system (CNS),  $Ca^{+2}$  plays a very important role in the neuronal synapse, mainly promoting exocytosis of the synaptic vesicles in the presynaptic region, meanwhile in the postsynaptic site is important for regulating the morphology of dendritic spines and spinogenesis [76, 77]. Calcium homeostasis



is fundamental for correct cellular function, and the mitochondria are structures important for maintaining the intracellular calcium concentrations [78]. They participate in the local regulation of cellular  $\text{Ca}^{+2}$  homeostasis, since it captures  $\text{Ca}^{+2}$  from the cytosol in response to ion fluxes through channels in both the inner and outer plasma membranes or by release of  $\text{Ca}^{+2}$  from the endoplasmic reticulum (ER) [79]. Thus, when the cytosolic concentration of calcium increases, mitochondria capture and accumulate large amounts of the ion in order to control intracellular concentrations. Therefore, for appropriate neuronal functioning, adequate parameters of intracellular calcium concentrations must be maintained [80].

Interestingly, aged brain neurons are incapable of regulating intracellular calcium, mainly due to dysfunctional mitochondria and increased oxidative stress [78, 81].

Mitochondrial dysfunction substantially contributes to biological aging [78]. In aging, oxidative stress affects mitochondrial function and, therefore, its role in  $\text{Ca}^{+2}$  homeostasis [78, 82]. When calcium homeostasis is altered, it has a detrimental role on the aging brain and is also associated with the development of neurodegenerative diseases [83]. Several studies showed that an increase of the  $\text{Ca}^{+2}$  affects synaptic communication, neurotransmitter release, and signal transduction, all this generating excitotoxicity and neuronal loss [84]. In addition, these alterations could also contribute to memory impairment [16, 84].

In this way, since the aging is associated with a marked cognitive decline, the calcium imbalance hypothesis proposed by Khachaturian turns out to be well accepted [85, 86]. This hypothesis proposes that changes in calcium regulation gradually modulate normal brain aging and, at the same time, increase their vulnerability to neurodegenerative diseases such as AD [87]. Calcium signaling depends of the transient elevation of its intracellular concentration. In brain cells, reduced regulation of calcium homeostasis is an early event during aging, altering multiple signaling pathways and affecting various molecular and cellular functions [88].

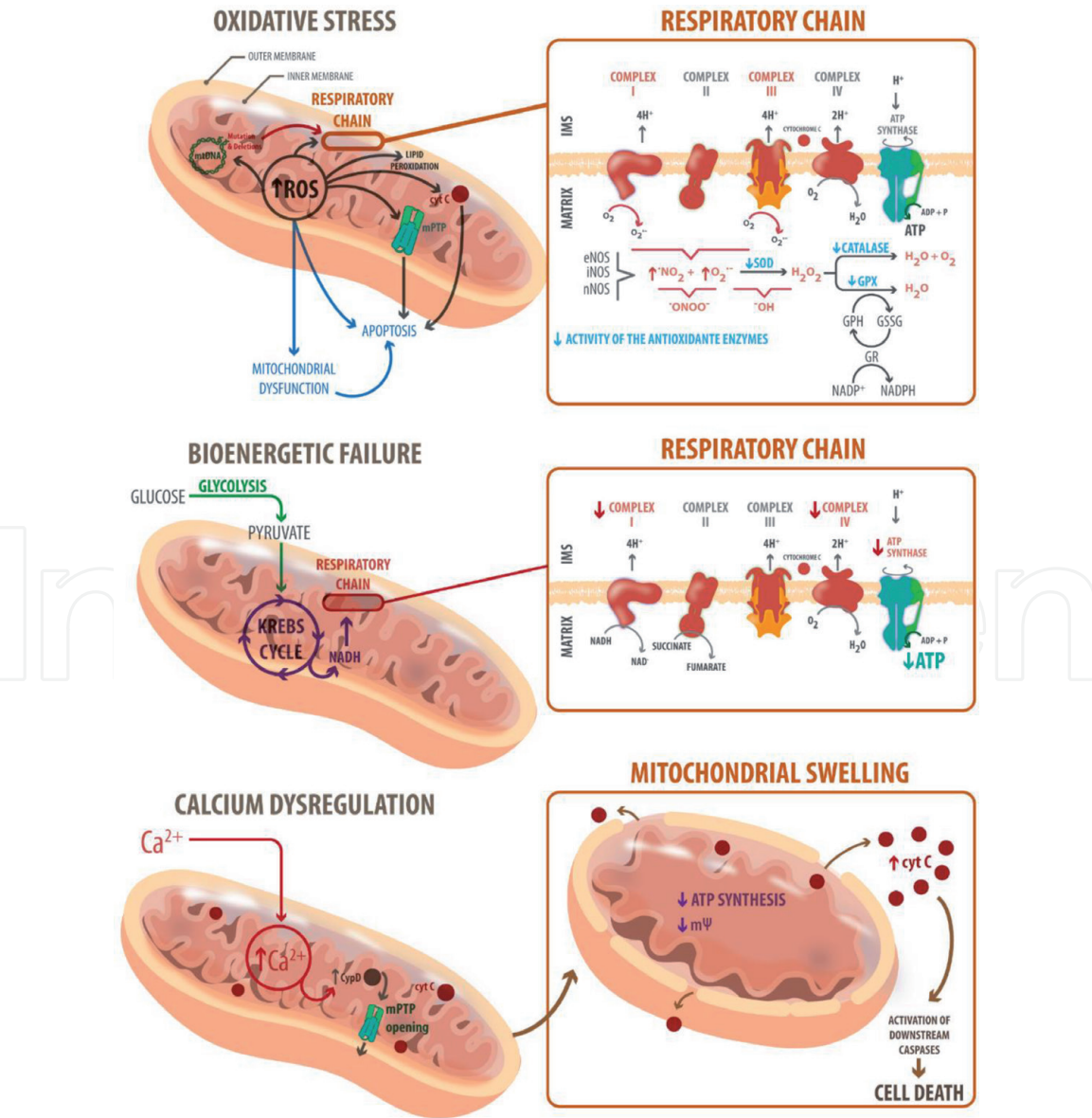
Due to their high buffering capacity, mitochondria are an essential component for maintaining calcium homeostasis, due to their involvement in the regulation of intracellular calcium signaling [89]. Also, other mitochondrial characteristics that facilitate its role in the regulation of calcium signaling is its structural plasticity produced by fusion and fission processes in the mitochondrial network, as well as its distribution within the neuron [90]. Aging affects mitochondrial dynamics leading to mitochondrial fragmentation and alterations to these functions [90]. Studies in mitochondria isolated from the cortex of aged animals exhibited more ROS production and mitochondrial swelling after increased  $\text{Ca}^{+2}$  loading than that of young animals [78]. Therefore, these findings suggest that the aging increased the sensitivity of the mitochondria to calcium overload, generating mitochondrial swelling [81]. Mitochondrial swelling results in the opening of the mPTP [91], and in aged animals, mPTP opening occurs prematurely, indicating reduced  $\text{Ca}^{+2}$  buffering during aging [78, 81].

The mPTP is a large nonselective channel located in the inner mitochondrial membrane and communicates the mitochondrial matrix directly with the cytoplasm [81]. Their opening is activated by  $\text{Ca}^{+2}$ , phosphate, ROS, increased pH, and magnesium ( $\text{Mg}^{+2}$ ) [92]. Transitory opening of mPTP allows the release of excessive calcium ions that accumulate in the mitochondria, but prolonged opening leads to the movement of ions and small molecules generating depolarization of the mitochondrial membrane and in turn releasing pro-apoptotic factors, which results in a reduction of ATP and finally causes cell death [81, 91].

The structure of mPTP is not completely clear. Experimental approaches have distinguished several protein components such as VDAC, the adenine nucleotide translocase protein (ANT), and the mitochondrial matrix protein cyclophilin D (Cyp-D) [91]. Recent research incorporates the F1FO subunits of ATP synthase, a



key enzyme of the OXPHOS complex, which participates in ATP production and maintenance of the membrane potential [91]. Interestingly, deregulation of this enzyme associated with aging has been reported, showing decreased expression of OSCP and in F1FO ATP synthase activity [81, 91]. These changes have also been observed in imaged brains that present age-related neurodegenerative pathologies [81, 91]. Cyp-D is a specific mitochondrial protein and generally considered to be a critical component of mPTP formation [91]. Several studies indicate that Cyp-D is the most important component facilitating mPTP formation, thus leading to decreased ATP production, increasing ROS generation, and eventually causing cell death [81, 91], although it is not yet completely clear how Cyp-D triggers mPTP formation [92]. The opening of mPTP dissipates  $\Delta\psi_m$ , uncoupling the mitochondria and causing swelling [91]. The expression of Cyp-D increases with age and is related to several age-associated neurological diseases such as AD [91, 93]. For example, Gauba et al. have reported that Cyp-D promotes the dysfunction of ATP synthase F1FO, in the mitochondria of aged brains, observing a significant increase in the expression of this protein with age [91]. In contrast, it has been observed that deletion of Cyp-D improves cognitive and mitochondrial functions in both aging and in neurodegenerative diseases [91, 93].



**Figure 1.**  
*The mitochondrial functions are impaired during aging.*

The increased life expectancy and the high incidence of neurodegenerative diseases require a better understanding of the aging processes and the mechanisms associated with it. Thus, comprehension of the interactions between calcium homeostasis and calcium-dependent processes during aging can help in the design of more effective therapeutic strategies. Maintaining calcium homeostasis and controlling the opening of mPTP are important factors that can be considered as a potential therapeutic objective to maintain the quality of life during aging and prevent mitochondrial damage and progressive cognitive deterioration associated with age that contribute to the development of neurodegenerative diseases.

**Figure 1** is a schematic representation of the main mitochondrial functions affected during normal aging. It shows increased oxidative stress as a result of a REDOX imbalance due to decreased activity of antioxidant enzymes and increased reactive oxygen species. It also shows the characteristic bioenergetics failure, as a consequence of diminished OXPHOS functioning, specifically by decreased activity of complexes I and IV of the ETC, which lead to reduced ATP production and, finally, calcium dysregulation, which leads to mitochondrial swelling due to a permanent opening of the mitochondrial permeability transition pore.

## 5. Mitochondrial dysfunction and cognitive impairment

Synaptic plasticity in the adult nervous system is a response to changes in the environment and synaptic activity, involving dendritic spine growth or retraction and synaptogenesis, which are believed to be responsible for learning and memory [94]. In the hippocampus, one form of synapse plasticity is LTP, which produces a stronger transmission for consolidation of long-term memory [95]. For this process, neurons need to synthesize proteins *de novo* at the dendritic spines where different neurotrophic factors play a key role [96]. An impairment in this process leads to neurodegeneration, as a result of the initial loss of synaptic structure and function and finally cell death [96].

The previously described mitochondrial dysfunction could be an important factor in synapse loss associated with cognitive decline observed during aging and in neurodegenerative disease [97]. Since mitochondria are present in axonal terminals and dendrite spines playing a critical role in calcium flux, ROS homeostasis, and ATP production in the synapses, this organelle is a key element for neuronal plasticity [94]. In addition, mitochondrial transport to the synaptic regions is essential for the correct function of this neuronal network [98].

Multiple pathological conditions present cognitive impairment related with a mitochondrial dysfunction. For example, chronic kidney disease (CKD) patients with cognitive damage have increased oxidative stress and decreased antioxidant enzymes (SOD, CAT, GPx, and GSH levels in plasma) compared to CKD patients without cognitive impairment [99]. Also, patients with hypoxia, ischemia induced by a traumatic brain injury (TBI), and diabetes showed cognitive decline and different signs of mitochondrial impairment such as glutamate excitotoxicity, calcium overload, opening of mPTP (which dissipates the mitochondrial electrochemical gradient leading to cell death), and increased ROS levels [100–102]. Interestingly, pyramidal neurons in the cerebral cortex and hippocampus are more susceptible to this type of injury [103], suggesting that these cellular defects may affect mainly synaptic plasticity, learning, and memory.

In the context of neurodegenerative disease, mitochondrial impairment and oxidative stress are the target of A $\beta$  neurotoxicity, promoting cognitive impairment in AD [104]. The degree of cognitive impairment in AD has been related to the amount of A $\beta$  accumulated in mitochondria [105], resulting in a loss of the  $\Delta\psi_m$  in

synaptic regions and ultimately leading to the characteristic synaptic loss observed in AD [106]. It has been suggested that Cyp-D can interact with A $\beta$  contributing to synaptic perturbations. A Cyp-D deficiency can notably improve synaptic function and therefore improve learning and memory in an AD mouse model [107]. It was recently proposed that tau protein can regulate synaptic activity, affecting mitochondrial function and axonal transport [108], and post-transductionally modified tau can induce mitochondrial damage, leading to synaptic dysfunction [109]. In fact, hyper-phosphorylated tau impairs mitochondrial respiratory chain function, increases ROS levels, decreases the activity of detoxifying enzymes, and produces  $\Delta\psi_m$  dissipation [108]. Thus, the accumulation of tau can lead to synaptic deficits and cognitive impairment [110].

Interestingly, cognitive decline is not only characteristic of disease and injury, since cognitive impairment is also observed during aging. During normal aging, it is well established that there is a reduction in the surface area and cortical thickness, resulting in a volume loss in the whole brain, being the non-cortical regions, such as the hippocampus and striatum, more vulnerable to this age-related atrophy [111]. In this context, a study performed with Sprague-Dawley rats of 14, 18, 23, and 27 months of age showed changes in the volume of different brain parts using magnetic resonance imaging (MRI) [112]. In that study they showed enlargement of lateral ventricles and a decrease in the volume of the medial prefrontal cortex, hippocampus, and striatum in 27-month-old rats, which correlates with cognitive deficiency. Twenty-three- and twenty-seven-month-old rats have decreased recognition memory and decreased spatial learning and memory [112]. Another common symptom of aging is cognitive fatigue (CF) characterized by an increase in the facility of becoming tired, lack of energy, and failure to sustain attention when performing cognitively demanding tasks with a high mental effort [113]. There is evidence of a correlation between the decreased connectivity strength of the neuronal network established between the cortical and the striatum areas and a higher CF at an advanced age, suggesting that the cortical-striatal network plays a crucial role in the CF phenomenon [114].

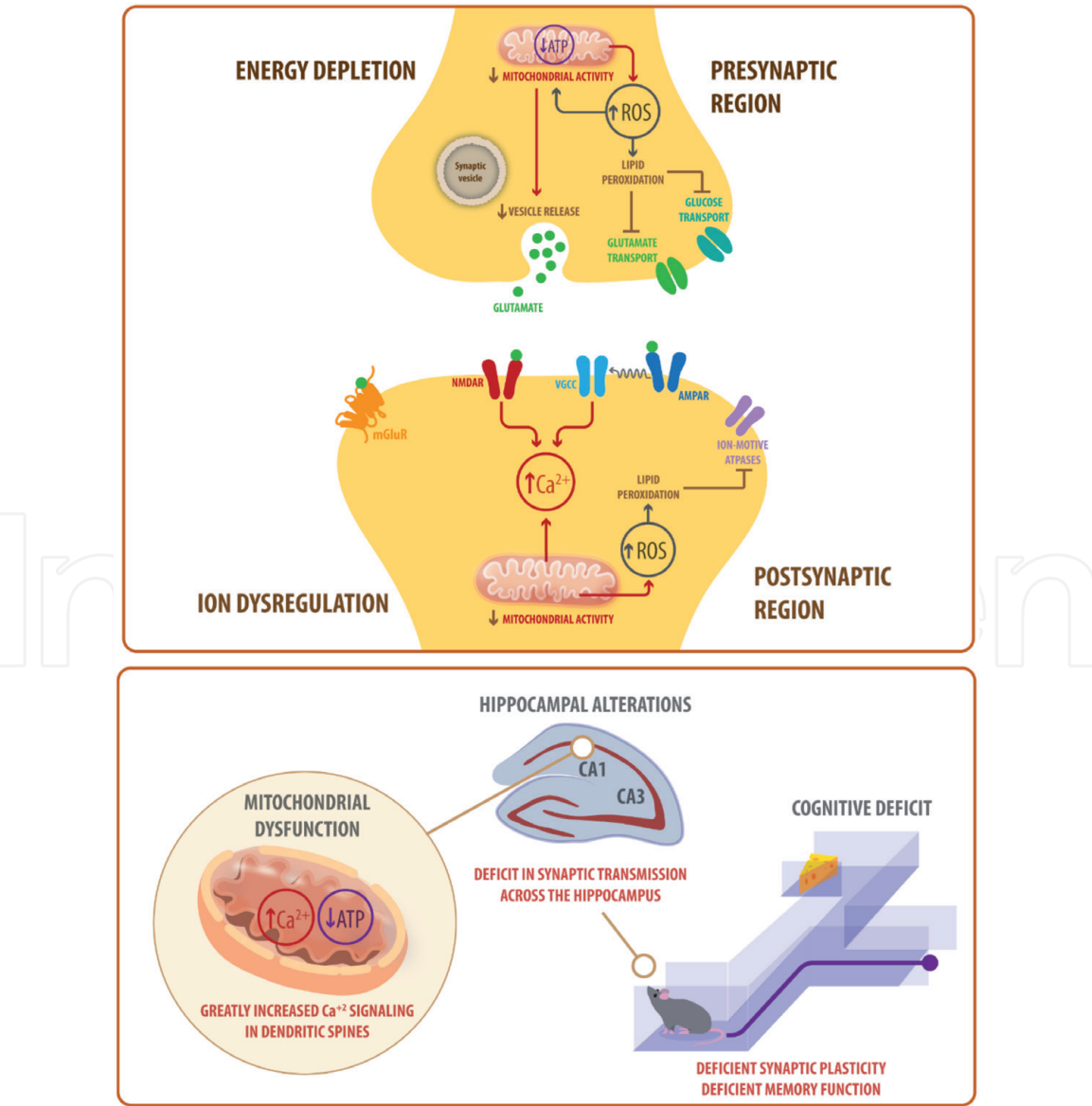
In humans, similar cognitive decline is observed during aging, present as a deficit in episodic or declarative memory, spatial learning, working memory, and attention [115]. These processes are mainly dependent on an adequate function of the hippocampus. Structural and functional changes in the hippocampus are related to the severity and development of neurodegenerative disorders associated with cognitive decline. In fact, many of the cognitive deficits seen with aging can be replicated in animal models with bilateral hippocampal damage [116]. The connection between dentate gyrus (DG) and the CA3 area of the hippocampus is responsible for the formation of new memories, and this is naturally decreased in the aged brain [117], with different biochemical modifications that affect its ability to generate and consolidate LTP [117]. Diverse studies have shown that during aging, the auto-associative network of CA3 is strengthened, and the processing of new information coming in from the entorhinal cortex is weaker [118]. Thus, the stored information becomes dominant in contrast to the ability to encode new information [118]. Also, there is a decrease in gray matter volume, where age-related changes in the temporal lobe involve mainly changes in the hippocampus [4].

Also, different studies show high levels of tau in cerebrospinal fluid (CSF) during aging [119, 120]. For example, the characteristic hearing loss (HL) present in aging influences neurodegeneration by promoting tau pathology in CSF [120], which produces cognitive impairment via synapsis dysfunction and neuronal loss [110]. Other studies evidence the age-related impairment of executive functions, verbal and nonverbal cognitive switching (independent of gender, education, and IQ), and the ability to focus attention and/or multitask [121, 122]. Studies have



shown that during aging, there is a reduction in inhibitory mechanisms in the CA3, where short-term plasticity and LTP are compromised [123]. Interestingly, mitochondria play a central role in LTP, enhancing mitochondrial gene expression [124], satisfying the ATP demand by producing changes in mitochondrial energy production, and regulating calcium homeostasis by increasing calcium pump activity [125]. Also, there is evidence that mitochondrial dysfunction can lead to failure in connectivity of brain cortex producing cognitive impairment [126]. Thus, mitochondrial dysfunction during aging can be related with degeneration of synapses, triggering cell death.

In this mitochondrial context of aging, it is interesting that in brain regions highly associated with cognitive function, such as the hippocampus and cortex, there is a high amount of impaired mitochondria, with dysfunctional respiration, excessive ROS production, loss of  $\Delta\psi_m$ , and decreased cytochrome c oxidase activity. Meanwhile mitochondria are less affected in areas of the brain that are less involved in cognitive abilities [105]. Therefore, mitochondrial function is a key component in cognition. It allows proper information processing through the brain network, being an important player in synaptic transmission. Mitochondrial dysfunction generates deficits in synapsis that trigger cognitive impairment in



**Figure 2.**  
*A synaptic failure leads to cognitive impairment in aging.*



neurodegenerative disease but also in natural aging. Thus, the understanding of these processes may be critical in these times where the aged population is increasing; therefore, improving their quality of life is a priority.

**Figure 2** above shows the synaptic effects of mitochondrial failure. In the presynaptic region, decreased mitochondrial activity diminishes ATP content, altering the exocytosis of synaptic vesicles. Also, increased ROS production induces lipid peroxidation, affecting glutamate and glucose transport. In the postsynaptic region, decreased mitochondrial activity disrupts calcium homeostasis, altering postsynaptic signaling. Besides, the increased ROS production and consequent lipid peroxidation impaired ion-motive ATPases. **Figure 2** below schematizes that mitochondrial dysfunction at the CA1 of the hippocampus impaired synaptic transmission resulting in cognitive impairment.

## 6. Mitochondrial therapies as an antiaging treatment

Since mitochondrial dysfunction is a key event promoting aging, interventions that focus on maintaining or restoring the correct functioning of the mitochondria seem fundamental. For this purpose, two different experimental strategies could be used [127], physiological approaches or pharmacological approximations, which will be briefly summarized in this section.

From the physiological point of view, maintaining a lifestyle that includes recurrent physical exercise preserves mitochondrial function [127]. During aging a loss of age-associated muscle mass is directly related with decreased mitochondria-dependent metabolic capacity, as well as with reduced mitochondrial biogenesis [128]. Biogenesis of new mitochondria is regulated by the transcriptional coactivator peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 $\alpha$ ), which also regulates redox balance and energetic function [129]. Interestingly, PGC-1 $\alpha$  expression is decreased in aging reducing its signaling pathway and gene target [129], an effect that could be counteracted by exercise, demonstrating that exercise also increases mtDNA content in the muscle of aged rats [130]. In addition, exercise increases the expression of the CAT enzyme, reducing ROS levels [131]. Similarly, exercise promotes both fission and fusion events as indicated by upregulated levels of Fis1 and Mfn1 protein in the muscle tissue of old animals and by increased Mfn2 and Drp1 mRNA in the skeletal muscle of older women [132]. Finally, exercise could contribute to restoration of mitochondrial Ca<sup>+2</sup> homeostasis, increasing the protein levels of mitochondrial Ca<sup>+2</sup> uniporter (MCU) [132]. Thus, exercise during aging could promote the genesis of new mitochondria or could attenuate the mitochondrial dysfunction observed at an advanced age.

A second physiological approximation important for simulating mitochondrial function is caloric restriction, which has been demonstrated in different models that are able to reduce the age-related phenotype and to increase lifespan [133]. The beneficial effects of caloric restriction are directly associated with the bioenergetic defects observed in aging, activating ATP production through fatty acid metabolism [134]. Mechanistically, caloric restriction increases the activity of complexes I, III, and IV of the ETC, as well as MnSOD, which results in increased ATP and reduced ROS levels [135]. Likewise, caloric restriction enhances Ca<sup>+2</sup> mitochondrial buffering, decreasing Cyp-D levels [135]. Therefore, regulating caloric ingestion is possible for maintaining mitochondrial activity during aging.

Mitochondrial function can also be regulated pharmacologically, for example, through the administration of polyphenols such as resveratrol, green tea, and red

wine [127, 136]. Specifically, they act by promoting mitochondrial OXPHOS and activating cellular antioxidant mechanisms [137]. Another possibility is the use of antioxidant compounds such as MitoQ, an electron scavenger that prevents the formation of mitochondrial free radicals [138]. Similarly,  $\alpha$ -tocopherol (MitoVitE),  $\alpha$ -phenyl-tert-butyl nitron (MitoPBN), the piperidine nitroxide MitoTEMPOL, the antioxidant SkQ1, and elamipretide (SS-31) enter and accumulate in the mitochondria preventing oxidative stress and preserving mitochondrial function [139, 140]. The numerous studies probing the clinical efficacy of these compounds validate the importance of mitochondria in aging [139]. To promote the natural antioxidant effect in the cell, treatment with N-acetylcysteine, vitamin C and other physiological antioxidant molecules have also been shown to be effective as palliative treatment of senescence [141, 142].

It is also important to highlight the positive effects induced by the direct administration of fatty acids including omega-3 fatty acid  $\alpha$ -linolenic acid, due to studies in vivo that have shown its capacity to extend lifespan [143]. This could be a consequence of increased  $\beta$ -oxidation, which results in higher mitochondrial energy production, by increasing mitochondrial biogenesis or by reducing oxidative stress [144]. Finally, we will mention the effects of Metformin, a drug commonly used for the treatment of type 2 diabetes. Metformin has a hypoglycemic effect in the plasma and promotes increased insulin sensibility by a mechanism that remains unclear [145]. However, favorable effects have been observed, where DNA damage and inflammation are prevented, impeding cellular damage by reducing ROS production [146].

Therefore, these approaches highlight the key role that mitochondrial function play during aging, where correct mitochondrial activity could extend lifespan, whereas metabolic alterations could compromise mitochondrial function, accelerating the aging phenotype.

## **7. Future directions: importance of synaptic mitochondrial dysfunction in aging**

It is now known that the mitochondria have a fundamental role during the aging process. In neurons, the mitochondria are classified into two groups according to their localization, such as synaptic and non-synaptic mitochondria. Non-synaptic mitochondria are distributed throughout the cell body and in the neural prolongations, meanwhile synaptic mitochondria are exclusively found in synapses, both at the pre- and postsynaptic level [147]. Thus, it is not surprising that synaptic mitochondria, which have a higher energy requirement in order to sustain synaptic activity, present functional differences compared to non-synaptic mitochondria. For example, synaptic mitochondria have higher peroxide production than non-synaptic ones [148]. During aging, it seems that these differences are accentuated between these two mitochondrial populations. Aged cortical synaptic mitochondria present decreased oxidative capacity and higher susceptibility to calcium overload, in contrast to non-synaptic mitochondria that preserve their respiratory capacity [16]. Similarly, we observed that hippocampal synaptic mitochondria fail previous to non-synaptic mitochondria during aging and suffer premature mitochondrial swelling with age, contributing hippocampus-dependent memory loss (manuscript in preparation). Thus, maintaining adequate function of synaptic mitochondria seems to be the new challenge in order to attenuate the aging phenotype, reducing the synaptic and cognitive failure characteristics of older individuals.

## 8. Conclusions

Taken together, the evidence presented in this chapter strongly suggests a close relationship between mitochondrial function and a wide range of processes associated with aging. In general, it is possible to propose an age-dependent decline observed in several organs such as the brain correlated with a loss of mitochondrial activity, generating a bioenergetic deficit and redox imbalance that promote oxidative stress. This promotes additional mitochondrial fail, affecting cellular calcium homeostasis, critical for neurons due to its important roles in the synapses. Thus, synaptic defects conduce to cognitive impairment. Finally, we propose that the synaptic mitochondria are a critical mitochondrial pool to preserve synaptic communication despite the passing of the years.

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