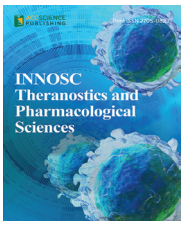
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REVIEW ARTICLE

Modulation of Mitochondrial Function in Elderly Brain: Involvement of Autophagy and Apoptosis

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Abstract:

Mitochondria are crucial cellular organelles that regulate energy production, oxidative balance, and calcium homeostasis, among other things. Aging is a natural, multifactorial, and multi-organic process, in which both pathological and physiological changes occur gradually over time. Autophagy capacity and mitochondrial processes such as mitophagy, biogenesis, and dynamics are associated with aging. These processes are important for maintaining the structural integrity of mitochondria and thus cell life since mitochondrial dysfunction leads to an impairment in energy metabolism and an increased production of reactive oxygen species, both of which may stimulate mechanisms of cellular senescence and apoptotic cell death. Furthermore, in both model organisms and humans, a decline in mitochondrial activity can contribute to age-related disease phenotypes. As people age, mitochondrial damage and malfunction may induce apoptosis, thus explaining the rise in cell death. Many aging processes are believed to be driven by oxidative stress. Taken together, the evidence strongly suggests a relation between mitochondrial function and a wide spectrum of aging processes. Although there is no general consensus among the studies reviewed, it appears that aging reduces mitochondrial biogenesis and dynamics, as well as the mitophagy capacity of the organism involved. This review describes the involvement of autophagy and apoptosis in the modulation of mitochondrial function in the brain.

Keywords: Aging, Apoptosis, Autophagy, Mitochondria, Mitophagy, Oxidative stress

1. Introduction

Aging is a well-studied phenomenon, with an increasing interest in understanding how and why cognitive activities are affected from a neurobiological perspective [1]. Aging is a multidimensional biological process, marked by a decline in physiological and cellular capabilities, including brain function [2]. Age is the main causative factor for the development of pathologies, including cancer, diabetes, cardiovascular disease, and neurodegenerative diseases [3]. Aging causes cognitive degeneration, in which reasoning, attention, and memory, among other processes, deteriorate over time [4]. Cellular senescence and changes in mitochondria and proteolytic systems are regarded as hallmarks of aging [3], with the mitochondria being one of the most studied [5]. In fact, mitochondrial dysfunction has been linked to the aging phenotype and the bulk of disorders that cause cognitive impairment. The structure and function of mitochondria have garnered widespread attention in recent decades due to their link to the aging brain [5].

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Autophagy is a catabolic process that involves the destruction of dysfunctional cellular and molecular elements by forming double-layered membrane structures known as autophagosomes, which fuse with lysosomes to produce autophagolysosomes, and these autophagolysosomes would surround the structures to be degraded [6]. Autophagy is classified based on the organelle it targets. When the target is a mitochondrion, the term used is mitophagy; when the target is a ribosome, the term used is ribophagy; when the target is a peroxisome, the term used is peroxyphagy; and when the target is an endoplasmic reticulum, the term used is reticulophagy [7]. Mitochondrial homeostasis is notably affected by aging [8], and it is recognized that mitochondria may have an important role in aging due to their critical involvement in the intricate balance of cellular functions [9]. Age-related alterations influence mitochondrial membrane potential ($\Delta\Psi m$) [10] by causing the opening of mitochondrial permeability transition pores in the membrane and thus resulting in mitochondrial depolarization or a drop in $\Delta\Psi m$ to -100 mV [11]. Furthermore, the age-related reduction in mitophagy hinders the elimination of malfunctioning or dysfunctional mitochondria and alters mitochondrial synthesis, resulting in a gradual accumulation of mitochondria. As a result of these effects, cellular function is damaged [12]. Hence, physiological aging could be associated with a decline in mitophagy activity and a reduction in mitochondrial activity.

Apoptosis is a form of programmed cell death and apoptotic cells are known to die by intent, while necrotic cells die as a result of lethal damage [13]. Aging is genetically controlled and so is programmed cell death. Senescent aging, on the other hand, could be attributed to "wear and tear" mechanisms that lead to apoptosis. Oxygen radicals, mitochondrial DNA damage, and the formation of glycoxidation products are all examples of these "wear and tear" mechanisms. Furthermore, in post-mitotic tissues, a programmed mechanism that initiates apoptosis may activate with aging [14]. There is evidence that apoptosis occurs in post-mitotic tissues as a result of normal aging, although the mechanisms are unknown.

According to the free radical hypothesis of aging, reactive oxygen species (ROS), which are produced as byproducts of biological oxidations of normal metabolism, cause oxidative injury to macromolecules, leading to cellular malfunction and finally cell death as people age [15]. Mitochondria are presumed to play an important role in aging [16]. According to the mitochondrial theory of aging, ROS produced by the mitochondrial respiratory chain damage certain mitochondrial membrane constituents, such as proteins, lipids, and mitochondrial DNA (mtDNA), under normal physiological conditions [17,18]. Progressive oxidative damage to mtDNA with age may lead to mitochondrial DNA mutations, resulting in reduced respiratory chain complex activity, increased mitochondrial ROS generation, and the accumulation of additional mtDNA mutations [19-21]. This vicious cycle has been postulated to explain the rise in oxidative damage that occurs as people age, leading to a steady loss in cellular and tissue functions due to a lack of energy and/or increased vulnerability to apoptosis [22-24].

2. Functions and importance of mitochondria and aging

Mitochondria are the cell's powerhouses, producing a major portion of cellular adenosine triphosphate (ATP). Furthermore, mitochondria are associated with calcium metabolism, which leads to the induction of intracellular ROS, and they play an important role in the initiation of apoptosis. These functions render them complex for cellular homeostasis and as important signaling organelles in various tissues [25]. The size and quantity of mitochondria in a cell are determined by the cell's metabolic needs, differentiation stage, and many physiological factors [26]. Mitochondria maintain a healthy state by controlling their own biogenesis and engaging in certain dynamic behaviors. **Figure 1** illustrates the important elements. Mitochondrial biogenesis is the regulation of protein import, nuclear gene expression, and mtDNA transcription in a coordinated manner [27]. This process is influenced by peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) and mitochondrial transcription factor A (TFAM) [28]. Transport (directed movement within a cell) and decay (targeted destruction via the mitophagy pathway) are two further dynamic properties of the mitochondria. All of these pathways are required for the existence of a healthy mitochondrial cell [29].

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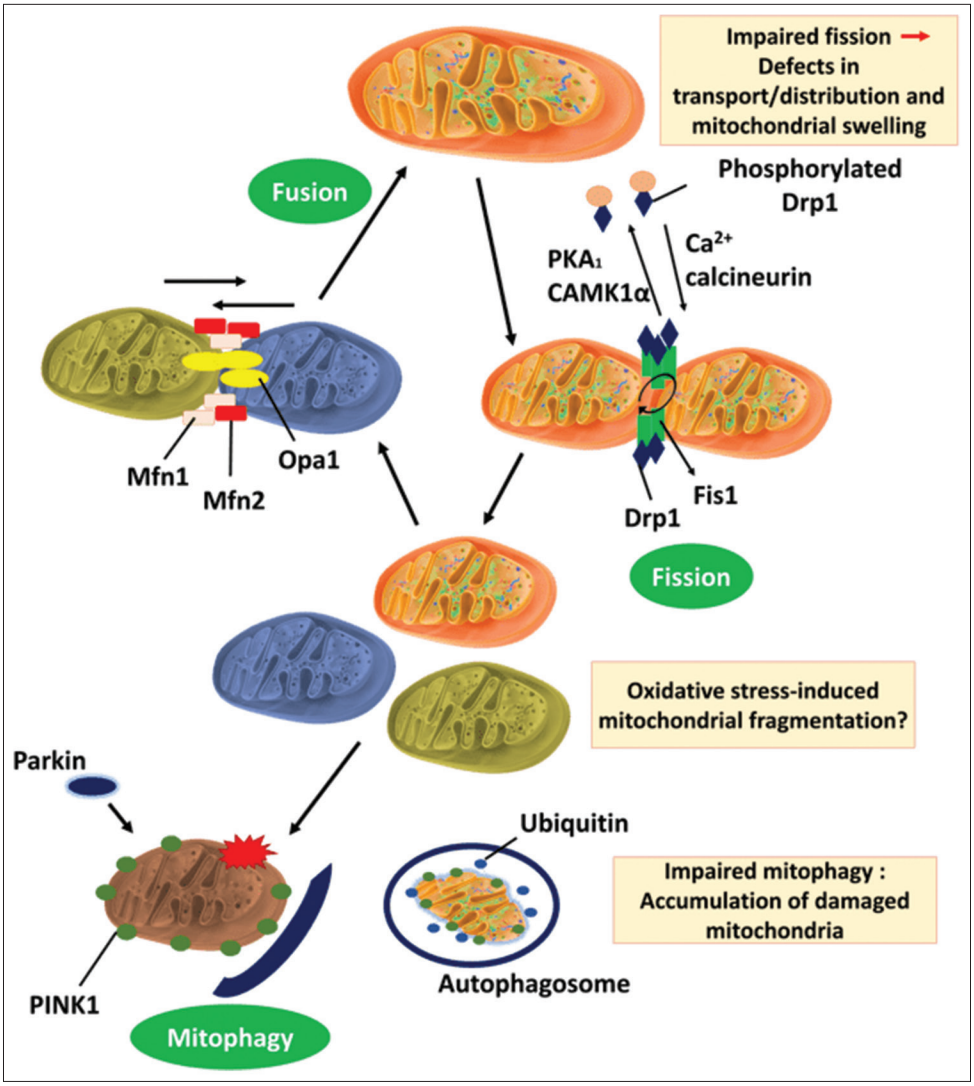


Figure 1. Overview of mitochondrial fusion-fission and mitophagy mechanisms. The major proteins involved in their modification and interaction processes are highlighted. DRP1 is drawn to the outer membrane by FIS1 following dephosphorylation. Following DRP1 oligomerization, mitochondrial fission and membrane constriction occur. After the fission event, the mitochondrion can either re-enter fusion or be transferred. The pro-fusion proteins OPA1 and MFN1/2 on the inner and outer membranes, respectively, oligomerize to fuse the membranes. PINK1 kinase, which ubiquitylates mitochondrial proteins and starts mitophagy, recruits the E3 ubiquitin ligase Parkin through faulty mitochondrial accumulation.
DRP1: Dynamin-related protein 1; FIS1: Fusion protein 1; MFN1/2: Mitofusion 1 and 2; OPA1: Optic atrophy 1; PINK1 kinase: PTEN-induced putative kinase 1; CAMK1α: Ca^{2+}/calmodulin-dependent protein kinase 1α; PKA: Protein kinase A.

Since mitochondrial failure can cause changes in energy metabolism, increase ROS generation, and subsequently trigger pathways of apoptotic cell death, maintaining the structural integrity, biogenesis, and function of the mitochondria is crucial for cells [25].

In recent decades, several lines of evidence from model organisms and humans have revealed that a decline in mitochondrial activity might contribute to aging and age-related illnesses [30-32]. The oxidative stress theory of aging was developed in response to the toxic potential of mitochondrial ROS (mtROS), which is produced by the mitochondrial respiratory chain. The theory proposes that oxidative damage to macromolecules plays an important role in the aging process [33]. Damaged mitochondrial DNA disrupts the respiratory chain, causing an increase in free radical generation and setting off

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a vicious cycle. Organic dysfunction and the aging phenotype result from these alterations [34]. The balance between mitochondrial fusion and fission appears to regulate the development of damaging mtDNA mutations within cells. While fusion may allow a mutant mtDNA species to be "diluted" into a group of wild-type molecules to reduce its functional effects, fission may allow aberrant mitochondria to be eliminated by selective mitophagy [9]. As a result, the fusion process activates the polarized mitochondrion, while mitophagy targets the depolarized mitochondrion [35].

3. Mitophagy

3.1. Mechanism of mitophagy

Mitochondria play a crucial role in adaptive metabolism and cellular stress survival. Hence, strong mitochondrial quality control is required to ensure excellent mitochondrial function [36]. Mitophagy has recently garnered attention as a result of the potential for mitochondrial injury to induce a slew of cell-wide effects. Damage-induced mitophagy and developmental-induced mitophagy are two primary mechanisms for eliminating defective mitochondria [26].

3.1.1. Damage-induced mitophagy

Its purpose is to eliminate mitochondria that are damaged or defective. The major drivers (Parkin) are PTEN-induced putative kinase (PINK), which can sense the mitochondrial polarization state, and E3 ubiquitin ligase. PINK1 is kept at low baseline levels, where mitochondria are polarized (**Figure 1**). PINK1 is transported into the inner mitochondrial membrane (IMM) and processed by mitochondrial peptidases like presenilin-associated rhomboid-like protein (PARL) protease [37]. However, this mechanism is blocked in damaged or defective mitochondria that are depolarized because of the inadequate $\Delta\Psi m$ to transport PINK1 into the IMM, resulting in the accumulation of PINK1 at the outer mitochondrial membrane (OMM) [38-40]. PINK1 phosphorylates certain mitochondrial proteins, causing autophagy cargo adaptors to attach to autophagosomes through light chain 3 (LC3) protein and then to lysosomes. Mitochondria can then be destroyed by autophagolysosomes in this manner [36]. PINK1 phosphorylates MFN1 and MFN2 to recruit Parkin from the cytosol, which amplifies the signal. PINK1 also phosphorylates Parkin's ubiquitin and ubiquitin-like (Ubl) domains, resulting in the activation of Parkin's E3 ligase activity and facilitating its attachment to the OMM. Parkin ubiquitinates OMM proteins in addition to ubiquitinating itself [35,41,42].

First, Parkin ubiquitinates both MFN1 and MFN2, limiting mitochondrial fusion and acting as a method of separation when organelles are injured, thus allowing them to be sequestered and destroyed through selective autophagy [43]. Parkin then ubiquitinates OMM proteins, such as voltage-dependent anion channel (VDAC) 1, to produce polyubiquitin chains via Lys27, which selects LC3-interacting region (LIR) containing autophagy receptors, such as sequestosome (p62/SQSTM), which binds to LC3 and simultaneously points to those mitochondria that should be eliminated [26,35].

3.1.2. Developmental-induced mitophagy

Its function is to eliminate an enormous number of mitochondria by a systematic process [26]. B-cell lymphoma 2 (BCL-2)/adenovirus E1B 19 kDa-interacting protein (BNIP) 3 and NIP3-like protein X or BNIP3L (NIX) are two essential pro-apoptotic proteins responsible for this type of mitophagy [44]. BNIP3/NIX-mediated mitophagy differs from PINK1/Parkin-mediated mitophagy in that Parkin and PINK1 proteins are unable to attach to autophagosome receptors directly, whereas NIX and BNIP3 can attach to the autophagy machinery components directly [45].

BNIP3 can trigger autophagy by depolarizing mitochondria, opening the mitochondrial permeability transition pore (MPTP), or interfering with the fission-fusion process [46]. The mitophagy activity of BNIP3 is regulated by phosphorylation. The phosphorylation of serine residue 24 promotes binding to LC3II and Golgi-associated ATPase enhancer of 16 kDa (GATE-16) as well as increases the affinity for these proteins. Although the phosphorylation of residues at BNIP3's C-terminus, which is close to the transmembrane domain, reduces mitochondrial damage and suppresses cell death, it does not limit autophagy or mitophagy [47]. NIX is essential for targeted mitophagy during reticulocyte maturation, which

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involves the elimination of membrane organelles, such as mitochondria, by a process that is identical to autophagy; however, the contents of the autophagy vacuole are not recycled but exocytosed instead [46]. It is possible that NIX's interaction with LC3 triggers mitophagy. Furthermore, NIX can interact with the *BECN1* gene-encoded protein BCL-2/Beclin-1 complex to release Beclin-1, thus allowing it to activate autophagy [26,44,48].

3.2. Mitochondrial function and mitophagy: As they change with age

PGC-1, DRP1, OPA1, TFAM, MFN1, MFN2, FIS1, BNIP3, VDAC1, PINK1, Parkin, and NIX are all proteins included in mitochondrial biogenesis, dynamics, and mitophagy. Most studies have reported a decrease in the expression of *PGC-1* mRNA and its protein when it comes to proteins included in biogenesis [49-52]. These data show that the deficiency of response of PGC-1 to various stimuli may play a role in decreasing mitochondrial biogenesis during aging [53]. OPA1, which is found on the IMM, affects mitochondrial fusion and ridge structure. OPA1 also regulates mitophagy by promoting the stabilization of mitochondrial ridges, which protects against mitochondrial malfunction and ROS overproduction. As a result, the increased expression of this protein indicates that mitophagy is decreasing, while mitochondrial fusion is increasing [38]. Most findings have suggested an increased expression of this protein in the muscles and brains of elderly rodents [54-58]. OPA1 functions as a fusion factor of mitochondria, possibly through interactions with mitofusin and other fusion factors of the outer membrane [59-61].

Furthermore, when mitochondrial dynamics become dysregulated with age, unhealthy mitochondria accumulate, potentially necessitating the activation of Parkin to regulate the number and quality of mitochondria [62]. VDAC1 not only controls the conductance and permeability of the outer membrane, but also functions as a regulator of membrane pore permeability [38]. In a study, the levels of VDAC1 in mitochondria that were isolated from the brains of aged rats were found to be significantly lower [63]. Based on these findings, it can be concluded that a rise in BNIP3 and NIX levels along with age may indicate a failure in the mitophagy system. Overall, aging is associated with a decrease in mitochondrial function, an increase in aberrant mitochondria, and a decline in the mitophagy ability of the organism involved.

4. Autophagy

4.1. Mitochondria's role in autophagy

Mitochondria and its structural properties are important at various stages of autophagy, from autophagosome formation to Beclin-1-mediated autophagy control and autophagy-mediated cell death [64]. ATG5 and LC3 are autophagy proteins transported to the mitochondrial outer membrane and share the lipid moieties required for the elongation of the first phagophore, rather than for mitophagy, which is the autophagic elimination of mitochondria. It has been further revealed that cells lacking mitochondrial protein MFN2, which mediates mitochondrial anchoring to the endoplasmic reticulum, do not exhibit ATG5 or LC3 recruitment in the area. The relevance of mitochondria and the endoplasmic reticulum in autophagy initiation is demonstrated by this finding [65]. Moreover, during serum deprivation, mitochondria form tubular structures by fusing with one another (mitochondrial fusion), thus prompting autophagy [66]. However, defective and larger senescent mitochondria that accumulate as a result of aging cannot fuse, thus preventing autophagy [67]. Mitochondria also regulate autophagy by interacting with autophagy start complexes through the proteins BAX-interacting factor 1 (BIF1) and sirtuin 1 (SIRT1) [68-71]. BIF1 (also found in the Golgi complex) is involved in endosome formation and promotes autophagy by binding to the positive regulator complex of autophagy, UV radiation resistance-associated gene protein (UVRAG), and Beclin-1 [69,72,73]. SIRT1 stimulates autophagy by interacting with ATG5, ATG7, and LC3/ATG8 directly [74]. Another mitochondrial protein involved in autophagy induction is smARF, a short mitochondrial form of the ARF tumor suppressor protein that induces cell cycle arrest and Type I programmed cell death (apoptosis) through a p53-dependent pathway. In its longer version, smARF induces excessive autophagy-mediated non-apoptotic cell death that can be prevented by knocking down ATG5 or Beclin-1 [75]. Mitochondria play an important role

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in autophagy-associated cell death by releasing cytochrome c, which is triggered by phospholipases and BAX/BAK, either by cleaved products of ATG4 and ATG5 or through leaky lysosomal protease [76-78]. With regard to mitochondrial aging, **Figure 2** depicts the interaction between mitochondria and lysosomes during autophagy.

5. Apoptosis

5.1. Regulation of apoptosis

The Nomenclature Committee on Cell Death (NCCD) describes apoptosis as the rounding up of a cell, chromatin condensation (pyknosis), decreased cellular volume, nuclear fragmentation (karyorrhexis), shrinkage of pseudopods, plasma membrane blebbing, and phagocyte ingestion [79,80]. Caspases are proteolytic enzymes that are selective for aspartate and cysteine in their active core and the principal propagators of the apoptotic program at the cellular level. They are detected in everything, from early nematodes to modern vertebrates [81-83]. Caspases are involved in mammalian cell apoptosis [84]. They can be divided into two classes depending on their hierarchical function in action: Initiator and effector caspases. Upstream signals activate the initiator caspases (caspases 8 and 9) [85] before the effector caspases (caspases 3 and 7) are activated [81,86]. The initiator caspases are activated by external cell death-triggering chemicals; for caspase-8, these chemicals include tumor necrosis factor-related apoptosis-inducing ligand [TRAIL], TNF-α, Fas, *etc*. [85,87], while internal stress, such as cellular malfunction and starvation, activates caspase-9, causing the mitochondrial release of cytochrome c, and thus resulting in the formation of the apoptosome complex (caspase-9 activating complex) [86]. In the intrinsic/mitochondrial apoptotic pathway, a shift in the proportion of proapoptotic BCL-2 family members (BAX, BAK, *etc*.) and anti-apoptotic members toward pro-apoptotic members causes their accumulation in the OMM, resulting in the formation of MPTP and subsequent cytochrome c release [86,88].

When there is ATP, cytochrome c and APAF1 (apoptotic protease activating factor 1) form an apoptosome with procaspase-9. The apoptosome

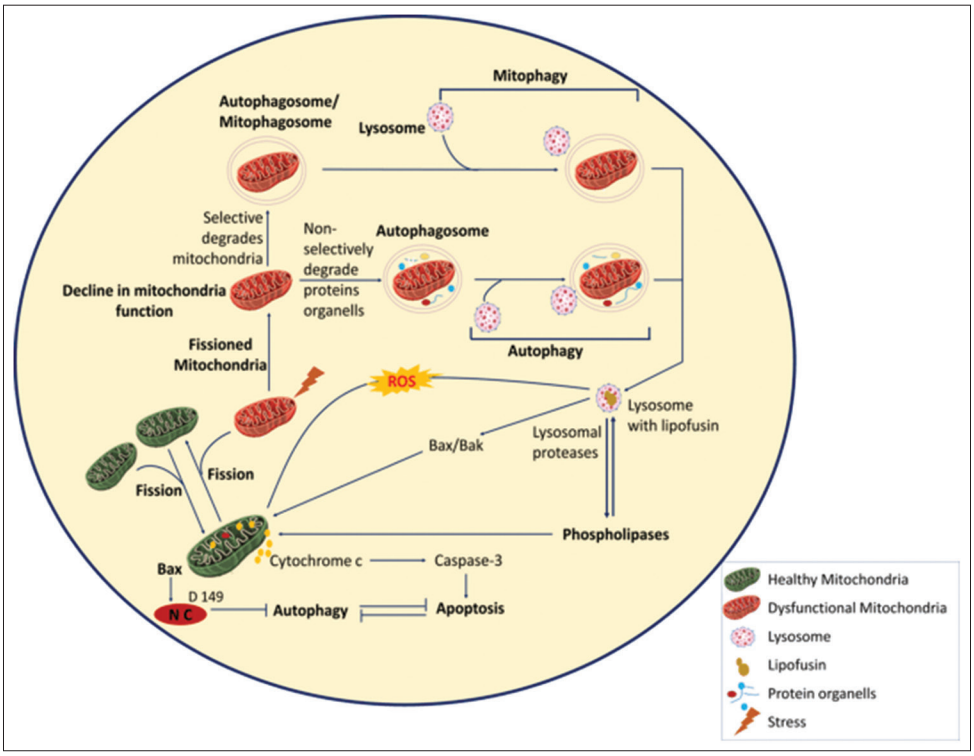


Figure 2. Involvement of mitochondria and lysosomes during autophagy. Reactive oxygen species are mediators of the severe cyclic damage caused by non-degradable lipofuscin accumulation in mitochondria and lysosomes. BAX, an apoptosis-promoting protein, increases the D149 caspase-mediated cleavage of Beclin-1, which reduces autophagy.

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acts as a caspase-9 activating complex [89]. Since proteolysis is an irreversible process, caspase activation is closely regulated by inhibitor of apoptosis proteins (IAPs) to prevent unintentional cell death [90-92]. IAPs are inhibited by second mitochondria-derived activator of caspase (SMAC)/ direct inhibitor of apoptosis-binding protein with low pI (DIABLO), which is released from the mitochondria [86]. Apoptosis-inducing factor (AIF) is a mitochondrial flavoprotein oxidoreductase that can trigger caspase-independent apoptosis. This protein is discharged from the mitochondria and translocated to the nucleus following apoptotic signals, where it causes chromatin condensation [93].

5.2. Mitochondrial control and apoptosis

Recent cell culture research has suggested that mitochondria undergo significant functional and structural changes that govern apoptosis.

i. The mitochondrial inner transmembrane potential ($\Delta\Psi m$) falls before the traditional morphological hallmarks of apoptosis.
ii. Research employing isolated mitochondria and cell-free systems has suggested that certain mitochondrial proteins (cytochrome c and AIF) are released to activate caspases and endonucleases that cleave substrates at Asp-Xxx bonds (*i.e.*, after aspartic acid residues) [94].
iii. Certain drugs that maintain mitochondrial membranes, such as cyclosporin, have been demonstrated to decrease apoptosis.
iv. Anti-apoptotic proteins, such as BCL-2, prevent the release of mitochondrial intermembrane protein cytochrome c, and thus prevent apoptosis [95-97].

These findings imply that mitochondria act as important regulators of apoptosis through the cytochrome c pathway (**Figure 3**). Although many cells employ this pathway to initiate apoptosis, they could potentially use mitochondrial pathways as well, including unknown chemicals found in the intermembrane area of mitochondria [98]. The holo form of cytochrome c (that is, without the heme group attached) forms an apoptosome with apoptotic protease activating factor 1 (APAF-1), caspase-9, and ATP. When an apoptosome is formed, caspase-9 is proteolytically activated, causing the caspase cascade (caspase-3 and caspase-6) to be activated and apoptosis to enter the breakdown phase [95,99]. These caspase inhibitors (IAPs) may play a significant role in post-mitotic tissue aging by limiting the death of irreplaceable cells in muscle and brain tissues. The BCL-2 family of proteins can regulate apoptosis by controlling the release of cytochrome c. BCL-2, BCL-XL, myeloid cell leukemia-1 (MCL-1), A1/Bfl-1, and BCL-W are all anti-apoptotic members of this family in mammals. Members of the BCL-2 family can undergo conformational changes, allowing them to embed themselves into the OMM and form channels. Members of the BCL-2 family may also generate channels by interacting with other proteins. In this circumstance, BCL-2 family proteins interact with mitochondrial membrane proteins to produce a channel that is large enough for intermembrane proteins to pass through. The voltage-dependent anion channel (VDAC) and the adenine nucleotide transporter are both channel proteins. VDAC is a potential candidate for such a role because it is known to bind to and be controlled by BCL-2 type proteins [100]. Since it is known to be a subunit of the MPTP, VDAC is a promising candidate. The loss of membrane potential, organelle swelling, and cytochrome c release all occur when MPTP opens [101]. In conclusion, changes in BCL-2 family proteins may be important for predicting when a cell will undergo apoptosis during aging.

5.3. Role of reactive oxygen and nitrogen intermediates in aging and apoptosis

The free radical theory of aging relates senescence to damage inflicted by superoxide-derived radicals as well as some other reactive intermediates produced primarily during mitochondrial respiration [102-104]. Similarly, mitochondria have been discovered to be a significant source of reactive nitrogen and oxygen intermediates [105-109]. According to the mitochondrial theory of aging, aging is caused by free radical damage to mtDNA. Defects in mtDNA lead to errors in the polypeptides encoded by mtDNA, resulting in mitochondrial respiratory channel complexes with defective proteins. More radicals are formed when the complex is faulty, leading to a cycle of increased mtDNA damage, radical generation, and possibly apoptosis [110-114]. Although aging is linked with the formation of radical intermediates in all tissues [110,115,116], the repercussions, such as increased mtDNA damage [113,117], may

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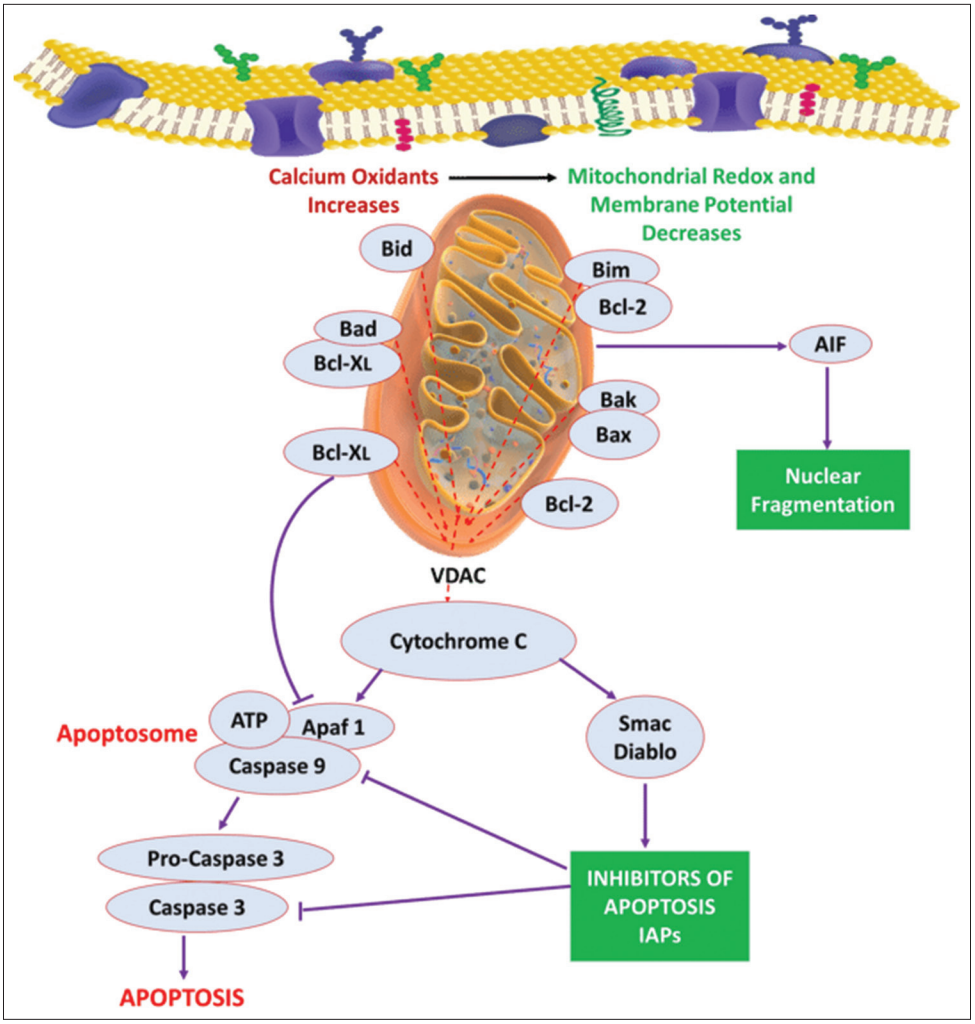


Figure 3. Mitochondrial mediated pathway. Oxidants, increased Ca^{2+} concentrations, a decline in redox status, and a collapse in mitochondrial membrane potential (m) are several factors that can cause mitochondrial dysfunction. VDAC, the mitochondrial outer membrane channel, which is involved in the release of cytochrome c from mitochondria, may be impacted by certain ratios of mitochondrial proteins, such as BCL-2, BCL-XL, BID, and BAX. Apoptosis might be triggered by the release of cytochrome c, which causes apoptosome formation. When given along with cytochrome c, SMAC/DIABLO suppresses the proteins that inhibit apoptosis (IAPs).
AIF: Apoptosis-inducing factor; APAF1: Apoptotic protease activating factor 1; ATP: Adenosine triphosphate; Ca^{2+}: Calcium ion; DIABLO: Direct inhibitor of apoptosis-binding protein with low pI; IAPs: Inhibitor of apoptosis proteins; SMAC: Second mitochondria-derived activator of caspase; VDAC: Voltage-dependent anion channel.

facilitate apoptotic induction over time (**Figure 4**). Apoptosis may thus be important in aging, since it may aid in destroying non-functional, toxic, aberrant, or misdirected cells, particularly in older people [118-120]. By altering cellular redox potentials, depleting reduced glutathione, lowering ATP levels, and decreasing reduced equivalents like reduced nicotinamide adenine dinucleotide (NADH) and reduced nicotinamide adenine dinucleotide phosphate (NADPH), oxidants may trigger apoptosis indirectly [121-123]. These modifications may make it easier for permeability transition holes to develop, thus allowing cytochrome c to be released. Several cell lines have been demonstrated to be induced by reactive nitrogen and oxygen species, such as hydrogen peroxide, peroxynitrite, and nitric oxide (NO), a free radical gas. Calcium ion (Ca^{2+}) and oxidants, such as hydrogen peroxide, for example, exert further effects on mega channel permeability

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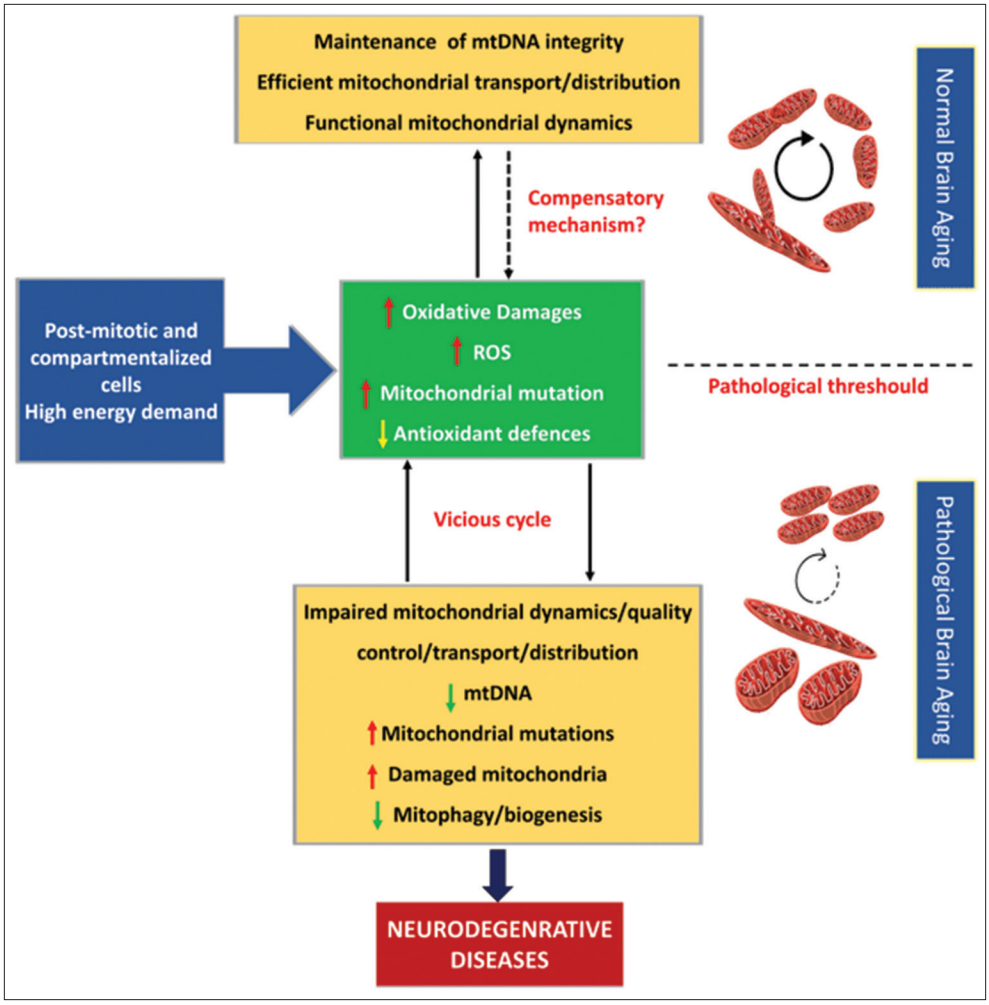


Figure 4. Mitochondrial function on brain aging. An aspect of brain aging accompanied by an increase in reactive oxygen species generation and/or deficiencies in the antioxidant system is increased oxidative stress. Cells are guarded by mitochondrial dynamics against the buildup of mitochondrial mutations. Normal aging results from the system being out of equilibrium. However, when a pathogenic threshold is crossed, altered mitochondrial dynamics may result in the accumulation of faulty organelles, setting off a series of events that can cause neurodegeneration.

transition (MPT) *in vitro* [124], which may play a key role in MPT susceptibility increasing with age.

Mitochondria from older cells (lymphocytes, brain, and liver) are more susceptible to MPT [124], an apoptotic event that causes apoptogenic proteins to be released into the cytosol. Increased mitochondrial oxidant production and raised intracellular Ca^{2+} levels have been associated not only with aging cells, but also with a favorable intracellular environment for MPT and the release of apoptogenic mediators [124,125]. NO is a key regulator of mitochondrial activity, cell communication, and gene expression; it is also a relaxing agent produced by endothelial cells [126]. NO may affect oxidant generation by regulating the activity of cytochrome c oxidase directly [127].

6. Conclusion

The evidence provided in this review clearly shows a link between the function of mitochondria and various aging processes. In general, age-related deterioration in numerous organs, such as the brain, might be linked to a decline in mitochondrial activity, resulting in a bioenergetic deficit and a redox imbalance that promotes oxidative stress. Mitophagy and the function of mitochondria must be maintained because mitochondria are involved in both adaptive metabolism and survival in response

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to cellular stress. Although there is no general agreement among the studies reviewed, it appears that aging reduces mitochondrial biogenesis, dynamics, and the mitophagy capacity of the organism involved. In addition, mitochondria are important mediators of apoptosis since MPT is a fundamental step in apoptosis. Indeed, apoptogenic substances are released from the intermembrane space when the MPTP opens. Mitochondria are both the target and the generator of ROS, which causes apoptosis. Increased mitochondrial peroxide generation, glutathione oxidation, and mtDNA oxidation are all hallmarks of apoptotic cells and cells from elderly animals.

7. Future directions

As people age, mitochondrial damage and malfunction may promote apoptosis, thus explaining the rise in cell death. Many aging processes are thought to be fueled by oxidative stress. Taken together, the evidence strongly implies a link between the function of mitochondria and a wide spectrum of aging processes. Ever since DNA damage signaling pathways have been discovered to regulate mitophagy and apoptosis, there has been a surge of interest in researching mitochondrial signaling mechanisms. Undeniably, further research is needed to understand the underlying mechanisms that lead to normal aging or neurodegenerative diseases. Understanding mitochondrial pathways in the context of brain aging could aid in the identification of therapeutic targets for various neurological disorders.

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Conflict of interest

The authors declare no conflict of interest.

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