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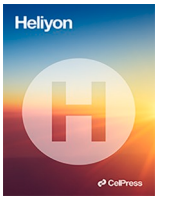

Review article

Molecular mechanisms of mitochondrial homeostasis regulation in neurons and possible therapeutic approaches for Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) is a neurological disease with memory loss and cognitive decline, which affects a large proportion of the aging population. Regrettably, there are no drug to reverse or cure AD and drug development for the primary theory of amyloid beta deposition has mostly failed. Therefore, there is an urgent need to investigate novel strategies for preventing AD. Recent studies demonstrate that imbalance of mitochondrial homeostasis is a driver in Aβ accumulation, which can lead to the occurrence and deterioration of cognitive impairment in AD patients. This suggests that regulating neuronal mitochondrial homeostasis may be a new strategy for AD. We summarize the importance of mitochondrial homeostasis in AD neuron and its regulatory mechanisms in this review. In addition, we summarize the results of studies indicating mitochondrial dysfunction in AD subjects, including impaired mitochondrial energy production, oxidative stress, imbalance of mitochondrial protein homeostasis, imbalance of fusion and fission, imbalance of neuronal mitochondrial biogenesis and autophagy, and altered mitochondrial motility, in hope of providing possible therapeutic approaches for AD.

1. Introduction

As the most common form of dementia, Alzheimer's disease (AD) is linked to a progressive neurodegenerative condition and has grown to be a significant health issue for the elderly. It is an irreversible neurological disorder that impacts approximately 50 million individuals worldwide [1]. However, due to its complex etiology, there is currently no drug to reverse AD, and over the past decades, drug development against the mainstream theory of Aβ has largely failed [2]. Although several monoclonal antibodies targeting Aβ have recently been approved to treat AD, such as Aducanumab, Lecanemab and Gantenerumab [3], they have been controversial due to safety concerns and reported adverse events [3–5]. Therefore, a novel approach for AD is urgently needed.

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Neuronal apoptosis is a central event in the occurrence and development of AD, and the main cause is an imbalance of mitochondrial homeostasis. In the early stages of AD, mitochondrial dysfunction can be detected, which is prior to the discovery of Aβ plaques and severe neuronal death [6–9] (Fig. 1). Cholinergic system dysfunction, oxidative stress, and neuroinflammation are all connected to mitochondrial dysfunction [10]. Mitochondria, as they are the most active cells in the body, are crucial for neuronal survival, differentiation and function. Mitochondria can provide ATP for neuron, which is essential for neuronal growth, function and regeneration. Neurons are especially sensitive to mitochondrial homeostasis imbalances [11,12]. An imbalance in mitochondrial homeostasis may cause oxidative stress, excessive production of reactive oxygen species (ROS), mitochondrial dysfunction and changes in calcium homeostasis in neurons, all of which may eventually cause neuronal apoptosis and contribute to the pathogenesis of nervous diseases, including AD. Accumulated evidence suggests that mitochondrial dysfunction caused by a mitochondrial homeostasis imbalance is one of the earliest and most striking characteristics of the brains of AD patients and model mouse [13]. Regulation of imbalanced mitochondrial homeostasis can reduce the accumulation of Aβ in the brain of AD model mice. More importantly, it can also improve the cognitive function of AD model mice [14,15]. Therefore, maintaining mitochondrial homeostasis and avoiding mitochondrial dysfunction to inhibit neuronal apoptosis may be a new approach to prevent AD [10].

At present, great progress has been made in the investigation of mitochondrial homeostasis in neurons of AD patients and model animals, as well as the mechanism of regulating mitochondrial homeostasis. This review emphasizes the importance of mitochondrial homeostasis in maintaining cerebral function and its imbalance in causing AD. In addition, the molecular mechanisms regulating mitochondrial homeostasis are outlined, with the aim of providing potential therapeutic approaches for AD.

2. Role of mitochondrial homeostasis in neurons

There are about 1500 proteins in mitochondria and most of them are encoded by nuclear genome. Proteins encoded by nDNA need to import the mitochondria in order to fold properly to perform their function. Above 90 % proteins encoded by nDNA import into the mitochondria via TOM complex, which is the translocator on the outer mitochondrial membrane. Tom 40 is the main component of the TOM complex, the other subunits including Tom 20, Tom 22, Tom 23, Tom 5, Tom 6, Tom 7, and Tom 70/Tom 71 perform supportive or regulatory roles [16], in addition, there are TIM complexes on the inner mitochondrial membrane such as TIM 23 [17]. Organelle homeostasis is maintained by a number of processes that mitochondria have developed. Mitochondria maintain mitochondrial protein homeostasis against mitochondrial protein damage through specific proteases and chaperones [18]. Chaperones, such as members of the HSP70 family proteins, can help mitochondrial protein folding, assembling and membrane transferring, and their categorical degradation of their clients via the proteasomal or autophagic pathways [19].

Neurons, as the most active cells in energy metabolism, are particularly dependent on mitochondria to produce energy. The normal function of neurons, including nerve impulse conduction, transmitter release, etc., needs mitochondria to provide energy. So it's important to maintain mitochondrial homeostasis in neurons to meet their energy and specific functional needs. In addition, mitochondria in neurons also have other special functions, such as regulating neuronal regeneration, regulating neuronal excitability, buffing Ca^{2+} homeostasis, regulating synaptic structural and functional plasticity, etc. Thus, it is critical to maintain mitochondrial homeostasis in neurons (Fig. 2).

2.1. *Mitochondria provide neurons with energy*

Mitochondrial homeostasis is crucial to maintain the normal activity and function of neurons. First, as the most active cells in energy metabolism, neurons particularly depend on the energy produced by mitochondria. Mitochondria maintain neuronal activity by providing ATP energy to neurons through the electron transport chain and adenosine triphosphate [20,21]. The specific process is as follows [22]: Pyruvate (Pyr), produced by glucose decomposition, is decarboxylated in the mitochondrial matrix to produce acetyl coenzyme A (AcCOA), which enters the tricarboxylic acid cycle (TCA) to produce NADH and $FADH_2$. The hydrogen or electrons produced during this process are transferred to the electron transport chain in the mitochondrial inner membrane through complex I (reduced coenzyme I - ubiquinone oxidoreductase) and complex II (succinate - ubiquinone oxidoreductase). Complex III (ubiquinol -

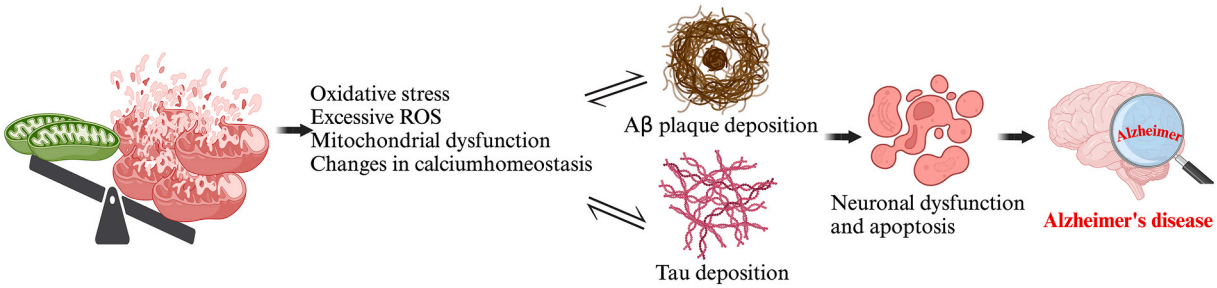

Fig. 1. The interaction of mitochondrial dysfunction with the pathology of Alzheimer's disease (AD), including amyloid beta plaque and tau deposition, contributes to neuronal dysfunction and apoptosis. While various factors have been identified as contributors to mitochondrial dysfunction, the correlation between AD pathology and neuronal apoptosis and dysfunction remains unclear.

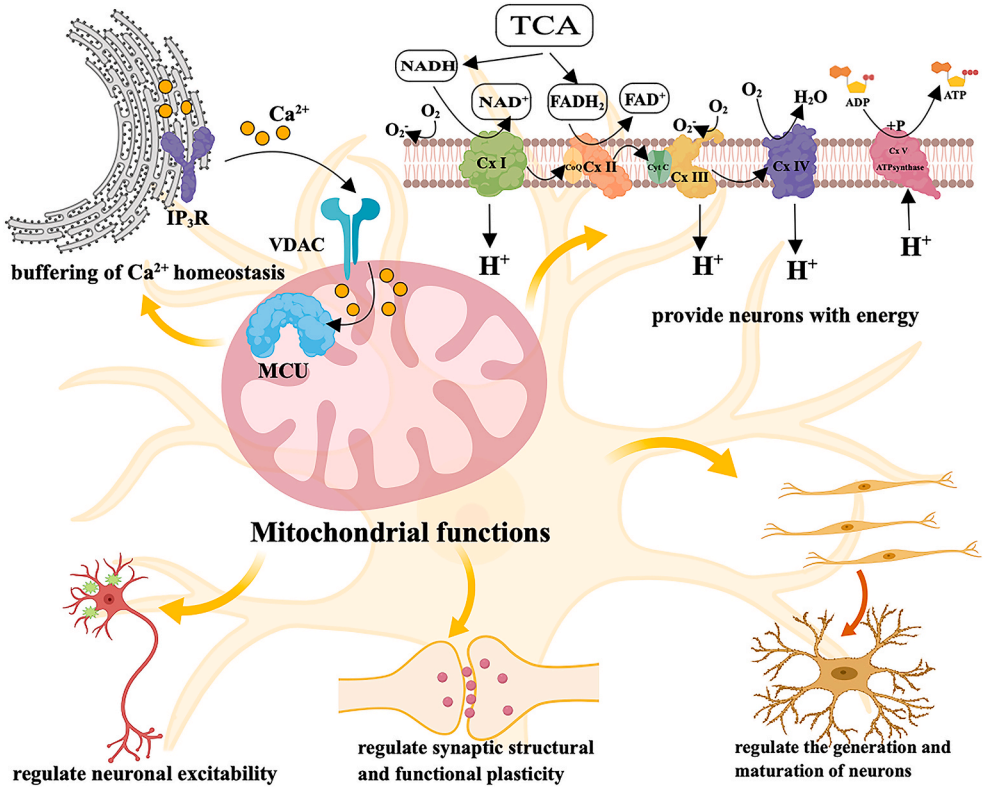

Fig. 2. Role of mitochondria in neurons, including buffering of Ca^{2+} homeostasis, providing neurons with energy, regulating neuronal excitability, synaptic plasticity and the generation and maturation of neurons. Mitochondria play a variety of key roles in neurons and are essential for maintaining normal function and homeostasis of neurons. IP3R: inositol 1,4,5-trisphosphate receptor. VDAC: voltage–dependent anion–selective channel. MCU: mitochondria calcium uniporter. TCA: Tricarboxylic acid cycle. NADH:Nicotinamide adenine dinucleotide. $FADH_2$:Flavine adenine dinucleotide. ATP:Adenosine triphosphate. ADP:Adenosine diphosphate. CxI: reduced coenzyme I - ubiquinone oxidoreductase. CxII: succinate - ubiquinone oxidoreductase. Cx III: ubiquinol - cytochrome *c* oxidoreductase. Cx IV: cytochrome C oxidase.

cytochrome *c* oxidoreductase) transfers electrons from reduced CoQ to Cytc, while complex IV (cytochrome C oxidase) transfers electrons from Cytc to O_2 to produce H_2O. Complex I, III and IV together form an electrochemical proton gradient across the inner mitochondria, and the subsequent proton power is utilized by complex V (ATP synthase) to produce ATP. Because neurons are not static, ATP production needs to be finely regulated according to cellular dynamics. For example, mitochondrial respiration is closely related to mitochondrial fission, and studies have shown that inhibition or depletion of dynamin - related protein 1 (DRP1, a mitochondrial fission dependent protein) is associated with reduced mitochondrial respiration in cultured cardiomyocytes [23].

2.2. *Mitochondria maintain neuronal calcium homeostasis*

As the second intracellular messenger, Ca^{2+} participates in a number of neuronal physiological functions, including neuronal excitation, neuronal proliferation and differentiation. Mitochondrial matrix calcium can activate ATP synthesis [24]. In addition to producing cellular ATP, mitochondria are also the main reservoirs of intracellular Ca^{2+} [25]. Mitochondrial Ca^{2+} homeostasis is regulated by cross-regulation between proteins located in the inner and outer mitochondrial membranes and Ca^{2+} signaling in the endoplasmic reticulum (ER) [26], mitochondria associated membrane (MAM) is a key microdomain in calcium homeostasis [27]. In addition, mitochondria maintain calcium homeostasis through mitochondrial calcium buffering capacity and functional interactions between mitochondria and other channels or organelles [28]. The disturbance of intracellular calcium homeostasis may lead to neurological loss and dysfunction. Thus, the concentration of free Ca^{2+} in neurons is precisely regulated by mitochondria to maintain a relatively stable homeostasis.

2.3. *Mitochondrial homeostasis is required for maintaining specific neuronal functions*

Mitochondria are critical in maintaining specific neuronal functions. For example, it can regulate neuronal proliferation and differentiation, regeneration, synaptic transmission, neuronal excitability and stress adaptation [29].

Appropriate distribution of mitochondria is important for normal neuronal cell physiology. Mitochondria are thought to be concentrated in sub-cellular regions of high metabolic demand to regulate neuronal proliferation and differentiation. Neurons consist

of cellular bodies, dendrites, axons and synapses in morphology. Due to their faster and longer growth than dendrites, axons require more energy to maintain their rapid growth. Thus, it is important to control mitochondrial biogenesis and mitochondrial transport in the direction of axons in order to maintain the number of mitochondria required by axons. With increasing numbers, mitochondria are distributed along dendrites and axons, distributed at the presynaptic terminals or at the base of dendritic spines [30]. Mitochondria distributed in dendritic are essential for supporting synapses and synaptic activity, which can also affect mitochondrial movement and lead to mitochondrial distribution at the base of dendritic spines and affect the structural plasticity of dendritic spines [31]. Studies of neuronal subcellular location and mitochondrial number changes have also confirmed the significance of mitochondrial biogenesis and motility in the formation of neuronal circuits [32]. Neurons with different states have different energy needs during the process of neuronal differentiation and maturation. Therefore, the number and distribution of mitochondria are different in neurons with different states. For example, during the growth of hippocampal neurons, mitochondria predominately exist in the cell body.

In addition, mitochondrial homeostasis aids in regulating nerve regeneration, which is crucial for the recovery of the injured nerve. Recent studies showed that mitochondrial dynamics in postmitotic cells could regulate neurogenesis [33]. The researchers observed a decrease in the number of newly formed neurons after pharmacologically promoting mitochondrial fusion or inhibiting mitochondrial fission. To confirm that conclusion, researchers used viral strategies to inhibit DRP1 to reduce mitochondrial fission and found that it resulted in a decrease in newborn neurons. Another piece of evidence also supports the effect of mitochondria on neuronal regeneration: When a mature axon is severed in mice, nearby mitochondria are destroyed and are unable to supply enough ATP to support regeneration of the injured nerve. This suggests that a decrease in mitochondrial transport may be the reason why adult neurons do not regenerate after injury [33].

3. Imbalance of mitochondrial homeostasis in neurons are involved in the occurrence and development of AD

Neuronal degeneration and apoptosis are the major pathological features of AD, and the imbalance of mitochondrial homeostasis is the main cause. Recent studies found that the degeneration of neurons in brain regions involved in cognition (hippocampus, entorhinal and frontal cortex) and emotional behavior (amygdala, frontal cortex inferior colliculus) is the major pathological feature [34]. Disrupted mitochondrial homeostasis and mitochondrial dysfunction are mainly manifested in mitochondrial morphology changes, decreased oxidative phosphorylation, decreased ATP synthesis, excessive ROS production, kinetic imbalance and mitochondrial DNA (mtDNA) damage, mitochondrial permeability transition pore (mPTP) opening, etc. Once mitochondrial homeostasis is broken, the function of mitochondria will be disturbed, which can affect the normal activity of neurons and eventually lead to neuronal apoptosis and promote the occurrence of AD.

3.1. Imbalance of mitochondrial homeostasis impaired mitochondrial energy production in neuron

The imbalance of mitochondrial homeostasis affects the oxidative posphorylation function of mitochondria, which cannot meet the energy required for neurons, inducing neuronal apoptosis and dysfunction and eventually leading to dementia [35]. Increasing evidence confirms that synaptic plasticity dysfunction and cognitive impairment in AD patients are related to decreased cellular ATP [36]. In addition, damage to ATP synthase, which is essential for cellular bioenergetics, is widely recognized as a hallmark of AD patients and animal models [37]. ATP synthase is involved in the conversion of ADP into ATP and in the morphological formation of the mitochondrial cristae. The enzyme is consisted with 18 protein subunits, 16 nuclear DNA encoded (nDNA) protein and 2 mtDNA encoded protein, which are arranged in two regions F0 and F1 [38]. Dysregulation of F1F0-ATP syntax has been widely proposed in AD patients. A decrease in ATP synthase activity can result in a decrease in ATP synthesis, which in turn triggers apoptosis. Recent studies found that the activity of ATP synthesis in AD entorhinal cortex samples was decreased by about 30 % [39]. Additionally, ATP synthase dysfunction can also cause an increase of ROS, causing oxidative stress to damage neurons [40]. Studies have shown that the α subunit of ATP synthesis in AD patients is oxidized lipids in the entorhinal cortex due to increased oxidative stress [38]. Age-related accumulation of mtDNA deletions can also cause defects in complex IV (the mitochondrial electron transport chain) and a decrease in the efficiency of mitochondrial energy generation, which in turn triggers neuronal death [10]. It can be seen that bioenergetic dysregulation can significantly affect neuronal populations, which is a major factor in the increased neuronal cell death in AD.

3.2. Imbalance of mitochondrial homeostasis induced oxidative stress

Although the etiology of AD is still unclear, it is becoming clear that oxidative stress and disturbed mitochondrial homeostasis are present in the brain and peripheral tissues of AD patients [41,42]. Increased oxidative stress can be found in damaged mitochondria, which is an early event of neurodegenerative diseases, and it can be found before Aβ accumulation and phosphorylated tau [40]. A number of studies show that the imbalance of mitochondrial homeostasis leads to excessive ROS production. It can cause mitochondrial membrane depolarization and mitochondrial protein damage, resulting in mitochondrial homeostasis imbalance, neuronal apoptosis and AD [43,44]. For instance, genetic factors associated with the early onset of AD include mutations in the human presenilin genes 1 and 2 [45], and the increase of the presenilin 2 expression can increase DNA fragmentation and induce apoptosis [46], which are serious consequences of oxidative damage.

Additionally, aging is a risk factor for oxidative stress and mitochondrial dysfunction. This theory postulates that mtDNA mutations can lead to respiratory chain dysfunction, resulting in the excessive production of ROS, which in turn leads to the accumulation of additional mtDNA mutations [47]. MtDNA is critical for normal mitochondrial function, and mtDNA depletion leads to reduce the activity of the oxidative phosphorylation (OXPHOS) complex and impaired production of ATP, causing severe neurological

dysfunction and neurodegeneration. Oxidative base modification of mtDNA may cause bioenergetic dysfunction that ultimately results in neuronal death [48]. More importantly, lacking the DNA-protecting histones and inefficient DNA repair mechanisms are susceptible to oxidative damage. If damaged DNA is not repaired correctly, it may lead to DNA mutations and deletions that disrupt its function to participate in ATP production, ultimately leading to mitochondrial dysfunction, ROS excessive production, and cell death. More importantly, increased mtDNA damage and base substitutions in neurons lead to decreased expression levels of mtDNA-encoded oxidative phosphatases, promoting the production of complex I and complex III superoxide (O^{2-}), and the accumulation of mitochondrial oxidative damage. So that with age, mitochondrial repair efficiency decreases, mitochondrial homeostasis is disrupted, and electron leakage occurs during the electron transport cascade, inducing ROS formation and leading to oxidative stress, causing severe damage to neurons.

3.3. Imbalance of mitochondrial calcium homeostasis in neuron and AD

As mentioned above, neuronal mitochondrial Ca^{2+} influx must be precisely regulated. When this process is abnormal, it can interfere with the mitochondrial oxidative phosphorylation process, causing excessive ROS production, which then leads to the occurrence of neurodegenerative disorders [49]. Neurodegeneration in AD can be caused by sustained increases in cytosolic Ca^{2+} concentrations [50]. In addition, oxidative damage is another mechanism by which Aβ causes disruption of Ca^{2+} homeostasis and neurotoxicity [51]. Accumulation of Aβ leads to the formation of ROS, which promotes DNA damage, and direct exposure to soluble Aβ oligomers (Aβo) leads to mitochondrial Ca^{2+} overload [52]. The increase in mitochondrial Ca^{2+} activates the mPTP [53] and the opening of the mPTP leads to loss of mitochondrial membrane potential and structural damage, resulting in mitochondrial dysfunction [54]. As mentioned earlier, MAMs are closely related to a variety of physiological functions such as calcium transport and mitochondrial function maintenance [11]. Since Aβ is generated in both ER and mitochondria, increasing evidence suggests that MAMs may play a critical role in Aβ generation [55]. Moreover, upregulation of MAMs function and increased ER - mitochondrial contacts were found in fibroblasts from presenilins knockout cells, sporadic AD patients and familial AD patients [56]. In addition, the concentration of 99-aa C-terminal fragment (C99) not cleaved by γ-Socrates was increased in MAMs in AD cell models, boosting the physical distance and function of ER-mitochondrial contacts [57]. In conclusion, mitochondrial calcium homeostasis is crucial for the normal functioning of neurons, and its breakdown is closely related to the occurrence and development of AD.

3.4. Imbalance mitochondrial fusion and fission in AD

Mitochondrial fusion and fission are essential to mitochondrial homeostasis and energy adaptation [58]. According to the body's metabolic requirements, mitochondria dynamically regulate their fusion and fission to regulate mitochondrial shape, size, number, and its transport in neurons to meet the metabolic needs of the body [59–62]. The balance between mitochondrial fusion and fission is an important factor in maintaining mitochondrial homeostasis in neurons and is also important in repairing mitochondrial damage [63]. However, it is vulnerable to neuronal physiological and pathological conditions. Disrupting the homeostasis between mitochondrial fusion and fission can result in mitochondrial morphological changes, swelling, and depolarization. In response, it can lead to the sensitivity of neurons to other forms of stress and lead to neuronal damage [64]. Studies have found that mitochondrial fission overpowers mitochondrial fusion in AD models, making it difficult for damaged mitochondria to operate properly and disrupting the balance of mitochondrial homeostasis [65]. Mitochondrial fission protein 1 (Fis1), mitochondrial fission factor (Mff), mitofusin (Mfn1, Mfn2), and optic atrophy protein 1 (OPA1) play important roles in mitochondrial fission and fusion [66,67]. In the neurons of AD patients, researchers have discovered significant expression changes of Drp1 and Fis1, which are related to mitochondrial fusion and fission, indicating that an imbalance of mitochondrial fusion and fission homeostasis is involved in the occurrence and development of AD [68]. Cell cycle exit and neuronal differentiation 1 (CEND1) is a neuron-specific protein located in the presynaptic mitochondrion. Deletion of CEND1 leads to an increase in mitochondrial fission mediated by up-regulation of Drp1, resulting in an abnormal mitochondrial function. Recent studies have found that overexpression of CEND1 in the hippocampus of 5xFAD mice can alleviate cognitive [69]. Thus, the breakdown of mitochondrial fusion and fission homeostasis is involved in the occurrence and development of AD. According to recent studies, improving mitochondrial fusion and fission homeostasis may be a potential treatment for AD [70].

3.5. Imbalance between neuronal mitochondrial biogenesis and autophagy

The balance between mitochondrial biogenesis and autophagy is crucially important for maintaining neuronal mitochondrial homeostasis and preventing neurodegeneration. Mitochondria increase their numbers through biogenesis and clear the damaged ones through autophagy, which is important for maintaining mitochondrial homeostasis to protect the cells when encountering stressful conditions [71]. Reduced mitochondrial autophagy capacity can result in the accumulation of damaged mitochondria in neurons. PTEN-induced kinase 1 (PINK1), correlated to mitophagy and cellular protection, has been reported to be downregulated in individuals with Alzheimer's disease [72] and 3xTg-AD mice [73]. Blocked mitochondrial biogenesis can lead to insufficient mitochondrial numbers of neurons and can not meet the needs of neuronal morphology and function. Peroxisome proliferator-activated receptor gamma coactivator - 1α (PGC-1α) and silent mating - type information regulation 2 homolog 1 (SIRT1) are important regulators of mitochondrial biogenesis. The expression levels of PGC-1α and SIRT1 are significantly decreased in Aβ - treated neuronal cells [74], and they must be carefully regulated to maintain healthy and robust neuronal mitochondria and prevent the occurrence of neurodegenerative diseases such as AD [75]. In AD subjects, the autophagy-lysosomal pathway (mitophagy) is impaired and damaged mitochondria cannot be cleared in time, finally leading to the accumulation of dysfunctional mitochondria in AD neurons [6].

Numerous AD studies have demonstrated that impaired mitophagy causes Aβ aggregation and Tau phosphorylation by increasing oxidative damage and cellular energy deficit, which in turn damage mitochondria, resulting in synaptic dysfunction and cognitive impairment and further promoting the occurrence and development of AD [6,76]. In AD neurons, not only the autophagy pathway but also the mitochondrial biogenesis pathway is impaired. AD is more common in the elderly, and the expression level of SIRT1 decreases with the increase of age. When nuclear NAD^+ decreases with age, PGC-1α activity is also declining. Increase the expression level of PGC-1α, the Aβ deposition in the brain of APP23 transgenic mice was significantly reduced, and their spatial and recognition memory abilities were significantly improved [77]. In addition, abnormal biogenesis and autophagy are often responsible for protein homeostasis imbalance. Neuronal mitochondrial protein homeostasis is important for mitochondrial homeostasis and cognitive function, and the broken of this homeostasis can lead to the occurrence of neurodegenerative diseases such as AD. The pathogenesis of Aβ accumulation in AD, for example, can be described as the formation of fibrillate aggregates of a specific protein that can accumulate in the nucleus, cytosol or mitochondria. Disruption of mitochondrial protein homeostasis impairs the ability of mitochondria to detect, repair and clear damaged proteins, leading to protein misfolding and aggregation in mitochondria, triggering mitochondrial dysfunction and ultimately leading to AD. Chaperones, which maintain mitochondrial protein homeostasis, have a crucial protective role in neurodegenerative diseases. For instance, overexpression of mitochondrial proteases and chaperones can be observed in AD patients and AD triple transgenic mice (3xTg-AD) mice before Aβ aggregation and Tau phosphorylation, indicating that disruption of mitochondrial protein homeostasis is an early event in AD progression [15]. Thus, imbalance of mitophagy and biogenesis homeostasis is involved in the occurrence and development of AD.

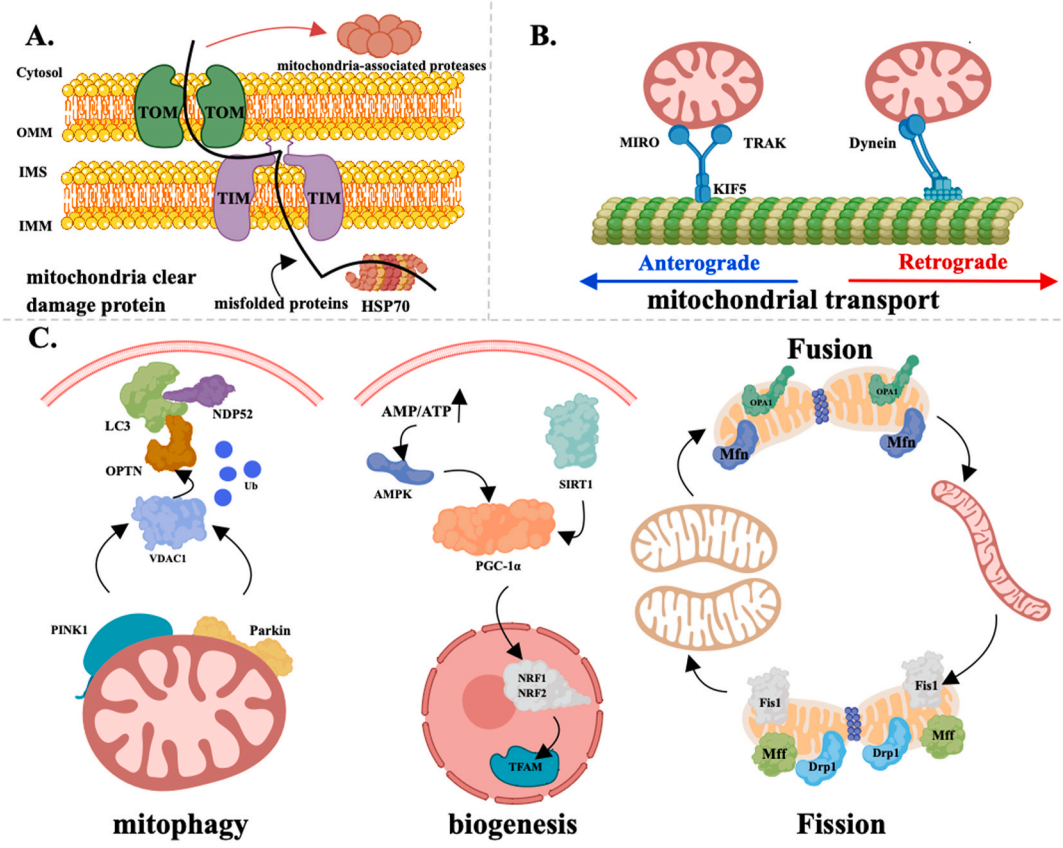

Fig. 3. Molecular mechanisms of mitochondrial homeostasis regulation in neurons. A. mitochondrial protein homeostasis regulation B. Molecular mechanisms of mitochondrial transport regulation C. Molecular mechanisms of mitochondrial biogenesis, mitophagy, fusion and fission regulation. OMM: outer mitochondrial membrane. IMS: intermembrane space. IMM: inner mitochondrial membrane. TOM:translocase of the outer membrane. TIM:translocase of the inner membrane. Miro: guanosine triphosphatase Rho GTPase. TRAK:Trafficking kinesin protei**n.** KIF5: inesin heavy chain isoform 5. LC3: autophagosomal protein. OPTN: optineurin. NDP52**:** autophagy receptor proteins. Ub: ubiquitin. PINK1:PTEN-induced kinase 1. Parkin: E3 ubiquitin-protein ligase parkin. AMPK: Adenosine 5'-monophosphate -activated protein kinase. SIRT1: silent mating-type information regulation 2 homolog 1. PGC-1α: Peroxisome proliferator-activated receptor gamma coactivator-1α. NRF1: Nuclear respiratory factor 1. NRF2: Nuclear respiratory factor 2. Mfn: mitofusin. OPA1: opticatrophy protein 1. Fis1: mitochondrial fission protein 1. Mff: mitochondrial fission factor. DRP1: dynamin-related protein 1. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

3.6. Imbalance mitochondrial transport and altered mitochondrial motility in AD

Mitochondria are not static organelles and have high motility driven by GTPase [78]. This intracellular movement is critical to maintain synaptic plasticity, neurotransmission, membrane potential, and normal neuronal polarity [79]. In PSEN1 and APP/PSEN1 mouse models, both impaired anterograde and retrograde transport were detected [80]. Damaged neurons' mitochondrial transport is more vulnerable to excitotoxicity, which ultimately results in neuronal apoptosis. In addition, mitochondrial microtubules, as essential components such as proteins or organelles, play a key role as the main channel for intracellular transport. It has been reported that changes in the normal microtubule structure surrounding Aβ in neurons may impair mitochondrial motility and trigger an apoptosis cascade in synapses and dendrites [81]. As a result, altered mitochondrial motility is involved in the occurrence and development of AD. The mitochondrial Rho family of guanosine triphosphatase Rho GTPase (Miro) proteins is a mitochondrial outer membrane protein, which plays a vital role in mitochondrial transport and the proteins can help ATP supply in response to energy demands as well as removing damaged mitochondria by attracting both anterograde and retrograde transport [82]. Several studies have shown that the accumulation of $A\beta_{42}$ plaques and defects in the induction kinetics of NFTs, leading to mitochondrial dysfunction, is one of the critical pathogenic mechanisms in AD [83–85]. Thus, Miro proteins also play an important role in AD. A study showed that knockout of Miro significantly reduced climbing activity in $A\beta_{42}$ overexpression flies by inducing defects in mitochondrial axonal transport [86]. In addition to this, a study showed that Miro overexpression induced mitochondrial fusion, maintained normal mitochondrial function, and promoted neuronal survival in an AD model of Drosophila [87]. Down-regulation and overexpression of Miro may affect mitochondrial axon transport and dynamics in AD, which may be a potential therapeutic target for AD.

4. How to regulate mitochondrial homeostasis in neurons and the potential therapeutic approaches for AD

In neurons, the morphologically different substructures require specific mitochondria pools. To meet the specific needs of different regions of neurons, mitochondrial shape and distribution are regulated to maintain mitochondrial quantity and quality to provide a healthy pool of mitochondria. Mitochondrial homeostasis in neurons can be achieved through regulating mitochondrial biogenesis and mitophagy, and mitochondrial transport, which is regulated by various molecules (Fig. 3).

4.1. Regulation mechanism and strategy of mitochondrial protein homeostasis

Maintaining mitochondrial function depends on maintaining mitochondrial protein homeostasis [88,89]. Mitochondrial proteins include proteins encoded by mitochondrial DNA and proteins encoded by nuclear DNA. However, the majority of mitochondrial proteins are encoded by nuclear DNA and are imported into mitochondria when necessary [90]. Moreover, certain proteins are encoded by both mitochondrial and nuclear DNA. For example, Complexes I, III, IV and ATP synthesis are encoded by both types of DNA. Therefore, all of the processes involved in protein encoding, synthesis and transport (including protein importing, folding, targeting, degenerating, etc.) should be precisely regulated to maintain mitochondrial protein homeostasis [91]. All proteins or genes involved in regulating mitochondrial protein homeostasis are potential targets for the treatment of AD. Damaged mitochondrial proteins can be refolded to their intrinsic three-dimensional conformations to maintain their functions by mitochondrial chaperones such as HSP60 and HSP70 [92], and irreversibly damaged proteins are degraded by mitochondria-associated proteases [93] and ultimately maintained mitochondrial protein homeostasis. For instance, injecting exogenous Hsp70 or raising endogenous Hsp70 levels can reduce neuronal degeneration and restore the memory of AD models [15]. What's more, Mitochondria have their own independent chaperones and proteases, such as Lon and ClpXP [94,95]. In addition, mitochondrial homeostasis is monitored by the unfolded protein response (mtUPR). When misfolded and damaged protein levels are elevated, mitochondrial mtUPR is activated, the expression level of mitochondrial chaperones and proteases is improved to reduce the concentration of damaged proteins [96]. Research has reported that the levels of all six mtUPR genes (including dnaja3, hspd1, clap, yme1l1, txn2, and hspe1) were significantly up-regulated in the frontal cortex of AD patients compared to normal subjects [97]. The mtUPR is usually regulated by activating transcription factors (ATFs) 4 and 5, and the transcription factor CHOP [98]. These molecules are cooperatively regulated to maintain mitochondrial protein homeostasis. Thus, targeting TOM complex, Chaperones, proteases ATFs and CHOP to maintain mitochondrial protein homeostasis may be a therapeutic strategy for AD.

4.2. Regulation mechanism and strategy of mitochondrial biogenesis and mitophagy in neurons

As mentioned above, it is important to maintain the balance between mitochondrial biogenesis and mitochondrial autophagy in neurons. Therefore, targeting proteins and genes associated with this regulatory process to maintain mitochondrial biogenesis and mitochondrial autophagy balance provides strategies for the treatment of AD. Mitochondrial biogenesis is triggered by increased energy expenditure, increased ATP demand, or in response to decreased mitochondrial numbers during neuronal proliferating, differentiating and function. PGC-1α is a key regulator of mitochondrial biogenesis [99]. By interacting with downstream NRF1 and NRF2 proteins, it might help regulate the expression of genes involved in mitochondrial respiration. NRF1 and NRF2 increase the assembly of the respiratory chain and promote the occurrence of mitochondrial biogenesis by activating the mitochondrial transcription factor TFAM and binding to the nuclear gene promoter region encoding the four complexes in the electron transport chain and the ATP synthase subunit [100]. Studies found that in HT22 cells, $A\beta_{42}$ treatment significantly reduced the levels of PGC-1α, NRF1 and TFAM compared to the control group, and in $A\beta_{42}$-treated cells, petunidin treatment restored these three protein levels [101]. SIRT1 regulates the activity of PGC-1α through deacetylation, and AMPK regulates the activity of PGC-1α through phosphorylation

[102]. In addition, evidence suggests that nuclear receptors peroxisome proliferator-activated receptors gamma(PPARγ) plays a crucial role in mitochondrial biogenesis [103]. It has been observed that both PPARγ and PGC-1α exhibit significant reductions in AD. Therefore, pharmacological agents that facilitate mitochondrial biogenesis by activating PPARγ and PGC-1α present themselves as prospective therapeutic interventions for addressing mitochondrial dysfunctions in AD [104]. Notable examples of such agents include metformin (Met) and resveratrol. AMPK signaling is particularly significant in the progression of AD, as it has been demonstrated to regulate both Aβ generation and tau phosphorylation [100]. An alternative and promising approach to addressing mitochondrial deficiencies involves targeting AMPK with Metformin (Met), a well-established compound that has shown efficacy in both *in vitro* and *in vivo* studies by influencing mitochondrial energy production and insulin signaling [100]. Met is believed to primarily target mitochondria, where it diminishes complex I of the electron transport chain, leading to a reduction in oxidative phosphorylation and ultimately ATP synthesis [105]. Increased AMP binds to the AMPK binding domain, causing an allosteric conformational change and activating the catalytic domain of AMPK [105]. Research has shown that resveratrol has the ability to stimulate SIRT1 expression, enhance AMPK activation and trigger PGC-1α [106,107]. By activating SIRT1, resveratrol has been found to protect against Aβ-induced microglial death and enhance cognitive function [108]. Furthermore, incorporating resveratrol into a long-term diet has been reported to alleviate learning and memory difficulties, as well as decrease amyloid levels and phosphorylated tau, through the activation of AMPK and SIRT1 [109]. Of particular interest, Sulforaphane (SFN) is a dietary molecule that activates Nrf2 and shows potential as a nutraceutical for AD [110].

When mitochondria are irreversibly damaged, the body selectively removes the damaged mitochondria by mitophagy. When mitochondria are damaged, their inner membrane continues to depolarize, and stimulates the protein PINK1 on the outer mitochondrial membrane (OMM). Together with Parkin, these proteins form phosphoubiquitin chains of mitochondrial outer membrane proteins such as VDAC1, which recruit autophagy receptors such as optineurin (OPTN) and NDP52. Then OPTN and NDP52 bind to both ubiquitin and LC3 (an autophagosomal protein) to induce autophagosome formation and recruit mitochondria to the autophagy pathway [6]. The mTOR complex plays a direct role in regulating mitophagy through its interaction with the ULK1 complex, which in turn regulates phagophore formation [111]. Studies on post-mortem AD brains and brains from mouse models of the disease suggest increased mTOR activity in the hippocampus and other brain regions, leading to impaired autophagosome formation [112–114]. Researchers have explored pharmacological agents aimed at enhancing mitophagy and improving mitochondrial health in animal models and, in some cases, in AD patients [115,116]. For instance, Rapamycin, a mTORC1 inhibitor, has been shown to effectively mitigate cognitive decline in various mouse models of AD and AD-like dementia [116–118]. Latrepirdine, an antihistamine drug, has demonstrated anti-Alzheimer's disease effects *in vitro* and *in vivo* studies [119,120]. It has been shown to reduce mitochondrial defects and Aβ toxicity by regulating the autophagic pathway in cell culture and AD mouse models. Thus, targeting PGC-1α, SIRT1, AMPK, and autophagy receptors such as PINK1 to maintain mitochondrial biogenesis and mitophagy may be a therapeutic strategy for AD.

4.3. Regulation mechanism and strategy of mitochondrial fusion and fission in neurons

Mitochondrial biogenesis is achieved through fission of parental mitochondria, and mitochondria can also repair damaged mitochondria through fusion. Mitochondrial fusion and fission are essential to mitochondrial homeostasis and energy adaptation. Fusion can regulate the morphology of organelles, which is critical for keeping the mitochondrial function. More importantly, fusion is crucial for rescuing damaged mitochondria. It can rescue damaged mitochondria by exchanging intrinsic proteins, lipids and mtDNA. In mitochondrial fusion, three GTPases are required: Mfn1, Mfn2 [121,122] and OPA1. OPA1 is the ortholog of Mgm1p, and mitofusins are orthologs of Fzo1p [123–125]. Fission is essential to the distribution of mitochondria in the cell, which requires MFF, Fis1 [62] and Drp1 [126]. Rapamycin, a mTORC1 inhibitor, has been shown to improve mitochondrial fission defects in glioblastoma cells by increasing the expression of Fis1 and Drp1 [118]. In addition, some studies have shown that mitochondrial elongation factor 1 and 2 (MIEF1 and MIEF2, also known as MiD51 and MiD49) act as a central hub, involved in fission and fusion, which in the fission and fusion mechanism interaction [127]. It has been reported that treated triple transgenic 3xTg-AD mice with Icariin can improve the cognitive ability of the mice, and it also finds that the expression level of Drp1 is decreased and the expression level of Mfn2 is increased [70]. What's more, studies found that bilberry anthocyanins significantly improved mitochondrial homeostasis by inducing Mfn2 expression in APP/PSEN 1 transgenic female mice [128]. Therefore, the proteins or genes involved in the balance regulatory process between fusion and fission can also be used as targets for treating AD.

4.4. Regulation mechanism and strategy of mitochondrial trafficking in neurons

Neurons are highly polarized cells with two characteristics complex, dendritic arbor and long axon [129]. Mitochondrial biogenesis of neurons mostly occurs in the cell body and is distributed in different parts through mitochondrial trafficking to play corresponding roles. Mitochondrial trafficking in neurons is related to a couple of proteins. For example, KIF5 of the Kinesin-1 family can regulate mitochondrial anterograde transport [130]. This process is mediated by KIF5 interacting with TRAK [131] and Miro [132] or the syntaxin syntabulin [133] binds to mitochondria. Besides, dynein and dynactin play key roles in mitochondrial retrograde transport [130]. It has been reported that overexpression of Armc 10 protein prevents Aβ-induced mitochondrial fragmentation, suggesting that Armc 10/SVH proteins have a protective role against Aβ-induced toxicity. Armc 10/SVH protein can regulate mitochondrial trafficking and interact with the kinesin/Miro/TRAK 2 complex [134]. Thus, regulating mitochondria trafficking proteins such as Miro in neurons may be a strategy for treating AD.

4.5. Regulation mechanism and strategy of mitochondrial calcium homeostasis in neurons

Mitochondria are crucial for maintaining neuronal calcium homeostasis. Ca^{2+} was released from ER by inositol 1,4,5-trisphosphate receptor (IP3R), then crossed the outer mitochondrial membrane mediated by voltage–dependent anion–selective channel (VDAC), and finally passed the inner mitochondria membranes into the mitochondrial matrix by mitochondria calcium uniporter (MCU). In addition, MAMs can regulate mitochondrial Ca^{2+} influx for Ca^{2+} exchanging to maintain neuronal Ca^{2+} homeostasis [135,136]. MAMs formation relies on the proteins of ER and mitochondrial membrane, they interact directly or indirectly to form multi protein - tethering complex [137]. A large number of calcium transport-related proteins are distributed on the MAMs, and these proteins mediate intracellular calcium flow and affect cell death by binding Ca^{2+} and regulating Ca^{2+} release and uptake. For example, SIRT3, a key deacetylase of mitochondrial proteins, has been shown to be an important regulator of mitochondrial function, including calcium exchange, and overexpression of SIRT3 has been reported to reduce mitochondria-associated endoplasmic reticulum membranes (MAMs) over-formation and protect hippocampal neurons from injury [138]. In the mitochondrial matrix, an increase in calcium concentration can activate the calcium-dependent signaling pathway, which can transport Ca^{2+} out of the mitochondrial matrix and maintain mitochondrial calcium homeostasis. This process was mediated by mitochondria Na^{+}/Ca^{2+} exchanger (mNCX) and mitochondria Na^{+}/Ca^{2+} exchanger (mHCX), and also can mediate mitochondrial Ca^{2+} efflux by mPTP [139,140].

As previously discussed, abnormal influxes of Ca^{2+} into neuronal mitochondria can precipitate the excessive generation of ROS. It is pertinent to highlight that specific compounds have been identified for their efficacy in mitigating mitochondrial ROS leakage. Among these, Vitamin E and Coenzyme Q10 (CoQ10) are notable for their antioxidant properties, providing a protective mechanism against oxidative stress by reducing the levels of ROS emanating from mitochondria [141]. This underscores the potential therapeutic value of these compounds in managing conditions associated with abnormal mitochondrial Ca^{2+} handling and ROS overproduction. Vitamin E, an antioxidant that is associated with lipids and membranes, may offer potential benefits as a supplement for patients with AD [142]. Several studies have demonstrated a decline in vitamin E levels in aging and dementia, which correlates with memory loss [143]. Supplementation with vitamin E has been shown to elevate the levels of this vitamin in AD patients and reduce the susceptibility of lipoproteins to oxidation [144]. Furthermore, vitamin E has been found to lower Aβ and tau levels in Tg2576 mice [142]. Dysken et al. discovered that vitamin E could significantly decelerate the rate of cognitive decline in individuals with mild to moderate AD [145]. CoQ10 serves as a co-factor for mitochondrial uncoupling proteins, functioning as a powerful antioxidant and thwarting apoptosis by impeding the permeability transition pore (PTP) [146]. Pretreatment with CoQ10 prevents a decline in mitochondrial transmembrane potential and diminishes the generation of mitochondrial ROS [147]. When administered to aged PS1 transgenic mice for 60 days, CoQ10 leads to a decrease in Aβ overproduction and intracellular Aβ deposits [148]. Moreover, a highly promising mitochondria-targeted antioxidant known as MitoQ, has emerged as a standout in the field [149]. The primary antioxidant in MitoQ is ubiquinone, which is the active antioxidant in CoQ10. It is selectively taken up by mitochondria due to the membrane potential, resulting in a significant concentration within the mitochondrial matrix [150]. Mito Q was studied for its potential to prevent AD-like pathology in mouse cortical neurons in cell culture as well as in a triple transgenic mouse model of AD (3xTg-AD). The research found that MitoQ mitigated Aβ-induced neurotoxicity in cortical neurons and also hindered the increased production of reactive species and loss of mitochondrial membrane potential (ψm) [149]. α-lipoic acid (LA) is a potent antioxidant with the ability to regenerate other antioxidants like vitamin E. LA naturally occurs as a cofactor of mitochondrial enzymes α-ketoglutarate dehydrogenase and pyruvate dehydrogenase, and has been shown to enhance acetylcholine (ACh) production and eliminate the harmful byproducts of lipid peroxidation [151]. In a clinical trial conducted by Hager et al., nine patients with probable Alzheimer's disease received a daily dose of 600 mg of LA in addition to either donepezil or rivastigmine, the results indicated that the cognitive decline in these patients was slowed after the introduction of LA compared to using AChEIs alone [152,153]. The drugs and their regulation mechanisms of mitochondrial homeostasis mentioned in this review see Table 1. Thus, regulating mitochondrial calcium homeostasis proteins in neurons is also a strategy for treating AD.

5. Conclusion

In conclusion, mitochondrial homeostasis is crucial for maintaining the normal function of neurons. It can not only provide neurons with the energy, but also regulate the growth and development of neurons, regulate the plasticity of synaptic structure and function, and stress adaptation. The imbalance of mitochondrial homeostasis and the dysfunction of mitochondria can lead to reduced ATP production, impaired mitochondrial bioenergy, and induced ROS excess, thus inducing oxidative stress,which further affetcs mitochondrial biogenesis, autophagy and kinetics, and ultimately leads to neurotoxicity or neuronal apoptosis, cognitive function decline, and AD. Regulating mitochondrial protein homeostasis, mitochondrial biogenesis and autophagy, mitochondrial dynamics and maintaining mitochondrial homeostasis to ensure the normal function of mitochondria can meet the needs of neuronal life activities and prevent the occurrence of AD. Hence, it is expected that novel therapeutics targeting mitochondria will inhibit or slow down the neurodegenerative process of Alzheimer's disease. Additional research is necessary to validate the efficacy of certain compounds for clinical application and to advance the development of promising new agents tailored to selectively target the mitochondria. Thus, regulating imbalanced mitochondrial homeostasis to inhibit neuronal apoptosis is a new strategy for preventing AD.

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Table 1
A list of the drugs and their regulation mechanisms of mitochondrial homeostasis.

Drug/active principle	Type of study/animal/cell model	Mechanism of action	References
Metformin	Primary neurons, obese mice	Influencing mitochondrial energy production and insulin signaling.	[100]
Resveratrol	AMPKα2−/− and AMPKα1−/− mice, Glial cells, C57BL/6J mice	Stimulating SIRT1 expression, enhancing AMPK activation, and triggering PGC-1α; protecting against Aβ-induced microglial death and enhance cognitive function; Incorporating resveratrol into a long-term diet has been reported to alleviate learning and memory difficulties, as well as decrease the levels of amyloid and phosphorylated tau, through the activation of AMPK and SIRT1.	[107–109]
Latrepirdine	Rats, Primary mouse cortical neurons and SH-SY5Y cells	Reducing mitochondrial defects and Aβ toxicity by regulating the autophagic pathway.	[119,120]
Rapamycin	Glioblastoma cells	Improving mitochondrial fission defects in glioblastoma cells by increasing the expression of Fis1 and Drp1.	[118]
Icariin	3xTg-AD mice	Improving the cognitive ability of the mice, it was also found that the expression level of Drp1 decreased and the expression level of Mfn2 increased.	[70]
Bilberry anthocyanins	APP/PSEN 1 mices	Improving mitochondrial homeostasis by inducing Mfn2 expression in APP/PSEN 1 transgenic female mice.	[128]
Vitamin E	Preclinical studies, Tg2576 mice	Reducing the susceptibility of lipoproteins to oxidation, lowering Aβ and tau levels in Tg2576 mice, and declining vitamin E levels in aging and dementia, which correlates with memory loss.	[142–144]
Coenzyme Q10	Preclinical studies, neuronal,ALS transgenic mice,PS1 transgenic mice	Serving as a co-factor for mitochondrial uncoupling proteins, functioning as a powerful antioxidant, and thwarting apoptosis by impeding the permeability transition pore (PTP). Pretreatment with CoQ10 prevents a decline in mitochondrial transmembrane potential and diminishes the generation of mitochondrial ROS, leading to a decrease in Aβ overproduction and intracellular Aβ deposits when administered to aged PS1 transgenic mice for 60 days.	[146–148]
Mitoquinone	3xTg mices, neurons	Mitigating Aβ-induced neurotoxicity in cortical neurons and hindering the increased production of reactive species and loss of mitochondrial membrane potential (ψm)	[149]
α-lipoic acid	Clinical studies, rats,rabbits	Enhancing acetylcholine (ACh) production and eliminating the harmful byproducts of lipid peroxidation; the introduction of LA slowed the cognitive decline in these patients.	[151–153]

Data availability statement

Data will be availible upon request.

CRediT authorship contribution statement

Jiale Ren: Writing – original draft. **Beibei Xiang:** Writing – original draft. **Lin Xueling:** Resources. **Xiaolu Han:** Resources. **Zhen Yang:** Writing – review & editing. **Mixia Zhang:** Writing – review & editing. **Yanjun Zhang:** Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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