Review Article

The Jour Multi Rese, 5(3), 2025, 17-26

The Journal of Multidisciplinary Research (TJMDR)

Content Available at www.saapjournals.org ISSN: 2583-0317

REVISITING ALZHEIMER'S DISEASE: THE MITOCHONDRIAL AND METABOLIC NEXUS SHAPING NEURODEGENERATION

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Received: 28 Sep 2025 Revised: 14 Oct 2025 Accepted: 06 Dec 2025

Abstract

Amyloid-β (Aβ) plaques and neurofibrillary tangles made of hyperphosphorylated tau protein are the two main indicators of Alzheimer's disease (AD), a progressive neurodegenerative illness. There is currently no cure, and symptomatic treatments including newly authorized anti-amyloid immunotherapies only slightly reduce cognitive loss. There is growing evidence that mitochondrial dysfunction appears early in the pathophysiology of AD and may be a primary cause of the disease's development rather than a subsequent one. Neurodegeneration is caused by a variety of mitochondrial abnormalities, including as decreased energy production, aberrant fusion and fission dynamics, elevated reactive oxygen species (ROS), and reduced mitophagy. Furthermore, mitochondrial failure is directly linked to metabolic problems such as brain insulin resistance, dysregulated lipid metabolism, and glucose hypometabolism. According to recent research, dysbiosis of the gut microbiota may exacerbate AD pathogenesis by causing neuroinflammation and metabolic abnormalities via the gut-brain axis. Restoring neuronal energy homeostasis and changing the course of illness may be possible by interventions that target these metabolic and mitochondrial pathways as well as gut bacteria.

Keywords: Alzheimer's disease, amyloid-β, neurofibrillary tangles, energy metabolism, reactive oxygen species, neuroinflammation, gut microbiota, metabolic disturbance, neurodegeneration.

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DOI: https://doi.org/10.37022/tjmdr.v5i3.780

Produced and Published by
South Asian Academic Publications

Introduction

Alzheimer's disease (AD) is characterized by a steady decline in cognitive function that ultimately leads to death. The hallmark pathological signs in AD brains include the buildup of amyloid-β (Aβ) plaques outside of cells and neurofibrillary tangles (NFTs) made of hyperphosphorylated tau protein inside neurons. Current FDA-approved therapies mainly provide symptomatic improvement, and recent anti-amyloid immunotherapies offer only moderate slowing of cognitive deterioration. No cure is available, and since treatments targeting Aβ and tau have not fully addressed the disease-suggesting these proteins may not be the root cause-research has shifted to other possible contributors, such as mitochondrial dysfunction [1-4]. Interest in mitochondria has increased because alterations in these organelles appear early in the disease and can trigger many of the neurodegenerative processes seen in AD [5–7]. Problems with mitochondrial balance cause organelle fragmentation, increased reactive oxygen species (ROS) production, and reduced cellular energy [8]. Impaired mitophagy further worsens these issues, preventing the cell from clearing away damaged mitochondria [9]. A disturbance in the gut microbiota can lead to an overproduction of proinflammatory cytokines like TNF-α and IL-6, which increase intestinal permeability and result in a "leaky gut". This compromised gut barrier enables harmful substances-such as endotoxins like lipopolysaccharide (LPS)-to enter the bloodstream and cross the blood-brain barrier, thereby promoting inflammation within the central nervous system. These inflammatory processes may drive insulin resistance, a feature associated with Alzheimer's disease (AD). Gut dysbiosis activates inflammatory pathways such as NF-kB, further impairing insulin signaling and linking systemic inflammation to metabolic abnormalities in the brain that are central to AD pathology. Emerging research even suggests that AD may start in the gut before affecting the brain: for instance, in animal studies, injection of Aβ1-42 oligomers into the gastric wall led to the migration of these amyloid proteins to the brain, triggering neuroinflammation and AD-like changes over time.

Additionally, exposure to curli-producing Escherichia coli in aged rats has been shown to increase α-synuclein production in the gut, which later aggregates in the brain. These rats displayed higher levels of inflammatory markers (TLR2, IL-6, TNF-α) in their brains, implying that bacterial amyloid proteins might promote α-synuclein aggregation and intensify microglial and astrocyte activation, thereby worsening AD pathology through a "cross-seeding" mechanism. Studies using APP transgenic mice have also demonstrated that alterations in the gut microbiota can affect brain amyloid deposition. Mice in germ-free environments, compared to those housed under normal conditions, exhibited a marked decrease in amyloid pathology, suggesting the gut microbiota's regulatory role over brain immune responses and AD-related changes. These findings underscore that gut microbiota imbalance can promote AD development by modulating immunity and neuroinflammatory mechanisms [10-12].

Mitochondria are often described as the cell's "powerhouses" because they generate ATP-the primary energy source for cellular processes-using oxidative phosphorylation. Besides energy production, mitochondria are essential for various other cellular activities, including metabolism, the synthesis of lipids, regulation of calcium levels, and intracellular signaling pathways. While mitochondria naturally generate small amounts of reactive oxygen species (ROS) during oxidative phosphorylation, these molecules normally function as important regulators of cellular processes. However, if mitochondrial activity becomes dysfunctional, it can result in excessive ROS generation, leading to oxidative stress that harms cellular components and disrupts normal functions. Additionally, mitochondria play a pivotal role in controlling apoptosis, or programmed cell death. When cells are stressed or damaged, the outer membrane of mitochondria becomes more permeable, causing the release of pro-apoptotic molecules such as cytochrome c, which subsequently triggers the cascade of events leading to cell death [13].

Mitochondria are self-replicating organelles found in nearly all cells except red blood cells. They perform numerous essential functions through various channels and transporters located on their outer membrane (OM). These channels facilitate the exchange of lipids, metabolites, and calcium ions (Ca^{2+}) between mitochondria, the cytosol, and other cellular structures. The outer membrane also plays a critical role in sensing mitochondrial dynamics such as fusion, fission, movement, and degradation, especially during apoptosis (programmed cell death).

Mitochondria are the primary suppliers of cellular energy, producing ATP (adenosine triphosphate) through oxidative phosphorylation (OXPHOS), which takes place in the inner mitochondrial membrane (IM). This process involves five enzyme complexes and two mobile electron carriers to transfer electrons and generate energy [14]. Besides their metabolic and energy-related roles, mitochondria also generate reactive oxygen species (ROS), which can function as signaling molecules involved in processes like cell proliferation, apoptosis, immune responses, and cellular recognition. In Alzheimer's disease (AD), the buildup of amyloid-β (Aβ) and phosphorylated tau (P-tau) proteins disrupts normal cellular activities, leading to neuronal loss, mitochondrial dysfunction, synaptic damage, and impaired mitophagy [15]. Mitophagy-the selective removal of damaged mitochondria-is a vital cellular mechanism ensuring mitochondrial quality control and proper function. Defects in mitophagy contribute significantly to mitochondrial abnormalities observed in AD pathology [16].

Reduced bioenergetic flux in AD

Mitochondria act as the central hub for producing energy and regulating metabolism. In neurons, oxidative phosphorylation (OXPHOS) continuously takes place on the inner mitochondrial membrane, generating large amounts of ATP. A single glucose molecule can produce about 36 ATP molecules through this process. Essential nutrients like glucose and lipids are transformed into acetyl-CoA, which enters the tricarboxylic acid (TCA) cycle, producing nicotinamide adenine dinucleotide (NADH) that donates electrons for ATP production during OXPHOS. The electron transport chain (ETC), made up of four protein complexes (I to IV), uses these electrons to create a proton motive force (PMF) that drives ATP synthase (Complex V) to synthesize ATP [17].

In Alzheimer's disease, brain mitochondria exhibit clear dysfunction, leading to impaired energy metabolism. The activities of enzymes critical for energy production, such as cytochrome c oxidase (COX), mitochondrial glutamate dehydrogenase (GDH), and α-ketoglutarate dehydrogenase (aKGDH), are notably reduced. Meanwhile, the activities of succinate dehydrogenase and malate dehydrogenase are significantly elevated [18-19]. This imbalance in enzyme activity contributes to mitochondrial inefficiency, resulting in reduced energy production that negatively affects neuronal health in AD. The increased activity of certain enzymes may represent either a compensatory reaction or a harmful metabolic alteration. Overall, these bioenergetic disruptions play an important role in the progression of Alzheimer's pathology [20-21].

Pathological abnormalities in Alzheimer's disease(AD)

The pathological abnormalities discussed as

- **Mitochondrial dysfunction ana Amyloid plague formation**

The clinical hallmark of Alzheimer's disease is induced neuronal injury and impairment caused by mitochondrial dysfunction and, specifically, amyloid-β (Aβ) plaque burden. Amyloid plaques begin as peptide fragments. They arise when the β-secretase and γ-secretase sequentially

hydrolyze the amyloid precursor protein, and these peptide fragments coalesce to form the plaques. In AD patients, Aβ aggregates accumulate as a result of the severe neuronal damage and dysfunction [22]. Notably, studies have shown that the deposition of Aβ plaques begins during the preclinical stages of the disease, often before the appearance of noticeable symptoms. However, emerging evidence suggests that mitochondrial impairment and disruptions in cellular energy metabolism occur even earlier, preceding Aβ accumulation. This temporal relationship supports the hypothesis that mitochondrial dysfunction may play a causative role in the initiation of Alzheimer's pathology, rather than being merely a downstream effect [23]. The interaction of mitochondria with the cellular organelles (i.e. endoplasmic reticulum (ER)) directly affects the synthesis of amyloid-b (Aβ) significantly [24]. These interactions occur in areas termed mitochondria-associated membranes (MAMs), which are unique sites of amyloid precursor protein (APP) synthesis (Area-Gomez et al., 2018). MAMs become dysregulated meaning APP, its substrates, and the γ-secretes may interact more closely when mitochondrial function fails. [25] suggest, this shifted relationship may accelerate Aβ production thereby advancing the pathophysiology of Alzheimer's disease. Furthermore, amyloid-β (Aβ) peptides can directly interact with the membranes of mitochondria which may aggravate the neuronal damage of Alzheimer's disease while also losing already weakened mitochondrial function.

Hyperpolarization of Tau protein

Tau protein plays a vital role in maintaining neuronal structure and function. It is crucial for the proper assembly and stabilization of microtubules, which are essential components of the cytoskeleton responsible for intracellular transport and maintaining neuronal polarity. As a microtubule-associated protein, tau supports synaptic plasticity by promoting microtubule polymerization, stabilizing their structure, and also participating in the regulation of autophagy processes within neurons [26-29]. Neurofibrillary tangles are harmful to brain cells and develop in neurons when misfolded, insoluble phosphorylated tau protein collects. Tau undergoes abnormal post-translational changes in pathological contexts such as hyperphosphorylation and caspase-3 cleavage [30] that ultimately trigger aggregation into insoluble filaments [31] explain that tau clumps impair synaptic function, and result in progressive neurodegeneration by not only destabilizing microtubule integrity, but also disrupt axonal transport processes such as the transport of mitochondria. It is mitochondrial dysfunction, in particular, that has been identified with abnormal phosphorylation of tau protein [32]. In summary, positron emission tomography (PET) preclinical studies have shown abnormalities in aerobic glycolysis, and increases in tau in the brain regions most vulnerable to Alzheimer disease. Aerobic glycolysis is the process whereby glucose is converted to pyruvate before being translocated into mitochondria where ATP can be synthesized [33]. Impairment to this process can indicate reduced glucose metabolism and underlying mitochondrial dysfunction in the affected brain regio ns. Caspase activation and cytochrome c leakage into the cytosol represent two different methods through which altered mitochondrial profiles predispose individuals to tau aggregation [34]. Revealed that, when cleaved by caspase-3, tau protein is cleaved in a selective fashion and tends to interact with itself compounding the risk for clustered hyperphosphorylated tau, hastening neurofibrillary tangle generation. Similarly, aging was demonstrated by [35] to be causative of mitochondrial fragmentation, which has been associated with cognitive reductions. The coupling of tau with voltage-dependent anion channel 1 (VDAC1) further highlights the link between tau-associated diseases with altered mitochondrial function. VDAC1 is an abundantly active protein situated on the outer mitochondrial membrane, which importantly, operates to permit the entry of various signals and chemicals such as pyruvate, Ca2+, and reactive oxygen species (ROS) to enter into mitochondria[36]. Pathologically, Aβ and hyperphosphorylated tau have been known to inhibit VDAC1's pore-opening activity, this disrupts normal VDAC1 functioning. This disruption hampers essential mitochondrial transport processes, aggravates mitochondrial dysfunction, and contributes to the initiation of apoptosis [37-38].

Metabolic Disturbance

Metabolic dysfunction is one of the trademarks of Alzheimer's disease, and the bioenergetic deficits that often accompany the progression of disease are attributable, at least in part, to mitochondrial dysfunction [39]. Furthermore, impaired mitochondrial function also interferes with lipid metabolism, further disrupting synaptic deficits and the accompanying neuroinflammatory responses, thereby accelerating progression of the disease [40]. The decrease in glucose metabolism is one of the earliest metabolic changes in Alzheimer's disease and is identified as a reduced ability for cerebral glucose utilization by positron emission tomography (PET) imaging [41-42]. The primary causes of decline are compromised glucose transport across the blood-brain barrier (BBB) and disrupted intracellular glucose catabolism dependent on sufficient mitochondrial functioning [43]. Glucose transporters (GLUT) modulate cerebral glucose metabolism enabling glucose transport into neurons and glial cells, ensuring adequate energy production [44]. Due to significant reductions in the expression of GLUT1 in brain endothelial and glial cells and GLUT3 in neurons, Alzheimer's disease significantly limits the glucose supply for mitochondrial oxidative phosphorylation (OXPHOS). Therefore, ATP production is inhibited and reactive oxygen species (ROS) accumulate The oxidative stress refers to damage to cell membranes,

and disruption of key signaling pathways that control transporter function and post-translational modifications . The glucose restriction produces mitochondrial dysfunction which produces even more bioenergetic failure [45-46]. There does seem to be compensatory increases in GLUT4 and GLUT12 in specific brain regions due to inadequate glucose metabolism [47]. The decreased expression of GLUT4 has been associated with tau pathology and alterations in insulin signaling, while GLUT12 may provide an increase in protection by reducing metabolic stress in insulin-responsive brain areas [48-49]. In addition, poor absorption of glucose also limits the available substrates in the tricarboxylic acid cycle (TCA cycle) which limits NADH and $FADH_2$ production - cofactors for correct functioning of the electron transport chain (ETC) [50-51]. Insulin resistance in the brain is a key cause of Alzheimer's disease, and is directly linked to mitochondrial dysfunction. Under normal circumstances, insulin binds to its receptors (IR), one of which is a receptor tyrosine kinase, starts a signaling cascade with insulin receptor substrate (IRS), phosphoinositide 3-kinase (PI3K) and protein kinase B (AKT) [52]. The effects of Alzheimer's disease reduce AKT phosphorylation by disrupting this receptor signaling pathway. As a result of disinhibited glycogen synthase kinase-3β (GSK-3β) activity, tau is hyperphosphorylated, and neurofibrillary tangles (NFTs) develop, contributing to neurodegeneration while inducing oxidative stress [53-54]. Insulin resistance also disrupts mTOR signaling pathway, limiting mTORC1, mTORC2 and common regulators of autophagy, mitochondrial biogenesis, protein synthesis and cellular metabolism, to allow damaged mitochondria to accumulate. The pathophysiology of mitochondrial dysfunction can proceed, with consequences of loss of mitophagy, a selective elimination of damaged mitochondria, greatly accelerating neurodegeneration. Mitochondria play a crucial role in lipid metabolism because they generate acetyl-CoA from fatty acids through a process known as β-oxidation. Such a molecule then powers oxidative phosphorylation for generating ATP after it is introduced to the tricarboxylic acid (TCA) cycle. It has been demonstrated that dyslipidemia, one of the metabolic risk factors for Alzheimer's disease (AD), exacerbates mitochondrial dysfunction and inflammatory responses. Dyslipidemia produces variations in phospholipid composition along with elevated oxidized low-density lipoproteins (oxLDL) [55]. These defects in β-oxidation lead to an accumulation of deleterious lipid intermediates, such as acylcarnitines, which hinder the action carnitine palmitoyltransferase 1, as well as ceramides, that can impair mitochondrial complexes I and III. In the end, this can result in compromised integrity of the mitochondrial membrane [56]. Furthermore, lipid peroxidation and the production of reactive aldehydes are encouraged by the excess reactive oxygen species (ROS) generated by malfunctioning mitochondria, which further deteriorates the electron transport chain (ETC) and exacerbates neuroinflammatory processes [57]. The complex interactions among insulin signalling, mitochondrial dysfunction, lipid homeostasis, and glucose metabolism in the aetiology of Alzheimer's disease are highlighted by these metabolic abnormalities taken together. There is great potential for disease modification with therapeutic approaches that focus on these interrelated pathways. Interventions that favorably alter mitochondrial biogenesis, promote the use of glucose and lipids, manage dyslipidemia, and decrease reactive oxygen species may, in theory, restore energy homeostasis in neurons and possibly delay the worsening of disease.

Oxidative Stress and Mitochondrial Defects

Reactive oxygen species (ROS) are one of the most important markers of oxidative stress (OS). Oxidative stress is the result of an imbalance between the production and accumulation of ROS, which are intrinsic byproducts of cellular metabolism, and the effective modulation and neutralization of those ROS by the cell. Under strictly controlled circumstances, ROS are crucial for regular cellular signalling; yet, an excessive accumulation of them can upset cellular homeostasis and exacerbate pathogenic processes [58].

On the other hand, high reactive oxygen species (ROS) levels might be detrimental, causing cellular damage and compromising regular physiological processes [59]. The inner membrane of mitochondria contains the electron transport chain (ETC) that comprises protein complexes I to IV and is a vital process of aerobic respiration [60]. Complexes I to IV convert electrons from metabolic substrates (such as glucose and fatty acids) to molecular oxygen. This movement of electrons and translocating protons across the membrane generates an electrochemical gradient utilized by Complex V (ATP synthase) to synthesize ATP. However, some electrons may be lost in the process, producing free radicals. Excess free radicals result in oxidative stress it is complex I and III that have been associated with increased ROS formation and electron loss, which can promote oxidative damage to components of the cell. In Alzheimer's disease, oxidative stress and mitochondrial dysfunction can be accentuated by environmental factors, dietary habits, and lifestyle [61]. Diets rich in refined carbohydrates and saturated fats can invoke a greater demand on mitochondria due to an excessive metabolic load and movement into the range where the oxidative burden surpasses the measures of bodily antioxidants As ROS (reactive oxygen species) is produced in amounts larger than the antioxidant capacity of the body, they result in oxidative stress and cellular protein, lipid and nucleic acid damage precipitated by overly high amounts of ROS, compromised electron transport chain (ETC) functionality, and oxidative stress qualitatively damaging the mitochondria themselves [62]. Dysfunction of the ETC induces a mitochondrial-derived oxidative stress brings

significant structural and functional harms to the mitochondria [63]. The elevated oxidative stress that accompanied the dysfunctional mitochondrial status in neurodegenerative conditions like Alzheimer's is exacerbated, and paralleled, by neuroinflammatory responses to his oxidative stress causes further degeneration of the central nervous system [64]. The inability of the ETC to maintain homeostasis with the concentration of calcium and the unique role of mitochondria as calcium stores in the central nervous system complicate neuronal function, along with dysfunctional calcium signalling into neuronal membranes and ultimately neuronal deregulation and degeneration. Damaging ROS (reactive oxygen species) propagated into this scenario, as ROS not only damage mitochondrial membranes directly, but also damage some key initiating proteins involved with ETC (reactive moods along with cardiolipin a lipid substrate for initiating structural integrity of the ETC complexes) [65]. Complex IV function is especially impacted by oxidative damage to cardiolipin, which results in decreased oxygen consumption and impaired ATP synthesis. Furthermore, mitochondrial DNA (mtDNA) mutations and changes brought on by oxidative stress might impede the production of proteins required for ETC function, exacerbating mitochondrial dysfunction and cellular energy deficits [66].

Calcium Homoeostasis Disruption

Mitochondria are important for keeping calcium levels inside cells in balance, which is necessary for neurones to stay alive and for synaptic transmission to work properly [67]. When mitochondria don't work right, calcium levels in the cell become unbalanced, which can cause calcium to build up in the cytosol. Part of the reason for this is because calcium transport systems, including the mitochondrial calcium uniporter (MCU), don't work well [68]. The calcium imbalance that results from this causes excitotoxicity by overstimulating glutamate receptors. This starts signalling pathways that lead to neuronal cell death and cognitive impairment, which are two primary pathogenic characteristics that occur during the progression of Alzheimer's Disease. An excess of calcium in cells may lead to the opening of the mitochondrial permeability transition pore (mPTP), signaling the start of cell death pathways and leading to and accounting for the type and number of dying brain cells observed in Alzheimer's disease subjects [69]. When researchers looked at older mice, they found that calcium signalling was very different from that of younger mice. For example, the cytosol had more calcium, and the mitochondria were less able to effectively control and recycle calcium [70]. Abnormal protein aggregation has also been associated with disruption of the intracellular calcium control system, which is essential for mitochondrial health [71]. Such disruption allows for a negative feedback loop within the disease pathology of Alzheimer's disease, contributing to its progression [72]. Mitochondrial dehydrogenases need calcium to assure adequate amounts, and calcium ions are crucial for regulating Ca2+ levels in cells [73]. High concentrations of calcium in cells can also disrupt important physiological functions (including protein folding in the endoplasmic reticulum [ER] and oxidative phosphorylation in the mitochondria), thus increasing ROS production and opening the mPTP (Ca2+ increased ROS). This all leads to decreased energy production and mitochondrial membrane potential [74]. Disturbances in synaptic plasticity can occur from imbalances in calcium, contributing to neuronal degeneration and programmed cell death [75].Too much calcium can cause apoptosis by activating pro-apoptotic proteins like Bax and p53, which make the mitochondrial membrane more permeable. This mechanism causes cytochrome c to be released into the cytosol and caspases to be activated, which leads to programmed cell death.Disrupted calcium signalling in mitochondria is substantially linked to higher levels of reactive oxygen species (ROS) [76]. Free calcium accumulates in the cytosol and mitochondrial matrix when the body is ill because defense mechanisms like the sodium-calcium exchanger and mitochondrial calcium uniporter are not functioning as well [77]. Prior research has shown that excessive calcium in mitochondria can cause neuronal death and is a significant contributing factor to the onset of Alzheimer's disease [78]. Furthermore, studies utilizing Alzheimer's disease models have demonstrated that calcium is more readily transferred from hippocampus reserves, as seen by epifluorescence imaging, an early indicator of the onset of the disease [79]. So, fixing calcium levels that are out of whack looks like a good way to treat Alzheimer's disease. Preclinical investigations have shown that medicines that target L-type calcium channels [80] and the mitochondrial calcium uniporter (MCU) [81] might be helpful. These therapies have been demonstrated to lower calcium excess and are linked to less amyloid plaques and neurofibrillary tangles forming.

Imbalance In Mitochondrial Fusion and Fission

Mitochondria are very active organelles that constantly fuse and split in the cytoplasm. These actions are important for keeping mitochondria healthy, making sure they are distributed properly, and keeping the mitochondrial network working well [82]. Dynamin family members of big guanosine triphosphatases (GTPases) control the fusion and fission of mitochondria. For cells to be healthy, they need to keep these two processes in balance. If this equilibrium is thrown off, as by too much fission, mitochondria can break apart. On the other hand, too much fusion can make mitochondria longer and cause more reactive oxygen species (ROS) [83]. Researchers are still looking into the molecular mechanisms that control mitochondrial fusion and fission, however there is more and more evidence that numerous big GTPase-containing proteins are very important for these processes. Proteins such as DLP1 (also called Drp1) help mitochondria split

apart, whereas Mfn1, Mfn2, and OPA1 help them come together [84]. In people with Alzheimer's disease, the brains show structural problems and damage in neuronal mitochondria, which is caused by increased mitochondrial fission [85-87]. Li et al. used primary hippocampus neurones from rats to show that problems with mitochondrial fusion can also be harmful. Specifically, when cultured neurones had too much tau protein, it caused proteins associated to fusion to be made more, which made the mitochondria longer and made the neurones less healthy.

Mitophagy Deficiency

In 2001, Hirai, K et al [88] was the first study to identify dysfunction in the mitophagy pathway in Alzheimer's disease. The researchers found that the accumulation of proteins and mitochondrial DNA (mtDNA) within the cytoplasm and autophagic vacuoles (AVs) of neurons in AD patients contributed to increased oxidative damage. Clinical evidence further revealed elevated levels of mitochondrial proteins, including TOMM20 and COX IV, along with a significantly higher mtDNA to nuclear DNA ratio in AD neurons, highlighting the extent of mitochondrial abnormalities in the disease. More research has showed that mitophagy decreases in neurones of Alzheimer's disease patients, especially those with high levels of phosphorylated tau (pTau). This suggests that tau pathology may play a role in this impairment [89]. Additionally, researchers have found that the hippocampus areas of AD brains contain higher amounts of mitochondrial markers and proteins associated to mitophagy, such as Parkin in the early stages and PINK1 in the later stages of AD [90]. In the hippocampus tissue of Alzheimer's disease patients, researchers have found higher levels of Parkin in the early stages and PINK1 in the later stages, as well as higher levels of mitochondrial markers in both stages. These results might mean that the dynamics of mitophagy are off, which could be because the Parkin/PINK1 signalling pathway isn't working well (Figure 3). Other studies have also made similar discoveries [91-92]. Several studies have also shown that brains affected by Alzheimer's disease have lower levels of important genes involved in mitophagy and autophagy, such as Optineurin (OPTN), BNIP3L, FUNDC1, VDAC1, Beclin-1 (Bcl-1), ULK1, class III PI3K, ATG5, ATG12, BNIP3, AMBRA1, and VCP/P97 (Martín-Maestro et al., 2017). In addition, the decrease in mitophagy was shown by the buildup of mitochondria that were damaged in both structure and function. This was shown by disorganised cristae, smaller mitochondria, and less ATP generation. This drop also included stopping the early phases of the mitophagy process, such as less recruitment of LC3 to mitochondria and less activation of AMPK (AMP-activated protein kinase) signalling, which was shown by lower levels of AMPK phosphorylation. Furthermore, TBK1 and ULK1 blocked routes that come after them [93]. A group of human sporadic Alzheimer's disease (SAD) neurones showed defective mitophagy when levels of p62, LC3-I, and LC3-II were high and levels of Parkin and PINK1 were low in mitochondrial-associated areas [94].

Conclusion

A growing body of research underscores mitochondrial dysfunction as a central and possibly initiating factor in Alzheimer's disease pathogenesis, preceding and potentially amplifying amyloid-β and tau pathology. Disruptions in energy metabolism, glucose and lipid homeostasis, oxidative stress, and impaired mitochondrial dynamics all intersect to drive neuronal injury and cognitive decline. Moreover, gut microbiota alterations and the resulting inflammatory responses further exacerbate these metabolic and mitochondrial impairments. Given the multifaceted role of mitochondria and interconnected metabolic processes in AD, therapeutic strategies that restore mitochondrial function, modulate metabolic pathways, reduce oxidative stress, and address gut dysbiosis hold significant potential to modify disease progression. Future research and clinical interventions targeting these intertwined mechanisms could pave the way for more effective treatments and possibly prevention of Alzheimer's disease.

Desclasare Satamente

There are no conflictos of inertes.

Acknowledgment

It's our privilege to express the profound sense of gratitude and cordial thanks to our respected chairman **Mr. Anil Chopra** and Vice Chairperson **Ms. Sangeeta Chopra**, St. Soldier Educational Society, Jalandhar for providing the necessary facilities to complete this review work.

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