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Mitochondrial Perturbation in Alzheimer's Disease and Diabetes

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Abstract

Mitochondria are well-known cellular organelles that play a vital role in cellular bioenergetics, heme biosynthesis, thermogenesis, calcium homeostasis, lipid catabolism, and other metabolic activities. Given the extensive role of mitochondria in cell function, mitochondrial dysfunction plays a part in many diseases, including diabetes and Alzheimer's disease (AD). In most cases, there is overwhelming evidence that impaired mitochondrial function is a causative factor in these diseases. Studying mitochondrial function in diseased cells vs healthy cells may reveal the modified mechanisms and molecular components involved in specific disease states. In this chapter, we provide a concise overview of the major recent findings on mitochondrial abnormalities and their link to synaptic dysfunction relevant to neurodegeneration and cognitive decline in AD and diabetes. Our increased understanding of the role of mitochondrial perturbation indicates that the development of specific small molecules targeting aberrant mitochondrial function could provide therapeutic benefits for the brain in combating aging-related dementia and neurodegenerative diseases by powering up brain energy and improving synaptic function and transmission.

1. INTRODUCTION

Emerged evidence suggests that the deleterious and advanced cellular changes in aging and diabetes are linked to mitochondrial dysfunction.[1,2] Brain aging is often characterized by neuronal loss and synaptic alteration, which are associated with mitochondrial abnormalities, energy failure, respiratory chain impairment, generation of reactive oxygen species (ROS), and neuronal perturbation.[3] Further, various evidences suggest that mitochondrial dysfunction is a prominent and early oxidative stress-associated factor that produces neuronal abnormalities in aging and diabetes, resulting in susceptibility to aging-related neurodegenerative diseases.[4] In the neurons, mitochondria are distributed throughout the length of the axons, presynaptic terminals, and dendrites. Mitochondria play active roles in regulating synaptogenesis and morphological/functional responses to synaptic activity; thus, mitochondrial dysfunction can lead to a stark neuronal energy deficit and, in the long run, to modifications in neuronal synapses and neurodegeneration in the aging brain.[1]

Alzheimer's disease (AD) is a chronic aging-related disease with two pathological features: abnormal accumulations of amyloid beta peptide (Aβ) and phosphorylation of tau protein in

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the brain. Increased evidence indicates that mitochondrial and synaptic dysfunction is an early pathological feature of AD.[5] Aβ has deleterious effects on mitochondrial function and structure and contributes to energy failure, respiratory chain impairment, ROS generation, induction of mitochondrial permeability transition pore (mPTP), imbalance of calcium homeostasis, disruption of mitochondrial dynamics, and mitochondrial DNA/RNA mutations.[6] Although Aβ directly and indirectly causes abnormal mitochondrial and neuronal function, recent studies have highlighted the association between early mitochondrial dysfunction and the accumulation of Aβ in mitochondria, implicating mitochondrial Aβ in AD pathogenesis.[7–28] These observations provide a better understanding of the relationship between mitochondria and AD pathogenesis.

Mitochondrial malfunction, synaptic damage, and the resultant impairment in cognitive function are pathological features of diabetes-affected brains.[2] Diabetes adversely affects the brain and increases the risk for depression and dementia.[29–39] In neurons, synaptic mitochondria are vital for the maintenance of synaptic function and transmission through normal mitochondrial dynamics, distribution, and trafficking as well as energy metabolism and synaptic calcium modulation. Imbalance of mitochondrial dynamics contributes to oxidative stress and hyperglycemia-induced alterations in mitochondrial morphology and function.[38,40,41] Diabetes elicits AD-like brain changes linked with cognitive decline and neurodegeneration, such as elevated tau expression and phosphorylation and accumulation of Aβ,[42–46] mitochondrial dysfunction, disruption of mitochondrial dynamics,[37,38,41,47–51] oxidative stress,[40,49] neuroinflammation, loss of synapses, impaired learning and memory, and synaptic plasticity deficits.[29,35,36,44,52–55] The underlying mechanisms and strategies to rescue such injury and dysfunction are not well understood. Studies have identified several cellular and mitochondrial cofactors that are directly or indirectly involved in AD- and diabetes-mediated alterations in mitochondrial and synaptic structure and function. Such factors include cyclophilin D (CypD), presequence protease (PreP), Aβ, mPTP, *N*-methyl-D-aspartate, and the receptor for advanced glycation endproducts (RAGE).

This chapter addresses several aspects of AD- and diabetes-induced mitochondrial dysfunction with a special focus on mitochondrial molecular mechanisms underlying synaptic pathology and cognitive dysfunction.

2. MITOCHONDRIAL FUNCTION

Mitochondria are essential organelles for cell survival, playing a crucial role in calcium homeostasis, energy metabolism, detoxification of ROS generation, and induction of cell death, including apoptosis and necrosis. Mitochondria in different types of cells or in different subcompartments of one cell differ significantly in their morphology and function and can be divided into multiple subgroups within one cell.[56] The recent recognition of mitochondrial heterogeneity facilitates our understanding of mitochondrial biology.

Mitochondria are the major site of ATP synthesis and are also the site of amino acid biosynthesis, fatty acid oxidation, steroid metabolism, calcium homeostasis, and ROS production and detoxification. The inner mitochondrial membrane is largely impermeable and contains a variety of enzymes, including those responsible for making ATP, and forms

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the major barrier between the cytosol and the mitochondrial matrix. The five complexes of the respiratory chain [complex I (NADH ubiquinone oxidoreductase), complex II (succinate ubiquinone oxidoreductase), complex III (ubiquinone-cytochrome *c* reductase), complex IV (cytochrome oxidase), and complex V (ATP synthase)] are embedded in the inner mitochondrial membrane. The transmission of electrons along the respiratory chain provides the energy to pump protons from the matrix into the intermembrane space, thereby generating the electrochemical gradient required to drive ATP synthesis.[56]

3. SYNAPTIC MITOCHONDRIAL PATHOLOGY IN AD

Synapses are the neuronal contact sites through which neurons receive and send information.[57,58] Energy provision and calcium fluctuation in synapses are prerequisite for interneuronal communication.[59] To meet the high energy demands and to cope with constant calcium flux, synapses are enriched with mitochondria for on-site energy provision and calcium modulation.[60]

Although the detrimental impacts of Aβ on synapses and synaptic function are extensive, multiple studies demonstrate that mitochondrial structure and function are particularly susceptible to the effects of mitochondrial Aβ accumulation.[7–28] Further, synaptic mitochondria serve as a reservoir for Aβ accumulation in aging and AD[1,5,61–64]; thus mitochondrial dysfunction is a major player in the synaptic alterations seen in AD and diabetes.[3,56,65]

First, mitochondrial and neuronal malfunction in AD is linked to the progress accumulation of Aβ in the mitochondria of both human AD and transgenic AD mouse brains.[1,7–9,11,15–18,66–68] Aβ can directly import into mitochondria via the translocase of the outer membrane machinery,[67] RAGE,[69] or other unknown mechanisms. Aβ may also be locally produced in mitochondria via gamma-secretase that is localized in mitochondria.[70–72] Notably, accumulation of mitochondrial Aβ precedes extracellular Aβ deposition in AD brains, increases with age, and associates with early onset synaptic loss, synaptic damage, and mitochondrial oxidative damage,[5,7,10,11,22,73–83] suggesting that early accumulation of Aβ in mitochondria may be an initiating pathological event, leading to mitochondrial and neuronal perturbation. Second, interaction of Aβ with mitochondrial matrix proteins such as amyloid-binding alcohol dehydrogenase (ABAD)[7,10,11,84] and CypD[23,85–87] exacerbates Aβ-induced mitochondrial and neuronal stress. Increasing PreP activity by antagonizing the Aβ-ABAD interaction decreases mitochondrial and cerebral Aβ accumulation in AD mice overexpressing Aβ and improves mitochondrial function.[88] Third, increasing neuronal PreP expression and activity in Aβ-enriched synaptic mitochondria of mAPP mice greatly reduces mitochondrial accumulation. Accordingly, synaptic function and learning and memory are significantly improved in PreP-overexpressed mitochondria.[28] These data strongly indicate that PreP is critical for maintaining mitochondrial integrity and function by clearance of mitochondrial Aβ. Strategies that reduce Aβ levels in mitochondria in addition to the brain by increasing PreP expression and activity are critical to consider as new avenues for both preventing and halting AD progression at the early stage. One such therapeutic strategy involves the development of a small-molecule agonist of PreP in order to safely decrease mitochondrial and cerebral Aβ accumulation by accelerating Aβ clearance.

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These recent studies highlight the significant role of Aβ in synaptic mitochondrial pathology and significantly advance our understanding of the mechanisms underlying mitochondrial dysfunction in AD, especially in the early stage when the presence of Aβ has not yet set in motion the devastating cognitive impairments often associated with AD. Ameliorating alterations in mitochondrial function could improve synaptic function and reverse cognitive decline in AD.

In AD and non-AD cell and animal models, treatment of mitochondria-targeted molecules mitoQ and SS31 significantly reverses Aβ-induced CypD elevation, mitochondrial fusion/fission proteins imbalance, and neurite growth.[89] MitoQ and SS31 also reduce mutant huntingtin-induced mitochondrial toxicity and synaptic damage.[90] Additionally, antioxidants attenuate mitochondrial transport and function in cybrid cells containing AD-derived mitochondria.[4,91] These results suggest a close relationship between neuronal mitochondrial dysfunction and synaptic perturbation and the value of eliminating neuronal mitochondrial oxidative stress in the treatment of neuronal/synaptic alterations in AD.[1,90]

4. IMPACT OF CypD-DEPENDENT mPTP ON MITOCHONDRIAL DEFECTS

CypD is a crucial component of the mPTP. CypD released from matrix can bind to the adenine nucleotide translocase in the inner mitochondrial membrane and the voltage-dependent anion channel in the outer mitochondrial membrane to trigger the opening of mPTP, a nonselective, high conductance pore allowing the transport not only calcium but any solute below the pore size. The opening of mPTP results in osmotic swelling, dissipation of the mitochondrial membrane potential, reduced mitochondrial calcium retention capacity, decreased membrane potential, increased ROS production, and eventually, cell death (Fig. 1).[92] Increased expression of CypD occurs in neurodegenerative diseases including AD, Parkinson's disease (PD), Huntington's disease (HD),[23,87,93–97] and diabetes, and con tributes to mitochondrial perturbation.[5,23,65,98]

Studies from in vitro cellular and in vivo animal models have demonstrated that blockade of CypD significantly attenuates mPTP-related mitochondrial dysfunction and cell death, which are relevant to the pathogenesis of stroke, AD, and diabetes.[23,65,87,98–102] Furthermore, blockade of mPTP by genetic depletion or pharmacological inhibition of CypD rescues axonal mitochondrial trafficking and protects synapses from Aβ toxicity. The potential mechanisms underlying the protective effect of CypD deficiency on axonal mitochondrial trafficking include the reduction of Aβ-induced calcium perturbation, the suppression of axonal ROS accumulation, and the activation of the downstream P38/MAPK signaling pathway.

The protein kinase A/cAMP regulatory element-binding (PKA/CREB) signaling pathway, a crucial regulator of synaptic plasticity and learning memory, is adversely affected by an Aβ-rich environment, leading to dendritic spine architecture changes in an AD mouse model.[102] Aβ reduces phosphorylation of PKA, thus disrupting PKA/CREB signal transduction and causing synaptic and cognitive dysfunction.[100,102] Notably, neurons lacking CypD reverse Aβ-induced synaptic dysfunction and are protected against Aβ-induced alterations in PKA and CREB phosphorylation. These results indicate the involvement of CypD in Aβ-induced

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abnormalities in signal transduction including PKA/CREB signaling. Sustained CypD-induced neuronal/synaptic mitochondrial stress is a potential mechanism underlying synaptic failure in the pathogenesis of AD.

Recently, Wang *et al.* demonstrated that CypD expression levels were significantly elevated in the hippocampi of streptozotocin-induced diabetic mice.[56] The CypD expression levels are further elevated in Aβ-enriched diabetic brain compared to nondiabetic mAPP mice.[56] These results suggest that CypD expression is increased in diabetes mellitus and further enhanced in an Aβ-rich environment. Increased levels of CypD in mitochondria trigger/enhance the mPTP opening, leading to colloidal osmotic swelling of the mitochondrial matrix, dissipation of the inner membrane potential, generation of ROS, and release of many proapoptogenic proteins and procaspases.[99] Hence, blockade of CypD may be a potential therapeutic strategy for preventing and halting synaptic and mitochondrial pathology in AD. Specifically, the development of small-molecule CypD inhibitors could hold therapeutic potential for the treatment of neurodegenerative diseases including AD and diabetes.[103,104]

5. EFFECT OF NEURONAL PreP ACTIVITY AND RAGE SIGNALING ON MITOCHONDRIAL DYSFUNCTION

PreP is a mitochondrial peptidasome that is localized in the mammalian mitochondrial matrix.[105] It is the key for maintenance of mitochondrial health and integrity. PreP proteolytic activity is significantly reduced in AD-affected brain mitochondria and transgenic AD mouse models[106] and is negatively correlated to mitochondrial Aβ accumulation. Du *et al.* demonstrated that increased expression and activity of neuronal PreP significantly reduced mitochondrial Aβ load and the production of proinflammatory mediators, improved mitochondrial function and synaptic plasticity, and attenuated cognitive decline in AD mice.[28] Furthermore, PreP proteolytic activity is required for degradation and clearance of mitochondrial Aβ. Mitochondrial Aβ accumulation may interfere with normal mitophagy and release of mitochondria-derived damage-associated molecular patterns from the injured neurons, leading to increased production of TNF-α, IL-1β, and MCP1, the cytokines known to be involved in the inflammatory process of AD.[107] Thus, dysfunctional or damaged mitochondria can produce excessive inflammation and tissue damage possibly via overproduction of cytokines and ROS.

RAGE-dependent signal transduction via Aβ-RAGE interaction plays an important role in mitochondrial dysfunction. RAGE serves as an important cell-surface receptor mediating chemotactic and inflammatory reaction to Aβ and other proinflammatory ligands.[69,108–113] RAGE signaling in neurons and microglia is known to promote induction of proinflammatory mediators, including cytokines and chemokines, and activation of microglia by increased expression of microglial markers (CD4 and CD11).[107,110] Additionally, over-expression of neuronal PreP in mAPP mice not only reduces Aβ accumulation in the brain but also remarkably suppresses RAGE expression as compared with mAPP mice,[69] suggesting a possible connection between mitochondrial defects and RAGE signaling relevant to the activation of transcription and the proinflammatory

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response.[28,69,107,109,110,112] Further investigation is required to elucidate the role of RAGE in mitochondrial dysfunction relevant to the pathogenesis of AD and diabetes.

6. EFFECTS OF METHIONINE SULFOXIDE REDUCTASE ON Aβ SOLUBILITY AND MITOCHONDRIAL FUNCTION

Accumulation of oxidized proteins, especially Aβ, is thought to be one of the common causes of AD. Induced ROS generation is one of the earliest consequences of toxic insults mediated by soluble Aβ oligomers.[81] Mitochondria are particularly sensitive to ROS, and reduced metabolic activity resulting from oxidative damage to vital mitochondrial components has been demonstrated in AD.[10]

Methionine (Met) is highly susceptible to oxidation in vivo, particularly under conditions of oxidative stress. The sulfoxide form comprises 10%–50% of Aβ in amyloid plaques of AD brain.[114] Oxidation of Met to Met(O) is reversible and the reverse reaction is catalyzed in vivo by the methionine sulfoxide reductase (Msr) system, composed of peptide-methionine (*S*)-S-oxide reductase (MsrA) and peptide-methionine (*R*)-S-oxide reductase (MsrB), which, respectively, reduce the *S* and *R* enantiomers of the sulfoxide group. These enzymes provide both an efficient repair mechanism for oxidative damage to Met residues and general protection against oxidative stress by scavenging ROS through the recycling of Met.

Studies from primary hippocampal and cortical neurons show increased total Msr activity, ascribed to increased activity in both MsrA and MsrB, in conjunction with protection against cell death induced by the sulfoxide forms of Aβ40 or Aβ42. Exposure of wild-type and *MsrA* knockout mouse cortical neurons to Aβ42 and Met(O)-Aβ demonstrated that lack of MsrA abolishes the protective effect induced by Met(O)-Aβ.[115] Furthermore, lack of MsrA promotes a shift from aggregated forms of Aβ toward soluble oligomers. Given that soluble oligomer Aβ are thought to be more toxic to neurons and synapses than aggregated Aβ forms,[115] enhancing MsrA activity by regulating transcription may have therapeutic applications. Alterations in MsrA expression levels and Aβ structure during normal aging might be a cofactor in AD-related mitochondrial malfunction.[115]

7. IMPACT OF MITOCHONDRIAL DYNAMICS IN MCI AND AD

Mitochondria are highly dynamic organelles that undergo continuous fission and fusion, which are regulated by the GTPase hydrolysis activity mitochondrial fission proteins (DLP1 and Fis1) and mitochondrial fusion protein [mitofusin 1 and 2 (Mfn1 and 2) and optic atrophy (Opa1)]. Mitochondrial dynamics are important for the proper distribution of mitochondria within cells, which is particularly critical for morphologically complex cells such as neurons.[116] Alterations in mitochondrial dynamics significantly impact almost all aspects of mitochondrial function including energy metabolism, calcium buffering, ROS generation, and apoptosis regulation.[117,118] Unbalanced fusion and fission lead, respectively, to mitochondrial elongation and excessive mitochondrial fragmentation, both of which impair the function of mitochondria. It has been shown that exchange of mitochondrial contents is important for mitochondrial function as well as organelle distribution in neurons. Mitochondrial fusion, in particular that mediated by Mfn2, is required for proper

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development and maintenance of the cerebellum.[119] Mutations in the Mfn2 gene cause neurodegenerative diseases, such as Charcot–Marie–Tooth type 2A, and mutations in OPA1 cause dominantly inherited optic atrophy. Increasing evidence implicates altered mitochondrial trafficking and fusion–fission dynamics in aging-related AD, PD, HD, and amyotrophic lateral sclerosis.

7.1 Effect of Mfn2 on Mitochondrial Function

Mitofusins Mfn1 and Mfn2 are outer membrane GTPases that mediate outer mitochondrial membrane fusion. Mfn2 expression is crucial for maintaining the morphology and operation of the mitochondrial network and mitochondrial metabolism. Recent studies demonstrate that markedly reduced mitochondrial mass and transport may contribute to neuronal loss due to the specific loss of Mfn2 but not Mfn1.[120] Du *et al.* examined the role of Mfn2 in the human-induced pluripotent stem cells (hiPSCs) differentiation system and reported that knockdown of Mfn2 results in mitochondrial dysfunctions and defects in neurogenesis and synapse formation.[119] By contrast, Mfn2 overexpression in neural progenitor cells directs differentiation and maturation into neurons with enhanced mitochondrial functions, suggesting that Mfn2 is crucial for mitochondrial development, and thereby essential to hiPSCs differentiation. Importantly, this also provides a novel neurophysiologic model of mitochondrial development in neurogenesis, which enhances our understanding of the involvement of dysfunctional mitochondria in aging and neurodegenerative diseases.[119] Under pathological conditions, Mfn2 expression levels are increased such as mild cognitive impairment (MCI)-derived mitochondria, leading to aberrant mitochondrial fusion and fission event evidenced by abnormal mitochondrial morphology and function.

7.2 Oxidative Stress and MCI- and AD-Related Mitochondrial Dynamics

MCI is characterized by a decline in cognitive abilities that is noticeable yet not severe enough to completely disrupt an individual's daily activity. MCI is generally considered to be a transitional phase between normal aging and early dementing disorders, especially AD.[121]

In cybrid model, MCI-induced mitochondrial defects manifest as alterations in mitochondrial dynamics, function, and morphology. These dysfunctional MCI cybrid mitochondria exhibit impaired fission/fusion events, impaired mitochondrial respiratory chain enzyme activity, decreased membrane potential, increased mitochondrial and intracellular ROS, and impairment in energy metabolism with decreased ATP levels when compared to non-MCI cybrid mitochondria. Given that mitochondrial Mfn2 is involved in mitochondrial fusion,[119] increased mitochondrial Mfn2 levels in MCI cybrids suggest that altered Mfn2 expression likely contributes to enhanced mitochondrial fusion. Accordingly, changes in MCI mitochondrial morphology display as elongated mitochondria. Interestingly, suppression of Mfn2 overexpression by inhibiting oxidative stress-mediated activation of extracellular signal-regulated kinases (ERK) reverses abnormalities in mitochondrial structure and function.[122] Thus, generation of Mfn2 antagonist may hold potential for prevention and treatment at the early stage of AD.[123]

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In contrast to MCI-derived mitochondria, AD mitochondria exhibit fragmentation as shown by overabundant fission, elongate, and aggregated mitochondria, compared to cybrid cells containing mitochondria from normal age-matched subjects with the relatively normal cognitive function. DLP1, which plays a key role in balancing mitochondrial dynamics by regulating mitochondrial fission, was significantly increased in AD mitochondria.[123] Additionally, the abnormal interaction of DLP1 with hyperphosphorylated tau was found in AD neurons.[124] Interaction of DLP1 with glycogen synthase kinase-3 (GSK3β) mediates changes in mitochondrial morphology and dynamics.[125–127] Mitochondrial dynamics modulates the induction of proinflammatory mediators in microglial cells.[128,129] ROS-induced activation of the mitogen-activated protein (MAP) kinase family appears to play a key role in mediating cellular responses to multiple stresses. ERK signaling is involved in mitochondrial function and neuronal stress.[123,130] Taken together, this suggests that oxidative stress-induced activation of MAP kinase via upregulation of DLP1 or Mfn2 expression contributes to mitochondrial dysfunction and abnormal mitochondrial dynamics[122,123] by disrupting the balance of mitochondrial fission and fusion and promoting translocation of DLP1 to mitochondria, leading to mitochondrial fragmentation in AD. Most importantly, suppression of ERK signaling and inhibition of mitochondrial fission or fusion pathways rescues defective mitochondrial morphology and function induced by AD or MCI[123] (Fig. 2). Antioxidant treatment attenuates AD mitochondrial defects, leading to improvements in axonal mitochondrial transport and mitochondrial bioenergy and function.[4,91]

8. DRP1-MEDIATED MITOCHONDRIAL ABNORMALITIES IN DIABETES

Mitochondria are dynamic organelles that undergo continuous fission and fusion. Fission events are regulated by dynamin-related protein (Drp1), while fusion events are regulated by the large dynamin-related GTPases known as Mfn1 and Mfn2 as well as optic atrophy 1 (OPA1).[131] Alterations in mitochondrial dynamics affect mitochondrial numbers and shape, respiratory enzyme activity, and ATP production. Imbalance between mitochondrial fission and fusion in diabetes results predominantly from upregulation of Drp1, which induces mitochondrial dysfunction (impaired respiration and ATP production) in a variety of cell types, including dorsal root ganglion neurons and β cells.[41] Mitochondrial dysfunction has been implicated in the development of insulin resistance in skeletal muscle cells and hyperglycemia.[132]

A novel and pivotal role of mitochondrial dysfunction in diabetes-induced synaptic impairment involves a GSK3b/Drp1-dependent connection between mitochondrial dysfunction in diabetic neurons and synaptic dysfunction including decline in long-term potentiation. These findings are consistent with diabetic neuropathy as shown by increased Drp1 expression and mitochondrial fission in dorsal root ganglion neurons of 6-month-old type II diabetes (db/db) mice.[2] In contrast to the greater numbers of mitochondria in dorsal root ganglion neurons, hippocampal neurons in 5- to 6-month-old db/db mice displayed smaller numbers of mitochondria, such a decrease was not seen in mice younger than 3 months. Between 3 and 6 months of age, complex I enzyme activity significantly declined by 15%–35% and ATP content was significantly altered. Pharmacologic or genetic inactivation of Drp1 prevented changes in mitochondrial morphology and function in db/db

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mouse hippocampus or human neuronal cells under hyperglycemic conditions, indicating the role of Drp1 in diabetes-induced mitochondrial dysfunction.[2] Furthermore, genetic activation of GSK3β without high glucose treatment can also promote mitochondrial fragmentation, while inactivation of GSK3β prevents high glucose-induced mitochondrial dysfunction. Taken together, these data suggest that GSK3β likely acts as an upstream signaling mechanism for Drp1 upregulation in diabetes-induced mitochondrial dysfunction.[2]

9. CONCLUSION

Several lines of evidence suggest that age-related AD and diabetes are predominantly associated with mitochondrial dysfunction. Mitochondrial defects result in increased ROS generation, abnormal protein–protein interactions, and decreased mitochondrial ATP production. Overproduction of ROS and mPTP formation with attendant compromised mitochondrial function contribute importantly to neuronal perturbation. Several other factors including intracellular Ca^{2+}, Aβ, and CypD also play an important role in mPTP formation, leading to mitochondrial dysfunction. In addition, disruption of mitochondrial dynamics by altered mitochondrial fusion and fission events contributes to mitochondrial and synaptic injury and cognitive decline relevant to the pathogenesis of AD and diabetes (Fig. 3). Thus, inhibition of mPTP opening by blocking CypD and regulation of mitochondrial dynamics are rational targets for potential therapeutic strategies for AD and diabetes.

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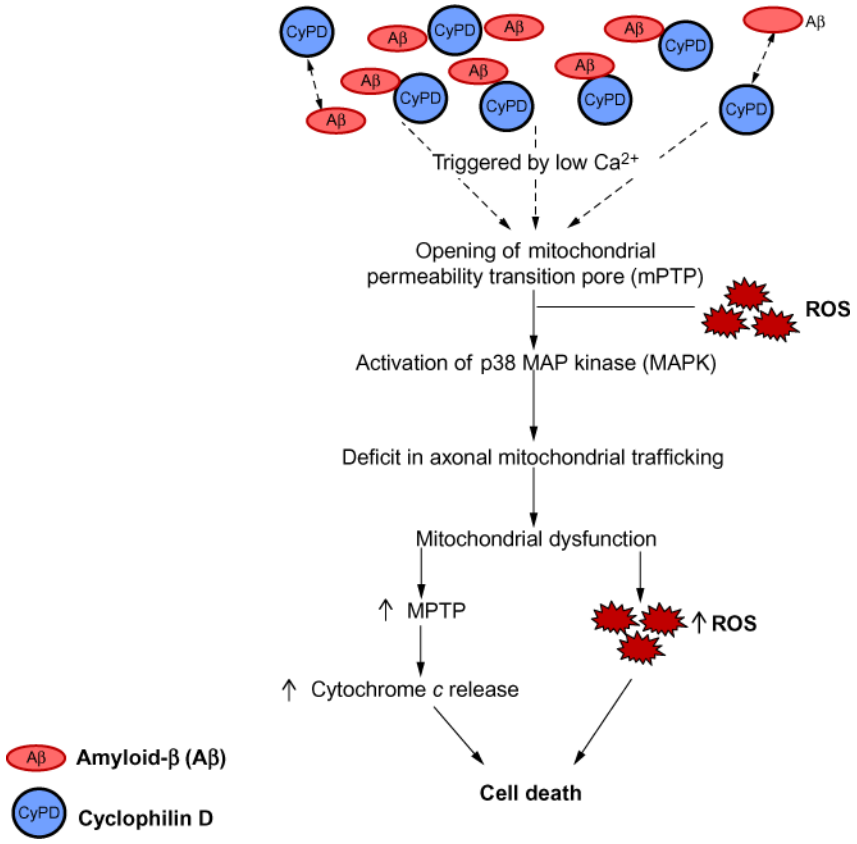

Fig. 1.

Effect of Aβ on CypD-involved mPTP formation. Aβ-cyclophilin D interaction mediates impairments in axonal mitochondrial transport due to an increase in the opening of CypD-mediated mitochondrial permeability transition pore (mPTP). This leads to the disruption of Ca^{2+} balance and increases the production/accumulation of reactive oxygen species (ROS). Elevation of Ca^{2+} and oxidative stress activates the downstream p38 MAP kinase signaling pathway, thus contributing to mitochondrial dysfunction.

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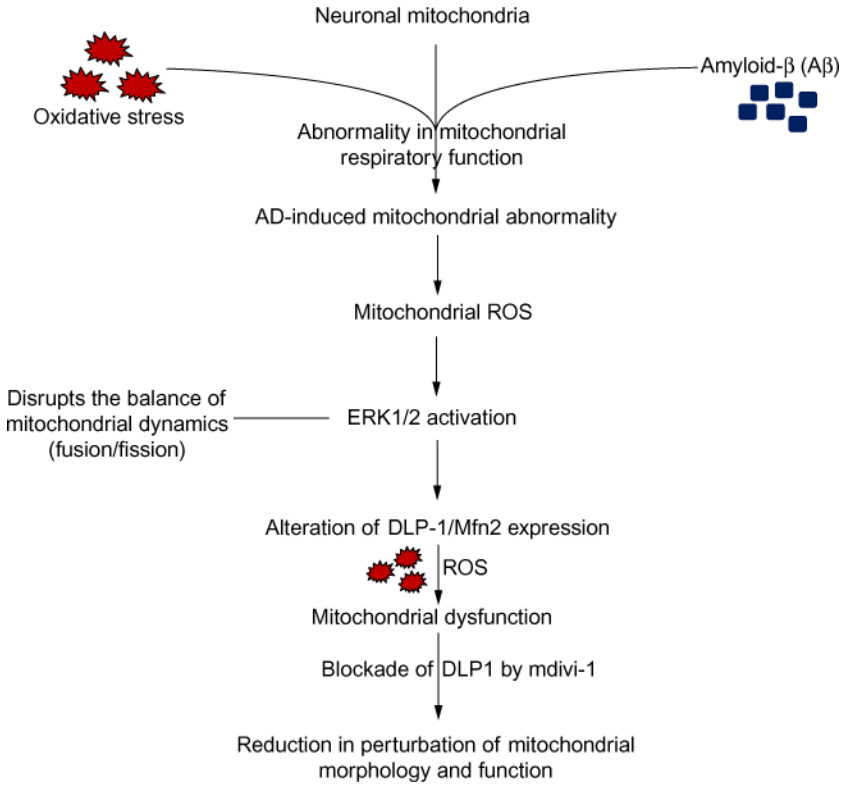

Fig. 2.

Effect of AD on mitochondrial dynamics. AD-induced mitochondrial respiratory function abnormality orchestrates ROS generation and accumulation and subsequently activates ERK signal transduction. Activation of ERK signaling disrupts mitochondrial dynamics and results in altered DLP1 and Mfn2 expression, which eventually leads to mitochondrial dysfunction. Inhibition of DLP1 or Mfn2 expression attenuates AD- or MCI-derived mitochondrial and neuronal dysfunction (Mdivi-1, an inhibitor for DLP1).

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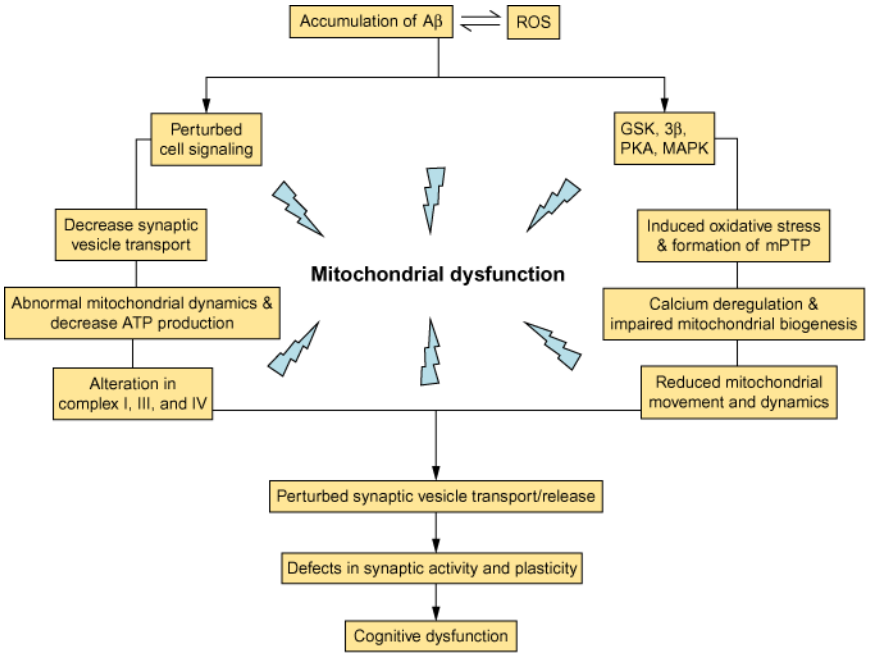

Fig. 3.

The cellular factors and related pathways contribute to Aβ-mediated mitochondrial defects and synaptic damage. Aβ accumulation perturbs mitochondrial transport and dynamics, cell signaling, synaptic mitochondrial structure and function, leading to decreased energy metabolism/ATP production, deregulation of calcium homeostasis, perturbed cell signaling cascades, altered key enzymes associated with mitochondrial respiratory chain, induced oxidative stress, and, eventually, synaptic injury and cognitive decline.