Factors Debilitating Mitochondrial Function

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Contributor: Sang Ryong Kim

Alzheimer's disease (AD) is the most frequent cause of age-related neurodegeneration and cognitive impairment, and there are currently no broadly effective therapies. The underlying pathogenesis is complex, but a growing body of evidence implicates mitochondrial dysfunction as a common pathomechanism involved in many of the hallmark features of the AD brain, such as the formation of amyloid-beta (Aβ) aggregates (amyloid plaques), neurofibrillary tangles, cholinergic system dysfunction, impaired synaptic transmission and plasticity, oxidative stress, and neuroinflammation, that lead to neurodegeneration and cognitive dysfunction. Indeed, mitochondrial dysfunction concomitant with progressive accumulation of mitochondrial Aβ is an early event in AD pathogenesis. Healthy mitochondria are critical for providing sufficient energy to maintain endogenous neuroprotective and reparative mechanisms, while disturbances in mitochondrial function, motility, fission, and fusion lead to neuronal malfunction and degeneration associated with excess free radical production and reduced intracellular calcium buffering. In addition, mitochondrial dysfunction can contribute to amyloid-β precursor protein (APP) expression and misprocessing to produce pathogenic fragments (e.g., Aβ1-40).

Keywords: mitochondria ; free radical ; mitophagy

1. Aging

Advanced age is a major risk for multiple neurodegenerative disorders due to accrued damage and impaired self-repair. Aging is associated with marked changes in mitochondria structure and function. For instance, several reports have revealed profound age-dependent changes in mitochondrial membrane architecture, such as the disappearance of cristae and inner membrane vesicles. Furthermore, the dissociation of ATP synthase dimers into monomers ruptures the outer membrane and releases apoptogens into the cytoplasm. In addition, inner membrane vesiculation and dissociation of ATP synthase dimers impairs the capacity to maintain sufficient ATP (energy charge) for essential cellular functions. Age-dependent accumulation of somatic mtDNA deletions and base substitution results in reduced expression of mtDNA-encoded OXPHOS enzymes, enhancing superoxide (O_2^-) production at OXPHOS complexes I/III and reducing ATP generation efficiency, thereby increasing the probability of metabolic failure and apoptosis. Impaired mitochondrial homeostasis during aging appears to be associated with disequilibrium between fusion and fission, with the predominance of fission over fusion preventing functional complementation of damaged mitochondria and thus accelerating deterioration [1]. Further, age-dependent accumulation of synaptic mitochondria is reported to interfere with synaptic activities, including the ATP production, and calcium homeostasis required for efficient depolarization-evoked release of neurotransmitter vesicles and plasticity, thereby impairing cognition and memory [2][3]. Compared to nonsynaptic mitochondria, synaptic mitochondria are more prone to age-dependent alterations and accumulation of Aβ aggregates.

Aging is the most important risk factor for the development of sporadic AD, which increases in the prevalence of only 2% between 65–69 years to 25% in individuals older than 90 [4]. Therefore, several cohort studies have emphasized that age must be considered when assessing the likely efficacy and safety of interventions against AD [5]. In addition to metabolic failure, the aging process may be driven by the accumulation of free radical damage. As mitochondria are the principal source of free radicals in the cell, oxidative damage would be most severe to mitochondrial macromolecules, in particular mtDNA [6]. Prolonged accumulation of free radicals is further associated with reduced activities of antioxidant enzymes, such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione reductase in the AD brain [7][8].

Furthermore, increased free radical generation, reduced ATP synthesis, loss of tissue regeneration capacity, and impaired DNA repair mechanisms will contribute to misfolded protein formation and aggregation, including aggregates that enhance the activities of the APP lytic enzymes β- and γ-secretase. This enhancement augments APP amyloidogenic processing, leading to Aβ plaque formation and resulting in AD-associated impairments, such as focal neurodegeneration and cognitive decline [6][9]. Further, a secondary mitochondrial cascade may mediate damage caused by a primary Aβ cascade, or Aβ produced as part of a primary mitochondrial cascade could itself cause harm [10]. Reports also suggest

that an aging-mediated reduction in proteasome activity may further promote Aβ and tau accumulation [11][12]. Collectively, these aging-related processes form a vicious cycle, resulting in progressive increases in mitochondrial dysfunction as well as Aβ and tau accumulation, the two major pathological hallmarks of AD.

2. Genetically Induced Mitochondrial Dysfunction

Alzheimer's disease is characterized by the abnormal processing and accumulation of mutant or damaged intracellular and extracellular proteins, increasing neuronal vulnerability to dysfunction. Several studies have revealed a higher occurrence of both nuclear and mtDNA mutations in AD brains [13][14]. Genetic mutations in presenilin 1 (PSEN1), presenilin 2 (PSEN2), APP, tau, and APOE4 genes are strongly associated with Aβ aggregation and AD development [15][16]. Among these genes, mutations in APP (21q21), PSEN1 (14q24), and PSEN2 (1q42) are fully penetrant and follow an autosomal dominant inheritance pattern, resulting in aggressive forms of early-onset AD that account for approximately 5% of all AD cases [17]. In addition, other susceptibility genes are believed to increase AD risk or drive pathogenesis through complex interactions with environmental factors. For instance, APOE (19q13) allele polymorphisms are associated with increased risk for late-onset AD, typically at 65 years or older [18].

Mitochondria DNA is composed of complementary H- and L-strands in a circular form with an approximate length of 15.5 kb [19]. Human mtDNA possesses 37 genes, of which 13 encode for respiratory and electron transport chain (ETC) components, 2 for ribosomal (r)RNAs, and 22 for transfer (t)RNAs necessary for mitochondrial protein synthesis [20]. Among the 13 mtDNA genes associated with the respiratory system and ETC, seven encodes complex I (NADH dehydrogenase, ND) components ND1, ND2, ND3, ND4, ND4L, ND5, and ND6, one encodes the complex III (cytochrome reductase), three encode complex IV (cyt c oxidase or COX) components COX I, COX II, and COX III, and two encode complex V (ATP synthase) components ATPase6 and ATPase8. Other subunits of complex II are encoded by nuclear nDNA. While mtDNA is critical for the proper functioning of mitochondria, it is prone to oxidative damage due to proximity with free radical generation sites, the lack of DNA-protective histones, and less efficient DNA repair mechanisms; indeed, it is estimated that mtDNA is ten times more prone to mutations than nDNA [21]. These mutations can occur at sites of known mtDNA transcription and replication regulatory elements, disrupting ETC component expression, and mitochondrial homeostasis. Moreover, mtDNA mutations (e.g., partial deletions, duplications, and point mutations) can be inherited maternally. These mutations then propagate through clonal expansion, eventually reaching a threshold for significant deleterious effects on mitochondrial function, resulting in cell death, and other age-related changes. Mitochondrial dysfunction is strongly associated with cognitive deficits and dementia due to high metabolic requirements, including for the synaptoplastic processes underlying higher-order cognitive functions [22]. For instance, Tanaka et al. (2008) reported impaired retention and consolidation of memory traces in mice harboring mtDNA mutations (Mito-mice) [23]. Hence, mutations in mtDNA, such as somatic mutations in OXPHOS genes, as well as several allelic polymorphisms (e.g., in APOE) are strongly associated with particular pathophysiological features of AD, including cognitive impairment and OS from excessive free radical generation [24][25][26].

3. Environmental Toxins and Mitochondrial Dysfunction

Recent studies have proposed that various lifestyle × environmental interactions can increase AD risk. Mitochondrial dysfunction is exacerbated by toxins such as pesticides, organic pollutants, heavy metals (Pb, MeHg, Cd, and As), xenobiotic compounds, industrial toxic waste products, and polychlorinated biphenyls among others. Exposure to such toxic agents has been well documented to cause neurotoxicity via mitochondrial dysfunction, leading to symptoms similar to those of AD [27][28]. Much ongoing research aims to determine the direct role of metal toxicity in mitochondrial dysfunction and AD progression [29]. In addition to mitochondrial function and morphology, some toxins have been shown to impair mtQC systems in AD models. For example, high-dose scopolamine administration induced several AD critical features in experimental animals, such as free radical generation, cognitive impairment, and accumulation of Aβ [30][31], and to increase mitochondrial vulnerability to swelling and membrane potential (ΔΨm) dissipation, which is required for coupling of the ETC to ATP production [32]. Streptozotocin was also found to induce cognitive impairments and brain accumulation of both Aβ and hyperphosphorylated tau [33][34]. Further, treatment was associated with decreased activity of complex I and complex IV, increased dynamin-related protein 1 (Drp1) protein expression, and decreased (depolarized) ΔΨm [33][35]. Treatment of cells with Aβ has also been found to induce mitochondrial defects, including ΔΨm depolarization, membrane fragmentation, and generation of free radicals. These examples strongly suggest that mitochondrial dysfunction contributes to AD risk and pathogenesis, underscoring mitochondria as promising targets for AD treatment.

4. Metabolic Syndrome (MetS)-Induced Mitochondrial Dysfunction

Multiple lines of evidence indicate that an imbalanced diet (high-calorie or calorie-deficient) results in mitochondrial failure and metabolic syndrome (MetS), which in turn can increase the risk for AD [36]. Characteristic features of MetS include metabolic disturbances that facilitate tissue stress and dysfunction leading to insulin resistance (IR), a closely related event to mitochondrial dysfunction [37]. Hyperglycemia due to obesity is reported to disrupt the normal TCA cycle in the mitochondrial matrix [38]. Middle-age obesity is strongly correlated with cognitive impairment and increased susceptibility to AD [36][39]. Further, MetS also result in the accumulation of advanced glycation end products (AGES) that can initiate hyperactive free radical generation, leading to oxidative stress, and seed aggregation of Aβ fibrils in neurons and microglia [40]. Mounting evidence suggests a complex reciprocal association between mitochondria dysfunction and MetS disorders such as diabetes, obesity, and non-alcoholic fatty liver disease, which may, in turn, elevated AD risk. Further study is required to verify associations between MetS and AD and to elucidate the underlying molecular pathways linking these disorders.

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