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MITOCHONDRIAL DYSFUNCTION IN THE PATHOGENESIS OF ALZHEIMER'S DISEASE: A REVIEW

Maitrayee Banerjee Mukherjee*

Ph.D, Assistant Professor, Department of Physiology, Krishnagar Govt. College, Krishnagar, University of Kalyani.

***Corresponding Author: Maitrayee Banerjee Mukherjee**

Ph.D, Assistant Professor, Department of Physiology, Krishnagar Govt. College, Krishnagar, University of Kalyani.

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ABSTRACT

Alzheimer's Disease (AD) is a type of dementia that causes loss of memory, cognitive impairment and development of some non cognitive features such as myoclonus, seizures etc. Biomarkers of important categories of neuropathologic change of AD, i.e., β-amyloid (Aβ) deposition, pathologic tau, and neurodegeneration, have been developed. Although AD is defined on the basis of amyloid-β plaque and tau neurofibrillary tangle deposition within the neocortex but the biochemical and metabolic changes in the brain that characterize the disease remain incompletely understood. The functional and metabolic changes of mitochondria in both the nervous tissue and rest of the body is observed early in this disease, and both amyloid and tau have detrimental effects on mitochondrial function. ROS generated cause damages in mitochondrial DNA (mtDNA) and other mitochondrial components, inducing a dysfunctional mitochondrial state. These include mitochondrial DNA damage, dysfunctional mitochondrial DNA expression, increased mitochondrial DNA mutations, reduced mitochondrial DNA copies, increased oxidative damage, reduced mitochondrial axonal transport, and overall impaired mitochondrial dynamics In this review article, various changes in the function and structure of mitochondria and its role in the pathogenesis of AD is discussed.

KEYWORDS: Dementia, Alzheimer's Disease, Mitochondria DNA , Mutation.

INTRODUCTION

Alzheimer's disease (AD) is one of the most prevalent neurodegenerative disease which is characterized by impaired loss of memory and decline in cognitive function due to progressive loss of neurons in the brain.[1] AD is the leading cause of dementia worldwide. In developed countries, 1 in 10 people over the age of 65 are affected by dementia of some form, with the frequency of AD almost doubling within this specific population every 5 years. By mid-century, the number of Americans age 65 and older with Alzheimer's dementia may grow to 13.8 million[1,2] The major symptom presents as deterioration of cognition and memory functions due to the progressive and selective loss of neurons in forebrain and other brain areas. The key clinical features are **impairment of episodic memory (** relative preservation of distant memory and amnesia for more recent events), **language deficit, apraxia (**inability to carry out skilled motor activities), **agnosia(** failure to recognize objects such as clothing, places and people**), impaired frontal executive function** (inaptitude of organizing, planning and sequencing of work), **posterior cortical atrophy (**least common presentation of AD with visual disorientation due to initial involvement of occipital lobes and occipitoparietal regions that results complex visual symptoms), **anosognosia** (lack of insight to seek medical attention or counseling) and development of some **late non-cognitive features** (myoclonus followed by seizures,reversal of sleep-wakefulness cycle, impaired swallowing leading to aspiration pneumonia).[3,4]

DIAGNOSIS

Magnetic Resonance Imaging (MRI) of brain typically shows characteristic atrophy of mesial temporal lobe structures, including hippocampi which progresses subsequently to generalized cerebral atrophy. In the early stages the imaging may be normal and selective regional atrophy is seen in AD variants such as posterior cortical atrophy (PCA) with occipital lobe atrophy.[1] Characteristic MRI and pscychometric testing abnormalities are sufficient to make a diagnosis if the clinical history is suggestive. CSF tau and beta amyloid measurement is helpful in cases of diagnostic difficulty but not yet widely available.[5] The *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition [*DSM-IV*]) criteria for diagnosing dementia requires the loss of 2 or more of the following: memory, language, calculation, orientation, or judgment.[6] The National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) Work Group criteria requires the presence of dementia documented by clinical examination, deficits in at least 2 cognitive domains,

absence of other systemic disorders, progressive worsening of memory for the diagnosis of "probable AD."[7]

The Mini-Mental State Examination (MMSE) is a bedside test which can help to evaluate changes in a patient's cognitive abilities. In addition, a diagnosis of probable AD necessitates the exclusion of other neurodegenerative disorders associated with dementia such as frontotemporal dementia (including frontotemporal dementia with Parkinsonism 17 and Pick disease).[6]

PATHOGENESIS AND ETIOLOGY OF ALZHEIMER' S DISEASE

The disease is believed to originate with neuronal degeneration in the second layer of the entorhinal cortex and progresses to the hippocampus, temporal cortex, front-parietal cortex, and further to the subcortical nuclei.[7] AD brains and cerebrospinal fluid contain elevated levels of malondialdehyde (MA) and 4-hydroxy nonenal (4-HNE). Several years of intense research have revealed that multiple cellular changes are implicated in the development and progression of disease, including mitochondrial damage, synaptic damage, Aβ formation and accumulation, inflammatory responses, deposition of hyperphosphorylated tau (P-Tau) and neurofibrillry tangles (NFTs), hormonal imbalance, and neuronal loss.[1,5.7] The amyloids could occlude cerebral blood vessels which leads to amyloid angiopathy. Among these cellular changes, mitochondrial dysfunction and synaptic damage are early changes in AD pathogenesis.[8] Electron microscopic analysis of postmortem brain shows that all forms of plaques, including diffuse plaques those are associated with neuropathology, are distinctly characterized by neuritic and synaptic dystrophie.[9] Preplaque increased levels of Aβ correlate with AD-characteristic alterations in synapses as evident on microscopy labeling the presynaptic protein synaptophysin in brain.[7,10]

Molecular Pathology of Alzheimer's Disease

A great deal about molecular pathology of Alzheimer's disease is now understood due to extensive cellular studies using biotechnological tools in last few decades. The main pathological hallmarks of AD are deposition of β amyloid (Aβ) in amyloid plaques in cortical areas.[7] Amyloid precursor protein (APP) is an integral membrane protein concentrated in the synapse and implicated as a regulator of synapse formation, neural plasticity. Proteolysis of APP by secretase enzyme releases $A\beta_{1-42}$ amyloid monomers, which are the building blocks of amyloid plaques.[8] First, α-secretase (nonneurotoxic "normal" cleavage) or β-secretase (potential neurotoxic "abnormal" cleavage) cleaves APP, and a second cleavage of the β-secretase product, by γ-secretase, cleaves APP further to produce Aβ. Depending on the point of cleavage by γ-secretase, 2 main forms of Aβ are produced consisting of either 40 or 42 amino acid residues (Aβ40 or Aβ42).[9] The most common form of Aβ in humans is 40 amino acids long and is called Aβ40. A 42-amino-acid–long fragment, Aβ42, is less abundant than Aβ40 and differs only in that it has 2 additional amino acid residues at the C-terminus.[8,9] Studies indicate that the Aβ42 fragment is associated with AD. Amyloid-β is derived from the amyloid precursor protein (APP) after cleavage by secretases. The proportion of Aβ40 to Aβ42 is particularly important in AD because Aβ42 is far more prone to oligomerize and form fibrils than the more abundantly produced Aβ40 peptide.[9,10,11]

This Aβ molecules can aggregate to form flexible soluble oligomers which may exist in several forms and are toxic to nerve cells. It seems that the excessive deposition of β-amyloid (Aβ) peptides and intracellular neurofibrillary tangles of tau protein hyperphosphorylated forms contribute to the damage of both DNA and RNA. Furthermore, it is believed that RNA-interference can affect both the level of pathological proteins (Aβ, tau protein) and the onset and progress of AD.[12] Additionally Aβ in a form other than amyloid plaques are also able to damage synapses and neurons. Transgenic mice engineered to secrete directly high amounts of Aβ not generated from APP readily form extensive plaques but do not show behavioral decline which supports the hypothesis that that secreted Aβ may not be the primary toxic form of Aβ.[10] Other molecular factors related to the immunological cause (TREM2) of the disease are a disorder of the lipid (ABCA1, ABCA7) or biothiol (MTHFD1) metabolism and of the transport of metabolites (BIN1).[12]

Genetics of Alzheimer's Disease

A first degree relative with Alzheimers Disease confers a double lifetime risk of AD and approximately 60% of early onset AD cases have multiple cases of AD within their families.[13] There are rare autosomal dominant monogenic early onset forms of familial AD with high penetrance, caused by mutations in specific genes which account for only 1% of cases of AD.[6] The E4 allele of the apolipoprotein A gene confers an increased risk of AD (2-3 times lifetime risk),especially if two copies of the E4 allele are inherited (6-8 times risk).[14] Several other candidate genes have been identified as risk factors for AD in large genome-wide association studies. Point mutations in the amyloid precursor protein (APP) gene can cause AD and the occurrence of three copies of the APP gene on chromosome 21 in Down syndrome patients is responsible for the high incidence of AD.[13] Mutations of Presenilin (PS) 1 and 2 affects the γsecretase enzyme function. The PS1/2 and APP genes may be sequenced for mutations in selected early –onset cases with a family history.[15]

Mitochondrial Dysfunction in Alzheimers Disease

Mitochondria play major role in cellular function including cell survival, energy metabolism, balancing reactive oxygen species (ROS), and mediating cell death pathways. Even though mitochondria are ubiquitous organelles, their complex mitochondrial proteome

exhibits tissue-heterogeneity to meet the metabolic and energy needs specific to each cell type. They are responsible for producing coenzyme A, a critical constituent of neurotransmitter acetylcholine, and converts fatty acids to readily available energy sources.[16]

Mitochondrial dysfunction causes a range of diseases spanning from incurable neonatal neurodevelopmental diseases to adult-onset neurodegenerative diseases.[16,17] Proteomic and protein expression studies confirmed exclusion of some proteins and enzymes of oxidative phosphorylation pathway as one of the most affected processes in the cortex of AD patients.[17] Amyloid precursor protein (APP) contains a mitochondrial targeting signal and an internal sequence rich in acidic amino acids, which can form stable complexes with the translocase of the outer membrane 40 (TOM40) and the translocase of the inner mitochondrial membrane 23 (TIM23). This translocation is independent of the membrane potential and differs from the conventional mechanism of mitochondrial protein.[18] Different studies suggest that accumulation of APP into mitochondria membranes and cristae alters the activities of enzyme such as COX, pyruvate dehydrogenase, and α-ketoglutarate dehydrogenase complex.[19] A positive correlation between levels of soluble Aβ and hydrogen peroxide in brain mitochondria isolated from APP transgenic mice was established which supports the hypothesis that mutant APP or soluble Aβ impairs mitochondrial metabolism.[20]

Various studies pursuing mitochondrial dysfunction in AD reported mtDNA fragmentation, dysfunctional mtDNA expression, increased mtDNA mutations, reduced mtDNA copies and reduced axonal transport and overall impaired mitochondrial dynamics.[18,21] The pathogenesis of AD includes reduced mitochondrial biogenesis and ATP formation. Simultaneously the energy of synaptic vesicles for delivering neurotransmitters to the synapse is compromised which further aggravates the situation.[21]

Oxidative Stress and Mitochondrial Dysfunction in Alzheimer's Disease

Mitochondria is the chief consumer of cellular oxygen, and also produce many byproducts, including reactive oxygen species (ROS) (1% and 5% of total cellular ROS in physiological conditions) such as superoxide (O_2^-), hydroxyl radical (OH), and hydrogen peroxide (H_2O_2).[20] Additionally peroxidation of mitochondrial membrane phospholipids may result in the release of Ca^{2+} and even the electron transport chain enzyme cytochrome *c*, which can signal cell death.[22] In AD where oxidative stress is attributed as the primary cause of disease progression, ROS increase the expression of β-secretase through activation of p38 mitogen-activated protein kinase (MAPK)[23] and increase abnormal tau phosphorylation by activation of glycogen synthase kinase 3, GSK3[24] Moreover, the activity of a mitochondrial enzyme α-ketoglutarate dehydrogenase complex (KGDHC) is reduced in brains of AD patients which is extremely sensitive to various oxidants whether they are added to cells or generated internally in cells.[25]

Studies with redox proteomics of AD brain tissue also confirmed oxidative modification and reduced cellular activity of some mitochondrial enzymes involved with glucose metabolism.[26] It was proposed that the metabolic changes appeared earlier than the onset of the histopathological markers and symptoms.[27] The glucose uptake in the brain is usually measured with the positron emission tomography (PET) tracer 18-fluorodeoxyglucose (fDG). In subjects with AD, PET studies have consistently demonstrated a decreased glucose metabolism (between 20% and 30% lower than healthy individuals) in hippocampus, posterior cingulate, temporal, and parietal lobes.[28] Also cell lines containing mtDNA from AD patients displayed an increased ROS and free radical production, compared to controls.[29] Furthermore, oxidative modifications to creatine kinases and ATP synthase in brain mitochondria help to explain the relationship between ROS overproduction and metabolism in mild cognitive impairment (MCI) and AD.[30] The oxidative modification–induced reduction of ATP production in AD is responsible for the synaptic disintegrity and transmission.[31] Dysfunctional mitochondria are removed from cytoplasm through mitophagy but in AD it is suppressed by excessive levels of ROS and Aβ. Increased ROS inhibits the fusion between late endosomes and lysosomes and thus enhance Aβ processing.[29,31]

Alteration of Mitochondrial Gene Expression in Alzheimer's Disease

Evidences suggest that oxidative damage stimulates an upregulation of genes relating to mitochondrial metabolism.[23] Decreased mRNA levels of the mitochondrial-encoded cytochrome oxidase (COX) subunits I, II and III in brains of AD patients were observed.[32] mRNA studies in transgenic amyloid precursor protein (APP) mice at different age groups revealed that genes which are responsible for mitochondrial energy metabolism and apoptosis are up regulated in all age groups induce an excessive production of free radicals, and cause mitochondrial dysfunction. Scientists propose that an increase in cytochrome oxidase gene expression might be the result of functional compensation by the surviving neurons or an early mitochondrial alteration related to increased oxidative damage.[33]

Mitochondrial Ca^{2+} Disturbance in Alzheimers Disease

Ca^{2+} is involved in most aspects of neuronal function: differentiation and migration, synaptic transmission and plasticity, vesicle release, cell death and survival or neuronal–glial communication.[18] Mitochondria play a key role in cellular Ca^{2+} homeostasis, and Ca^{2+} is an important regulator of vital neuronal processes, such as

secretion, motility, metabolic regulation, synaptic plasticity, proliferation, gene expression, and apoptosis.[18,21] Different studies suggest that the dysregulation of Ca^{2+} homeostasis is a critical factor in accelerating AD pathology. Increase in mitochondrial Ca^{2+} can certainly rise the permeability transition (PT), that is the permeability of the inner mitochondrial membrane (IMM) to ions and solutes mediated by the PT pore (mPTP), a high-conductance, a voltage-dependent channel which requires a permissive Ca^{2+} matrix load for opening. Persistent opening of mPTP is accompanied by membrane depolarization, Ca^{2+} release, matrix swelling with IMM remodeling, and eventually, rupture of the outer mitochondrial membrane (OMM) with the release of cytochrome c and other apoptogenic proteins.[35]

Furthermore tau and beta-amyloid dysfunction have been extensively coupled to altered cytosolic Ca^{2+} homeostasis through various mechanisms. These scenarios compromise mitochondria in two ways: challenging mitochondrial Ca^{2+} buffering capacity and, in addition, the cellular bioenergetics of cells in which mitochondrial function could be already impaired.[36]

Mitochondrial Dysfunction of Microglia in Alzheimer's Disease

Microglia are the highly dynamic resident innate immune cells which are critical to brain immunity and homeostasis. Proliferation and activation of microglia in the brain around the amyloid plaques is observed in AD. Aβ interacts with microglial receptors, such as triggering receptor expressed in myeloid cells 2 (TREM2) which activate downstream pathways those are responsible for mitochondrial damage, inflammation and cytotoxicity.[32] TREM2 binds to apolipoproteins apoE and clusterin which are themselves encoded by AD risk genes. TREM2–ligand interactions are impaired by TREM2 variants that increase AD risk, implying that these AD variants are at least partial loss-of-function mutants. [37] Fibrillar Aβ activates nicotinamide adenine dinucleotide phosphate (NADPH) oxidase in microglia which causes induction of mitochondrial ROS which further causes neurotoxicity.

Microglial mitophagy also plays a significant role in development of neuroinflammation in AD. Phagocytosis and clearance of Aβ depends on mitochondrial health.[29] It has been experimentally confirmed that the efficiency of microglia to clear Aβ plaques reduces chronic inflammation and mitochondrial dysfunction. Restoring mitochondrial function and mitophagy in microglia helps reduce neuroinflammation and is therefore neuroprotective.[38]

CONCLUSION

Mitochondrial function in AD is impaired which is evident to be associated with a decrease in neuronal ATP levels and overproduction of ROS which indicates that the organelle may fail to maintain the cellular energy needed. In short, there is decreased activity of many TCA cycle enzymes, Electron Transport Chains and also notable mitochondrial fragmentation that correlate with diminished ATP production.

Mitochondria also act as intracellular buffers of cytosolic calcium. It internalizes calcium by uniporters and releases by Na^{+}/Ca^{++} or H^{+}/Ca^{2+} exchanger. Dysregulation of calcium homeostasis can potentiate excitotoxicity that further cause neurodegeneration.

It has also been reported that there is increased oxidation of mitochondrial DNA in frontal, parietal and temporal lobes of AD patients. Also mitochondrial fission/fusion and mitophagy disruption may have consequences on the mitochondrial pool of neurons. Modification of mitochondrial function in early stages may be a target for management or prevention of sporadic AD related neurodegenation. Understanding the cellular mechanism of mitochondrial dysfunction and therapeutically targeting mitochondrial bioenergetics in AD could be a novel treatment approach and promise for preventing or slowing the onset of AD.

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