

Review Article

Amyloid Beta Mediated Mitochondrial Dysfunction in Alzheimer's disease: A Mini Review.

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ABSTRACT

Mitochondria, the sub cellular organelles inside cells transform oxygen and nutrients into adenosine triphosphate (ATP), the main source of fuel for cellular activity and survival. Mitochondria, sustain life through energy transformation and intracellular signaling. Increasing evidence implicates mitochondrial dysfunction induced bioenergetic failure in multiple neurodegenerative disorders including Alzheimer's disease (AD). Alzheimer's disease is the most tragic geriatric complication that takes away the essence of life. Beside tau hyper phosphorylation, cholinergic dysfunction and neuroinflammation, amyloid β are the prominent pathological markers of the disease. The major target of $A\beta$ is the mitochondrion and these cellular powerhouses differ between Alzheimer's brains and healthy brains. $A\beta$ block the transport of nuclear-encoded mitochondrial proteins to mitochondria, interact with mitochondrial machinery, disrupt the electron transport system, increase oxidative stress leading to mitochondrial damage and ultimately prevent neurons from functioning normally. This has led to the view that mitochondria play an important role in Alzheimer's, not only as contributors but also as drivers of disease.

KEYWORDS

Amyloid β , Alzheimer's disease, cognition, mitochondria.

1. INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia in the elderly. It is an epidemic with approximately 27 million people affected worldwide and this number is expected to rise (quadrupling by 2050) as the disease is still incurable despite vigorous research efforts. AD is becoming markedly more common with the aging of the world's population. It is estimated that by 2050, one in every 85 people will be living with AD (Cummings et al., 2018). The pathogenesis of Alzheimer's disease is very complex and involves molecular, cellular and physiological complexities. Soluble amyloid β ($A\beta$) oligomers, tau hyperphosphorylation, loss of basal forebrain cholinergic neurons, spine loss, abnormal spine morphology, reactive oxygen species, prolonged long-term depression and inhibition of long-term potentiation terminating in neuronal cell death has been strongly implicated in the pathology of Alzheimer's disease (Pitt et al., 2009; Worden et al., 2013).

Recent studies of postmortem brains from AD patients and transgenic mouse models of AD suggest that oxidative damage, induced by $A\beta$, is associated with mitochondrial dysfunction in AD progression. $A\beta$ and amyloid-precursor protein (APP) are known to localize to mitochondrial membranes, block the transport of nuclear-encoded mitochondrial proteins to mitochondria, interact with mitochondrial proteins, disrupt the electron-transport chain, increase reactive oxygen species production, cause mitochondrial damage and prevent neurons from functioning normally (Hemachandra and Bea, 2008).

1.1. Mitochondria in Brain

Mitochondria populate the cytoplasm of mammalian cells, including neurons, which rely on mitochondrial energy production for survival. These organelles contain their own genome—the mitochondrial DNA (mtDNA) which encodes essential subunits of the respiratory chain where electrons are combined with oxygen to enable the flow of energy through mitochondria. Energized mitochondria can then synthesize ATP that fuels energy-dependent intracellular reactions (such as endocytosis, ion transport and neurotransmitter biosynthesis) and sustain other critical mitochondrial functions (Ca^{2+} handling, reactive oxygen species production etc.), contributing to intracellular signaling (Wallace, 2010). Mitochondria also respond acutely to the metabolic environment by undergoing morphological and functional changes that may influence the cellular aging process (Picard, 2013). These changes in shape of mitochondria are regulated through processes of fusion and fission (making longer or shorter organelles, respectively) and actively traffic between cell compartments such as the soma, axon and presynaptic boutons (Chan, 2012).

Interestingly, although mitochondrial dysfunction resulting from mtDNA mutations often cause severe multisystemic diseases, and the brain appears most vulnerable to mitochondrial defects, as mitochondria regulate fundamental aspects of brain function (Picard and McEwen, 2014).

Mitochondria are indispensable for neuronal function as the limited glycolytic capacity of neurons cells makes them highly dependent on aerobic oxidative phosphorylation (OXPHOS) for their energetic needs. However, OXPHOS is a major source of endogenous toxic free radicals that are products of normal cellular respiration. Several efficient enzymatic processes are continuously operational to quench the reactive species including SOD, GPx, superoxide reductase (SRed), catalase (CAT), peroxiredoxin (Prx), thioredoxin/thioredoxin reductase (Trx/

TrxRed). Inevitably, if the amount of free radical species produced overwhelms the neuronal capacity to neutralize them, oxidative stress occurs, followed by mitochondrial dysfunction and neuronal damage. Reactive species generated by mitochondria have several cellular targets including mitochondrial components themselves (lipids, proteins and DNA). The lack of histones in mitochondrial DNA (mtDNA) and the diminished capacity for DNA repair render the mitochondria an easy target to oxidative stress event (Hoye, 2008).

Mitochondria also serve as high-capacity Ca^{2+} sinks, which allows them to stay in tune with changes in cytosolic Ca^{2+} loads and aid in maintaining cellular Ca^{2+} homeostasis that is required for normal neuronal function. Conversely, excessive Ca^{2+} uptake into mitochondria has been shown to increase ROS production, inhibit ATP synthesis, induce mitochondrial permeability transition pore (PTP) and release small proteins that trigger the initiation of apoptosis, such as cytochrome c and apoptosis-inducing factor (AIF), from the mitochondrial intermembrane space into the cytoplasm. Released cytochrome c binds apoptotic protease-activating factor 1 (Apaf-1) and activates the caspase cascade (Hengartner, 2000). Such alterations in mitochondrial function have been proposed as a causative mechanism in the pathogenesis of AD (Moreira, 2010).

Mitochondrial dysfunction- a primary event in AD mitochondrial cascade states that, in the sporadic AD, mitochondrial dysfunction is the primary event that causes $\text{A}\beta$ deposition, synaptic degeneration and NFTs formation (Swerdlow 2009). Mitochondria are abundant in synaptic terminals and ATP production by mitochondria is crucial for synaptic function. Impaired mitochondrial function associated with reduced ATP supply lead to synaptic dysfunction, reduced neuronal and synaptic outgrowth and finally apoptosis.

1.2. Brain –an easy prey to mitochondrial dysfunction

Although the brain represents only 2% of the body weight, it receives 15% of cardiac output and accounts for 20% of total body oxygen consumption. This energy requirement is largely driven by neuronal demand for energy to maintain ion gradients across the plasma membrane that is critical for the generation of action potentials. This intense energy requirement is continuous; even brief periods of oxygen or glucose deprivation result in neuronal death (Moreira et al., 2010).

Mitochondria are small organelles within cells that generate energy for cells. They can be considered to be a cell's "power-plant" (NINDS), 2018). Approximately 90 percent of the energy needs of the body's tissues are met by mitochondria. This energy is stored in a molecule known as Adenosine Triphosphate (ATP) which is the product of a long chain of biochemical and biophysical events that convert sugar and oxygen into energy.

ATP can also be used as a signaling molecule in its own right, for example as a neurotransmitter. ATP can be stripped of one or all three of its phosphate groups and become, respectively, adenosine diphosphate (ADP) or simply adenosine, and both these substances work as signaling molecules too. Dysregulation of the receptors of ATP, ADP, or adenosine has been implicated in various disorders including Alzheimer's disease (Burnstock, 2016).

All cells of the human body require ATP as the fundamental energy source to support life and mitochondria produce the majority of ATP, thus impaired mitochondrial function is implicated in the chronic and degenerative health conditions including obesity, cardiovascular disease, cancer, diabetes, sarcopenia and neurodegenerative diseases (Sebastian et al., 2017]. To produce ATP,

mitochondria burn down digested food with the help of the oxygen and during process they dump several waste products: carbon dioxide, water and *free radicals*.

Free radicals are chemicals that are highly corrosive, first and foremost to the mitochondria themselves but also to their hosts. Indeed, how healthy a cell is can be judged by the shape of its mitochondria. They are tubular when all is well, turn into donut forms under the stress of too many free radicals and into blobs when damage is irreversible. In a vicious cycle, the more its shape departs from normal, the more free radicals the mitochondrion produces (Ahmad et al., 2013).

The nervous system is the most important system that cannot possibly function without mitochondria (Markham et al., 2014). Neurons relay information by firing and mitochondria provide the energy for this. Transported by miniature motors along tubular tracks, they travel extensively inside the neuron to furnish ATP where it is needed (Sheng & Cai, 2012). Although neurons use up ATP even when all they are doing is basic housekeeping, energy is in highest demand at synapses, where most of the action occurs. Mitochondria are transferred and docked there only when they are in good shape. As soon as they become unfit and in need of replacement they are promptly destroyed, either on the spot (Ashrafi et al., 2014) or after having been removed and transported away (Lin & Sheng, 2015). Poor quality and poor transport of mitochondria precedes the onset of Alzheimer's diseases (Correia et al., 2016; Shlevkov & Schwarz, 2017) and might play a part in schizophrenia and depression as well (Deheshi et al., 2013).

Thus a place where mitochondrial trouble occurs frequently is the brain having mass mere 2% of the body's total but it uses 25% of the body energy (Houzel, 2012). By comparison, it is only 13% in other primates and 2% to 8% in the vast majority of vertebrates (Mink et al., 1981). A resting cortical neuron turns out to consume 4.7 billion ATP molecules per second; a resting human brain goes through nearly 6 kilograms of them per day (Zhu et al., 2012). Inevitably, brain mitochondria produce a lot of free radicals and this contributes to making the brain itself particularly vulnerable to free-radical damage—or “brain rust” as it has been called (de Oliveira et al., 2012). Cognitive symptoms in Alzheimer's disease are preceded by energy deficits in neurons (Kapogiannis & Mattson, 2011).

Mitochondria also affect synaptic plasticity as they supply the energy needed to strengthen neuronal connections; on the other hand, by delivering the same enzymes they use when forced to kill off their host cell, they can prune connections away (Jeanneteau & Arango-Lievano, 2016; Markham et al., 2014). As people age, their blood flow diminishes and the brain gets progressively less blood and thus less glucose and oxygen for mitochondria to make ATP with. Eventually (de la Torre, 2002), brain mitochondria no longer meet the normal energy demand and neurons degenerate, leading to dementia—whose prevalence, between the ages of 55 and 90, increases 400-fold (Prince et al., 2015).

The most disrupted region in Alzheimer's disease is the hippocampus—an area, involved in memory that compared to most other areas of the brain contains remarkably low levels of a protein that helps oxygen diffuse to the mitochondria (Burmester et al., 2000).

1.3. Mitochondrial dysfunction in AD

Mitochondria are involved in vital metabolic processes, such as calcium and iron homeostasis, redox signalling, programmed cell death, innate immunity and finally participate in the regulation of various physiological processes (Picard, 2016). In Alzheimer's disease mitochondria changes in many ways that include rate of decrease in metabolism (Santos, 2010) disruption in mitochondrial fission and fusion (Cunnane, 2010), mitochondrial concentration decreases in CSF (Podlesniy2016), number of cristae decreases (2013) and there are morphological changes as well (Bonda et al.,2011).

Alzheimer's pathology is accompanied by a decrease in expression and activity of enzymes involved in mitochondrial bioenergetics, which would be expected to lead to compromised electron transport chain complex activity and reduced ATP synthesis. In addition to the lowered mitochondrial bioenergetic capacity, impairment of oxidative phosphorylation is associated with increased free radical production and the resultant oxidative damage which is characteristic of brains from AD. Increased oxidative stress, coupled with dysregulation of calcium homeostasis and resulting apoptosis of vulnerable neuronal populations, are proposed to underlie the loss of synaptic activity and associated cognitive decline (Yao et al., 2009). Further, overproduction of the APP and A β may affect dynamics of mitochondrial fusion/fission, impair mitochondrial transport, disrupt the electron transfer chain, increase ROS production and impair mitochondrial function (Isaac G. Onyango, 2016).

1.4. Amyloid beta and AD

Amyloid β is the major component of neuritic plaques deposited in AD brain. A β is generated by abnormal processing of APP in AD neurons. The APP processing occurs in 2 pathways - amyloidogenic and non-amyloidogenic pathway. In the amyloidogenic pathway, APP undergoes sequential proteolysis by β - and γ -secretases, resulting in A β , and in the non- amyloidogenic pathway, cleavage occurs by the α -secretase, within the A β domain and prevents the formation of full A β (Reddy and Beal, 2008).

In early-onset AD, genetic mutations in APP, presenillin (PS1 and PS2) genes activate β - and γ -secretases and cleave A β . In late-onset AD, oxidative stress has been proposed to activate β -secretase and to facilitate the secretion of A β (Reddy and Weeney, 2006; Mattson 2004; Reddy2006). A β is generated in neurons and in several intracellular sites, including Golgi apparatus, endoplasmic reticulum, endosomal-lysosomal systems multivesicular bodies [LaFerla, 2007] including mitochondria, which causes cellular dysfunction (Reddy and Beal, 2008).

Mitochondria are important cell organelles that are responsible not only for the conversion of the bulk of nutritive energy, but also exert a major role in aging processes and in the development of age-related diseases. While accumulation of amyloid deposit as senile plaques is a hallmark feature of AD, growing evidence suggests that elevated Amyloid beta levels contribute to the mitochondrial abnormalities, which might evolve in the pathogenesis in AD. Both amyloid precursor protein (APP) and A β have been found in mitochondrial membranes and interact with mitochondrial proteins, overproduction of which might affect dynamics of mitochondrial fusion/fission (Manczak et al., 2011),impair mitochondrial transport, disrupt the electron transfer chain, increase ROS production (Manczak et al., 2006), and impair mitochondrial function (Reddy, 2009).

In the immediate vicinity of A β plaques, there is mitochondrial loss, structural abnormalities, and functional distress, suggesting that senile plaques are a focal source of toxicity in the living animals. The mitochondrial alterations would be expected to contribute to neural network disruptions and subsequent behavioral deficits observed in these animals, and by extension, to AD patients (Xie et al., 2013). Near plaques, there is loss of mitochondrial membrane potential (MMP) which is a surrogate to impaired energy production by mitochondria, which would have profound implications for local metabolism and activity. The robust deficits occur within a halo that surrounds individual plaques, resulting in a radius of toxicity. There are also local alterations in spine density, neuritic curvature, calcium dysregulation and oxidative stress (Koffie et al., 2009; Xie et al., 2013).

A β have been shown to localize mainly to the inner mitochondrial membrane, causing excessive reactive oxygen species (ROS) production (Lin and Beal, 2006). Besides the respiratory chain injuries, A β have been shown to enhance the expression of cyclophilin D, a mitochondrial protein regulating the opening of the transition pore (Du et al., 2008), and to promote S-nitrosylation of dynamin-related protein 1, a protein that governs mitochondrial dynamics (Cho et al., 2009).

A β also form a complex with the mitochondria. A β -peptide-binding alcohol dehydrogenase (ABAD), an interaction that leads to accelerated cell death (Yao et al., 2011; Raffaella Solito, 2013). In addition, A β induced ROS elevation activates lipid peroxidation pathways, that generate excessive amounts of highly toxic aldehydes, particularly 4-hydroxy-2-noneal (4-HNE). HNE forms stable adducts with a myriad of proteins required for mitochondrial functions (Petersen and Doorn, 2004; Schneider et al., 2008).

A β does not cause toxicity in cells depleted of mitochondria (Morais Cardoso, 2002) and a mitochondrial protein, the voltage-dependent anion channel (VDAC) has been shown to participate in A β -induced toxicity (Marin 2007; Reddy 2013).

2. CONCLUSION

Alzheimer's disease is a common, devastating, neurodegenerative and neuropsychiatric disorder that is pathologically defined by the accumulation of extracellular A β containing plaques, beside other characteristic features. A β and mitochondria interaction reveals A β accumulates in synapses and synaptic mitochondria, leading to abnormal mitochondrial dynamics and synaptic degeneration in AD neurons. A β initiate a complex pathology that leads to reduced mitochondrial mass, defective axonal transport, impaired mitochondrial biogenesis and synaptic degeneration. The present work advocates that A β is responsible for mitochondrial and synaptic deficiencies and future strategies may be designed keeping A β induced mitochondrial dysfunction at the center stage.

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