AUCTORES
Globalize Your research

Journal of Neuroscience and Neurological Surgery
Brian E. Staveley, J Neuroscience and Neurological Surgery

Open Article

Short Communication

The Role of Mitochondria in Alzheimer's disease: Neurodegenerative Disease and Future Therapeutic Options

P. Githure M'Angale and Brian E. Staveley*
Department of NeuroBiology

***Corresponding Author :** **Brian E. Staveley**, Department of NeuroBiology,

Received date: January 02, 2018;Accepted date : January 20, 2018 ; Published date: February 05,2018.

Citation for this Article: **Brian E. Staveley**, The Role of Mitochondria in Alzheimer's disease: Neurodegenerative Disease and Future Therapeutic Options . J Neuroscience and Neurological Surgery. **Doi:** 10.31579/2578-8868/026

Abstract

Mitochondria are cytoplasmic organelles responsible for life and death. Extensive evidence from animal and clinical studies suggests that mitochondria play a critical role in aging, cancer, diabetes and neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, and Huntington's disease. Several lines of research suggest that mitochondrial oxidative damage is an important cellular change in most late-onset neurodegenerative diseases. Further, emerging evidence suggests that structural changes in mitochondria, including increased mitochondrial fragmentation and decreased mitochondrial fusion, are critical factors associated with mitochondrial dysfunction and cell death in aging and age-related diseases. In addition, epigenetic factors and lifestyle activities may contribute to selective disease susceptibility for each of these diseases. This paper discusses research that has elucidated features of mitochondria that are associated with cellular dysfunction in aging and neurodegenerative diseases. This paper also discusses mitochondrial abnormalities and potential mitochondrial therapeutics in AD.

Alzheimer's disease (AD) is characterized by neuronal loss and gradual cognitive impairment. AD is the leading cause of dementia worldwide and the incidence is increasing rapidly, with diagnoses expected to triple by the year 2050. Impaired cholinergic transmission is a major role player in the rapid deterioration associated with AD, primarily as a result of increased acetylcholinesterase (AChE) in the AD brain, responsible for reducing the amount of acetylcholine (ACh). Current drug therapies, known as AChE inhibitors (AChEIs), target this heightened level of AChE in an attempt to slow disease progression. AChEIs have only showed success in the treatment of mild to moderate AD symptoms, with the glutamate inhibitor memantine being the most common drug prescribed for the management of severe AD.

Keywords

Alzheimer′s disease; mitochondria; Bioenergetics; Mitochondrial DNA; Neuroinflammation; Mitohormesis; caloric restriction; Hypometabolism; Mitophagy;

Introduction

AD is categorized into two major forms: sporadic AD (sAD) and familial AD (fAD) with < 10% of AD cases being familial (Thinakaran, 1999) and showing autosomal-dominant transmission within affected families. Although sAD has a heterogeneous etiology and heritability of 70% to 80% (Gatz et al., 2006; Wingo et al., 2012), age is its most prominent biological risk factor (Carr et al., 1997) with APOE4 gene being an additional risk factor (Dorszewska et al., 2016). Female gender is also an important contributor that is partially explainable by the fact that postmenopausal women lose the protection that estrogens confer to neuronal mitochondria against beta-amyloid (Aβ) toxicity. Older women are also more likely than age-matched men to suffer from metabolic diseases, such as diabetes and obesity that increase their chances of developing AD Most fAD patients have at least one affected first-degree relative (van Duijn et al., 1994; Campion et al., 1999; Jarmolowicz et al., 2014), and in 10% to 15% the mode of inheritance is autosomal dominant transmission (Campion et al., 1999; Jarmolowicz et al., 2014). fAD is triggered by gene mutations of amyloid precursor protein (APP) (chromosome 21), presenilin 1 (PSEN1) (chromosome 14), or presenilin 2 (PSEN2) (chromosome 1). This elicits Aβ aggregation in earlier years and the onset of the disease is as early as 20–30 years of age (Su et al., 2008; Muirhead et al., 2010) with the majority being diagnosed between 45 and 60 years.

Additional risk genes that have been identified by genome-wide association studies (GWAS) include: the gene for clusterin (CLU) also known as apolipoprotein J (localized on chromosome 8), the gene encoding the complement component (3b/4b) receptor 1 (CR1) (chromosome 1), the gene encoding PI-binding clathrin assembly protein (PICALM) (chromosome 11), the gene encoding the bridging integrator 1 (BIN1) (chromosome 2), and the disabled homolog 1 (DAB1) (chromosome 1). Additional novel risk loci associated with sAD are: sortilin-like receptor 1 (SORL1), triggering receptor expressed on myeloid cells 2 (TREM2), the membrane-spanning 4-domains, subfamily A (MS4A), ATP-binding cassette transporter A1 and A7 (ABCA1 and 7), methylenetetrahydrofolate dehydrogenase 1 (MTHFD1) and CD33 (Allen et al., 2012). These newly identified genes are involved in transport, lipid metabolism (Zhu et al., 2015; El gaamouch et al., 2016), immune response and APP metabolism (De Strooper and Karran, 2016).A mitochondrion contains 2–10 copies of mtDNA (Reddy, 2008). The human mtDNA consists of a 16.5 kb, double-stranded, circular DNA molecule (Anderson et al., 1981). mtDNA contains 13 polypeptide genes that encode essential components of the ETC. mtDNA also encodes the 12S and 16S ribosomal RNA (rRNA) genes and the 22 transfer RNA (tRNA) genes required for mitochondrial protein synthesis (Reddy and Beal, 2005). Nuclear genes encode the remaining mitochondrial proteins, metabolic enzymes, DNA and RNA polymerases, ribosomal proteins, and mtDNA regulatory factors, such as mitochondrial transcription factor A.

Nuclear mitochondrial proteins are synthesized in the cytoplasm and are subsequently transported into mitochondria. mtDNA is inherited exclusively from the mother and is present in thousands of copies per cell. Mitochondrial number and morphology are controlled by an equilibrium of mitochondrial fusion and fission (Chan, 2006) that is vital for metabolism, energy production, Ca^{2+} signaling, ROS production, apoptosis, and senescence Fusion allows the exchange of mitochondrial components including mtDNA between different mitochondria. mtDNA due to their proximity to the respiratory chain and a lack of protective histones have a very high mutation rate that is about ten times faster compared to the nuclear DNA (nDNA).

New mtDNA mutations arise frequently in the maternal lineage and initially present as a mixture of the wild-type and mutant mtDNAs, defining the so-called heteroplasmic state. mtDNA mutations are most often heteroplasmic (mixed population of normal and mutant mtDNAs). During cellular divisions, the mutant mtDNAs will be randomly segregated into the daughter's cells and the percentage of mutant mtDNAs in different cell lineages will drift toward either pure mutant or normal (or homoplasmy) (Stewart and Chinnery, 2015). As the percentage of mutant mtDNAs increases in the cell, energy output falls, resulting in an overall mitochondrial dysfunction in the cell. Hence, the ratio of mutant to normal mtDNA contributes to the severity of the disease. Severe mitochondrial damage impairs fusion resulting in fragmentation of mitochondria that are then selectively removed by an autophagic process called mitophagy.

Cellular Therapy

Cell-based therapies are a promising alternative currently being developed to enable the reversal of neurodegeneration in AD either directly by replacing injured neuron or indirectly by stimulating neuronal repair *via* paracrine signaling at the injury site (Baraniak and McDevitt, 2010). Neurons and glial cells have successfully been generated from embryonic stem cells (ESCs), neural stem cells (NSCs), neural progenitor cells (NPCs), mesenchymal stem cells (MSCs), induced pluripotent stem cells (iPSCs), and induced neuronal cells (iN), induced neuronal progenitor cells (iNPCs). Transplantation of NSCs into animal models of neurodegenerative diseases, including AD, increases the total amount of mtDNA, messenger RNA and protein levels of mitochondrial biogenesis-related factors as well as protein levels of mitochondrial fission genes.

Targeting ROS

Targeting detrimental neuronal ROS at the production stage without affecting ROS signaling would be ideal in preventing and treating AD. In this regard, it has been shown that mitochondria-targeted antioxidants potently sequester reactive oxygen intermediates and confer greater protection against oxidative damage in the mitochondria than untargeted cellular antioxidants. The ability of mitochondria-targeted antioxidants to confer greater protection against oxidative damage in the mitochondria than untargeted cellular antioxidants provide has been attributed to their ability to cross the mitochondrial phospholipid bilayer and eliminate ROS where it is being generated.

Targeting the proteasome

Proteosomal activity can also be enhanced by using Pyrazolone containing small molecules which block USP14, a proteasome-associated deubiquitinating enzyme that inhibits the processing of ubiquitin–protein complexes destined for degradation by the proteasome (Lee et al., 2010). PD169316 is a novel small molecule p38 MAPK inhibitor and a very potent activator of proteasome activity enhanced Proteolysis Targeting Chimeric (PROTAC)-mediated and ubiquitin-dependent protein degradation and decreases the levels of both overexpressed and endogenous α-synuclein in a bimolecular fluorescence complementation (BiFC) assay.

Role of Aging and Epigenetic Factors in Neurodegenerative Diseases

In AD and PD, there are no differences pathologically between early onset familial patients and late onset patients. Only difference is that in late-onset patients, pathological changes occur later than in the early-onset patients.

In early-onset cases, genetic mutations accelerate the disease process. In late-onset patients, in the absence of genetic mutations, age-related cellular changes control disease progression, which is why late-onset AD and PD patients take more time to exhibit pathological features. As described above, age-related mitochondrial abnormalities contribute to disease progression in late-onset AD and PD. However, if age-dependent mitochondrial abnormalities are likely factors affecting the development of AD and PD (and possibly even affecting cancer and diabetes in aged individuals), it is still unclear what makes some aged persons susceptible to PD development and others, to AD. Epigenetic factors and lifestyle activities may contribute to age-dependent susceptibility to these diseases.

Mitochondrial dysfunction is an early event in AD

Using in situ hybridization to mtDNA, immunocytochemistry of cytochrome oxidase (COX), and morphometry of electron micrographs of biopsy specimens, we demonstrated that neurons showing increased oxidative damage in AD also possessed a striking and significant increase in mtDNA and COX [. Moreover, we found that much of the mtDNA and COX was localized in the neuronal cytoplasm and, in the case of mtDNA, in vacuoles associated with lipofuscin, whereas morphometric analysis showed that mitochondria were significantly reduced in AD. Interestingly, the cellular expression of COX subunits II and IV is reduced during aging and these age-related changes are more marked in AD, suggesting that aging is a major risk factor for this disease. However, Cottrell et al. Observed that the distribution of amyloid plaques is anatomically distinct from the COX-deficient hippocampal pyramidal neurons, and the neurons containing NFT or apoptotic labeling were always COX-positive. The authors concluded that COX-deficient, succinate dehydrogenase-positive hippocampal neurons indicative of high mtDNA mutation load do not appear to be prone to apoptosis or to directly participate in the overproduction of tau or Aβ.

Mitochondrial-Directed Therapies

The discovery that mitochondrial dysfunction underlies the pathogenesis of many neurodegenerative diseases has opened a window for new therapeutic strategies aimed at preserving/ameliorating mitochondrial function. In nearly all cases where mitochondrial dysfunction contributes to disease, a major cause of damage is overproduction of ROS by mitochondria, either directly or as a secondary consequence of other malfunctions

Conclusion

Mitochondrial dysfunction is an early feature of AD pathology. Any damage to mitochondria by either Aβ or ROS can result in interrupting the usual mechanisms by which ROS are destroyed, therefore further increasing the number of ROS present in the organelle. It has been found that in post-mortem AD brains there is a deficit of COX, the terminal enzyme in the mitochondrial respiratory chain responsible for reducing oxygen radicals, supporting the theory that ROS are involved in the mitochondrial damage found in AD. Many antioxidants have been investigated as therapies for AD, and further studies have been carried out to find mitochondria specific antioxidants to enable a greater concentration of antioxidants to accumulate in the mitochondria, allowing a more specific method for combatting mitochondrial oxidative stress. It has been suggested that as early as 2025, prevention or effective treatment of AD may be realized.

References

1. Anandatheerthavarada HK, Biswas G, Robin MA, Avadhani NG. Mitochondrial targeting and a novel transmembrane arrest of Alzheimer's amyloid precursor protein impairs mitochondrial function in neuronal cells. J Cell Biol. 2003;161:41–54.k DOI: 10.1083/jcb.200207030
2. Anderson S, Bankier AT, Barrell BG, de Bruijn MH, Coulson AR, Drouin J, Eperon IC, Nierlich DP, Roe BA, Sanger F, Schreier PH, Smith AJ, Staden R, Young IG. Sequence and organization of the human mitochondrial genome. Nature. 1981;290:457–465.
3. Beal MF. Mitochondria take center stage in aging and neurodegeneration. Ann Neurol. 2005;58:495–505.

4. Caspersen C, Wang N, Yao J, Sosunov A, Chen X, Lustbader JW, G, Yan SD. Mitochondrial Abeta: a potential focal point for neuronal metabolic dysfunction in Alzheimer's disease. FASEB J. 2005;19:2040–2041
5. Chandrasekaran K, Giordano T, Brady DR, Stoll J, Martin LJ, Rapoport SI. Impairment in mitochondrial cytochrome oxidase gene expression in Alzheimer disease. Brain Res Mol Brain Res. 1994;24:336–340.https://doi.org/10.1016/0169-328X(94)90147-3
6. Coskun PE, Beal MF, Wallace DC. Alzheimer's brains harbor somatic mtDNA control-region mutations that suppress mitochondrial transcription and replication. Proc Natl Acad Sci U S A. 2004;101:10726–10731.https://doi.org/10.1073/pnas.0403649101
7. Crouch PJ, Blake R, Duce JA, Ciccotosto GD, Li QX, Barnham KJ, Curtain CC, Cherny RA, Cappai R, Dyrks T, Masters CL, Trounce IA. Copper-dependent inhibition of human cytochrome c oxidase by a dimeric conformer of amyloid-beta1-42. J Neurosci. 2005;25:672–679.DOI: https://doi.org/10.1523/JNEUROSCI.4276-04.2005
8. Devi L, Prabhu BM, Galati DF, Avadhani NG, Anandatheerthavarada HK. Accumulation of amyloid precursor protein in the mitochondrial import channels of human Alzheimer's disease brain is associated with mitochondrial dysfunction. J Neurosci. 2006;26:9057–9068.
9. DiMauro S, Schon EA. Mitochondrial disorders in the nervous system. Annu Rev Neurosci. 2008;31:91–123.
10. Doody RS, Gavrilova SI, Sano M, Thomas RG, Aisen PS, Bachurin SO, Seely L, Hung D dimebon investigators. Effect of dimebon on cognition, activities of daily living, behaviour, and global function in patients with mild-to-moderate Alzheimer's disease: a randomised, double-blind, placebo-controlled study. Lancet. 2008;372:207–215https://doi.org/10.1016/S0140-6736(08)61074-0
11. Du H, Guo L, Fang F, Chen D, Sosunov AA, McKhann GM, Yan Y, Wang C, Zhang H, Molkentin JD, Gunn-Moore FJ, Vonsattel JP, Arancio O, Chen JX, Yan SD. Cyclophilin D deficiency attenuates mitochondrial and neuronal perturbation and ameliorates learning and memory in Alzheimer's disease. Nat Med. 2008;14:1097–1105.
12. Gibson GE, Sheu KF, Blass JP. Abnormalities of mitochondrial enzymes in Alzheimer disease. J Neural Transm. 1998;105:855–870.
13. Hansson Petersen CA, Alikhani N, Behbahani H, Wiehager B, Pavlov PF, Alafuzoff I, Leinonen V, Ito A, Winblad B, Glaser E, Ankarcrona M. The amyloid beta-peptide is imported into mitochondria via the TOM import machinery and localized to mitochondrial cristae. Proc Natl Acad Sci U S A. 2008;105:13145–13150.
14. Hirai K, Aliev G, Nunomura A, Fujioka H, Russell RL, Atwood CS, Johnson AB, Kress Y, Vinters HV, Tabaton M, Shimohama S, Cash AD, Siedlak SL, Harris PL, Jones PK, Petersen RB, Perry G, Smith MA. Mitochondrial abnormalities in Alzheimer's disease. J Neurosci. 2001;21:3017–3023.
15. DOI: https://doi.org/10.1523/JNEUROSCI.21-09-03017.2001
16. Keil U, Bonert A, Marques CA, Scherping I, Weyermann J, Strosznajder JB, Müller-Spahn F, Haass C, Czech C, Pradier L, Müller WE, Eckert A. Amyloid beta-induced changes in nitric oxide production and mitochondrial activity lead to apoptosis. J Biol Chem. 2004;279:50310–50320.
17. Lin MT, Beal MF. Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. Nature. 2006;443:787–795.
18. Lin MT, Simon DK, Ahn CH, Kim LM, Beal MF. High aggregate burden of somatic mtDNA point mutations in aging and Alzheimer's disease brain. Hum Mol Genet. 2002;11:133–145.
19. Manczak M, Anekonda TS, Henson E, Park BS, Quinn J, Reddy PH. Mitochondria are a direct site of A beta accumulation in Alzheimer's disease neurons: implications for free radical generation and oxidative damage in disease progression. Hum Mol Genet. 2006;15:1437–1449.https://doi.org/10.1093/hmg/ddl066