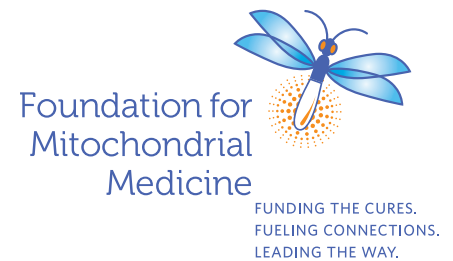


# Alzheimer's & Mitochondrial Disease

Mitochondrial disease can look like a number of better known diseases: Autism, Parkinson's, Alzheimer's, Lou Gehrig's disease (ALS), muscular dystrophy and chronic fatigue, among others. And it's this web of complexity and connectivity that makes mitochondrial disease research valuable to so many. Research shows that mitochondrial dysfunction is often at the crux of these more commonly recognized diseases.

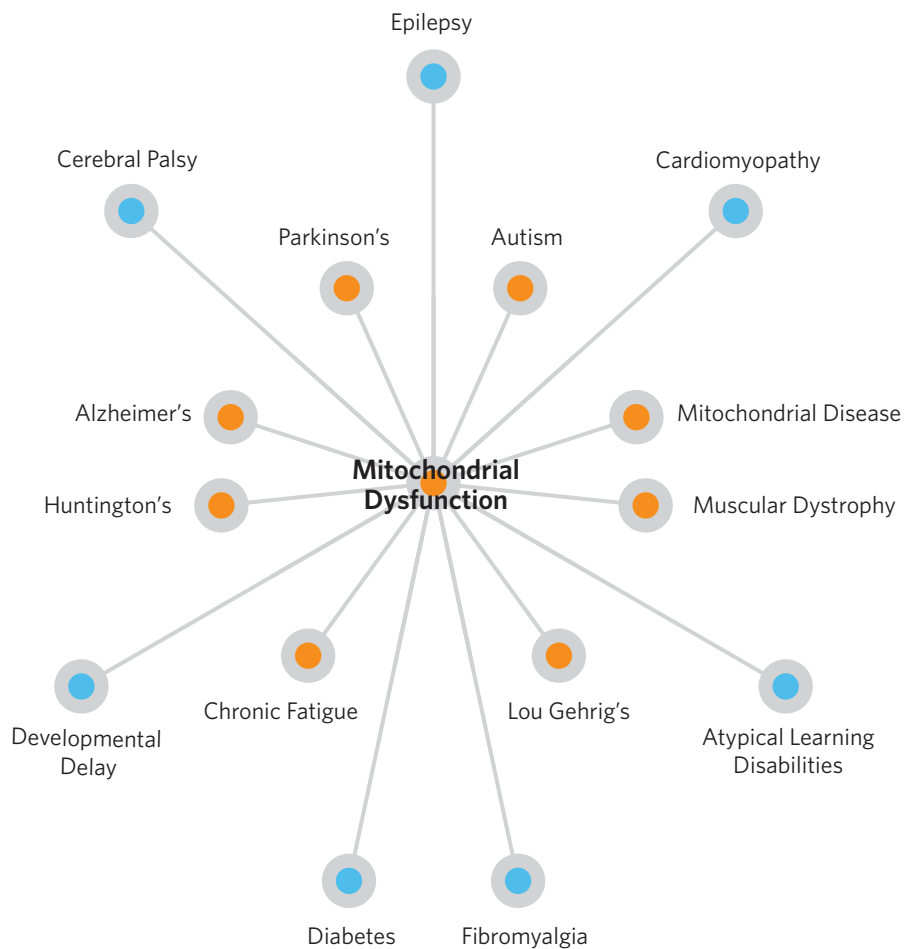


Recent reports and scientific studies linking mitochondrial disease to Alzheimer's include:

\* **A June 2010 article in the *International Journal of Experimental and Clinical Pathology*, found that Mitochondrial dysfunction has surfaced as one of the most discussed hypotheses acting as a trigger for the pathogenesis of Alzheimer's disease.** Mitochondria assume central functions in the cell, including ATP production, calcium homeostasis, reactive oxygen species generation, and apoptotic signaling. Although their role as the cause of the disease may be controversial, there is no doubt that mitochondrial dysfunction, abnormal mitochondrial dynamics and degradation by mitophagy occur during the disease process, contributing to its onset and progression. *Alzheimer's Disease: Diverse Aspects of Mitochondrial Malfunction*, Renato X Santos,1,2,3 Sónia C Correia,1,2,3 Xinglong Wang,3 George Perry,3,4 Mark A Smith,3 Paula I Moreira,1,5 and Xiongwei Zhu3 *IntJClinExpPathol.* 2010;3(6):570-581. Published online 2010 June 25. *Curr Alzheimer Res.* 2011 Jan 19. [Epub ahead of print]

## FAMILIAR CONNECTIONS

Mitochondrial dysfunction is a central element of familiar diseases.



Research shows that mitochondrial dysfunction is often a central element of these more commonly recognized diseases. Studies and reports indicate the "orange" ones are more influenced.

A cure for mitochondrial disease could impact cures for Autism, Parkinson's, Alzheimer's and Muscular Dystrophy

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# Mitochondria: The Common Upstream Driver of Abeta and Tau Pathology in Alzheimer's Disease.

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## Abstract

Mitochondrial dysfunction has been widely implicated in the etiology of Alzheimer's disease (AD). Evidence shows a mitochondrial-mediated impairment of autophagy that potentiates amyloid- $\beta$  (A $\beta$ ) deposition. Accordingly, recent data obtained from AD models, in which mitochondrial alterations are a prominent feature, demonstrated abnormalities in microtubule network, involving tubulin and tau post-translational modifications. In this review we will discuss mitochondrial-regulated processes where mitochondrial malfunction is likely to start a sequence of events leading to sirtuin-2 activation,

microtubule network breakdown, and impairment of the autophagic pathway. Because sirtuin-2 activity depends on cellular NAD<sup>+</sup> availability, mitochondrial regulation of NAD<sup>+</sup> levels may contribute to an increase in sirtuin-mediated tubulin deacetylation. A vicious cycle become installed which potentiates tau hyperphosphorylation, together with A $\beta$  overproduction and deposition. Overall, targeting microtubule network constitutes a promising strategy for pharmacological therapy in AD.

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# Early deficits in synaptic mitochondria in an Alzheimer's disease mouse model.

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## Abstract

Synaptic dysfunction and the loss of synapses are early pathological features of Alzheimer's disease (AD). Synapses are sites of high energy demand and extensive calcium fluctuations; accordingly, synaptic transmission requires high levels of ATP and constant calcium fluctuation. Thus, synaptic mitochondria are vital for maintenance of synaptic function and transmission through normal mitochondrial energy metabolism, distribution and trafficking, and through synaptic calcium modulation. To date, there has been no extensive analysis of alterations in synaptic mitochondria associated with amyloid pathology in an amyloid  $\beta$  (A $\beta$ )-rich milieu. Here, we identified differences in mitochondrial properties and function of synaptic vs. nonsynaptic mitochondrial populations in the transgenic mouse brain, which overexpresses the human mutant form of amyloid precursor protein and A $\beta$ . Compared with nonsynaptic mitochondria, synaptic mitochondria showed a greater degree of age-dependent accumulation of A $\beta$  and mitochondrial alterations. The synaptic mitochondrial pool of A $\beta$  was detected at an age

as young as 4 mo, well before the onset of nonsynaptic mitochondrial and extensive extracellular A $\beta$  accumulation. A $\beta$ -insulted synaptic mitochondria revealed early deficits in mitochondrial function, as shown by increased mitochondrial permeability transition, decline in both respiratory function and activity of cytochrome c oxidase, and increased mitochondrial oxidative stress. Furthermore, a low concentration of A $\beta$  (200 nM) significantly interfered with mitochondrial distribution and trafficking in axons. These results demonstrate that synaptic mitochondria, especially A $\beta$ -rich synaptic mitochondria, are more susceptible to A $\beta$ -induced damage, highlighting the central importance of synaptic mitochondrial dysfunction relevant to the development of Current Drug Targets.

*2010 Oct;11(10):1193-206.* 