

## MITOCHONDRIAL DYSFUNCTION IN NEUROPSYCHIATRIC DISORDERS

Mitochondrial disorders were first described in 1962 (Luft, Ikkos, Palmieri, Ernster, & Afzelius, 1962), and were initially thought to be uniformly progressive and fatal with onset in infancy or early childhood, typically associated with severe neurological manifestations, including stroke-like episodes, seizures, neuronal degeneration, organ failure and dementia. More recently, clinical observation and research has increasingly discovered a tremendous variety of more mild cases of adult-onset mitochondrial disorders and mitochondrial dysfunction in many diseases not previously thought of as “mitochondrial” in nature, suggesting that mitochondrial dysfunction not only manifests a diverse array of phenotypes, but may be a final common pathway in many disease states, as well as normal ageing. For a variety of reasons, the brain and nervous system are uniquely vulnerable to mitochondrial dysfunction, and many neurobehavioral symptoms may be related to impaired mitochondrial activity. This paper will discuss the origin and function of mitochondria, the pathogenesis of mitochondrial disease, and the neurobehavioral effects of mitochondrial dysfunction.

### Origin and Function of Mitochondria

Approximately 1.5 billion years ago, mitochondria were protobacteria appropriated by the primordial “anaerobic ancestor of the modern eukaryotic cell” (Cohen & Gold, 2001, p. 629). Mitochondria benefited these ancestral eukaryotes by removing oxygen, a toxic compound, and producing increased ATP as a byproduct, thus endowing eukaryotic host cells with the adaptive advantage of aerobic metabolism in exchange for shelter and a steady food supply (Kidd, 2005; Margulis & Bermudes, 1985). Because mitochondria were once autonomous microorganisms, only later becoming double membrane organelles within human cells, they have their own genomic DNA (mtDNA) separate from the host organism’s nuclear genome (nDNA).

This advantageous evolutionary symbiosis allowed for the development of multicellular life forms and rendered mitochondria endosymbionts critical for the survival of complex organisms, including human beings. For instance, the process of “burning food in the presence of oxygen” to produce energy, termed oxidative phosphorylation (OXPHOS), synthesizes adenosine triphosphate (ATP) from adenosine diphosphate (ADP), producing over 80% of the total energy needed by normal human adults (the remaining 20% is generated from glycolysis) (Cohen & Gold, 2001, p. 629). The vital OXPHOS process is carried out by the respiratory (electron transport) chain, a set of five protein and enzymatic complexes (complex I-V), which uses “the energy generated [...] to pump protons [...] between the inner and outer mitochondrial membranes” in order to maintain the electrochemical proton gradient necessary for ATP production (Dimauro & Davidzon, 2005, p. 222). Besides synthesizing crude fuels (nutrient precursors) into usable energy currency (ATP) through OXPHOS, mitochondria evolved to also become responsible for a number of other vital cellular functions, including: providing pathways of intermediate metabolism; manufacturing the building blocks of cells; maintaining organellar and cellular calcium homeostasis; carrying out amino acid biosynthesis, fatty acid oxidation and steroid metabolism; and making cellular life-death decisions as the gatekeepers of apoptosis (programmed cell death) (Cohen & Gold; Schon & Salvatore, 2003).

However, the sophisticated life of complex organisms came with a price: intrinsic to OXPHOS is the creation of highly reactive free radicals termed “reactive oxygen species” (ROS). ROS are “sparks of metabolism” producing toxic biochemical “smoke,” whose erosive effects on cellular structure and function damages mitochondria and cells themselves, leaving metabolic “ash,” further causing mitochondrial dysfunction and many disease states, typically including neurodegenerative disorders (Kidd, 2005, p. 271).

## Pathogenesis of Mitochondrial Disease

Mitochondrial disorders are “primary” or “secondary,” and can manifest in infancy or childhood, or in adolescence or adulthood (late-onset). Primary diseases result from mutations, most typically in nDNA, but also in mtDNA, usually inherited, but also acquired sporadically. They directly impact the composition and “function of the electron transport chain [and impair

mitochondrial OXPHOS]” resulting in damaged, dysfunctional or destroyed mitochondria (Hass et al., 2007, p. 1330). Some primary mitochondrial disorders are not inherited, rather result from spontaneous mutation (Schon & Salvatore, 2001).

In addition, some late-onset, secondary sporadic mitochondrial disorders are acquired, resulting from “mutations in mtDNA [which are] caused by exposure to an environmental toxin [e.g. drug or medication,] such as [the antibiotic] amino-glycoside-induced ototoxicity” (Cohen & Gold, 2001, p. 631). Mutations in mtDNA are also thought to accumulate with ageing, or from other stressors, such as chronic hypoxia, viral infection, radiation, chronic stress (and elevated cortisol levels), and chemical pollution (Cohen & Gold; Vernon et al., 2006). These “respiratory-chain-deficient-cells are apoptosis [programmed cell death] prone,” contributing to loss of vulnerable cells such as, for example, neuronal loss in the brain (Trifunovic & Larsson, 2008, p. 167).

Genotype and phenotype are not tightly linked, and each disorder is unique in its presentation in each individual. Mechanisms causing phenotypic variation include: maternal inheritance, in which mitotic segregation results in heteroplasmy, the variable ratio of normal-to-mutated mtDNA in a given cell, tissue, or organ (Cohen & Gold, 2001); threshold effect, when the number of mutant mitochondria in a particular postmitotic tissue reaches a critical mass (Dimauro & Davidzon, 2005); heterozygosity (different alleles at a corresponding chromosomal loci) which can show incomplete dominance (“manifesting carrier”) and the synergistic interaction of different alleles at different genetic loci (combinatorial heterozygosity) (Vladutiu, 2001); the excessive vulnerability of mitochondria to damage because they “lack protective histones” and “repair mechanisms,” and are “in close proximity to the electron transport chain, exposing it [mtDNA] to high concentrations of free radicals [ROS]” (Cohen & Gold, p. 631); and the triggering of apoptosis, which can cause excessive losses of often critical cells (Szewczyk & Wojtczak, 2002).

## Neurobehavioral Effects of Mitochondrial Dysfunction

Because mitochondrial diseases are multisystemic and heterogeneous, they affect “virtually any organ or tissue”, causing “any symptom in any organ at any age”, particularly in the central

(CNS) and peripheral nervous systems (PNS) (Haas et al., 2007, p. 1327). The brain is particularly vulnerable to mitochondrial dysfunction for a number of reasons: 1) it is postmitotic tissue and therefore, generally cannot create new cells (with the primary exception of the hippocampus [Nasrallah, 2007]), “diseased cells cannot be replaced by healthier neighbor cells”, and “no selection process weeds out sick cells” resulting in accumulation of mutant mitochondria (Cohen & Gold, 2001, p. 631); 2) the brain is restricted to the use of glucose, precluding neurons from alternative energy sources when mitochondria fail; 3) the brain has the highest concentration of mitochondria (due to its high energy demand) and is therefore more likely to accumulate ROS and secondary damage; 4) the brain “uses more oxygen and produces more energy per unit mass than any other organ”, requiring extremely high OXPHOS activity (Kidd, 2005, p. 272); 5) the brain is “loaded with unsaturated fatty acids” (such as in the myelin sheath cell membranes), causing cells to be particularly vulnerable to peroxidation caused by such ROS as H<sub>2</sub>O<sub>2</sub> (Kidd, p. 272); 6) the brain is “poorly equipped with antioxidant enzyme defenses” (Kidd, p. 273); and 7) neurons in the brain have a constant calcium flux and therefore need efficient mitochondria to “provide backup for calcium homeostasis. Thus, mitochondrial insufficiency could tip the delicate intracellular calcium balance toward cell death” (Kidd, p. 273).

In addition to the extreme vulnerability of the brain, because “nerve cells and Schwann cells are [also] extremely active metabolically, [requiring] a tremendous amount of energy to maintain the electrochemical gradient necessary for nerve transmission”, mitochondrial dysfunction often leads to neuropathy, causing “neuropathic pain and weakness, acute and chronic inflammatory demyelinating polyneuropathy”, “or autonomic [nervous system] features such as [absent deep tendon reflexes,] temperature instability [temperature dysregulation with low baseline temperatures], inappropriate sweating (or lack of sweating), orthostatic hypotension, [gastrointestinal dysmotility,] or bladder dysfunction” (Cohen & Gold, 2001, pp. 630-633; Dimauro & Davidzon, 2005).

In primary, inherited mitochondrial diseases, mitochondrial dysfunction often leads to severe neurobehavioral symptoms. For instance, in Leigh syndrome, typically an early-onset and progressive, fatal neurodegenerative disease, mutations in mtDNA (loci 8993 and 8994) “reduces

mitochondrial ATP synthesis by blocking the [enzyme] ATP synthase”, resulting in “ataxia, developmental delay, optic atrophy, [...] ophthalmoplegia (paralysis of the extraocular eye muscles resulting in immobility of the eyeball)”, eventual degeneration of the basal ganglia, brainstem dysfunction, and necrosis of subcortical regions of the brain “including thalamus, basal ganglia, brainstem, and spinal cord, accompanied by demyelination, gliosis, and vascular proliferation of affected areas”, which cause the “rapid decline in function [...] marked by seizures, dementia, [motor and mental regression] and ventilatory failure” characteristic of the syndrome (Cohen & Gold, 2001, p. 632; Schon & Manfredi, 2003, p. 305; Wallace & Lott, 2002, p. 978).

In Leber hereditary optic neuropathy (LHON) mutations in mtDNA, encoding subunits of complex I and V of the electron transport chain, cause selective neuronal degeneration of the optic nerve, resulting in “bilateral visual failure and blindness” (Schon & Manfredi, 2003, p. 304). However, in “LHON-plus” syndrome, more extensive mutations in these same mtDNA genes cause “basal ganglia degeneration and dystonia” and an “inherited form of levodopa-responsive parkinsonism” (Schon & Manfredi, p. 304).

Furthermore, a growing body of research has found mitochondrial dysfunction to be a significant causative feature of many neurodegenerative and psychiatric disorders, which are not primary mitochondrial disorders, including: Alzheimer disease, Parkinson disease, stroke, Amyotrophic Lateral Sclerosis (ALS), schizophrenia, bipolar disorder, and major depressive disorder, among others (Kidd, 2005; Shao et al., 2008).

For instance, in Parkinson disease (PD), a progressive neurodegenerative disorder characterized by “rigidity, tremor, and bradykinesia”, mitochondrial mutations are believed to be instrumental in the significant loss of “dopaminergic neurons in the substantia nigra”, typical of PD (Schon & Manfredi, 2003, p. 307). Specifically, the outer membrane of mutated mitochondria produces excessive amounts of *N*-methyl-4-phenylpyridinium ion (MPP<sup>+</sup>) which causes complex I deficiency, and progressive depletion of glutathione in affected neurons in the substantia nigra, resulting in parkinsonism (Kidd, 2005; Schon & Manfredi). Moreover, because complex I is a “principal source of free radicals [ROS] in the cell, altered complex I function in the substantia

nigra is responsible for the increased DNA damage and lipid peroxidation found in PD brains” (Schon & Manfredi, p. 307). Interestingly, stroke has also been associated with high concentrations of ROS, as it is the “flood of ROS generated in the neuronal and glia mitochondria during hypoxic-hyperoxic” ischemia that causes neuronal death and catastrophic brain tissue damage (Kidd, p. 273).

Mitochondrial dysfunction has also been strongly linked to Alzheimer disease (AD). Mutant nDNA and mtDNA, impaired OXPHOS, high concentrations of ROS, and alterations in mitochondrial enzymes have been found to cause “morphological and functional [mitochondrial] modifications [adversely] affecting dendritic trees and synapses, neurotransmitters, tissue perfusion and metabolism” in the frontal, temporal (middle temporal gyrus), and parietal cortexes of AD brains (Kidd, 2005, p. 273). Metabolic abnormalities in these brain regions cause the impaired motor and sensory system, memory and learning, and disrupted sleep typical of AD. Regarding psychiatric disorders, evidence from “morphological, genetic, comorbidity, and imaging data”, and studies of bioenergetics, have shown that mitochondrial dysfunction plays a significant role in schizophrenia (SZ), bipolar disorder (BPD), and major depressive disorder (MDD) (Shao et al., 2008, p. 290). For example, diminished energy production mitochondria (ATP levels) in neurons in the frontal cortex of subjects with SZ as compared to controls has been found using phosphorous magnetic spectroscopy (Volz et al., 1997). “Related to psychiatry, monoamine oxidase A and B enzymes”, believed to effect levels and activity of the neurotransmitters dopamine and norepinephrine, as well as “peripheral benzodiazepine [GABA] receptors”, all important in the regulation of mood and anxiety, “have been shown to be localized in the outer membrane of mitochondria” (Shao et al., p. 282). Thus, widespread mitochondrial dysfunction is associated with diminished neurotransmitter signaling in the brain, implicated in mood dysregulation. Additionally, mitochondrial abnormalities in structure, density, and number have been found in the prefrontal cortex and caudate nucleus (SZ); frontal and temporal lobes (BPD); and frontal cortex, hippocampus and anterior cingulate cortex (MDD) (Grover et al., 2006; Shao et al., p. 290; Strakowski, Delbello, Adler, Cecil, & Sax, 2000).

## Conclusion

Mitochondrial dysfunction can be a primary disease entity with encephalopathy as a main symptom due to the high energy demands of the brain, dependence on glucose metabolism and vulnerability of postmitotic tissues. It is implicated in many diseases not typically thought of as “mitochondrial” disorders, with current evidence strongly suggesting an important role of mitochondrial dysfunction as a final common pathway in neurological and psychiatric disorders, in the expression of myriad neurobehavioral symptoms, as well as in the “final disease state,” ageing. As research into the phenotypic variability of mitochondrial dysfunction and its role as a final common disease pathway is a burgeoning field, more studies must be done to develop a clearer understanding of etiology (inherited and acquired), pathophysiology, and involvement in other non-primary mitochondrial diseases. Additionally, research must address more effective methods of diagnosis and treatment, as currently there are, with rare exceptions, no targeted therapeutic approaches for mitochondrial disease and dysfunction, only nonspecific vitamin and cofactor supplementation.

## Bibliography

- Cohen, B. H., & Gold, D. R. (2001, July). Mitochondrial cytopathy in adults: What we know so far. *Cleveland Clinic Journal of Medicine*, 68(7), 625-642.
- Dexter, D. T., Sian, J., Rose, S., Hindmarsh, J.G., Mann, V. M., Copper, J. M., et al. (1994). Indices of oxidative stress and mitochondrial function in individuals with incidental Lewy body disease. *Annals of Neurology*, 35, 38-44.
- Dimauro, S., & Davidzon G. (2005). Mitochondrial DNA and disease. *Annals of Medicine*, 37(3), 222-232.
- Grover, S., Padhy, S. K., Das, C. P., Vasishta R. K., Sharan, P., & Chakrabarti, S. (2006). Mania as a first presentation in mitochondrial myopathy. *Psychiatry and Clinical Neurosciences*, 60, 774-775.
- Hass, R. H., Parikh, S., Falk, F. J., Saneto R. P., Wolf N. I., Darin, N., et al. (2007, December). Mitochondrial disease: A practical approach for primary care physicians. *Pediatrics*, 120(6), 1326-1333.
- Kidd, P. M. (2005). Neurodegeneration from mitochondrial insufficiency: Nutrients, stem cells, growth factors, and prospects for brain rebuilding using integrative management. *Alternative Medicine Review*, 10(4), 268-293.

- Luft, R., Ikkos, D., Palmieri G., Ernster, L., & Afzelius B. (1962). A case of severe hypermetabolism of nonthyroid origin with a defect in maintenance of mitochondrial respiratory control: A correlated clinical, biochemical and morphological study. *Journal of Clinical Investigation*, 41, 1776-1804.
- Margulis, L., & Bermudes, D. (1985). Symbiosis as a mechanism of evolution: Status of cell symbiosis theory. *Symbiosis*, 1, 101-124.
- Nasrallah, H. A. (2007). Remember the hippocampus!: You can protect the brain's 'regeneration center.' *Current Psychiatry*, 6(10), 17-19.
- Schon, E. A., & Salvatore D. (2001). Mitochondrial dysfunction in chronic fatigue syndrome. In Lemasters J. J. & Nieman, A. (Eds.), *Mitochondria in Pathogenesis* (pp. 53-80). New York: Kluwer Academic/Plenum Publishers.
- Schon, E. A., & Manfredi, G. (2003). Neuronal degeneration and mitochondrial dysfunction. *The Journal of Clinical Investigation*, 111(3), 303-312, doi: 10.1172/JC117741, The American Society for Clinical Investigation.
- Shao, L., Martin, M. V., Watson, S. J., Schatzberg, A., Akil, H., Myers, R. M., et al. (2008). Mitochondrial involvement in psychiatric disorders. *Annals of Medicine*, 40, 281-295.
- Strakowski, S. M., Delbello, M. P., Adler, C., Cecil, K. M., & Sax, K. W. (2000). Neuroimaging in bipolar disorder. *Bipolar Disorders*, 2, 148-164.
- Szewczyk, A., & Wojtczak L. (2002). Mitochondria as a pharmacological target. *Pharmacological Reviews*, 54, 101-127.
- Trifunovic, A., & Larsson, N. G. (2008). Mitochondrial dysfunction as a cause of ageing. *Journal of Internal Medicine*, 263, 167-178, doi: 10.1111/j.1365-2796.2007.01905.x.
- Vernon, S. D., Whistler, T., Cameron, B., Hickie, I. B., Reeves, W.C., & Lloyd, A. (2006, January). Preliminary evidence of mitochondrial dysfunction associated with post-infective fatigue after acute infection with Epstein Barr Virus. *BMC Infectious Disease*, 6(15), doi: 10.1186/1471-2334-6-15.
- Vladutiu, G. D. (2001). Heterozygosity: An expanding role in proteomics. *Molecular Genetics and Metabolism*, 74, 51-63, doi: 10.1006/mgme.2001.3240.
- Wallace, D. C., & Lott, M. T. (2002). Mitochondrial defects in common disease. In King, R. A., Rotter, J. I. & Motulsky, A. G. (Eds.), *The Genetic Basis of Common Diseases*. (2<sup>nd</sup> ed.). (pp. 975-988). USA: Oxford University Press.
- Volz, H. P., Rzanny, R., May, S., Hegewald, H., Preussler, B., Hajek, M., et al. (1997). 31P magnetic resonance spectroscopy in the dorsolateral prefrontal cortex of schizophrenics with a volume selective technique – preliminary findings. *Biological Psychiatry*, 41, 644-648.