Mitochondrial Nutrition and Beyond:
Mitochondrial Optimization for Optimal Health

Brief introduction and review: Bioenergetics, physiology, roles in inflammation, microbial responsiveness, cancer and apoptosis

Mitochondrial interventions:
- Physiologic requirements
- Mitochondrial liberation, interventional disinhibition
- Biogenesis
- Therapeutic mitophagy
- Resuscitation
- Further optimization

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DrV’s “Functional Inflammology Protocol”

1. Food and Diet
2. Infections and dysbiosis
3. Nutritional immunomodulation
4. Dysfunctional mitochondria
5. Stress, lifestyle, sleep, spinal health, pSychology
6. Endocrine and hormonal imbalances
7. Xenobiotics and toxins/toxicants

Mitochondrial structure:

Image from Wikimedia Commons: http://en.wikipedia.org/wiki/Mitochondrion
**Mitochondrial bioenergetics, ATP production:**

- Everyone knows that the major role of mitochondria is ATP production; unfortunately, this is the sum total that most people—including doctors—know about mitochondria.

- My way of viewing ATP production is as follows:
  1. Glycolysis
  2. Pyruvate dehydrogenase shuttle/complex
     1. Alternate inputs: fructose, ethanol, fatty acids, ketones/KB
  3. Krebs’ cycle = citric acid cycle = TCA cycle
  4. Electron transport chain (ETC), ending with ATP synthase
Mitochondria in inflammation, microbial responsiveness, and apoptosis:

Required reading: Green DR, Galluzzi L, Kroemer G. Mitochondria and the autophagy-inflammation-cell death axis in organismal aging. Science. 2011 Aug 26;333:1109-12

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Mitochondria in inflammation, microbial responsiveness, and apoptosis: Science 2011 Aug

- “Mitochondria participate in the detection of infectious microorganisms and cellular damage to activate innate immune responses.”
- “…likely that accumulation of damaged mitochondria is an important cause of inflammation.”
- “…the removal of mitochondria that have a rather low threshold for permeabilization (mitochondrial “purging”).”
  - Mitophagy/autophagy is the body’s self-protective mechanism for deleting or purging dysfunctional mitochondria to protect the body from inflammation and oxidative stress.
- “Exercise and caloric restriction stimulate autophagy in most tissues…”
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Infections Toxins, and nutritional deficiencies

Antioxidants (depletion, supplementation) Inflammatory diseases: DM, HTN, allergy, autoimmunity

Induction of apoptosis: pancreas, cartilage, brain (Alzheimer’s disease, PD) NFkB modulators, diet, dysbiosis, antimetabolites from gut and diet

Lack of apoptosis = immortalization = cancer Excess mitophagy = ATP depletion, fatigue, cell death

Inflammatory diseases: DM, HTN, allergy, autoimmunity

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Mitochondrial dysfunction = vicious cycle

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Mitochondrial dysfunction = disease:

1. Inflammation: mitochondrial dysfunction contributes to cell senescence, chronic inflammation, and “inflammaging”
2. Allergy: especially asthma,
3. Autoimmunity: especially SLE and RA,
4. Metabolic Syndrome, Diabetes Type-2, Hypertension: mitochondria are required for insulin secretion and reception,
5. Heart failure: failure of energy production,
6. Fibromyalgia: histologic and biochemical evidence of mitochondrial failure, mitophagy,
7. Migraine: biochemical evidence of mitochondrial impairment,
8. Neurodegeneration—Parkinson’s Dz, Alzheimer’s Dz: I think pretty much everyone should know this by now, especially regarding Parkinson’s disease.
Mitochondrial dysfunction = disease:

2. Mitochondrial dysfunction increases the inflammatory responsiveness to cytokines in normal human chondrocytes. *Arthritis Rheum* 2012 May
4. Age-Related Mitochondrial Dysfunction Sensitizes Human Synoviocytes to Inflammatory Response [abstract]: "The present study identifies for the first time mitochondria as organelles implicated in the proinflammatory response in human synoviocytes, since mitochondrial dysfunction sensitizes these cells amplifying the inflammatory response induced by cytokines." *Arthritis Rheum* 2011
5. Mitochondrial dysfunction and biogenesis: do ICU patients die from mitochondrial failure? "Collectively the data discussed in this review suggest that appropriate diagnosis and specific treatment of mitochondrial dysfunction in ICU patients may significantly improve the clinical outcome." *Ann Intensive Care* 2011 Sept
6. Effects of mitochondrial dysfunction on the immunological properties of microglia. *Journal of Neuroinflammation* 2010

Mitochondrial dysfunction = diabetes type-2:

Proper mitochondrial function is essential for insulin secretion due to hyperglycemia:

- "In the pancreatic beta-cell, glucose carbons are quantitatively funneled to the mitochondria, where signals for the initiation and potentiation of insulin secretion are generated. After mitochondrial activation, the plasma membrane is depolarized with ensuing cytosolic calcium transients and exocytosis of insulin."

Proper mitochondrial function is essential for insulin action in tissues:

- "Normal mitochondrial activity appears to be equally important in the action of insulin on its target tissues."

Treatment:

- Both prevention and treatment of type 2 diabetes should focus on mitochondrial targets for the improvement of nutrient-stimulated insulin secretion and their utilization in peripheral tissues.

Wiederkehr. *Endocrinology* 2006 Jun

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Mitochondrial Dysfunction = Disease: Diabetes, Hypertension, Metabolic Syndrome

"Insulin resistance emanating from mitochondrial dysfunction may contribute to metabolic and cardiovascular abnormalities and subsequent increases in cardiovascular disease. Furthermore, interventions that improve mitochondrial function also improve insulin resistance."

Restoring Mitochondrial Function = Health

- Treat with plant-based diet, low-carb diet, and antioxidant supplementation, especially CoQ10, lipoic acid, vitamins E and C, selenium, NAC
- Treat with caloric restriction, exercise, ketogenic diet, and mitochondrial nutrients such as CoQ-10, lipoic acid, acetyl-carnitine, riboflavin and others

Figure 4. Mechanism of mitochondrial dysfunction. Excess intake of nutrients, including overloaded FFAs or hyperglycemia conditions, increases ROS production and reduces mitochondrial biogenesis, causing mitochondrial dysfunction. Mitochondrial dysfunction leads to decreased β-oxidation and ATP production and increased ROS production, resulting in insulin resistance, diabetes, and cardiovascular disease.

Jeong-a, Circulation Research, 2008
Mitochondrial dysfunctions and their associated diseases:

1. **Inflammation**: mitochondrial dysfunction contributes to cell senescence, chronic inflammation, and “inflammaging”

2. **Allergy**: especially asthma,

3. **Autoimmunity**: especially SLE and RA,

4. **Metabolic Syndrome, Diabetes Type-2, Hypertension**: mitochondria are required for insulin secretion and reception,

5. **Heart failure**: failure of energy production,

6. **Fibromyalgia**: histologic and biochemical evidence of mitochondrial failure, mitophagy,

7. **Migraine**: biochemical evidence of mitochondrial impairment,

8. **Neurodegeneration—Parkinson’s Dz, Alzheimer’s Dz**: I think pretty much everyone should know this by now, especially regarding Parkinson’s disease.

Mitochondrial dysfunction and molecular pathways of disease

Steve R. Pieczenik, John Neustadt *

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Abstract

Since the first mitochondrial dysfunction was described in the 1960s, the medicine has advanced in its understanding the role mitochondria play in health, disease, and aging. A wide range of seemingly unrelated disorders, such as schizophrenia, bipolar disease, Down’s, Alzheimer’s disease, epilepsy, migraine headaches, stroke, stroke, amphetamine abuse, Parkinson’s disease, ataxia, transient ischemic attack, cardiomyopathy, coronary artery disease, chronic fatigue syndrome, fibromyalgia, retinitis pigmentosa, diabetes, hepatitis C, and primary biliary cirrhosis, have underlying pathophysiological mechanisms in common, namely reactive oxygen species (ROS) production, the accumulation of mitochondrial DNA (mtDNA) damage, resulting in mitochondrial dysfunction. Antioxidant therapies hold promise for improving mitochondrial performance. Physicians seeking systematic treatments for their patients might consider testing urinary organic acids to determine the best treatment. If in the last 50 years advances in mitochondrial treatments match the immense increase in knowledge about mitochondrial function that has occurred, mitochondrial diseases and dysfunction will likely be a medical triumph.

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Mitochondrial dysfunction and molecular pathways of disease

Table 2
Acquired conditions in which mitochondrial dysfunction has been implicated

- Diabetes (Wallace, 2005; Fosslien, 2001; West, 2000)
- Huntington’s disease (Stavrovskaya and Kristal, 2005)
- Cancer (Wallace, 2005), including hepatitis-C virus-associated hepatocarcinogenesis (Koike, 2005)
- Alzheimer’s disease (Stavrovskaya and Kristal, 2003)
- Parkinson’s disease (Stavrovskaya and Kristal, 2005)
- Bipolar disorder (Stork and Renshaw, 2005; Fatati et al., 2006)
- Schizophrenia (Fatati et al., 2006)
- Aging and senescence (Wallace, 2005; Savitha et al., 2005; Sá Longo, 2005; Corral-Debrinski et al., 1992; Ames et al., 1991)
- Anxiety disorders (Einat et al., 2005)
- Nonalcoholic steatohepatitis (Lieber et al., 2004)
- Cardiovascular disease (Fosslien, 2001), including atherosclerosis (Puddu et al., 2005)
- Sarcopenia (Bua et al., 2002)
- Exercise intolerance (Conley et al., 2000)
- Fatigue, including chronic fatigue syndrome (Folle et al., 2004)
- Fibromyalgia (Park et al., 2000; Yunus et al., 1983), and my (Yunus et al., 1988)

Table 3
Inherited conditions in which mitochondrial dysfunction has been implicated

- Kearns-Sayre syndrome (KSS)—ocular, optokinetic nystagmus, cardiac conduction defects, and sensorineural hearing loss
- Leber hereditary optic neuropathy (LHON)—visual loss in young adulthood
- Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like syndrome (MELAS)—various degrees of cognitive impairment and dementia, lactic acidosis, strokes, and transient ischemic attacks
- Myoclonic epilepsy and ragged-red fibers (MERRF)—progressive myoclonic epilepsy, clumps of damaged mitochondria accumulate in the subaxonal central region of the muscle fiber
- Leigh syndrome (subacute necrotizing encephalopathy)—seizures, altered states of consciousness, dementia, ventricular failure
- Neurontic neuropathy, axonal, retinitis pigmentosa, and pigmented retinopathy (NARP)—dementia, in addition to the symptoms described in the acronym
- Myoneuronal gastrointestinal encephalopathy (MNGIE)—gastrointestinal pseudo-obstruction, neuropathy