

Mitochondrial dysfunction and molecular pathways of disease

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FROM ABSTRACT

Since the first mitochondrial dysfunction was described in the 1960s, the medicine has advanced in its understanding of the role mitochondria play in health, disease, and aging.

A wide range of seemingly unrelated disorders, such as schizophrenia, bipolar disease, dementia, Alzheimer's disease, epilepsy, migraine headaches, strokes, neuropathic pain, 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 how best to treat them.

Keywords: Mitochondria; Antioxidant; L-carnitine; Coenzyme Q10; Lipoic acid; Thiocetic acid; Electron Transport Chain; Krebs's cycle

THESE AUTHORS ALSO NOTE:

"Mitochondria are the powerhouses of our cells. They are responsible for generating energy as adenosine triphosphate (ATP) and heat."

Mitochondria are the only other subcellular structure aside from the nucleus to contain DNA.

"Unlike nuclear DNA, mitochondrial DNA (mtDNA) are not protected by histones. Nuclear DNA wraps around histones, which then physically shield the DNA from damaging free radicals and are also required to repair double-stranded DNA breaks. Since mtDNA lacks the structural protection of histones and their repair mechanisms, they are quite susceptible to [free radical] damage."

"Oxidative phosphorylation (ox-phos) is the major cellular energy-producing pathway. Energy, in the form of ATP, is produced in the mitochondria through a series of reactions in which electrons liberated from the reducing substrates nicotine

adenine dinucleotide (NADH) and flavin adenine dinucleotide (FADH) are delivered to O_2 via a chain of respiratory proton (H^+) pumps."

"Mitochondrial dysfunction has been implicated in nearly all pathologic and toxicologic conditions."

"Cellular energy requirements control how many mitochondria are in each cell."

A single somatic cell can contain from 200 to 2000 mitochondria.

"The largest number of mitochondria is found in the most metabolically active cells, such as skeletal and cardiac muscle and the liver and brain."

Mitochondria are found in every human cell except mature erythrocytes.

"Mitochondria produce more than 90% of our cellular energy by ox-phos."

Energy production is the result of two closely coordinated metabolic processes:

- 1) The tricarboxylic acid (TCA) cycle = the Krebs's cycle = citric acid cycle
- 2) The electron transport chain (ETC)

The Krebs's cycle converts carbohydrates and fats into some ATP.

However, the major job of the Krebs's cycle is producing the coenzymes NADH and FADH that enter into the ETC.

- The catabolism of glucose in the cytosol produces 2 molecules of pyruvate.
- These 2 pyruvate molecules are enzymatically converted into 2 molecules of acetyl-coenzyme A (acetyl CoA). This conversion requires:
 - Coenzyme A (CoA), which is derived from pantothenic acid (vitamin B5)
 - NAD^+ , which contains niacin (vitamin B3)
 - FAD^+ , which contains riboflavin (vitamin B2)
 - Lipoic acid
 - Thiamine pyrophosphate (TPP), which contains thiamine (vitamin B1)
- Acetyl CoA then passes through the mitochondria's double membrane to enter the Krebs's cycle.
- The Krebs's cycle has 9 steps, and its completion requires the following cofactors: cysteine, iron, niacin, magnesium, manganese, thiamine, riboflavin, pantothenic acid, and lipoic acid.

- In the Krebs's cycle, each acetyl-CoA produces 3 molecules of NADH and 2 molecules of FADH, for a total of 6 NADH and 4 FADH per one molecule of pyruvate.
- Acetyl-CoA can be produced by oxidation of fatty acids, which then requires the nutrient l-carnitine to shuttle the acetyl-CoA into the mitochondria to enter the Krebs's cycle.
- The electron transport chain (ETC) is embedded in the inner mitochondrial membrane and consists of a series of five enzyme complexes, designated I–V.
- NADH and FADH carry electrons to the ETC.
- Electrons donated from NADH and FADH flow through the ETC complexes, passing down an electrochemical gradient to be delivered to oxygen (O₂).
- Electron transport complexes I–IV require ubiquinone (Coenzyme Q10, or CoQ10).
- Electron transport complex IV is a cytochrome (cytochrome c) enzyme.
- Electron transport complexes I–IV contain flavins, which contain riboflavin, iron, sulfur, and copper.
- CoQ10 shuttles electrons from complexes I and II to complex III.
- Cytochrome c, an iron-containing heme protein that transfers electrons from electron transport complex III to IV.
- "During this process, protons are pumped through the inner mitochondrial membrane to the intermembrane space to establish a proton motive force, which is used by complex V to phosphorylate adenosine diphosphate (ADP) by ATP synthase, thereby creating ATP."

"Proper functioning of the Krebs's cycle and the ETC requires all the nutrients involved in the production of enzymes and all the cofactors needed to activate the enzymes."

"Damage to mitochondria is caused primarily by reactive oxygen species (ROS) generated by the mitochondria themselves."

The majority of ROS are generated by complexes I and III by the release of electrons by NADH and FADH into the ETC.

"Mitochondria consume approximately 85% of the oxygen utilized by the cell during its production of ATP."

“During normal ox-phos, 0.4–4.0% of all oxygen consumed is converted in mitochondria to the superoxide (O_2^-) radical.”

“Superoxide is transformed to hydrogen peroxide (H_2O_2) by the detoxification enzymes manganese superoxide dismutase (MnSOD) or copper/zinc superoxide dismutase (Cu/Zn SOD), and then to water by glutathione peroxidase (GPX).”

When these endogenous anti-oxidant enzymes cannot convert ROS fast enough, oxidative damage occurs and accumulates in the mitochondria.

“Glutathione in GPX is one of the body's major antioxidants. Glutathione is a tripeptide containing glutamine, glycine, and cysteine, and GPX requires selenium as a cofactor.”

“Within the mitochondria, elements that are particularly vulnerable to free radicals include lipids, proteins, oxidative phosphorylation enzymes, and mtDNA.”

Free radical damage to mitochondrial proteins decrease their affinity for substrates or coenzymes and, thereby, decreases their function.

Compounding the problem, once a mitochondria is damaged, mitochondrial function is reduced, producing more free radicals which cause additional mitochondrial damage.

Hyperglycemia induces mitochondrial superoxide production which contributes to diabetes, cardiovascular disease, atherosclerosis, hypertension, heart failure, aging, sepsis, ischemia–reperfusion injury, and hypercholesterolemia.

Inflammatory mediators are associated with mitochondrial dysfunction and increased ROS generation, causing damage to mtDNA.

“Vitamins, minerals, and other metabolites act as necessary cofactors for the synthesis and function of mitochondrial enzymes and other compounds that support mitochondrial function, and diets deficient in micronutrients can accelerate mitochondrial decay and contribute to neurodegeneration.”

Deficiencies of any component of the Krebs’s cycle or ETC lead to increased production of free radicals and mtDNA damage.

“Iron-deficiency anemia is a major contributor to the global burden of disease, affecting an estimated 2 billion people, mostly women and children.”

“Low iron status decreases mitochondrial activity by causing a loss of complex IV and increasing oxidative stress.”

“Toxic metals, especially mercury, generate many of their deleterious effects through the formation of free radicals, resulting in DNA damage, lipid peroxidation, depletion of protein sulfhydryls (eg, glutathione) and other effects.”

The major mechanism for metals toxicity appears to be direct and indirect damage to mitochondria via depletion of glutathione which results in excessive free radical generation and mitochondrial damage.

Increased urinary organic acid pyroglutamate is a specific marker for glutathione depletion.

A hallmark symptom of mitochondrial damage is fatigue.

Mercury can accumulate in mitochondria because of their high affinity for binding thiols (sulfur-containing molecules), leading to the depletion of mitochondrial glutathione.

“The central nervous system is particularly sensitive to damage by MeHg induced glutathione depletion.”

Exposure to mercury depletes glutathione, damaging human neurons, astrocytes, and neuroblastoma cells.

Exposure to mercury also damages the pancreas, inhibiting insulin secretion, and impairing kidney function through depletion of glutathione, generation of free radicals, and mitochondrial damage.

N-acetyl-cysteine (NAC) increases intracellular glutathione and a decrease in reactive oxygen species formation from mercury exposure.

Arsenic also damages cellular energy production pathways by inhibiting the transformation of pyruvate to acetyl-coenzyme A (acetyl-CoA), and inhibiting the cytochrome C oxidase enzyme.

“Since the major reason for mitochondrial dysfunction is ROS production and the accumulation of mitochondrial damage, antioxidant therapy is a viable strategy for attenuating the situation.”

Along with providing the antioxidants, a systematic medical approach would also ensure that any cofactors required for detoxification enzyme function (e.g., selenium for GPX) are also present in clinically relevant amounts.

In animals, 30 days of combined supplementation with l-carnitine and alpha-lipoic acid resulted in a significant increase in production of energy production enzymes.

Diets rich in antioxidants increase glutathione.

“Based on known molecular pathways, consumption of whey protein, which increases glutathione levels in vivo, might also be part of an effective therapeutic strategy.”

“The most important test for mitochondrial dysfunction is urinary organic acid testing.”

The clinical relevance of organic acid testing is its ability to determine dysfunction of mitochondrial energy production, the presence of functional nutrient deficiencies, and the presence of toxins that adversely affect detoxification pathways.

KEY POINTS FROM DAN MURPHY

- 1) “Mitochondria are the powerhouses of our cells. They are responsible for generating energy as an adenosine triphosphate (ATP).”
- 2) Mitochondria are the only other subcellular structure aside from the nucleus to contain DNA.
- 3) The mitochondria play a key role in health, disease, and aging.
- 4) The common underlying pathophysiological mechanism in many diseases is the generation of reactive oxygen species (ROS), the accumulation of mitochondrial DNA (mtDNA) damage, resulting in mitochondrial dysfunction. **[Key Point]**
- 5) Antioxidant therapies hold promise for improving mitochondrial performance.
- 6) “Unlike nuclear DNA, mitochondrial DNA (mtDNA) are not protected by histones. Nuclear DNA wraps around histones, which then physically shield the DNA from damaging free radicals and are also required to repair double-stranded DNA breaks. Since mtDNA lacks the structural protection of histones and their repair mechanisms, they are quite susceptible to [free radical] damage.”
- 7) “Mitochondrial dysfunction has been implicated in nearly all pathologic and toxicologic conditions.”
- 8) “Cellular energy requirements control how many mitochondria are in each cell.” A single somatic cell can contain from 200 to 2000 mitochondria.
- 9) “The largest number of mitochondria is found in the most metabolically active cells, such as skeletal and cardiac muscle and the liver and brain.”
- 10) Mitochondrial energy production uses 2 metabolic processes: the Krebs cycle and the electron transport chain (ETC).

- 11) The major job of the Krebs's cycle is producing NADH and FADH that enter into the ETC.
- 12) "Proper functioning of the Krebs's cycle and ETC requires all the nutrients involved in the production of enzymes and all the cofactors needed to activate the enzymes."
- 13) "Damage to mitochondria is caused primarily by reactive oxygen species (ROS) generated by the mitochondria themselves."
- 14) "Mitochondria consume approximately 85% of the oxygen utilized by the cell during its production of ATP."
- 15) "During normal ox-phos, 0.4–4.0% of all oxygen consumed is converted in mitochondria to the superoxide (O_2^-) radical."
- 16) "Superoxide is transformed to hydrogen peroxide (H_2O_2) by the detoxification enzymes manganese superoxide dismutase (MnSOD) or copper/zinc superoxide dismutase (Cu/Zn SOD), and then to water by glutathione peroxidase (GPX)."
- 17) When these endogenous anti-oxidant enzymes cannot convert ROS fast enough, oxidative damage occurs and accumulates in the mitochondria.
- 18) "Glutathione in GPX is one of the body's major antioxidants. Glutathione is a tripeptide containing glutamine, glycine, and cysteine, and GPX requires selenium as a cofactor."
- 19) "Within the mitochondria, elements that are particularly vulnerable to free radicals include lipids, proteins, oxidative phosphorylation enzymes, and mtDNA."
- 20) Once the mitochondria are damaged by free radicals, mitochondrial function is reduced, producing more free radicals, which cause additional mitochondrial damage.
- 21) Inflammation increases mitochondrial dysfunction and increased ROS generation, causing damage to mtDNA.
- 22) "Diets deficient in micronutrients can accelerate mitochondrial decay and contribute to neurodegeneration."
- 23) Deficiencies of any component of the Krebs's cycle or ETC lead to increased production of free radicals and mtDNA damage.
- 24) "Toxic metals, especially mercury, generate many of their deleterious effects through the formation of free radicals, resulting in DNA damage, lipid peroxidation, depletion of protein sulfhydryls (eg, glutathione) and other effects."

- 25) The major mechanism for metals toxicity appears to be direct and indirect damage to mitochondria via depletion of glutathione, which results in excessive free radical generation and mitochondrial damage.
- 26) A hallmark symptom of mitochondrial damage is fatigue.
- 27) Mercury can accumulate in mitochondria because of their high affinity for binding thiols (sulfur-containing molecules), leading to the depletion of mitochondrial glutathione.
- 28) "The central nervous system is particularly sensitive to damage by MeHg induced glutathione depletion."
- 29) Exposure to mercury depletes glutathione, damaging human neurons, astrocytes, and neuroblastoma cells. Exposure to mercury also damages the pancreas, inhibiting insulin secretion, and impairing kidney function through depletion of glutathione, generation of free radicals, and mitochondrial damage.
- 30) N-acetyl-cysteine (NAC) increases intracellular glutathione and decreases reactive oxygen species formation from mercury exposure.
- 31) Arsenic also damages cellular energy production pathways by inhibiting the transformation of pyruvate to acetyl-coenzyme A (acetyl-CoA), and inhibiting the cytochrome C oxidase enzyme. **[Important for Low Level Laser Therapy]**
- 32) "Since the major reason for mitochondrial dysfunction is ROS production and the accumulation of mitochondrial damage, antioxidant therapy is a viable strategy for attenuating the situation."
- 33) Along with providing the antioxidants, a systematic medical approach would also ensure that any cofactors required for detoxification enzyme function (e.g., selenium for GPX) are also present in clinically relevant amounts.
[Also important for Low Level Laser Therapy]
- 34) Supplementation with l-carnitine and alpha-lipoic acid can significantly increase generation of energy production enzymes.
- 35) Diets rich in antioxidants increase glutathione.
- 36) "Based on known molecular pathways, consumption of whey protein, which increases glutathione levels in vivo, might also be part of an effective therapeutic strategy."
- 37) "The most important test for mitochondrial dysfunction is urinary organic acid testing."

Key Nutrients Required for Proper Mitochondrial Function

Required for the Kreb's cycle

Iron, sulfur, thiamine (vitamin B1), riboflavin (vitamin B2), niacin (vitamin B3), pantothenic acid (vitamin B5), cysteine, magnesium, manganese, lipoic acid, copper, zinc, riboflavin, and pyridoxine (vitamin B6)

Required for the electron transport chain complexes

Ubiquinone (CoQ10), riboflavin, iron, sulfur, copper

Key enzymes required for oxidative phosphorylation

Manganese superoxide dismutase (MnSOD), copper/zinc superoxide dismutase (Cu/Zn SOD), glutathione peroxidase (GPX)

Key nutrients required for oxidative phosphorylation

Manganese, SOD, copper, zinc, glutathione (glutamine, glycine, and cysteine), selenium

COMMENTS FROM DAN MURPHY

In accordance with this article, certain nutrients are required to enhance the mitochondria production of ATP energy and reduce the damage caused by free radicals to the mitochondria DNA. I am most familiar with the nutrition company **Nutri-West [(800) 443-3333]** because I use their products and they sponsor my **Nutritional Neurology** class:

Complete AG Contains Acetyl-L-Carnitine, Alpha-Lipoic Acid and CoQ-10.

Complete Glutathione Contains N-Acetyl Cysteine and Superoxide Dismutase.

LazerMins Contains endogenous antioxidant enzyme minerals: Zinc, Copper, Manganese, and Selenium.

ALSO, there is evidence that low level laser therapy increases the production of ATP by improving electron transfer at cytochrome C oxidase enzyme. Step in the electron transport chain.

Arsenic damages ATP production. Our primary exposure to arsenic is through eating chicken. [USA Today and The Meat You Eat by Ken Midkiff, 2004] Midkiff notes: Chicken "feeds are specially formulated to ensure maximum growth at minimum cost." "Appetite enhancers. Such as arsenic, are added to the feeds to force the chickens to keep eating." pp. 72-73

**From Biology, Life on Earth
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Sixth Edition, 2002
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