THE PATH AHEAD

Strategies for Protecting Mitochondria From Metals and Chemicals

Joseph Pizzorno, ND, Editor in Chief

Abstract

Mitochondria are required for life, and dysfunction leads to chronic disease and shortened life expectancy. Unfortunately, suboptimal mitochondrial function is very common. While genetic mutations play a role, far more common is the damage from nutrient deficiencies and regular accidental and intentional exposure to mitotoxic metals and chemicals. Alcohol, antibiotics, metals, bisphenols, phthalates, pesticides and herbicides, and statins—the list is long—all impair mitochondrial function. Fortunately, toxins can be avoided and their elimination from the body can be enhanced. In addition, many natural health molecules help protect mitochondria and restore function.

Joseph Pizzorno, ND; Editor in Chief, *IMCJ;* co-author, *Textbook of Natural Medicine;* Founding President, Bastyr University; Chair, Board of Directors, Institute for Functional Medicine.

Introduction

While clinicians are, of course, aware that mitochondria are required for life, few realize the remarkably high level of their activity. Over the past decade I have several times asked audiences of health care professionals to estimate how much ATP (adenosine triphosphate) is produced every day by a healthy 70 kg person at rest. For many years, the closest correct answer was 500 g a day—which is a gross underestimation. The stunning number is 70 kg/d, i.e., the person's body weight. During maximal exercise, like sprinting, ATP production increases to 0.5 to 1.0 kg/min! But here is a key issue: the body does not store ATP. The average amount of ATP in the body at any given moment is only about 250 g or 4.25 W, the equivalent of an AA battery, and only enough for about 5 minutes of metabolism.[1] Easy to see why mitochondrial poisons like cyanide kill so quickly—stop the electron transport chain and death ensues immediately.

In addition, all that metabolic activity uses a lot of oxygen and even in a healthy person, 1% to 2% of the oxygen and high energy electrons are leaked during ATP production. Mitochondrial ROS (reactive oxygen species) production and leakage are the major source of intracellular oxidants and increase with age as mitochondrial DNA (mtDNA) damage accumulates and control of high energy electrons and molecules is further eroded.[2] Since this leakage is happening physically right next to the mtDNA, it experiences a 10-fold higher level of oxidative stress than nuclear DNA, resulting in a 17-fold higher mutation rate.[3] It is not surprising then that virtually every chronic disease, even the aging process itself, is highly correlated with mitochondrial damage.[4,5] Protecting mitochondria and optimizing their function is a key strategy for a healthy and long life.

Obviously, optimizing nutrients needed for mitochondrial function (virtually all of them) and aggressive avoidance of mitochondria-damaging environmental metals and chemicals is critical. Unfortunately, humans are regularly exposed—both intentionally and accidentally—to many metals and chemicals that directly damage mitochondria. Many of these mitotoxins are difficult to avoid and some have very long half-lives in humans.

This editorial discusses how mitochondria function is impaired by toxins. It is not, of course, a comprehensive treatise. Rather it highlights some key toxins which substantially impact mitochondrial function in a significant portion of the population and provides example interventions for each.

Prevalence of Mitochondrial Dysfunction

Assessing function of any physiological activity is challenging. Rarely is the assessment simply functional or

dysfunctional. Function can be refined as dysfunctional, minimally functional, of average functionality, and optimally functional. Very challenging is that virtually all measures define functional as within the 95% range, i.e., is the function within the range of 95% of the average "healthy" population. And unfortunately, "healthy" is typically poorly defined as lack of overt disease. Considering the high prevalence of subjective "ill health" and objective evidence of undiagnosed disease, the population standard is suspect. For example, 20 years ago a comprehensive study in Norway found that over 80% of those aged 15-84 years in the general population reported subjective symptoms of ill health, while over one-third reported substantial symptoms of ill health that impacted daily life.[6] In addition, there is substantial research showing that much overt disease is underdiagnosed. For example, according to the CDC, in 2019, 14.5% of adults aged 45-64 had been diagnosed with diabetes, but an additional 4.5% had diabetes but were unaware they had it.[7] A significant portion of the population suffers poor function or undiagnosed disease, making average function a poor measure.

Easiest to define are inherited mitochondrial DNA diseases which affect about 1 in 4300.[8] This implies mitochondrial dysfunction is rare. However, if we use the broader definition of inadequate ATP production for vitality and disease resistance, we need a better measure. One way to do this is to look at diseases where mitochondrial dysfunction plays a causative or contributory role. Table 1 shows that this is surprisingly common.

Table 1. Acquired Conditions Associated With Mitochondrial Dysfunction[a]

- Aging and senescence
- Alzheimer disease
- Anxiety disorders
- Atherosclerosis
- Bipolar disorder
- Cancer
- Cardiovascular disease
- Diabetes
- Exercise intolerance
- Fatigue, chronic fatigue syndrome
- Fibromyalgia
- Hepatitis-C virus-associated hepatocarcinogenesis
- Huntington disease
- Myofascial pain
- Nonalcoholic steatohepatitis
- Parkinson disease
- Sarcopenia
- Schizophrenia

[a]Adapted from Pieczenik and Neustadt.[9]

Those interested in further exploring the role of overt mitochondrial dysfunction in disease will find the annotated database at http://www.mitodb.com/ intriguing.

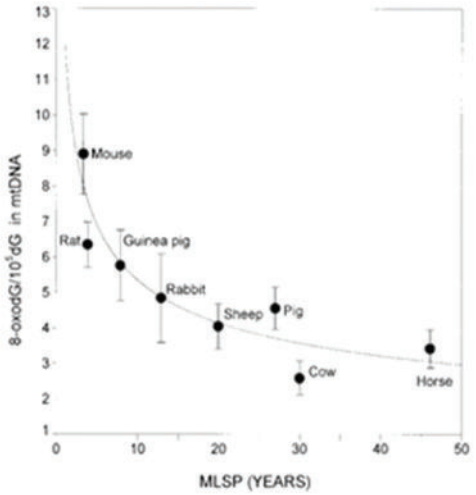
I have now written many editorials on environmental medicine showing that environmental metals and chemicals significantly contribute to virtually all of these diseases. This raises an interesting question: What portion of these diseases is due to mitochondrial dysfunction secondary to environmental exposure?

Metals and Chemicals That Damage Mitochondria

Determining which metal and chemical toxins at the levels typically experienced by the general population damage the mitochondria the most is subject to considerable judgment calls. In addition, while the inclination is to attribute all the damage to environmental contamination, this is a limited and inaccurate assumption. The research is clear that significant mitochondrial damage comes from common intentional exposures such as alcohol consumption and commonly prescribed classes of drugs like statins, NSAIDs, and antibiotics. Several of these are discussed below. They are listed alphabetically since I don't think there is enough research to prioritize and an individual's polymorphisms hugely impact ability to detoxify and protect against these toxins.

Protecting mitochondria requires limiting exposure to mitotoxins as much as possible as well as ensuring adequate levels of nutrients critical for function and protection from oxidative stress. The research is clear that the animal species are the most effective at protecting their mitochondria live the longest, as shown in Figure 1. Of particular interest, measures of mtDNA damage are far more predictive of longevity than measures of nuclear DNA damage.

Figure 1. mtDNA Damage Inversely Correlates With Longevity in Multiple Animal Species[10]



Abbreviations: mtDNA, mitochondrial DNA; MLSP, maximum life span.

Alcohol

In the body, ethanol is converted to acetaldehyde, which is converted to acetate which then increases NADH (reduced nicotinamide adenine dinucleotide) and increases ROS production as shown in Figure 2. Interestingly, while consuming 40 g/d of alcohol for 30 days in the form of beer or wine has no effect on ATP production, spirits decrease production by 12%.[11] The assumption is that beer and wine contain molecules, such as resveratrol, that protect the mitochondria from the damaging effects of alcohol.

Antibiotics

Entering the search terms "antibiotics" and "mitochondria" into PubMed produces almost 10 000 hits. Table 2 shows how in a cell study, later reproduced in rabbits, several antibiotics decrease ATP production, increase ROS, increase measures of lipid peroxidation (malondialdehyde [MDA]), and, perhaps most importantly, increase measures of mtDNA damage (8-OHdG).

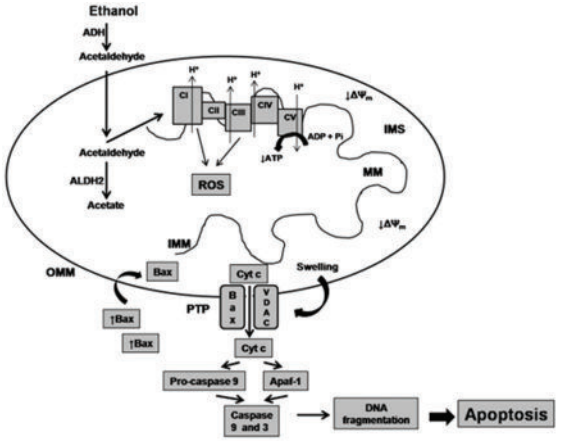
The good news is that the same study showed that cotreatment of the rabbits with NAC decreased damage by about 50%.

Arsenic

The International Agency for Research on Cancer (IARC) ranks arsenic as a Group I carcinogen.[14] Much of its carcinogenesis appears to be due to induced ROS overproduction which leads to mitochondrial dysfunction and inhibition of DNA repair.[15] An example mechanism is impairment of mitochondrial succinate dehydrogenase as shown in Figure 3. This impacts both the citric acid cycle and the electron transport chain.

Since arsenic has a short 2-4 day half-life, reduction in exposure is very effective for decreasing body load. If levels can't be decreased enough, consumption of fermented foods and methylated natural folates (but not folic acid if the patient has a MTHFR polymorphism which impairs methylation) increase the rate of detoxification.

Figure 2. Alcohol damages mitochondria.[a]



[a]Reproduced from Manzo-Avalos and Saavedra-Molina.[12]

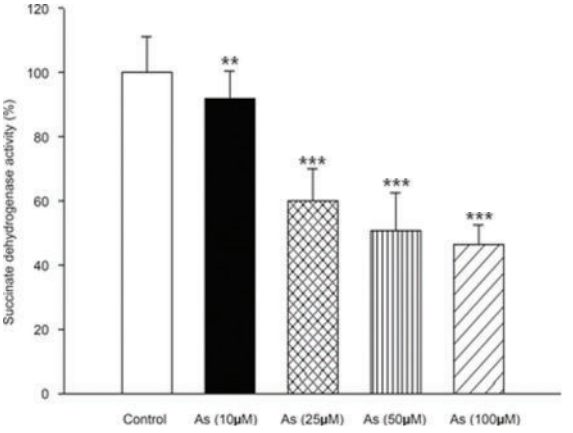
Abbreviations: ΔΨm, mitochondrial membrane potential; ADH, alcohol dehydrogenase; ADP, adenosine diphosphate; ALDH2, mitochondrial aldehyde dehydrogenase 2; Apaf-1, apoptotic protease activating factor-1; ATP, adenosine triphosphate; (CI-CIV), electron transport complexes; Cyt c, cytochrome c; IMM, inner mitochondrial membrane; IMS, intramitochondrial space; MM, mitochondrial matrix; OMM, outer mitochondrial membrane; PTP, permeability transition pore; ROS, reactive oxygen species; VDAC, voltage-dependent anion channel.

Table 2. Antibiotics Damage Mitochondria[13]

After 4 days	Ciprofloxacin	Ampicillin	Kanamycin	Tetracycline
ATP Production	-90%	-75%	-80%	-20%
ROS	+250%	+200%	+240%	+40%
MDA	+90%	+80%	+75%	+20%
8-OHdG	+100%	+720%	+400%	230%

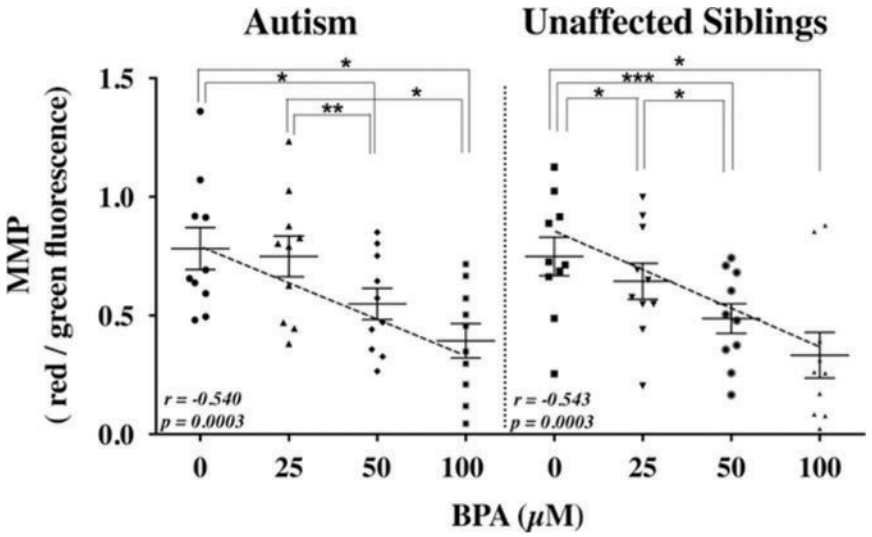
Abbreviations: 8-OHdG, 8-Hydroxyguanosine; ATP, adenosine triphosphate; MDA, malondialdehyde; ROS, reactive oxygen species.

Figure 3. Arsenic inhibits mitochondrial succinate dehydrogenase in liver cell cuture.[16]



Abbreviation: As, arsenic.

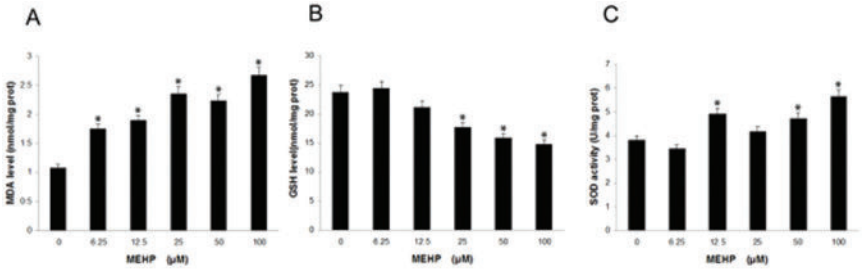
Figure 4. BPA decreases ATP production in both autistic and non-autistic children.[a]



[a]Reproduced from Kaur et al.[17]

Abbreviations: BPA, bisphenol A; MMP, mitochondrial membrane potential.

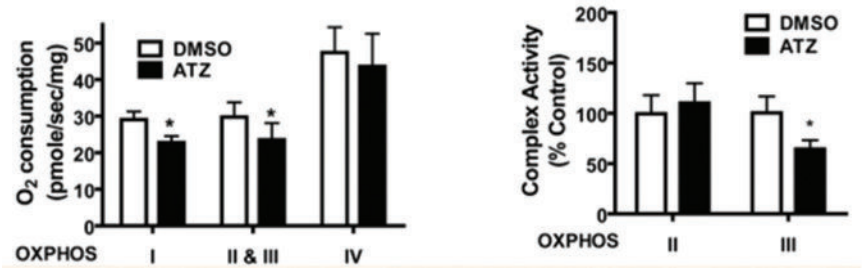
Figure 5. Phthalates Increase Mitochondrial Oxidative Stress.[a]



[a]Reproduced from Ban et al.[19]

Abbreviations: GSH, glutathione; MDA, malondialdehyde; MEHP, mono-(2-ethylhexyl) phthalate; SOD, superoxide dismutase.

Figure 6. Atrazine Inhibits the Electron Transport Chain.[22]



Bisphenols

Figure 4, a human cell culture, shows decreases in mitochondrial ATP production (measured by MMP—mitochondrial membrane potential) in both autistic and non-autistic siblings. While the good news is that bisphenol A (BPA) levels are decreasing in the population, the bad news is that they are being replaced by other bisphenols that show similar toxicity.

Since bisphenols have short half-lives of about a day, reduction in exposure is very effective for decreasing body load. If levels can't be decreased enough, enhancing glucuronidation through consumption of cabbage family foods and/or supplementation with sulforaphane increases the rate of detoxification.

Phthalates

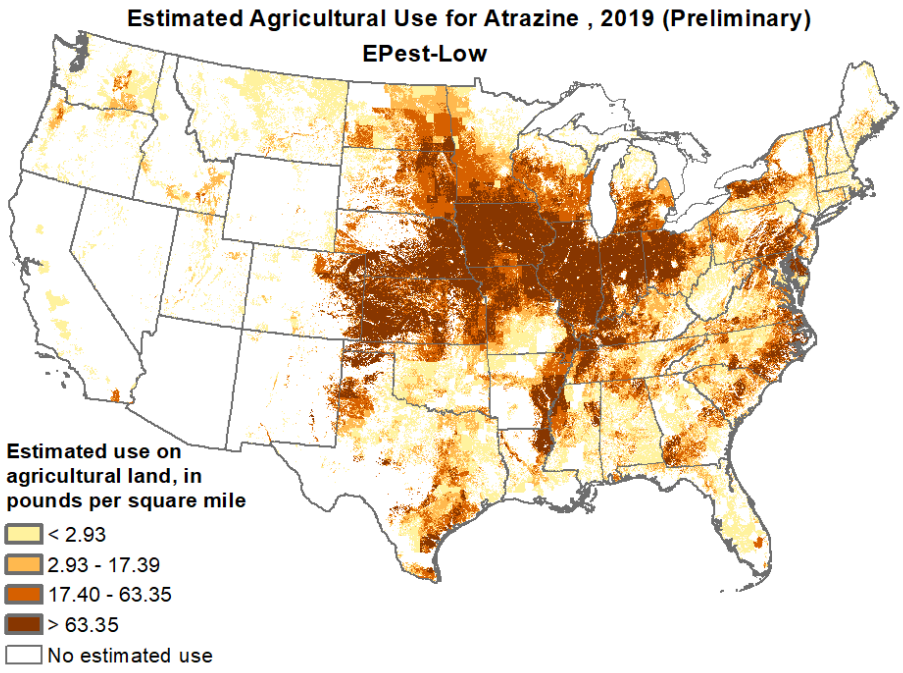
The mitochondrial toxicity of phthalates has been known for almost half a century (Figure 5). Phthalate esters, in a dose-dependent manner, alter the permeability of the inner membrane, increase oxidative stress, increase MDA and inhibit succinate dehydrogenase activity.[18]

Since phthalates have short half-lives of about a day, reduction in exposure is very effective for decreasing body load. Phthalate excretion can be increased with the use of saunas.[20]

Pesticides and Herbicides

Many pesticides and herbicides are mitochondrial poisons. The herbicide atrazine has been widely used in the United States since the 1960s—even though it was banned by the European Union in 2004.[21] It inhibits both photosynthesis and mitochondrial function. As can be seen in Figure 6, in cell cultures atrazine inhibits all the complexes in oxidative phosphorylation.

Figure 7. Atrazine Use in the United States.[23]



Unfortunately, much of the United States is highly contaminated with atrazine as shown in Figure 7. Over 80% is used for growing corn. While much of that corn is used to produce ethanol for transportation, not only is corn for humans and animal feed contaminated, but so is the ground water.

The intervention is obviously to not eat chemically-grown foods and to ensure the water supply is not contaminated. The only way to be sure is for the food and water to be measured for toxin levels.

Statins

Statins damage mitochondrial function in many ways: they reduce coenzyme Q10 levels, inhibit respiratory chain complexes, induce mitochondrial apoptosis, dysregulate calcium metabolism, and decrease carnitine palmitoyltransferase-2 expression.[24] The degree of damage is hugely impacted by the chemical structure of a specific statin and how it interacts with key enzymes according to a person's unique genetics. For the average person, the typical dose of 40 mg/d simvastatin causes decreased oxygen uptake during exercise training and reduction in citrate synthase activity.

Vitamin D has been shown in patients with type 2 diabetes mellitus to reverse almost all of the mitochondrial dysfunction caused by simvastatin. In a study which used exercise performance and skeletal muscle mitochondrial content as the measure, 60 000 IU of vitamin D once a week decreased the loss of respiratory fitness induced by 12 weeks of 40 mg/d of simvastatin from 8.4% to 0.6%.[25] I thought it especially interesting that vitamin D alone increased cardiorespiratory fitness and muscle cell mitochondrial content by 7.1% and 16.7%, respectively, suggesting deficiency. While the study provided vitamin D weekly, the bone health research clearly shows that daily administration of vitamin D is far more effective.

Conclusion

Mitochondria are necessary for life, and dysfunction leads to chronic disease and shortened life expectancy. Unfortunately, suboptimal mitochondrial function is very common. While genetic mutations play a role, far more common is the damage from nutrient deficiencies and regular accidental and intentional exposures to mitotoxic metals and chemicals. Fortunately, toxins can be avoided and elimination from the body can be enhanced. In addition, many natural health molecules can help protect mitochondria and restore function.

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