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How Aging Affects Mitochondria in Brain Cells

Analysis by Dr. Joseph Mercola Fact Checked | March 28, 2023

STORY AT-A-GLANCE

- Mitochondria are the powerhouses of your cells, producing a majority of the energy generated in your body. They also coordinate apoptosis, or programmed cell death — an important process that ensures the death of malfunctioning cells that might otherwise turn into cancer
- Your brain, being the most energy-dependent organ, is particularly susceptible to impaired energy production due to faulty mitochondria, and researchers now suggest this is what makes the human brain susceptible to age-related diseases in the first place
- In older individuals, mitochondrial genes related to energy generation become progressively less active. The mitochondria tend to be less dense and more fragmented, and generate much lower amounts of energy
- Free radicals formed at the level of the mitochondria are typically extremely harmful, which is why you need to minimize them. Effective strategies include cyclical ketosis, calorie restriction (fasting), meal timing, exercise and EMF avoidance
- Supplements that help optimize mitochondrial function include CoQ10, PQQ, berberine, magnesium, nontimed-release niacin and D-ribose

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In recent years, it's become increasingly apparent that most of what we refer to as health and disease really links back to the function of your mitochondria — tiny

organelles inside your cells that play an important role in the production of adenosine triphosphate (ATP), required for all biological functions.

If your mitochondria are not functioning well, your risk for chronic degenerative diseases will radically increase. Not surprisingly, optimization of mitochondria is also vital for life extension strategies.

Your brain, being the most energy-dependent organ (consuming up to 20 percent of the energy used by your entire body[1]), is therefore particularly susceptible to impaired energy production due to faulty mitochondria, and researchers now suggest this appears to be what makes the human brain susceptible to age-related diseases in the first place. As reported by Salk News:[2]

> *"Salk researchers used a new method to discover that cells from older individuals had impaired mitochondria — the power stations of cells — and reduced energy production. A better understanding of the effects of aging on mitochondria could reveal more about the link between mitochondrial dysfunction and age-related brain diseases such as Alzheimer's and Parkinson's."*

Mitochondrial Dysfunction and Age-Related Brain Disease

The research[3] in question, published in the May issue of Cell Reports, supports "a bioenergetic explanation for the high susceptibility of the brain to aging." With age, your mitochondria tend to decrease both in number and function, and this age-related dysfunction is caused by impaired ATP production and an increase in oxidative damage. According to the authors:

> *"Mitochondrial dysfunction is characterized by the loss of the mitochondrial membrane potential, which is directly linked to a loss of energy generated through the electron transport chain that performs oxidative phosphorylation (OXPHOS); the failure of OXPHOS is believed to set the stage for the development of age-related disorders.*

Interestingly, inherited mitochondrial diseases that can be caused by mutations in genes encoded on the nuclear DNA, which encodes the vast majority of mitochondrial genes, or in genes that are encoded in mtDNA are often associated with neurodegenerative phenotypes, indicating a particular vulnerability of brain neurons to mitochondrial defects.

Similarly, the human brain is an organ that is strongly affected by aging, and advanced age is by far the strongest risk factor for most neurodegenerative disorders."

While most investigative methods employ chemical stressors on cells to simulate cellular aging, the Salk group, led by Rusty Gage, a Salk Laboratory of Genetics professor, used a novel method previously developed by Gage that directly converts skin cells into neurons, referred to as "induced neurons" or iNs. These iNs allowed them to observe the effects of natural aging on mitochondria.

Mitochondrial Genes Are Turned Off in Older Individuals

For the featured study, the team collected skin cells from individuals ranging in age from newborn to 89, and then created iNs from each donor. They then studied the mitochondria within each set, using a variety of different methods. Interestingly, while the mitochondria in the skin cells showed few variations between age groups, once the cells were converted to neurons, significant differences emerged.

In the iNs of older individuals, mitochondrial genes related to energy generation were turned down. The mitochondria were also less dense and more fragmented, and generated much lower amounts of energy. The mitochondrial membrane potential was on average 43 percent lower in old iNs compared to young iNs.

"Pretty much every area we looked at — functional, genetic and morphological — had defects," Jerome Mertens, a Salk staff scientist and co-corresponding study author said.

The authors also noted that the differences in susceptibility to mitochondrial aging between various cell types appears to depend on the level of oxidative phosphorylation

the cell in question performs, and that "the metabolic profile of neurons might render them particularly vulnerable to mitochondrial aging." As reported by Salk News:

> *"The researchers hypothesized that the reason the mitochondria of iNs were more impacted by aging than the mitochondria of skin cells was that neurons rely more heavily on mitochondria for their energy needs. 'If you have an old car with a bad engine that sits in your garage every day, it doesn't matter,' Mertens says. 'But if you're commuting with that car, the engine becomes a big problem.'*
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> *The finding shows how aging can impact organs differently throughout the body. The researchers next want to begin to apply their method to study age-related diseases, including Alzheimer's and Parkinson's. In the past, mitochondrial defects have been implicated in these diseases.*
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> *By collecting skin cells from patients and creating iNs, the team can look at how neuronal mitochondria from patients with those diseases are different from neuronal mitochondria from unaffected older individuals."*

Mitochondrial Function Is Important for Tumor Protection

Aside from turning the food you eat into energy, your mitochondria also have other radically important functions. For example, they act as the coordinator for apoptosis, or programmed cell death — an important process that ensures the death of malfunctioning cells that might turn into tumors lest they be cleaned out.

Over the course of a cell's life, damage will inevitably occur. Once that damage reaches a certain threshold, signals are sent to the cell with instructions to self-destruct.

Your mitochondria determine whether that threshold has been reached, and are the initiators of the subsequent cell suicide program. If your mitochondria are not functioning well, they might not be able to make a proper determination of when the damage threshold has been reached, and/or may not give the damaged cell the signal for apoptosis. The result is obvious: You end up with severely damaged cells hanging around, accumulating and contributing to further dysfunction.

Moreover, in order for the apoptosis cascade to happen, energy input is required. So, even if your mitochondria are able to make the determination that the threshold has been reached and are able to signal apoptosis, if there's insufficient energy, defective cells will still survive and multiply. This, in a nutshell, is how dysfunctional mitochondria end up causing cancer.

Peroxynitrite Likely Causes Most of the Damage

While your mitochondria can be damaged in a number of ways, much of it stems from superoxide free radicals — created when electrons leak out of the electron transport chain (ETC) and react with oxygen. This is a normal and healthy process, but when superoxide is created at higher levels than healthy, it will damage the DNA in your mitochondria.

What causes excess leakage of electrons out of the ETC in your mitochondria? In short, not being metabolically flexible and burning a higher percentage of carbohydrate than fat, which leaks far more of these electrons that combine with molecular oxygen to form superoxide.

With a name like superoxide, you would think this molecule would be really damaging and dangerous but it is relatively benign. It was thought that its conversion to hydrogen peroxide and combining with iron (Fenton reaction) to form hydroxyl free radical caused most of the damage.

However, this view has radically shifted this century. It is now appreciated that while hydroxyl radicals are damaging, they don't travel very far, only the distance of one protein, and their damage is relatively restricted. The major problem with generations of excess superoxide is that it is available to combine with nitric oxide to form what is likely the most dangerous molecule in your body, peroxynitrate.

EMF Exposure

I just concluded hundreds of hours of reading thousands of pages on this topic and finished writing a 30-page paper for a peer-reviewed publication that extensively details the concept of how one can use molecular biology to understand and remediate most chronic disease. I hope to publish it on the site later this year, once it is accepted for journal publication.

But briefly, the perfect storm of DNA, cellular protein and membrane destruction is created when you aren't burning fat for fuel and creating excess superoxide and then get exposed to electromagnetic fields (EMFs).

This causes a radical increase in nitric oxide release that nearly instantaneously combines with superoxide to create enormous levels of peroxynitrate, which triggers a cascade of destructive events to your cellular and mitochondrial DNA, membranes and proteins.

Although all biologic damage is of concern, it is the DNA strand breaks that are most concerning as they will lead to a radical increase in inflammation and virtually all degenerative diseases. Thankfully, your body has the ability to repair this damaged DNA with a family of enzymes called PARP (poly ADP ribose polymerase). It is a very effective repair system and works wonderfully to repair the damage as long as it has enough fuel.

And what is that fuel? It is NAD+ that you might have heard a bit of in the news recently. When excess peroxynitrate activates PARP to repair the DNA damage, it consumes NAD+ and if you run out you can't repair the damage, which is likely the central cause for most of the diseases we are seeing in the modern world now.

I have previously written extensively about EMF and how you can mitigate your exposure. The key here is to understand that it is the combination of EMF exposure and the inability to burn fat as a primary fuel that causes the domino cascade of biologic destruction that we are currently observing.

NAD+ Is Central to Maintaining Cellular, Mitochondrial Health

Improving NAD+ levels is a very complex topic and really requires a book to carefully explain, which I am actually in the process of writing. But optimizing NAD+ levels may be the single most important strategy for improving your mitochondrial health.

The first step is to reduce NAD+ consumption by the correct diet, along with EMF avoidance. Then there are inhibitors of inflammatory pathways, like CD38, that consume NAD+ that can also increase NAD+ levels. Finally, there are strategies to convert NADH to NAD+, which is the beneficial form of NAD.

There is one simple inexpensive supplemental strategy to increase NAD+ from a biological precursor. There are four primary ones that will not be reviewed here but the least expensive one is simple nontimed-release niacin (vitamin B3) — yes, the same vitamin used to cure pellagra and improve heart disease for the last 50 years. Although niacinamide works, evidence suggests it is not as effective, and additionally suppresses important and beneficial sirtuins.

NAD+ (nicotinamide adenine dinucleotide) is one of the most important biomolecules in your body. It's involved in the conversion of food to energy, maintaining DNA integrity and ensuring proper cell function. Together, these functions help protect against or delay aging and virtually all chronic disease.

NAD+ also acts as fuel for longevity proteins called sirtuins. Sadly, NAD levels dramatically decline with age, contributing to aging and chronic disease states. NAD is also used up by DNA repair enzymes and enzymes involved in inflammation and immunity, such that chronic inflammation, or acute illness in old age, can rapidly result in depletion.

To restore NAD_, you need to fix the root cause for NAD+ depletion, which primarily involves addressing the decline in the NAD salvage pathway. By increasing enzymes in that pathway, which decline with age, your body can recycle NAD_ like it did naturally when it was younger. For more information, please review my **fantastic interview with molecular biologist Nichola Conlon**, Ph.D.

The best way to supplement niacinamide is by taking a very low dose of 50 mg three times a day. This is an order of magnitude less expensive than taking NAD precursors like nicotinamide riboside or nicotinamide mononucleotide to increase NAD+ levels. Please do NOT take high doses like 500 mg or even 1,000 mg, because taking more is not better and will be highly counterproductive as higher doses will impair your sirtuin longevity proteins.

You can purchase a niacinamide powder and take one-sixty-fourth of a teaspoon three times a day or take a 50 mg niacinamide tablet three times a day. Because a 50 mg niacinamide tablet currently is not being made commercially, we will be launching one very soon.

Efficient Fat Burning Minimizes Mitochondrial Damage

So, hopefully, you are now even more motivated to optimize your diet by what I just shared. The central theme of my book "**Fat for Fuel**," details strategies aimed at minimizing the production of excess superoxide by teaching your body to burn fat as a primary fuel.

What we're now finding is that it's the divergence from our ancestral diet — the massive prevalence of processed, unnatural foods and excessive amounts of added sugars, net carbs and industrial fats — that causes a majority of the damage.

High-carb, processed food diets prevent your body from efficiently burning fat as its primary fuel, and burning fats and ketones is far more efficient, inducing far less oxidative stress, than burning carbs. So, a foundational dietary strategy to optimize your mitochondrial health is to eat the right fuel.

Once you become an efficient fat burner, you automatically minimize the oxidative stress placed on your mitochondria, which is key. Other effective strategies include calorie restriction (fasting) and exercise (see section below).

Meal timing is another important factor. One of the worst things you can do to your mitochondria on a regular basis is eating shortly before going to bed. Ideally, you would

eat your last meal at least three hours or more before bedtime.

By supplying your body with food at a time when your body needs it the least (since you're sleeping), excessive amounts of free radicals end up being formed, which then spill out and damage mitochondrial DNA. Excess carbohydrates, in particular, result in a backup of electrons that causes the production of superoxide.

What's more, should you happen to have high iron levels — which is far more common than low iron — combined with high superoxide, then hydroxyl free radicals are produced, which are among the most harmful. The chemical reaction that creates these hydroxyl free radicals is known as the Fenton reaction.

While you certainly need enough iron, having too high an iron level can cause severe damage, and this is one way in which it does that. To learn more about the hazards of high iron, and simple ways to screen for and lower it, please see "**Why Managing Your Iron Level Is Crucial to Your Health**."

Practical Strategies to Optimize Your Mitochondrial Function

Thanks to living in a toxic environment, feeding your body inappropriate fuel, eating at the wrong time and not exercising enough, most people have less than optimized mitochondria. The good news is there are many ways to improve your mitochondrial function. The two best and most researched ways to optimize mitochondrial function are exercise and calorie restriction.

Exercise upregulates genes like PGC-1 alpha and nuclear gene factors like Nrf2. These genes help your mitochondria become more efficient. They also boost mitochondrial growth and division, so that you end up with a larger number of mitochondria. In simplified terms, the reason exercise benefits your mitochondria is because it places an increased energy demand on your cells.

In response, free radicals signal that you need more mitochondria. So, over time, your body adapts to higher levels of physical activity by triggering the creation of more mitochondria, and improving their efficiency.

As your fitness level improves, each individual mitochondrion is placed under considerably less stress (since there's more of them), and as a result, fewer free radicals are generated. As noted by Dr. Lee Know, author of "Mitochondria and the Future of Medicine," this is "one of the reasons why physically fit individuals have a lower risk of pretty much all degenerative diseases, including cancer, as well as a longer life span."

Molecular Hydrogen (H_2)

Molecular hydrogen acts as a selective antioxidant, meaning it doesn't indiscriminately suppress free radicals. Rather, it's unique in that it helps your body make its own endogenous antioxidants. This is important because excessive use of antioxidants can be counterproductive, while molecular hydrogen serves as a redox regulator.

Hydrogen gas is particularly useful for non-ionizing radiation and neutralizing the peroxynitrate that is produced when exposed to EMF. This is important as peroxynitrate causes most of the dangerous free radicals from EMF exposure. Hydrogen also stimulates many other important endogenous antioxidants like glutathione to further reduce oxidative stress.

The H_2 molecule is the smallest in the universe, which allows it to diffuse through all cell membranes, including the blood-brain barrier and subcellular compartments, and into the mitochondria. According to Tyler LeBaron, Ph.D., it's been shown to have therapeutic benefits in more than 170 different animal disease models.3 While there's no risk of overdosing on molecular hydrogen, intermittent exposure produces the best results.

Helpful Supplements

In addition to diet, meal timing and exercise, certain dietary supplements can also be useful. The following are particularly beneficial for optimizing mitochondrial function throughout your body:

Coenzyme Q10 (CoQ10) or its reduced (and more absorbable) form, ubiquinol, if you're over 40. CoQ10 is intimately involved in the energy production process, and having an excess amount of CoQ10 is by many considered an effective therapeutic strategy to ensure well-functioning mitochondria. CoQ10 also acts as a signaling molecule and helps protect cell membranes from damage.

Quercetin, an antioxidant that belongs to a class of water-soluble plant substances called flavonoids, which are present in certain fruits and vegetables. Aside from antioxidant properties, quercetin is known to have anticarcinogenic and anti-atherogenic capabilities, but for purposes of this discussion in can also increase NAD+ levels.

Pau D'Arco has been used for centuries to treat cancer and malaria. It is loaded with flavones, quercetin, alkaloids and other nutrients that can increase NAD+ levels.

Pyrroloquinoline quinone (PQQ), a vitamin-like substance and a cousin to CoQ10, helps with mitochondrial biogenesis. The greater number of mitochondria you have, the more energy your cells are able to produce, and the better they function overall. So, having sufficient amounts of PQQ encourages the proliferation of mitochondria.

Both animal and human studies using doses between 10 and 20 milligrams (mg) of PQQ shows significant improvement in mental processing and memory. The best results are obtained when you take PQQ in combination with CoQ10. PQQ has also been shown to protect against the development of alpha-synuclein, a protein associated with Parkinson's disease, and beta-amyloid, associated with Alzheimer's.

Berberine also benefits mitochondrial function and is a powerful AMPK activator, thereby stimulating mitochondrial autophagy (mitophagy) and mitochondrial biogenesis. It also helps protect against the type of oxidative stress that leads to Parkinson's disease.

Magnesium also plays an important role in the production of ATP, and is a required cofactor in the mitochondrial repair process. To learn more about how magnesium

impacts your mitochondrial health, see "Magnesium — A Key Nutrient for Health and Disease Prevention."

D-ribose is a five-carbon sugar required by ADP. While being a sugar, it has no impact on your blood glucose, so it's safe to consume even for diabetics. Ribose enters cells and converts into the adenosine triphosphate (ATP) base required for the creation of ADP and ATP.

While your body produces D-ribose on its own, it's a very slow process. According to Know, D-ribose is often a rate limiting factor in recovery for patients with cardiovascular disease, stroke, heart attack and chronic fatigue.

It's nontoxic and is virtually impossible to overdose on, and if you've suffered a stroke, heart attack or struggle with chronic fatigue, it's a really important supplement to include in your regimen. Taking D-ribose prior to cardiac surgery can also help minimize damage associated with reperfusion injury. Since most people have some degree of mitochondrial dysfunction, it may also be helpful for general health, especially if you exercise regularly.

Sources and References

- [1, 3] Cell Reports May 29, 2018; 23(9): 2550-2558
- [2] Salk News May 29, 2018