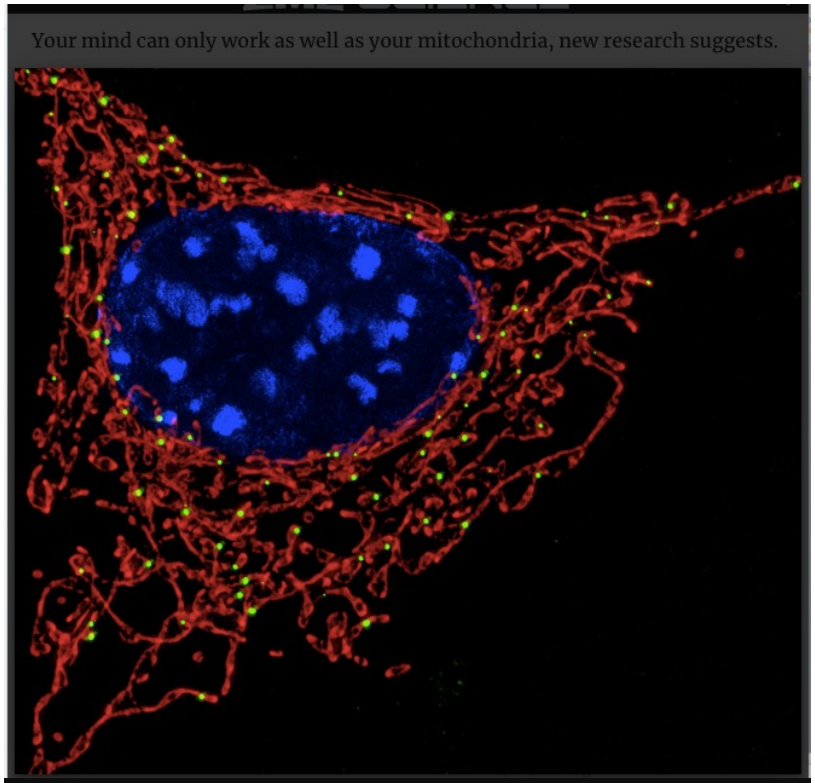

When mitochondria break down, so do our minds. When power runs low, neurons start going haywire.

Our (Mother's) Mitochondria and Our Mind

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Perspectives on Psychological Science 2018, Vol. 13(1) 88–100

Mindfulness In Biz
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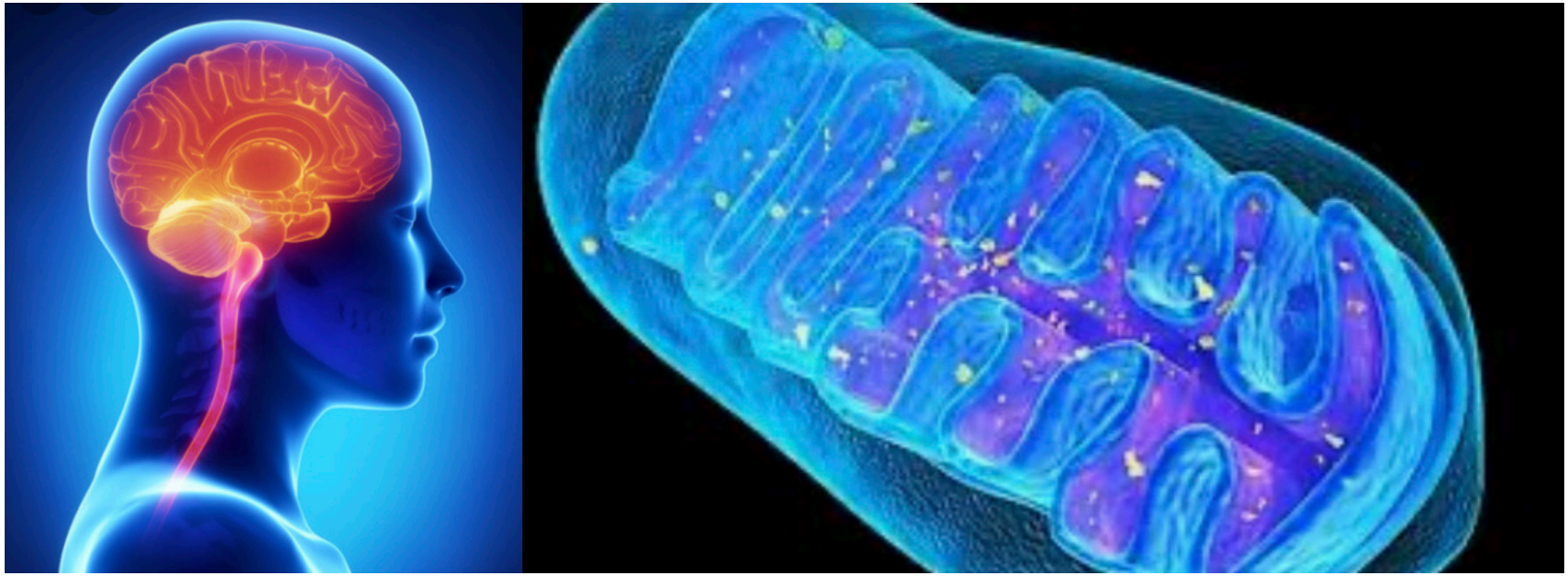
Discussions

Mitochondria… Energy Powerhouse



Mitochondria… Energy Powerhouse

Some people expend tremendous energy merely to be normal.
— Albert Camus, *Notebooks: 1942–1951*

Most of the energy we get to spend is furnished by mitochondria, tiny living structures sitting inside our cells or dispatched back and forth within them to where they are needed. Mitochondria produce energy by burning down what remains of our meal after we have digested it, but at the cost of constantly corroding themselves and us.

Here we review how our mitochondria evolved from invading bacteria and have retained a small amount of independence from us; how we inherit them only from our mother; and how they are heavily implicated in learning, memory, cognition, and virtually every mental or neurological affliction.

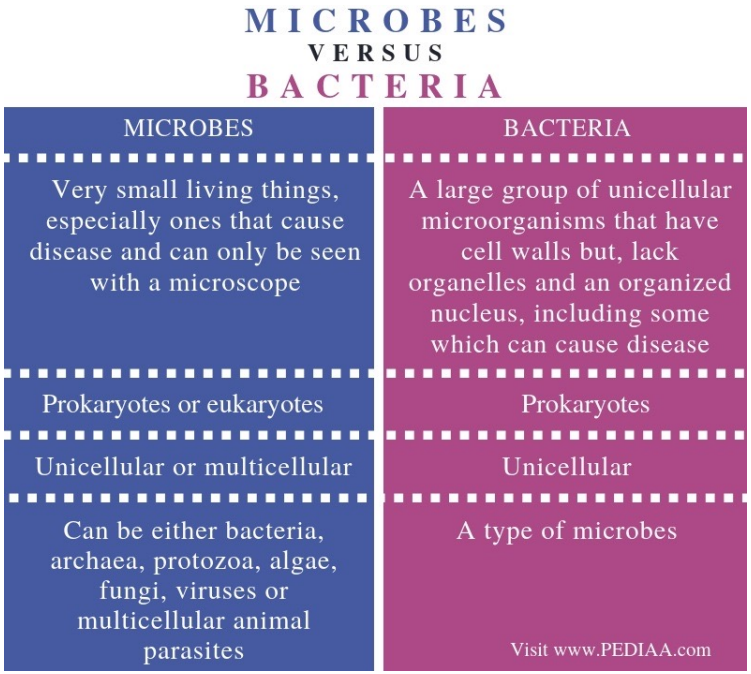
We discuss why counteracting mitochondrial corrosion with antioxidant supplements is often unwise, and why our mitochondria, and therefore we ourselves, benefit instead from exercise, meditation, sleep, sunshine, and particular eating habits.

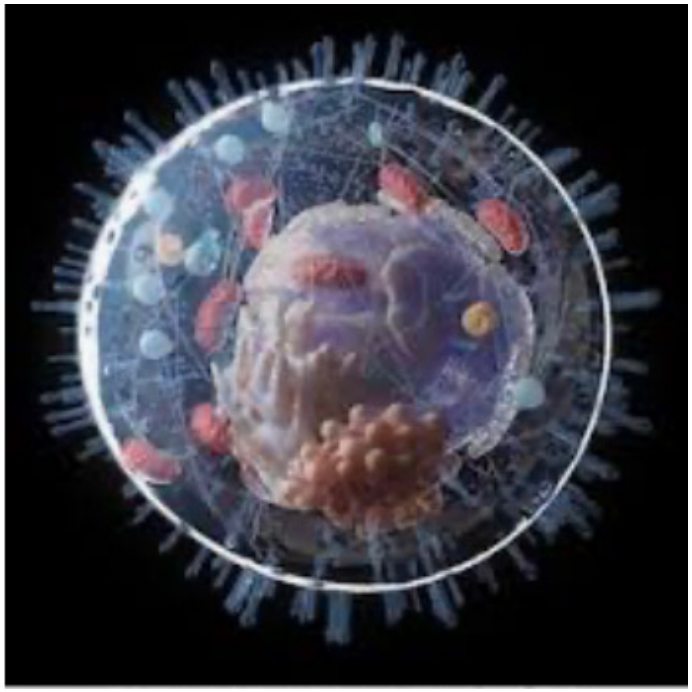
Love in a Cold Climate

Life on earth has existed for around 4 billion years (Dodd et al., 2017). For the first 2 billion, all creatures alive were single cells with no nucleus (Dacks et al., 2016).

Mitochondria are former prokaryotic cells (bacteria), at one point in the distant past "join forces" with the other microbes offering them nutrients and protection in exchange for their energy.

With mitochondria's energy, microbes build a kind of control center out of it—a cell "nucleus"—and evolve from prokaryotes (organisms made of one cell with no nucleus) into eukaryotes (organisms made of one or more cells with a nucleus, like us) (Lane, 2015; Lane & Martin, 2010).



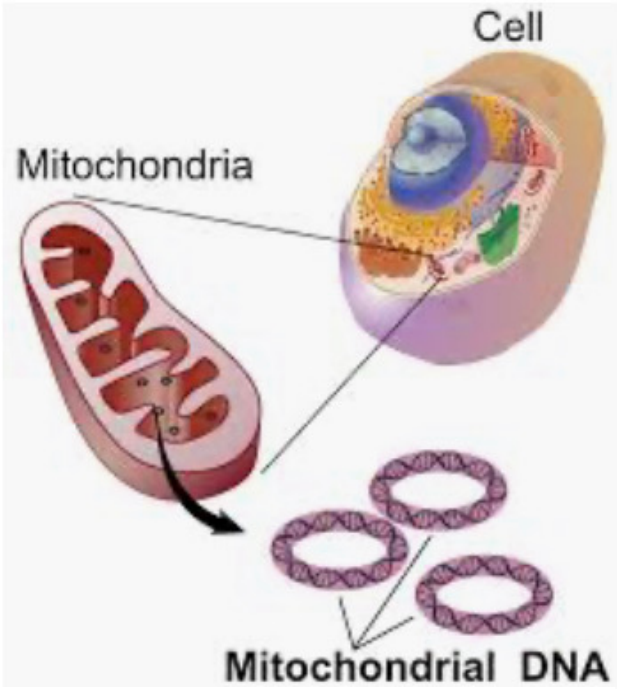


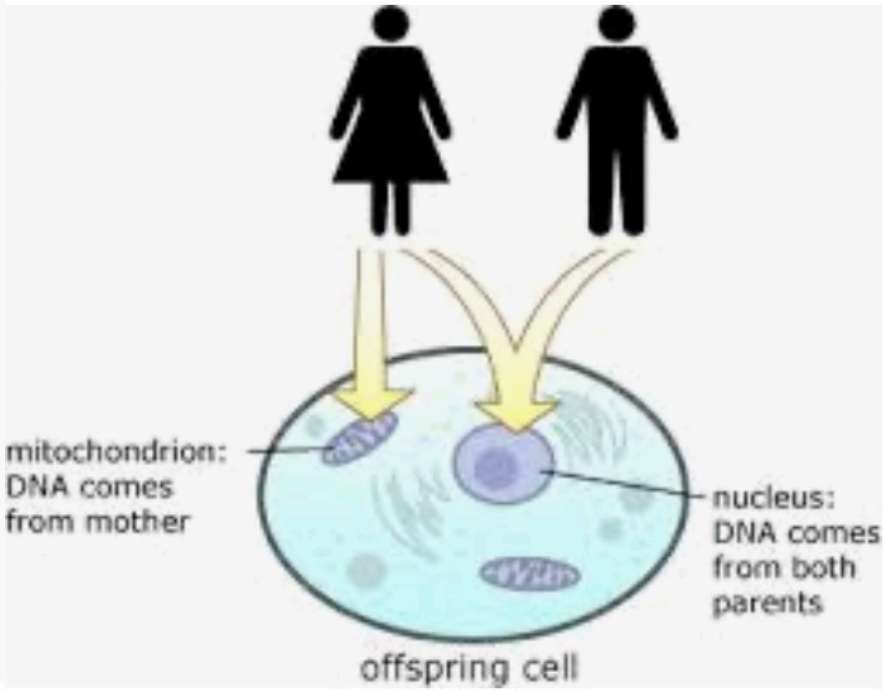
Love in a Cold Climate

Prokaryotes are sexless and reproduce by making copies of themselves.

Eukaryotes, in addition to cloning, will also reproduce sexually some of the time (Speijer, 2016). Only eukaryotes have mitochondria, only eukaryotes have sex.

Sexual reproduction involves passing on not only genes but also all the rest of the fertilized egg, including live mitochondria.



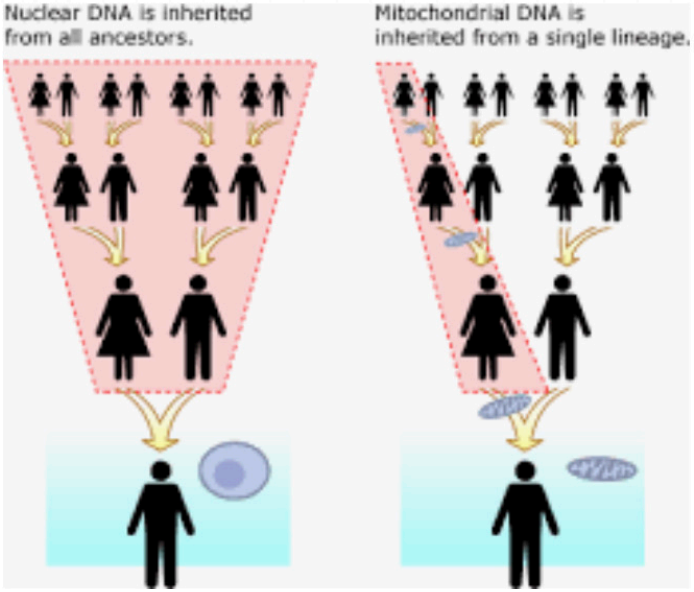


Love in a Cold Climate

Most of our DNA (including some 20,000 genes) sits in the nucleus of each of our cells, and this nuclear DNA regulates much of how our mitochondria function (Mattson, Gleichmann, & Cheng, 2008).

Outside the nucleus, however, mitochondria have retained some DNA of their own (including, in humans, 37 genes) and this gives them a small degree of independence.

Human mitochondrial DNA, unlike nuclear DNA, is passed on only from mothers (Pyle et al., 2015).

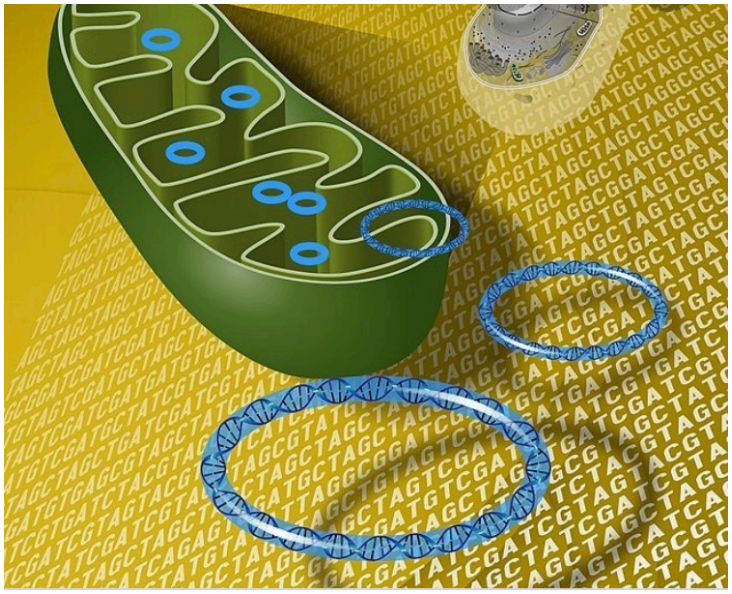


MITOCHONDRIAL DNA	NUCLEAR DNA
Mitochondrial DNA consists of the mitochondrial genome	Nuclear DNA consists of the cell's genome, including mDNA
Double-stranded & circular	Double-stranded and linear
Arranged into a single chromosome	Arranged into several chromosomes
Composed of 0.25% of the cell's genetic makeup in animal cells	Composed of 99.75% of the cell's genetic makeup in animal cells
Freely floating in the mitochondrial matrix	Found in the nuclear matrix, fixed to the nuclear envelope
Not enclosed by the nuclear envelope	Enclosed by the nucleus
Size is 16,569 base pairs	Size is 3.3 billion base pairs
Not packed with histone proteins	Tightly packed with histone proteins
Consists of 37 genes, encoding 13 proteins, 22 tRNAs, and 2 rRNAs	Consists of 20,000-25,000 genes, including three mt genes
Lacks non-coding DNA regions like introns	Contains non-coding regions of DNA like introns and untranslated regions
Replicated independently from nDNA	Replicated only during the S-phase of the cell cycle
Maternally inherited	Inherited equally from both parents

Love in a Cold Climate

Each mitochondrion can carry several up to hundreds or thousands of copies of DNA per cell. Each set is used in the production of the same proteins. Should one set no longer function properly, due for example to accumulation of mutations, another can compensate and this renders mitochondria much more resilient than they otherwise would be.

The number of copies of mitochondrial DNA is not the same for everyone, though, a smaller one should stand for reduced mitochondrial efficiency, and on such grounds reduced efficiency of body and brain (Cao, Zhao, Zhou, Chen, & Yang, 2012).



Air, Fire, and Dangerous Things

Mitochondria Corrode

Mitochondria generate energy then chemically store it as adenosine triphosphate (ATP) and ship it out to the cell. ATP is a molecule that virtually all the cells in your body 'spend' when they need energy. Without ATP, our bodies would completely stall – it's not only important, it's vital to our cells.

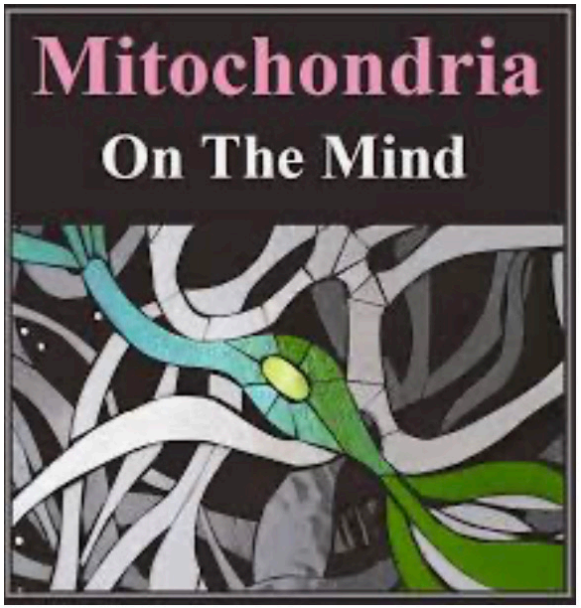
Through the process of creating this molecule, however, mitochondria also generate heat and waste products – carbon dioxide, water, and aggressive, corrosive compounds known as free radicals that degrade cells and the mitochondria themselves.

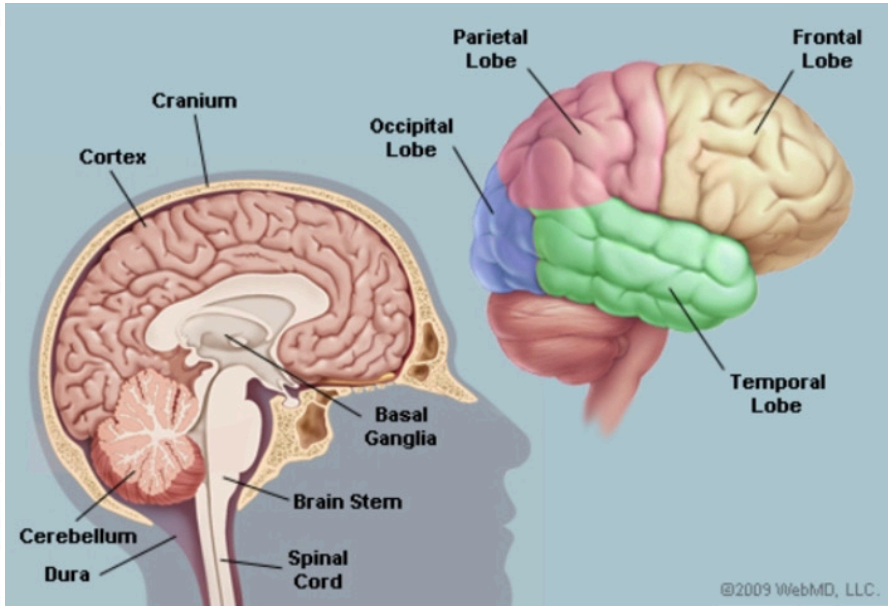
Air, Fire, and Dangerous Things

Mitochondria Corrode

Although mitochondria have a number of contingency measures they can employ to deal with this type of damage, they're only temporary. After a certain amount of time, damage builds up beyond the organelle's ability to fix – so over time, a certain level of mitochondrial dysfunction is inevitable.

The brain, which regularly guips down around 25% of the body's energy, bears the brunt of this wear and tear.

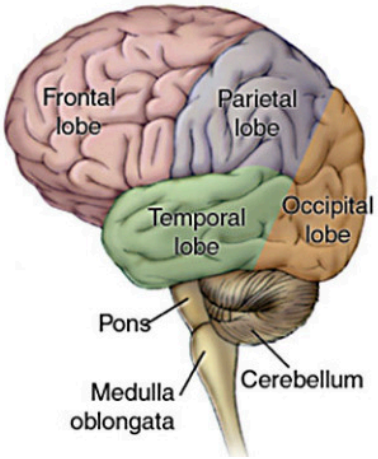


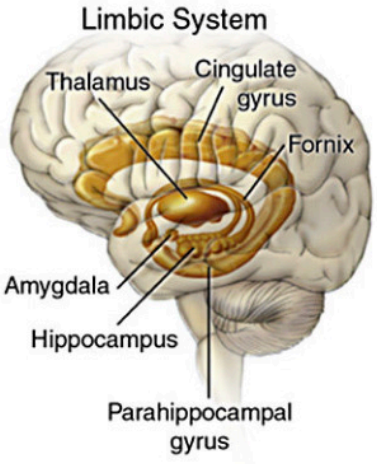


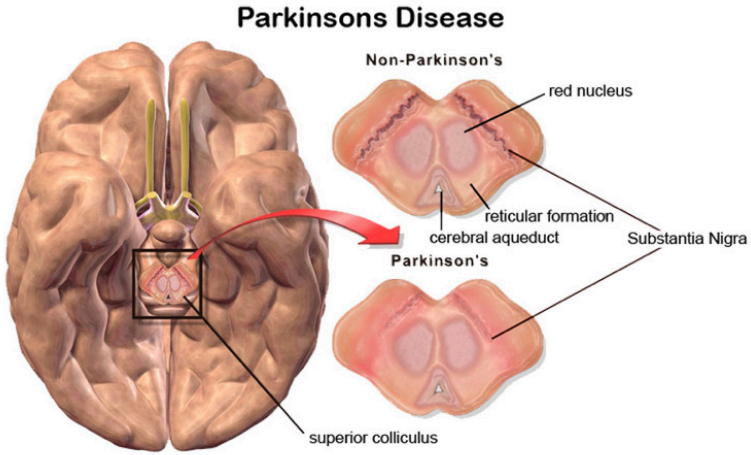
Air, Fire, and Dangerous Things

Mitochondria Corrode

In the case of degenerative conditions such as Alzheimer's or Parkinson's disease, decreased blood flow to the brain (a consequence of aging) limits the amount of glucose and oxygen that mitochondria there can burn to produce ATP. This shortage of fuel slowly causes neurons to degenerate in energy-intensive regions of the brain, such as those associated with memory (i.e., the hippocampus in Alzheimer's) or motor planning (i.e., the substantia nigra pars compacta in Parkinson's).







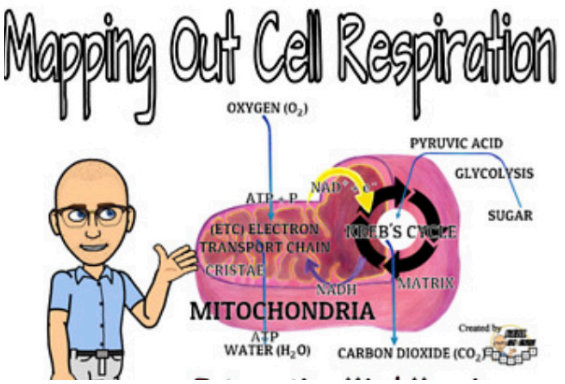
Air, Fire, and Dangerous Things

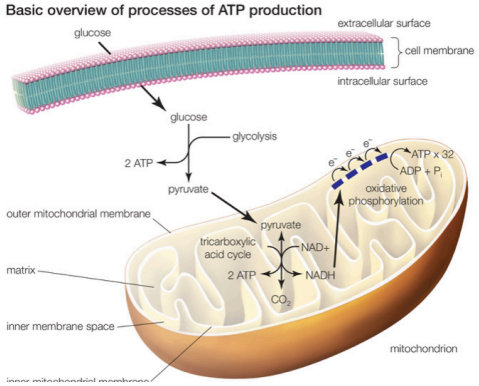
Mitochondria Multitask

On the one hand, mitochondria make our mental health. On the other, they also break it.

Furnish the energy for the brain to function

The nervous system cannot possibly function without mitochondria (Markham, Bains, Franklin, & Spedding, 2014; Mattson et al., 2008). Neurons relay information by firing and mitochondria provide the energy for this. Although neurons use up ATP, energy is in highest demand at synapses, where most of the action occurs. Mitochondria are transferred and docked there only when they are in good shape. As soon as they become unfit and in need of replacement they are promptly destroyed, either on the spot (Ashrafi, Schlehe, LaVoie, & Schwarz, 2014) or after having been removed and transported away (Lin & Sheng, 2015). Poor quality control at this stage is linked to neurodegenerative diseases (Martinez-Vicente, 2017); poor transport of mitochondria precedes the onset of Alzheimer's and Parkinson's diseases (Correia, Perry, & Moreira, 2016; Shlevkov & Schwarz, 2017) and might play a part in schizophrenia and depression as well (Deheshi, Pasqualotto, & Rintoul, 2013).





Air, Fire, and Dangerous Things

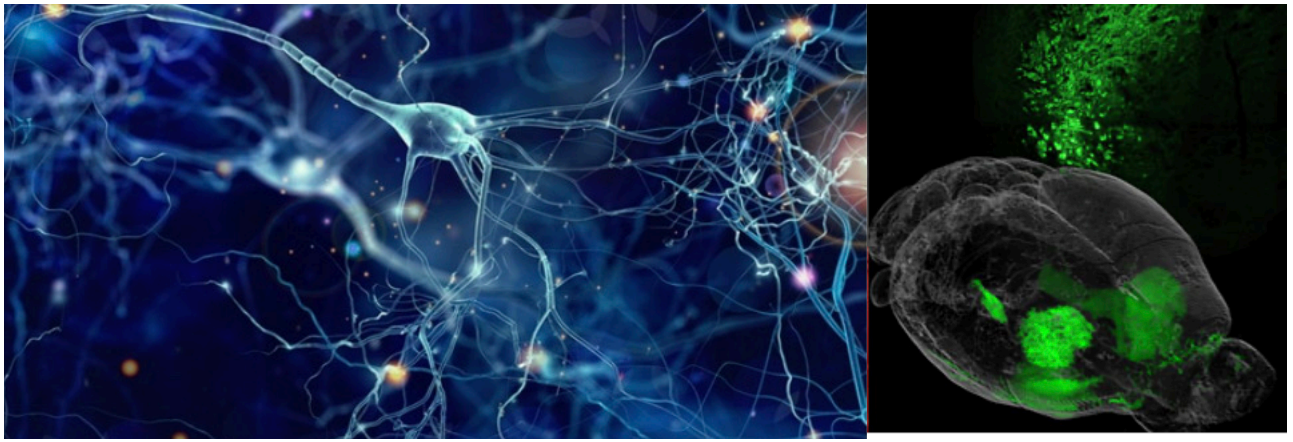
Mitochondria Multitask

On the one hand, mitochondria make our mental health. On the other, they also break it.

Enable synaptic plasticity

Calcium affects the synaptic plasticity in all kinds of manners, not least by sparking the release of brain-derived neurotrophic factor (BDNF), a protein that stimulates the growth and repair of active neurons and synapses (Markham et al., 2014).

Mitochondria affect synaptic plasticity both ways: On the one hand, prompted by BDNF, they supply the energy needed to strengthen neuronal connections; on the other, by delivering the same enzymes they use when forced to kill off their host cell, they can prune connections away (Jeanneteau & Arango-Lievano, 2016; Markham et al., 2014).



Air, Fire, and Dangerous Things

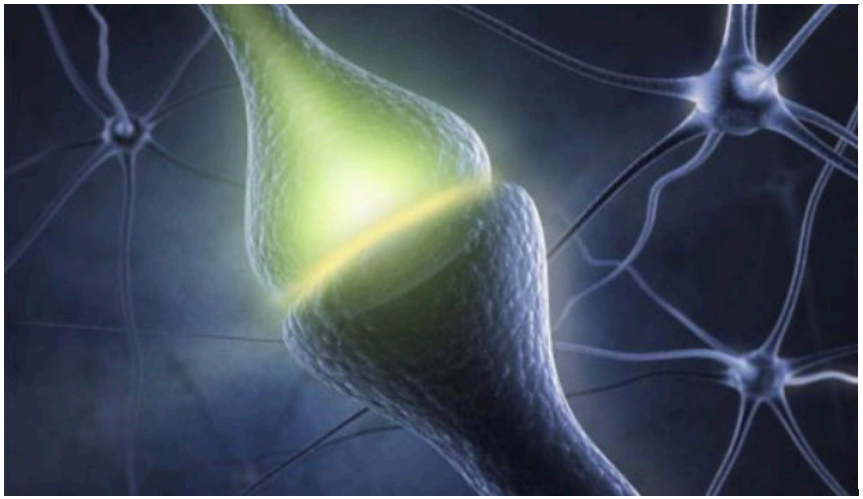
Mitochondria Multitask

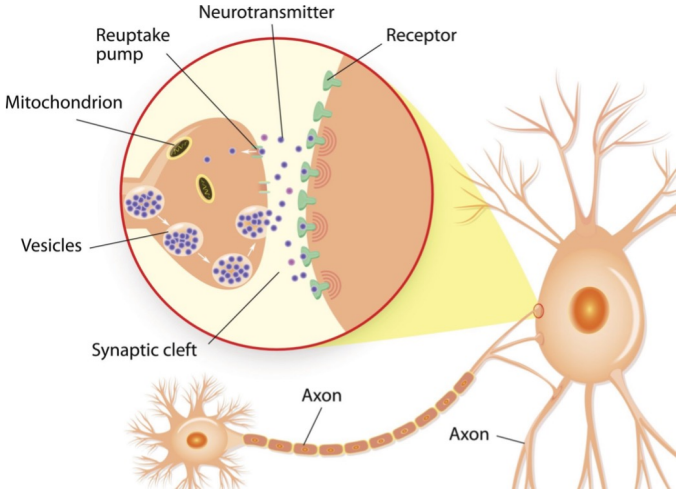
On the one hand, mitochondria make our mental health. On the other, they also break it.

Produce hormones and signaling molecules

ATP can also be used as a signaling molecule in its own right, for example as a neurotransmitter.

Dysregulation of the receptors of either ATP, ADP, or adenosine has been implicated in disorders ranging from a reduced urge to empty one's bladder (whose stretching releases ATP: Cook & McCleskey, 2000) to depression and schizophrenia (Krügel, 2016) and the early stages of Alzheimer's and Parkinson's disease (Burnstock, 2016).





Air, Fire, and Dangerous Things

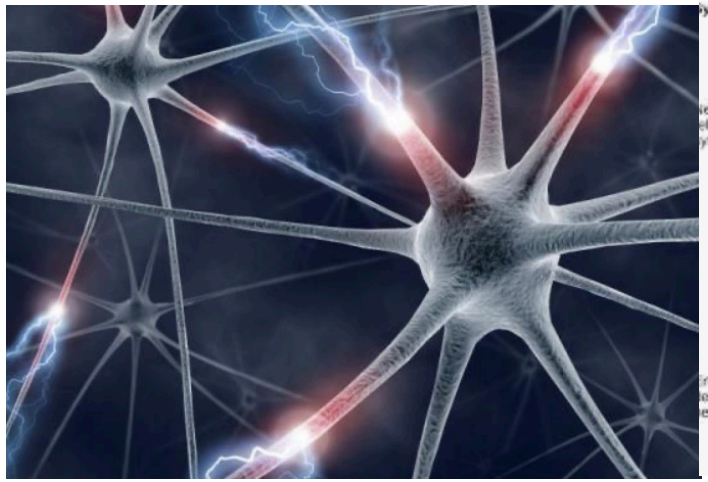
Mitochondria Multitask

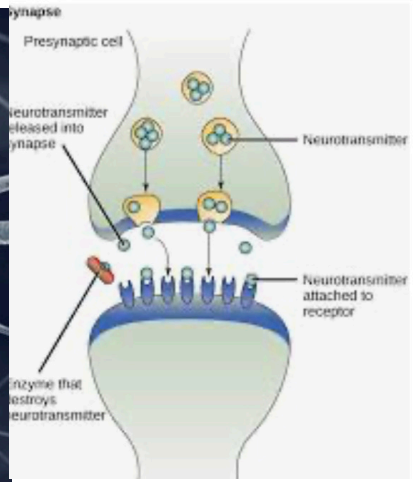
On the one hand, mitochondria make our mental health. On the other, they also break it.

Dish neurotransmitters out and rein neurotransmitters in

After use, or if present in excess, hormones and neurotransmitters tend to be stored away or broken down. The breaking down is partly accomplished by mitochondria, by way of two enzymes of their own: MAO-A and MAO-B. Both metabolize, and thus curtail, critical neurotransmitters such as serotonin, dopamine, and noradrenalin (Buckholtz & Meyer-Lindenberg, 2008).

If one directly knocks out the MAOA gene during development, as has been done in mice, MAO-A is no longer produced, serotonin and noradrenalin levels in the brain rise, and aggressiveness goes up (Buckholtz & Meyer-Lindenberg, 2008).





Air, Fire, and Dangerous Things

Mitochondria Derange

On the one hand, mitochondria make our mental health. On the other, they also break it.

Given the multiple jobs that mitochondria do in the nervous system, their malfunctioning is associated with cognitive deficits, intellectual disabilities, neurodegenerative disorders, and mental illness.

People diagnosed with an inherited disorder that affects all of their mitochondria have been reported to carry a 50% to 70% probability—more than two or three times as high as ordinary people's—of developing a psychiatric condition at some point in life (Fattal, Link, Quinn, Cohen, & Franco, 2007; Inczedy-Farkas et al., 2012; Mancuso et al., 2013; for a review, see Kaplan et al., 2015).

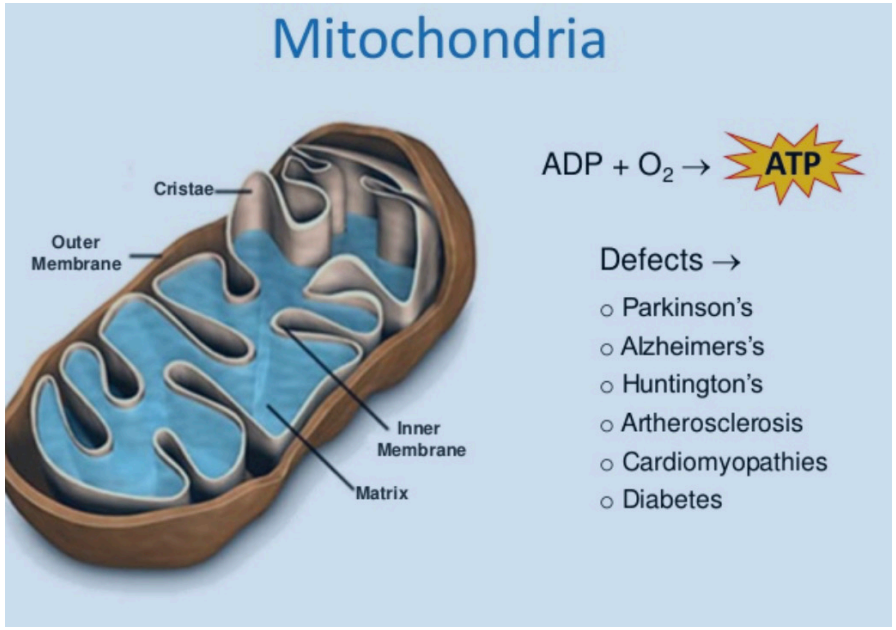
Not unexpectedly, given its effects on mitochondria, dysregulation of either calcium or BDNF has been implicated in numerous mental afflictions too (Autry & Monteggia, 2012; Markham et al., 2014). Mitochondrial malfunctioning also arouses the immune system (Markham et al., 2014), and an activated immune system drives mitochondria to produce even more free radicals (López-Armada et al., 2013).

Air, Fire, and Dangerous Things

Mitochondria Derange

On the one hand, mitochondria make our mental health. On the other, they also break it.

Considering all the above, mental disorders are apt to hinge together (Devaraju & Zakharenko, 2017). For example, schizophrenia patients are often depressed (Buckley, Miller, Lehrer, & Castle, 2009), autism patients are often anxious (van Steensel, Bögels, & Perrin, 2011), Down syndrome patients tend to develop premature dementia (N.C. Lee, 2017), and current depression predicts dementia later on (Manji et al., 2012; Mirza et al., 2016).



At recommended treatment durations and doses, drugs that directly target bacteria, such as common antibiotics, also cripple mitochondria in one or another of an assortment of ways.

For similar reasons, mitochondria get damaged by exposure to any of a wide array of regularly used pesticides and other environmental pollutants (Karami-Mohajeri & Abdollahi, 2013; Meyer et al., 2013; Mostafalou & Abdollahi, 2013).

The Art of Mitochondria Maintenance

Not all mental disorders can be cured, and at least for the time being we have no way of stopping the eventual degeneration of our body and brain. Yet we can improve our mental health and slow down our decline—if only we were willing to pay the unfashionable price at which this comes:

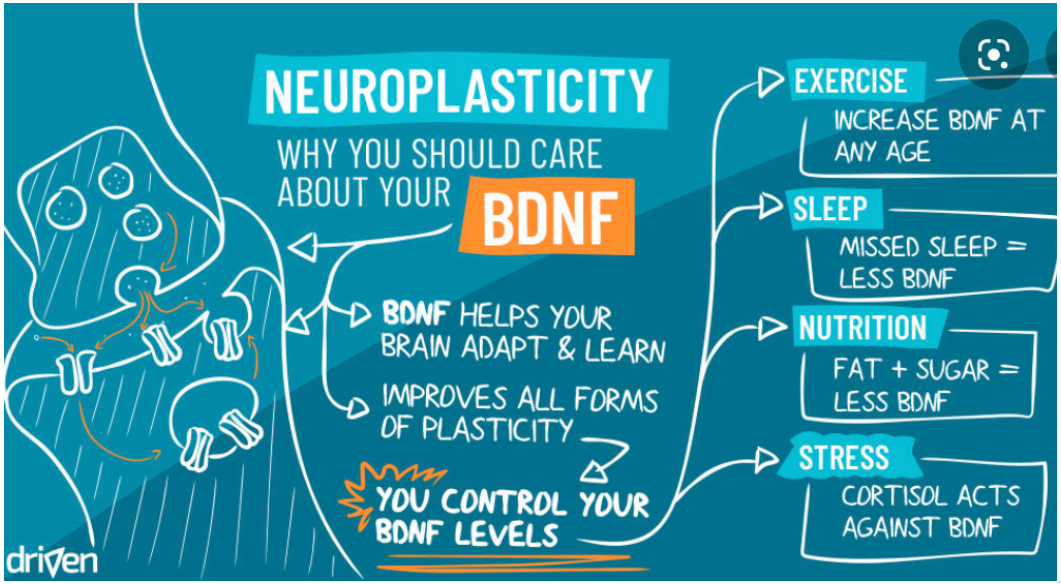
- getting enough sleep,
- exercising regularly,
- practicing relaxation techniques,
- eating less than we may like and less frequently, and
- choosing unprocessed, nutrient-rich foods.

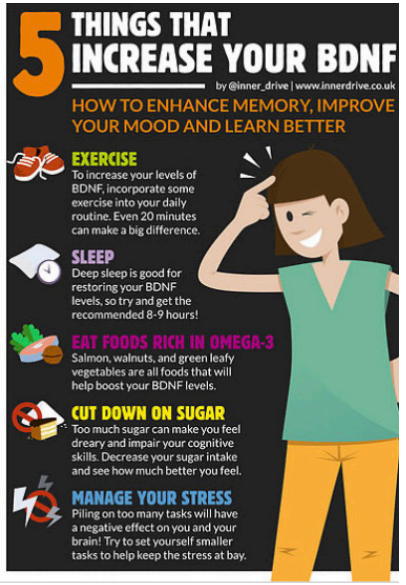
The Art of Mitochondria Maintenance

As soon as we fall asleep, our brain cells shrink in size (Xie et al., 2013). This move—possibly a side effect of reduced firing activity—expands the space between cells by more than 60%. Throughout the brain, the extra space strikingly increases the perpetual flow of cerebrospinal fluid that flushes waste products out into the bloodstream, for eventual detoxification in the liver. In particular, the main component of Alzheimer's plaques, beta-amyloid, is washed out of the brain twice as fast while one sleeps than while one is awake (shown in mice: Xie et al., 2013).

The Art of Mitochondria Maintenance

During sleep, the body and brain continue to spend energy, but the usual source of that energy, glucose, is gradually depleted and not replenished. The same happens during prolonged exercise. Mitochondria must switch to burning something else, and on that account the liver breaks down stored fat into molecules called ketone bodies. This switch means that metabolic circumstances have changed; besides acting as a circulating source of energy, ketone bodies appear to serve as carriers of this useful piece of information too (Newman & Verdin, 2014; Sleiman et al., 2016). Through the bloodstream, they reach the brain where they proceed to signal the news by regulating gene expression— targeting specifically the gene responsible for the production of BDNF.

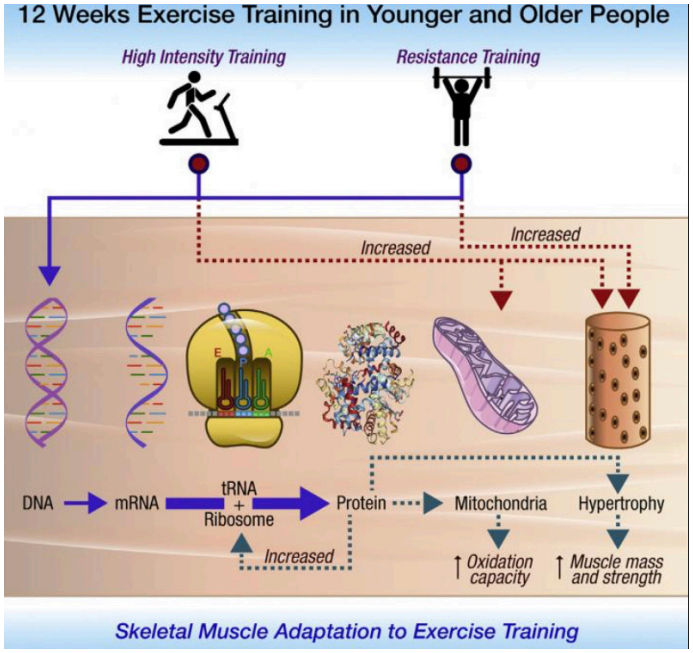




The Art of Mitochondria Maintenance

Exercise actually stimulates the production of BDNF in more than one way at the same time (e.g., Sleiman et al., 2016; Wrann et al., 2013). For our ancestors, after all, physical effort tended to occur at times when one had better be smart and learn fast: when responding to danger, locating hazards, tracking prey, or exploring unfamiliar environments (Mattson, 2015; Noakes & Spedding, 2012).

Rest rusts, say the Dutch, but of course the flip side of lack of rest is a greater production of ATP and thus of free radicals.



The benefits of regular exercise appear to outweigh its inescapable costs only so long as this is practiced at low-to-moderate intensities (Gradari, Pallé, McGreevy, Fontán-Lozano, & Trejo, 2016). Repeated mild stresses up-regulate various anti-oxidant and repair mechanisms so that the body is better placed to cope with major stresses at a future time (Goto, Naito, Kaneko, Chung, & Radák, 2007). Note, incidentally, that this chain of events—and with it the health-promoting effects of exercise—is blocked by taking antioxidant supplements (Peternelj & Coombes, 2011).

The Art of Mitochondria Maintenance

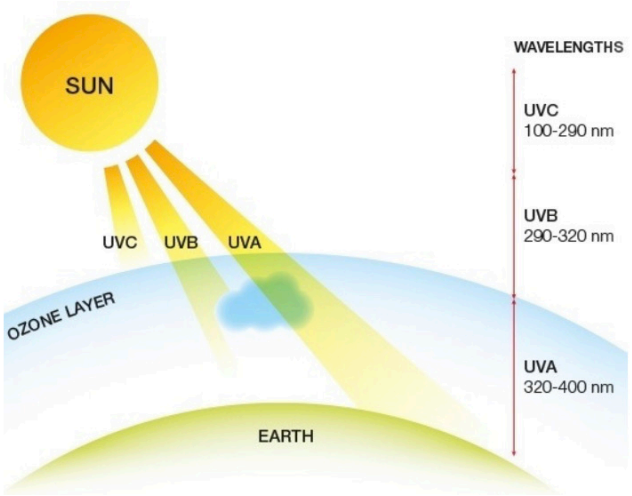
A rule of moderation seems to apply to all forms of stress. For example, low levels of the stress hormone corticosterone, even when chronic, strengthen mitochondria but higher levels harm them (shown in rats: Markham et al., 2014). The effects of constant intense stress counteract those of BDNF, increase free-radical production, and reduce mitochondria's capacity to create energy and lock away calcium. Practicing stress-management techniques that move one's attention away from everyday concerns—like meditation, yoga, tai chi, or repetitive prayer—can engender positive effects on body functions within minutes. Especially in people who practice them regularly, these techniques up-regulate genes that reduce free-radical damage, down-regulate those that foster inflammation, and support the production of ATP and its use by cells (Bhasin et al., 2013).

The Art of Mitochondria Maintenance

Similar benefits as those brought about by getting enough sleep and exercising, and at least partly via the same glucose-depletion mechanism, can be achieved by eating enough but less than one would be spontaneously inclined to do (Gano, Patel, & Rho, 2014; Maalouf, Rho, & Mattson, 2009; Mattson, 2012). Evolutionarily speaking, protracted food restriction may signal famine and dictate that energy be directed away from current reproduction efforts and toward maintenance and repair mechanisms that will allow one to reproduce at a future, more appropriate time.

The Art of Mitochondria Maintenance

Whether or not we manage to eat less, however, and more important, we can feed our mitochondria those vitamins, minerals, enzymes, cofactors, polyphenols, and other nutrients they need to do their job (Liu & Ames, 2005; Parikh et al., 2009). In combinations and concentrations that, unlike in supplements (Villanueva & Kross, 2012), tend to be harmless, some or other of these crucial substances can be found in unprocessed natural foods. These foods include fruit and vegetables, fish, shellfish and seaweeds, meats and organ meats like liver and heart, nuts and seeds, and fermented fare. Vitamin D, a hormone that forms rapidly in the unprotected skin during sunbathing, should be high on the list too. In people with low levels of vitamin D in the blood, vitamin D supplements make mitochondria work better, possibly by regulating the entry of calcium in them (Sinha, Hollingsworth, Ball, & Cheetham, 2013). Adoption of a lifestyle designed to help mitochondrial function, pivoting on an outstandingly nutrient-rich diet, has been reported to have gotten a physician with progressive multiple sclerosis out of her wheelchair (Wahls, 2011).



The Art of Mitochondria Maintenance

Summary

We tend to think of ourselves as human beings and human beings only: Yet 38 trillion microbes (Sender, Fuchs, & Milo, 2016), distributed into at least 2,172 known species (Hugon et al., 2015), populate each of us in places as supremely personal as our mouth, armpits, gut, genital and brain (Branton et al., 2013). It is a sobering thought that we house at least as many foreign as human cells (Sender et al., 2016), and those cells that we consider human stem from archaea and bacteria. With the single exception of red blood cells, which got rid of their nucleus too, each of these "human" cells is itself densely inhabited by direct descendants of bacteria in the form of mitochondria. They have made themselves indispensable and this is good and bad news. On the one hand, mitochondria *make* our mental health. On the other, they also *break* it. Whether as victims or as perpetrators, mitochondria are right in the middle of virtually all human afflictions. They still look a little like their bacterial forefathers and still retain a bit of independence from us. But because of the deal they struck with archaea 2 billion years ago, their health is now entwined with ours. So, to help get the best out of us as humans, we may actually want to do what is best for our bacteria-like components: **exercise, sleep, spend time in the sun, eat well, and meditate.**