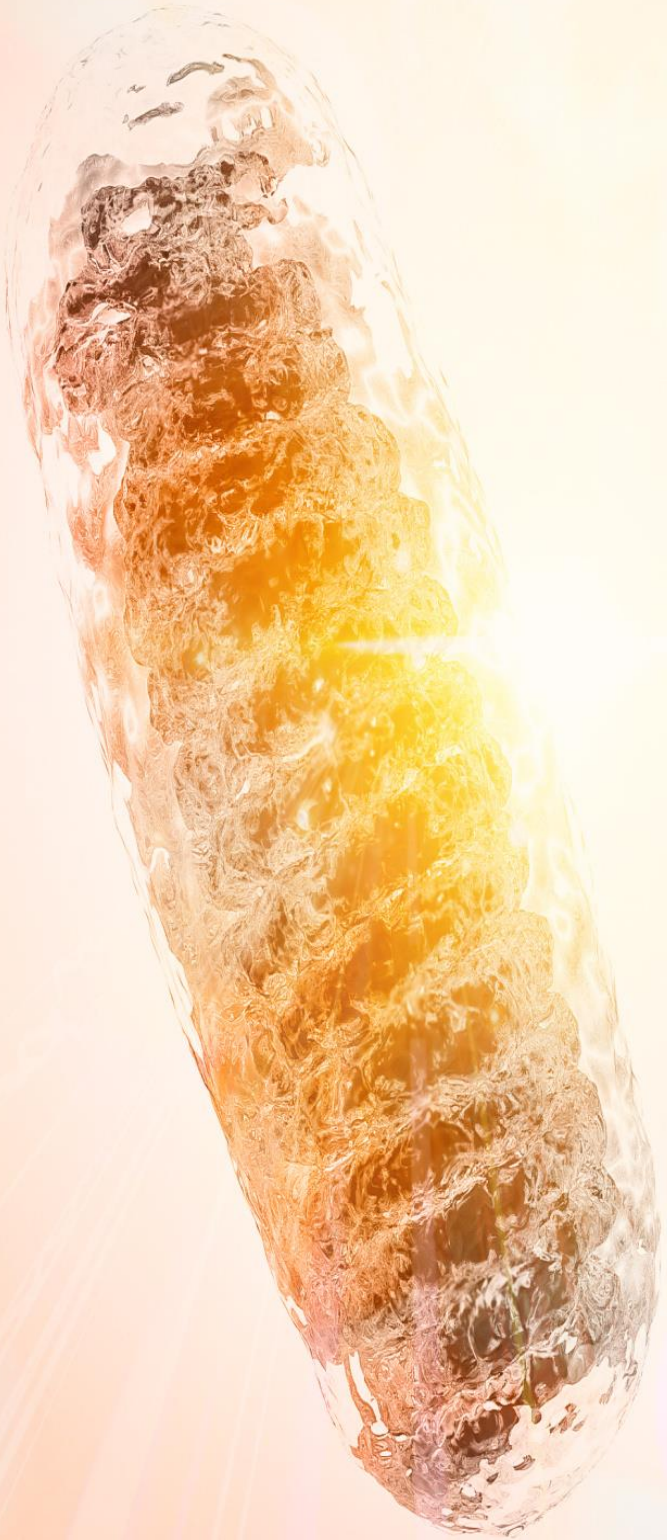
THE ENERGY BLUEPRINT



BUILDING THE CELLULAR ENGINE

(Hormesis)

Building the Cellular Engine

Here's what we covered in Masterclass video #2:

- What the cellular engine is, how it controls your energy levels and how to literally make it 50% to 200% bigger and stronger than it is now.
- The two most basic causes of fatigue issues and why one of them is overlooked by almost everyone, even natural health and functional medicine doctors.
- The world's best kept longevity and disease prevention secret, which also translates into massively greater energy levels.
- A revolutionary new understanding of stress that will likely blow your mind.
- The hidden reason behind why people lose their resistance to stress and become fragile and easily overwhelmed by stressors.
- How to massively increase your body's resilience, which is a critical piece of the puzzle of increasing your energy levels.
- Two powerful strategies to dramatically increase your energy levels, in just weeks (and, as an added bonus, how to track your improvements to literally watch your body's energy generating systems grow stronger and stronger).

(Note from Ari: There are some complex concepts in this video/summary document. If you are the type of person who wants to skip the video and just read the summary document, please be aware that you may come away confused. Watching the video will be extremely helpful for understanding the concepts here, so I strongly encourage you to do that, if you haven't already.)

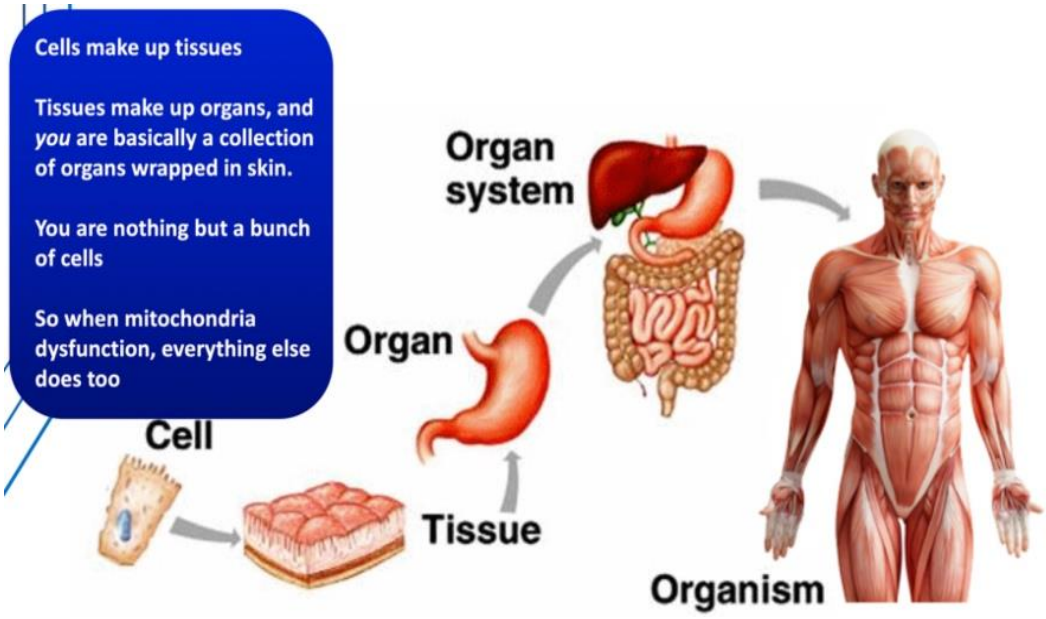
The Role of Mitochondria

If you want to understand fatigue and how to increase your energy levels, it's all about this: Mitochondria.

Without mitochondria you have no energy in the cells and without energy in the cells, they cannot do any of the things that cells do.

The basic idea that you were probably taught in your biology classes in high school or college was that mitochondria are the “powerhouse of the cell” or the energy generators of the cell. So you may be familiar with images like this...

And the basic description is generally that mitochondria take in fuel, primarily carbs and fats, and they turn them into something called ATP (Adenosine Triphosphate), and that is basically energy at the cellular level. ATP is what powers your cells.



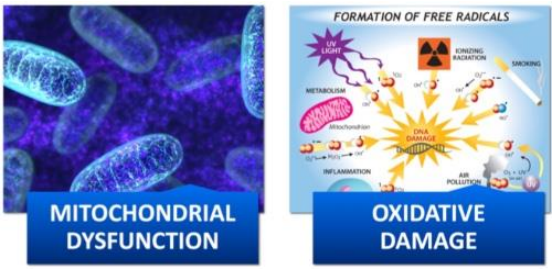
Think of the importance this way. At the most basic level we have cells, and then we have groups of cells that are tissues. Tissues compose organs, which in turn compose organ systems. And you—the trillions of cells of you as an organism, as a human organism—are basically a collection of these organ systems, organs, tissues, and trillions of cells.

Virtually all of those trillions of cells are powered by mitochondria. So, importantly, **when mitochondria dysfunction, everything has the potential to dysfunction.**

They are powering everything from your brain, to your heart, to your liver, to your muscles and much more.

In this masterclass, we learned why **mitochondria are the crux of health, energy and longevity**.

Mitochondrial Dysfunction in Fatigue: Two Key Cellular Mechanisms That Drive Fatigue



I want you to think about two key drivers at the cellular level of what's going on in fatigue, whether it's mild fatigue or severe chronic fatigue.

1. **Mitochondrial dysfunction.** Mitochondrial dysfunction is pretty much the key cellular driver of fatigue.
2. **Oxidative stress/damage.** Additionally, there is oxidative stress, also called free radicals, oxidants or reactive oxygen species, all different words for the same things.

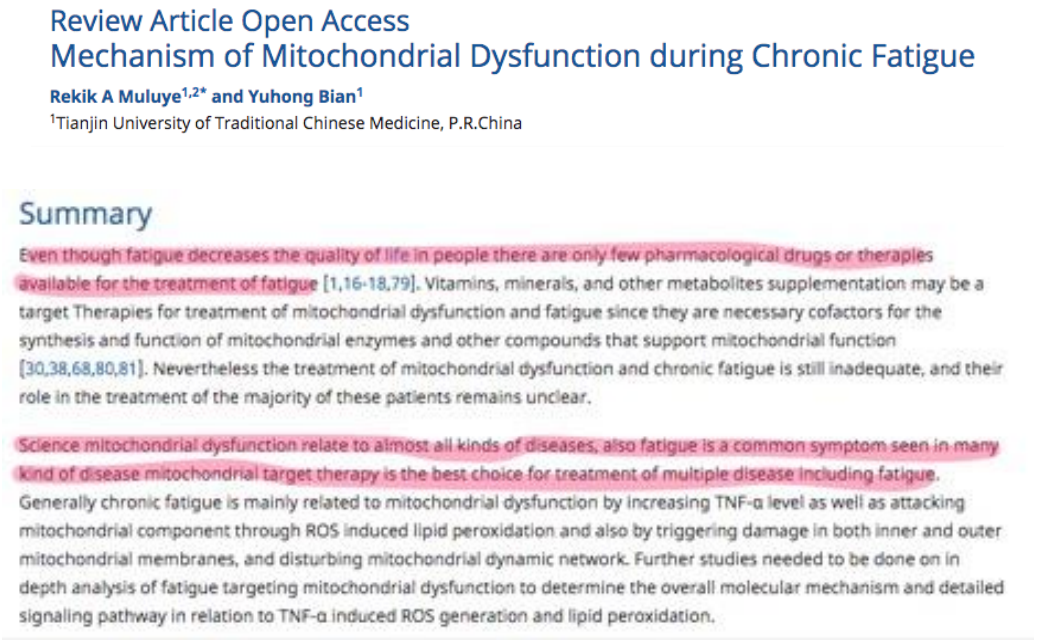
There is normally a balance between these free radicals or oxidants and the cellular antioxidant mechanisms. It's what is called the redox balance. There's constantly this sort of balancing act going on between how many free radicals (or “oxidants”) are present and how many things that neutralize free radicals, (a.k.a. antioxidants manufactured by the cells), are present. The cells are constantly trying to maintain a proper balance between these two things.

Oxidative damage occurs when there's an imbalance of too many oxidants and not enough of the cellular antioxidants.

We're going to talk more about this a little later on, but these are the two key cellular drivers of aging and fatigue issues at the cellular level.

I want you to understand that these two things almost always go together. **To the extent that you have mitochondrial dysfunction, you are pretty much guaranteed will also have oxidative damage going on.**

I also want to point out that mitochondrial dysfunction and oxidative damage are key drivers of not just fatigue, but the aging process itself, as well as many chronic diseases including some of the major killers in our world today.



Review Article Open Access

Mechanism of Mitochondrial Dysfunction during Chronic Fatigue

Rekik A Muluye[1,2*] and Yuhong Bian[1]

[1]Tianjin University of Traditional Chinese Medicine, P.R.China

Summary

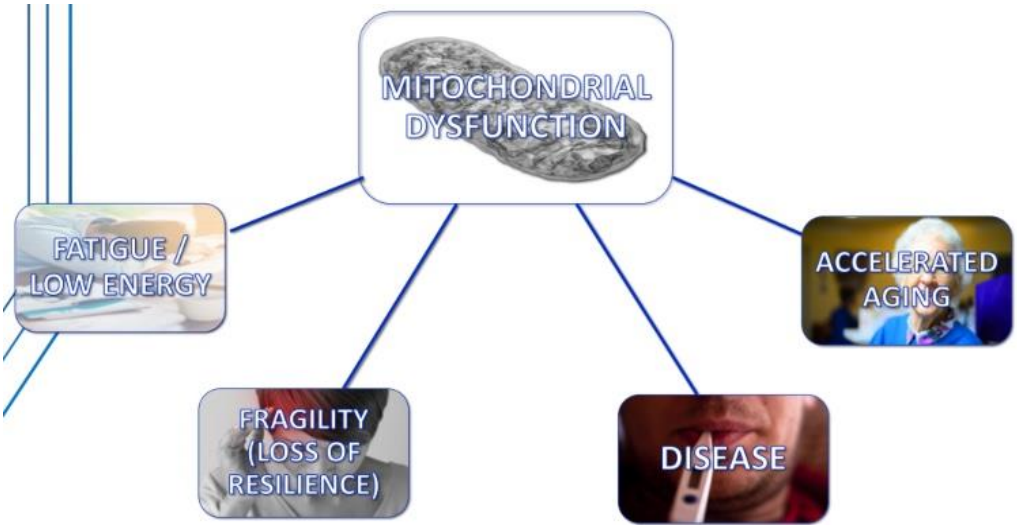
Even though fatigue decreases the quality of life in people there are only few pharmacological drugs or therapies available for the treatment of fatigue [1,16-18,79]. Vitamins, minerals, and other metabolites supplementation may be a target Therapies for treatment of mitochondrial dysfunction and fatigue since they are necessary cofactors for the synthesis and function of mitochondrial enzymes and other compounds that support mitochondrial function [30,38,68,80,81]. Nevertheless the treatment of mitochondrial dysfunction and chronic fatigue is still inadequate, and their role in the treatment of the majority of these patients remains unclear.

Science mitochondrial dysfunction relate to almost all kinds of diseases, also fatigue is a common symptom seen in many kind of disease mitochondrial target therapy is the best choice for treatment of multiple disease including fatigue. Generally chronic fatigue is mainly related to mitochondrial dysfunction by increasing TNF-α level as well as attacking mitochondrial component through ROS induced lipid peroxidation and also by triggering damage in both inner and outer mitochondrial membranes, and disturbing mitochondrial dynamic network. Further studies needed to be done on in depth analysis of fatigue targeting mitochondrial dysfunction to determine the overall molecular mechanism and detailed signaling pathway in relation to TNF-α induced ROS generation and lipid peroxidation.

One review article called “The Mechanism of Mitochondrial Dysfunction during Chronic Fatigue,” stated,

> *“Since mitochondrial dysfunction relates to almost all kinds of diseases, and fatigue is a common symptom seen in many kinds of diseases,* ***mitochondrial targeted therapy is the best choice for treatment of multiple diseases including fatigue.”***

If you want to understand fatigue, it's all about mitochondria, but it's more than just fatigue. **Mitochondrial dysfunction drives fatigue and low energy states, AND it also drives fragility and loss of resilience, many chronic diseases and accelerated aging.**

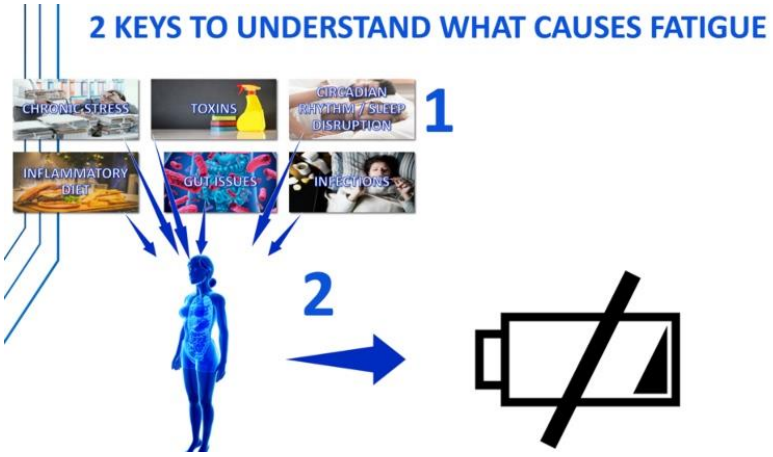


We're going to talk about why that is.

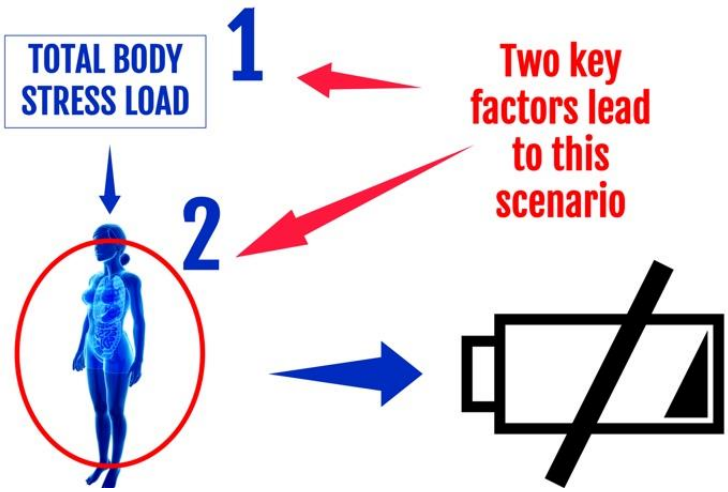
Optimal mitochondrial function, on the other hand, is the driver of high energy levels, high resilience, high resistance to disease and increased longevity.

Why Are Mitochondria So Darn Important?

I want you to think about fatigue as having two fundamental causes. One is total body stress load, or allostatic load, which is just the combination of all the different kinds of stressors that you can imagine. This is everything from psychological and emotional stress, to toxins, to pollutants in the environment, to a poor diet, to sleep deprivation, to poor gut health and many others. Then the second thing is our body's capacity to handle stressors.



The combination of lots of different stressors, and then the second big factor, our body's resilience systems—our body's capacity to deal with the stress load placed on it and to maintain balance and homeostasis—determines our energy levels.



Now there can be two different scenarios or different combinations here.

1. **You have way too many of these stressors and too large of a total body stress load.**
2. **Or you can have weakened, resilient systems in your body**

Or a combination of the two.

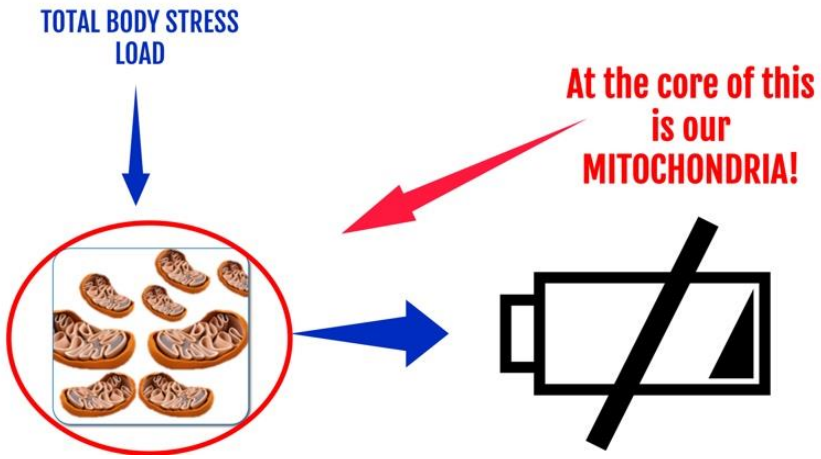
In most cases, we're dealing with a combination of the two.

To simplify this, total body stress load and the body's resilient systems determine your energy levels. At the most basic level, these are the two key factors that lead to how energetic or fatigued you are.

Most doctors, whether we're talking about conventional doctors or holistic or functional medicine doctors, **almost everybody is focused on point 1 (the total body stress load), and almost no one is talking about or even aware of the body's resilience systems and how they relate to health and energy.**

Even though hardly anyone talks about it, I want to make the case **that this is as important as, if not even more important than, the stressors you're being exposed to**.

It is a huge factor in why people are fatigued. (I will discuss this more later in this masterclass).



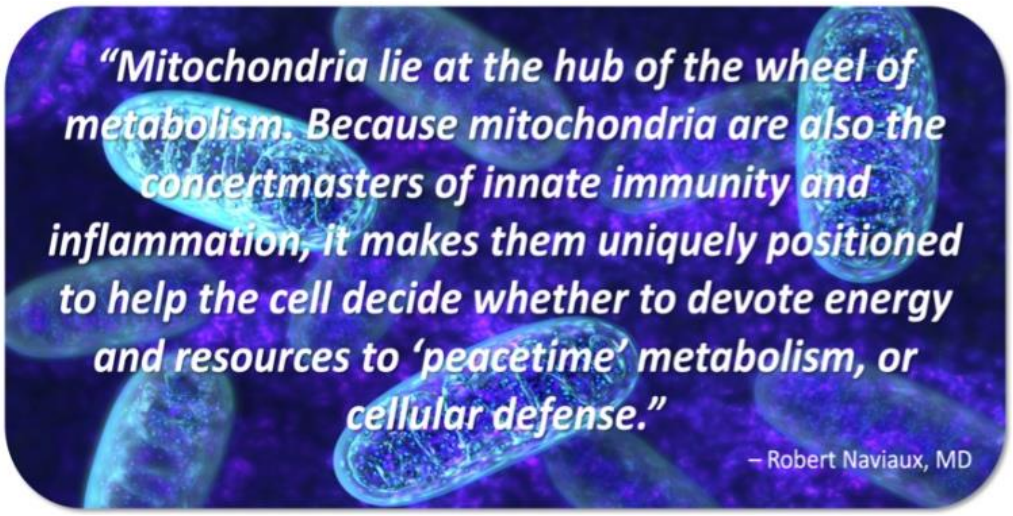
At the core of our body's resilience systems and capacity to deal with stress and maintain health, balance and high energy levels is our mitochondria.

This is where it's at when we're talking about resilience and our body's capacity to deal with stress and maintain high energy levels. It's all about the mitochondria.

There was a breakthrough paper published by Robert Naviaux, MD a couple years ago called "The Cell Danger Response."

Basically, this is an envisioning of kind of what I've been describing—showing that the mitochondria are the central hub of determining how all these signals and stressors from the

environment get translated into things like your energy levels and your disease risk and the rate of aging.



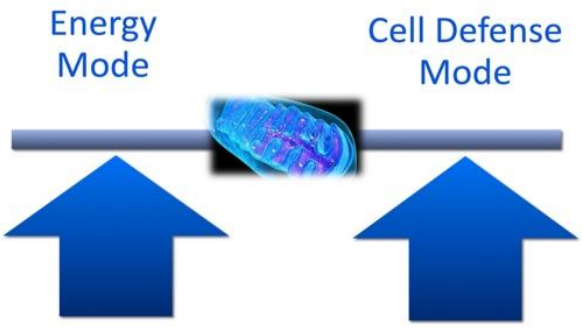
This is the critical line: "**whether to devote energy and resources to peacetime metabolism or cellular defense**."

Remember we talked about how in your high school or college biology classes, you probably learned that mitochondria are the powerhouse of the cell, just sort of these mindless energy generators?

Well, the big discovery of the last 10 years or so is that mitochondria have another key role that is just as important as their role in energy production, and that is that they are danger sensors!

They're sensors of what's going on in the body.

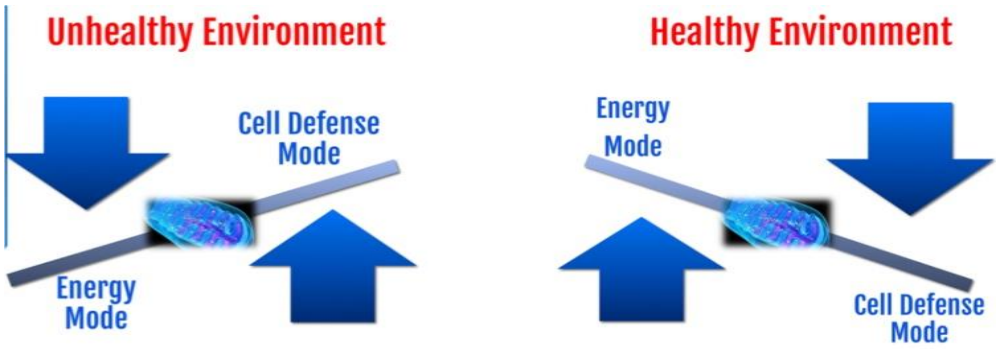
In response to the signals that they're picking up, they can either shift more into cellular Defense Mode if they're picking up lots of threats or stressors or danger signals, or they can stay in peacetime metabolism, as doctor Naviaux called it, or Energy Mode, as I call it.



Importantly, **these two things are mutually exclusive**!

The more that the mitochondria get shifted into cell Defense Mode, i.e. the more they're picking up on stress and danger signals, the more that Energy Mode gets turned off.

This is the fundamental cause of low energy levels at the cellular level.

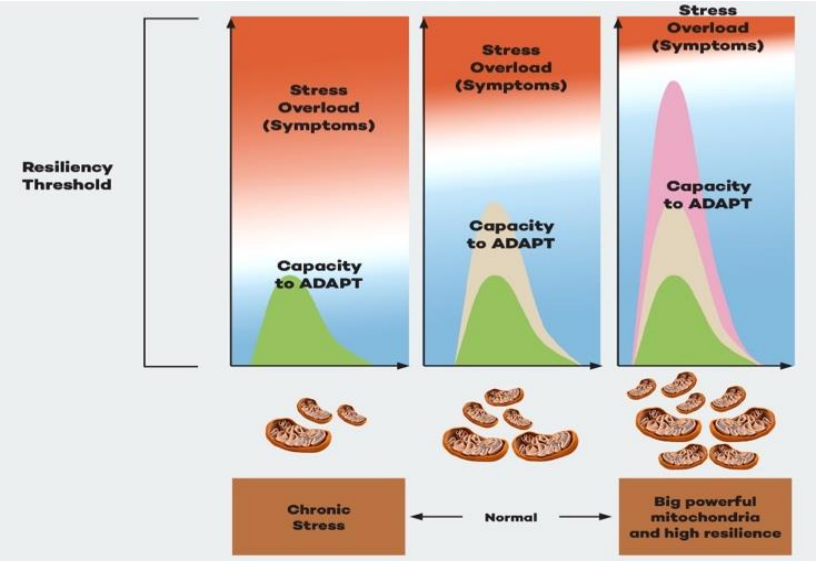


If you have the symptoms of fatigue and low energy, your mitochondria are in cellular Defense Mode.

The Resilience Threshold

The next key point: mitochondria are not just mindless energy generators or even just stress sensors. They also ultimately control something called your resilience threshold.

The Resilience Threshold

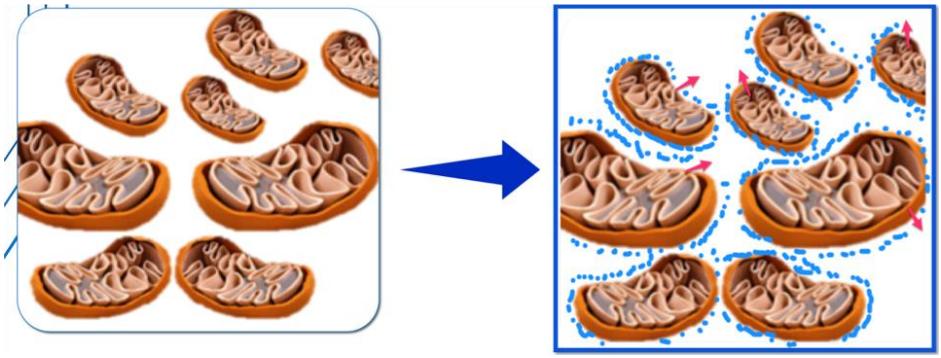


The basic idea here is that the more mitochondria you have, the greater your capacity to adapt to various kinds of stressors while maintaining balance, homeostasis and high energy levels.

The higher your threshold is, the bigger your body's capacity to maintain balance, maintain health, and maintain high energy levels. The more you lose mitochondria and have fewer of them, and the more they become weaker, fragile, damaged and dysfunctional, then the lower your resilience threshold gets. The lower your capacity to tolerate, handle and adapt to stressors, the easier it is for you to enter into stress overload, where you start to experience symptoms and start to get fatigued.

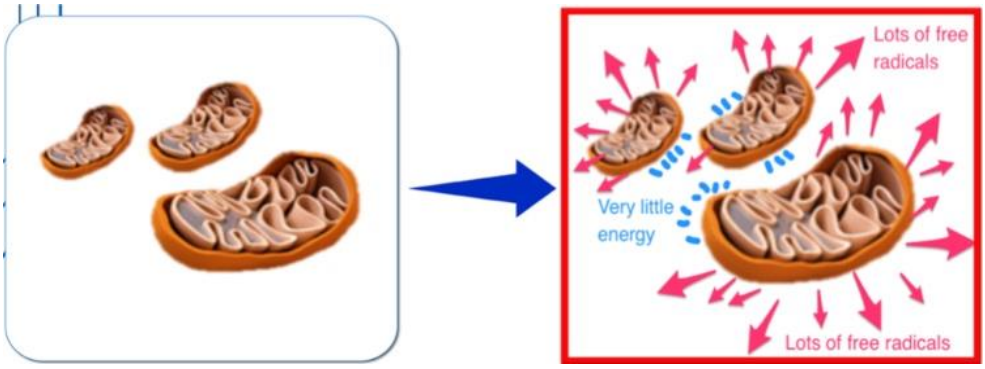
Essentially, your body becomes more fragile, you lose resiliency, and it becomes way easier to trigger your body into stress mode and fatigue mode.

The two sets of pictures below illustrate what happens when either big, strong, healthy mitochondria are subjected to stress vs. when small, weak, dysfunctional mitochondria are subjected to stress...

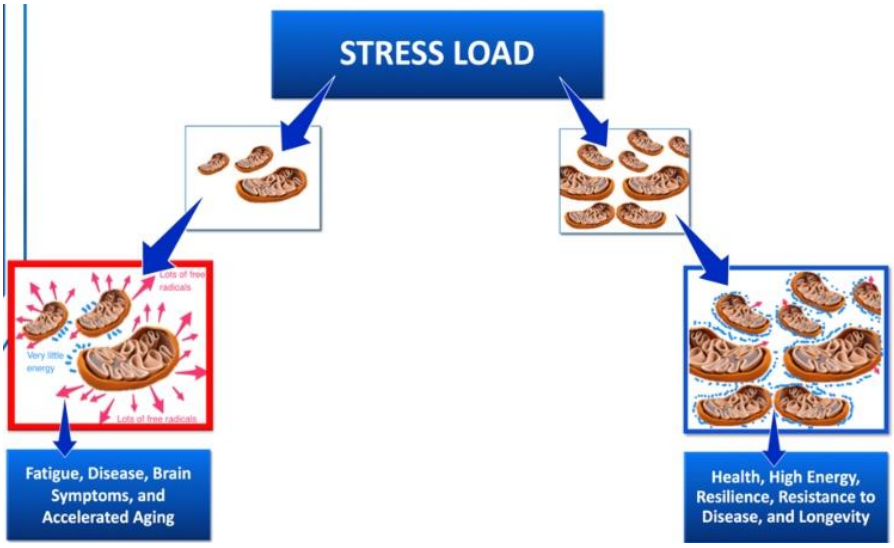


Think of it like this. The pictures above show how big, healthy, strong mitochondria handle a stress load. Normally, they're pumping out lots of energy, which I'm showing as these little blue dots here. At the same time, mitochondria also always have some little trickle of free radicals being produced pretty much all the time. I don't want to get too complex here, but it's perfectly normal and healthy for mitochondria to have some little trickle of free radicals coming out. **This is what happens while they're under stress: they maintain Energy Mode, pumping out very few free radicals and lots of energy.**

Now on the other hand, when you have smaller, weaker, more dysfunctional mitochondria, the same stress load will shift your mitochondria into Defense Mode, where you have the SYMPTOM of fatigue...



The pictures above show what happens when you have smaller, weaker, more fragile, more damaged and dysfunctional mitochondria. The same stress load now creates a situation where these mitochondria are shifted into Defense Mode. They're throwing off lots of free radicals and very little energy. The symptom of this scenario at the cellular level, at the mitochondrial level, is fatigue.



Putting this all together, there are just two different scenarios here. You can have the same total body stress load, but depending on the state of your mitochondria, the outcome is going to be either fatigue or high energy.

If you have the symptoms that we talked about in the last video such as fatigue and sleep problems, post-exertional malaise, trouble maintaining energy if you don't eat, or brain symptoms like anxiety, depression and brain fog, these are sure signs of a low resilience threshold and weakened and dysfunctional mitochondria.

Resistance to stress parallels the health of your mitochondria. And the health of your mitochondria predicts:

- **Your resistance to disease**
- **Your longevity**
- **Your resilience**
- **Your energy levels**

If you want to double or triple your energy levels, prevent dozens of diseases, live to a hundred and beyond, and make yourself resilient and build a High Energy Body, you must focus on rebuilding your mitochondria.

What Causes the Mitochondria to Become Fragile?

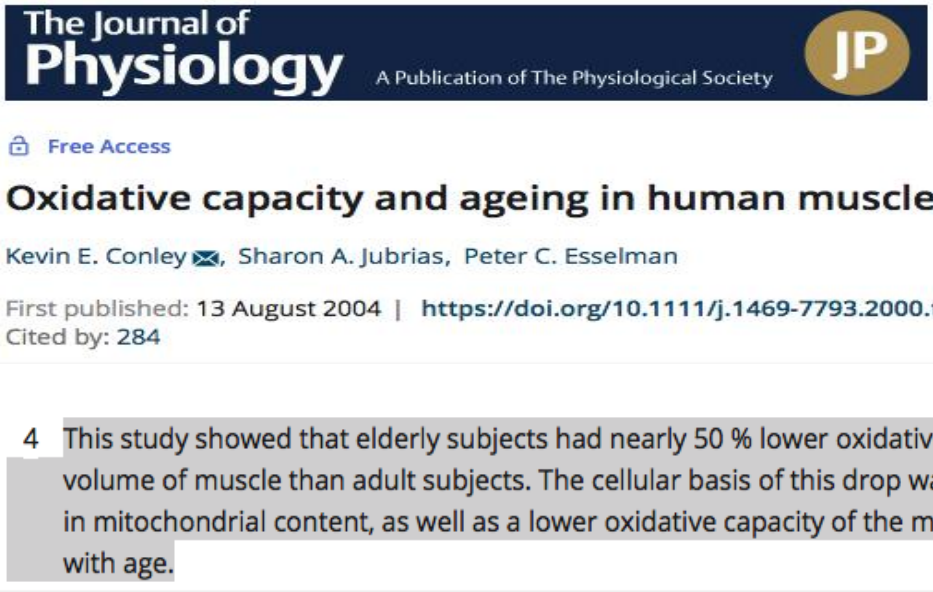
How do your mitochondria become weak, fragile, damaged and dysfunctional in the first place, and how do we lose mitochondria?

There are two basic causes of this:

1. Aging
2. Lack of mitochondrial stimulation/hormesis

First, let's talk about aging...

There are several studies that have shown that humans lose close to 75% of their mitochondrial capacity as they go from young adults (roughly 20) to older adults (70).



The Journal of Physiology A Publication of The Physiological Society JP

Free Access

Oxidative capacity and ageing in human muscle

Kevin E. Conley, Sharon A. Jubrias, Peter C. Esselman

First published: 13 August 2004 | https://doi.org/10.1111/j.1469-7793.2000.t01-1-00203.x | Cited by: 284

4 This study showed that elderly subjects had nearly 50 % lower oxidative capacity per volume of muscle than adult subjects. The cellular basis of this drop was a reduction in mitochondrial content, as well as a lower oxidative capacity of the mitochondria with age.

This study, titled “Oxidative Capacity and Ageing in Human Muscle,” showed that elderly subjects had nearly 50% lower oxidative capacity per volume of muscle than adult subjects.

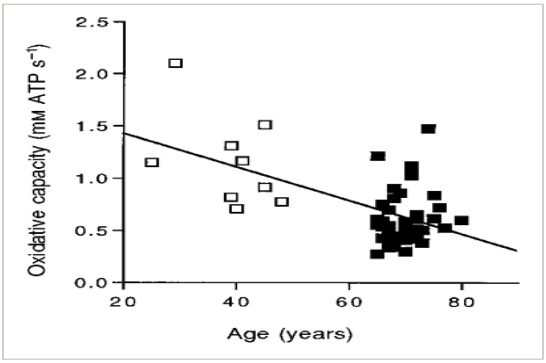


Figure 5 Open i

Oxidative capacity as a function of age

Here's a chart illustrating the decline in mitochondrial capacity as you go from 20 to 40 to 60 to 80 and so on.

J Aging Res. 2012; 2012: 194821.
Published online 2012 Jul 19. doi: 10.1155/2012/194821

Skeletal Muscle Mitochondria and Aging: A Review

Courtney M. Peterson, Darcy L. Johannsen, * and Eric Ravussin

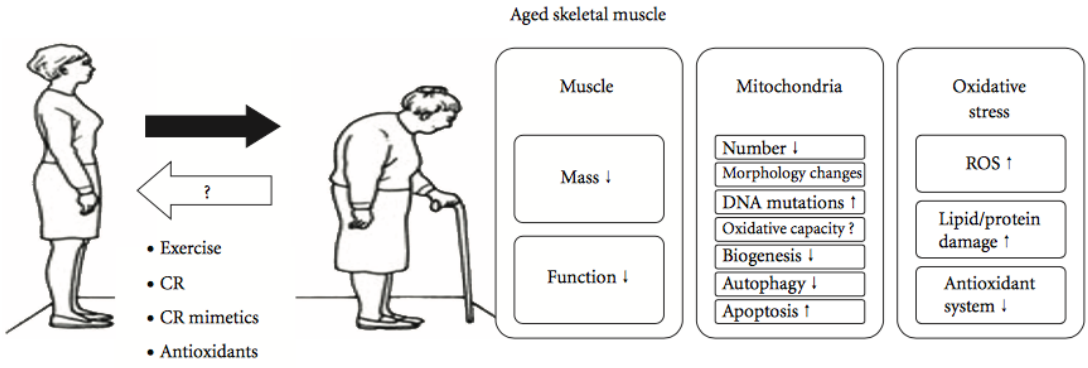


FIGURE 1: This cartoon describes the changes in skeletal muscle with aging on the right side of the figure. Both the mass and function of skeletal muscle are decreased in elderly people. Furthermore, at the mitochondrial level, the number of mitochondria is decreased in parallel with changes in mitochondrial morphology. Mitochondrial DNA, oxidative capacity, biogenesis, and autophagy are all decreased in conjunction with an increased number of DNA mutations and increased levels of apoptosis. Finally, oxidative stress is increased in the muscles of elderly people in association with cellular lipid, protein, and DNA damage. The bottom left of the cartoon shows that exercise, caloric restriction, caloric restriction mimetics, and antioxidants can all delay the aging of skeletal muscle.

But it’s not just that we're losing the number of mitochondria, there's a number of other changes.

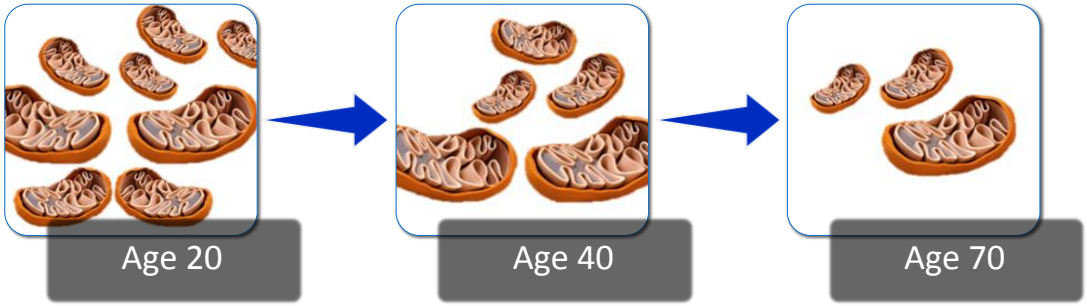
- There are changes in the structure of the mitochondria
- There is an increase in DNA mutations in the mitochondria
- There is a decrease in biogenesis
- There is a decrease in autophagy
- There is an increase in free radicals
- There is a decrease in the antioxidant system inside the cell

There are all these different changes, but **the fundamental idea is that aging is associated with a very big and significant decline in mitochondrial function.**

The basic idea here is that we accumulate mitochondrial damage and dysfunction and lose mitochondria over the years.

Also, research indicates that nearly 50% of people under the age of 40 have early onset mitochondrial dysfunction, and virtually everyone over the age of 40 has it to a very significant degree.

Here's a simple way of illustrating everything I just said...



Think of it like this. Between the ages of 40 and 70, what the research I just showed you indicates is that your mitochondrial capacity and number basically get cut in half.

In addition, it's actually worse than just that because not only does the number get cut in half, **but the mitochondria that are present are weaker, damaged, dysfunctional and less capable of producing energy.** A similar thing happens from the age of 20 to 40: your mitochondrial capacity gets cut in half, and then again from 40 to 70.

As you can imagine, this situation dramatically decreases our energy levels, but also it decreases our resilience to stress, accelerates aging and massively increases our likelihood of having symptoms or disease. So that's the aging part of the equation.

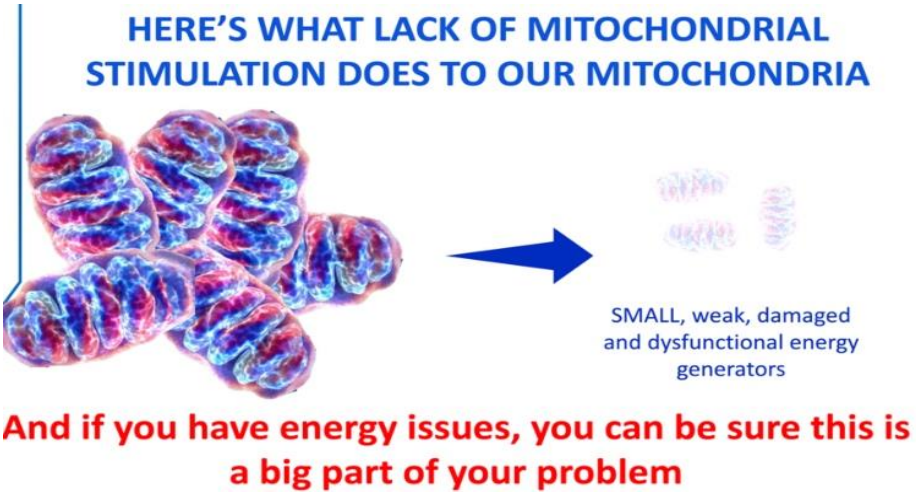
But the second part—lack of mitochondrial stimulation—is actually THE BIG KEY. It's actually way more important than aging!

What do I mean by lack of mitochondrial stimulation?

There are certain factors in our lifestyle that stimulate our mitochondria, that keep them big and strong and help us maintain lots of them. The loss of that mitochondrial stimulation leads to this. It leads to this decline over time.

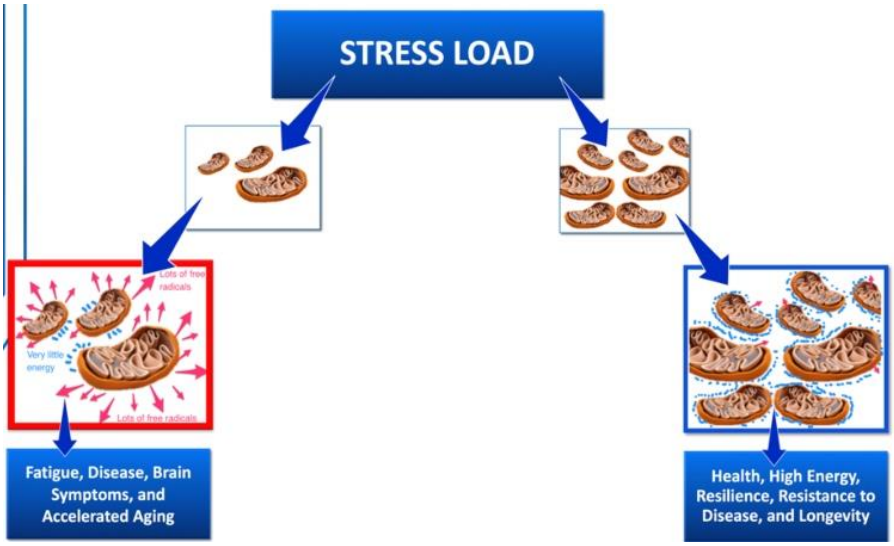
Like we saw with aging, it leads to this decline from lots of big, strong, healthy mitochondria to much fewer as time goes on.

This is fundamentally what lack of mitochondrial stimulation does to our mitochondria: it takes big, strong, healthy mitochondria and turns them into weak, fragile, and dysfunctional mitochondria.



Tying this back into the concepts we've been talking about, lack of mitochondrial stimulation is what takes you from a high resilience threshold to a lower resilience threshold over time.

In this situation it's much easier for the stressors of life, to which we're all exposed, to wear down out mitochondria



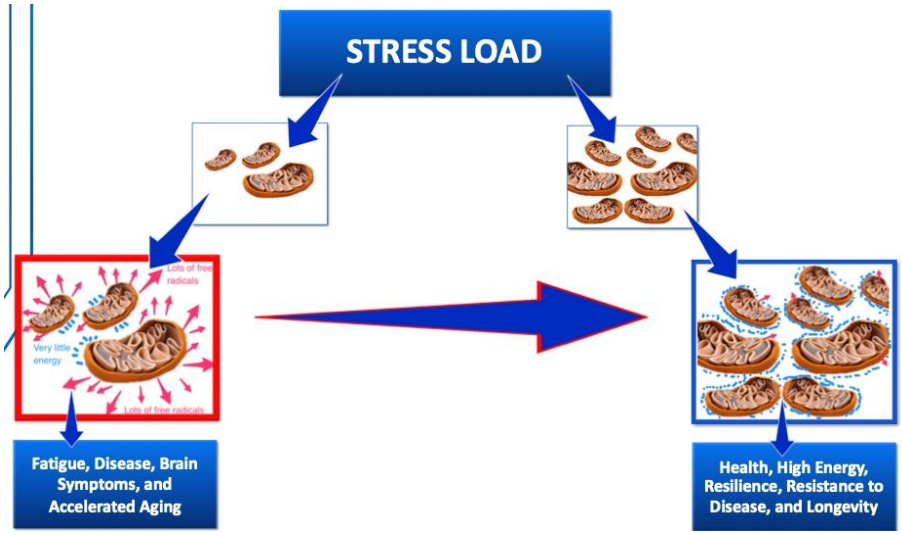
No matter how healthy we are, we're all being exposed to a significant number of stressors in the environment.

Key Point: When you have small, weak, damaged mitochondria (and few of them), It makes it much easier for those stressors to overwhelm your mitochondrial capacity to adapt and maintain balance, and then trigger cell Defense Mode and start to push you into fatigue.

How to Build and Increase Your Mitochondria

If you want to overcome fatigue and increase your energy, <u>rebuilding your mitochondria is the central goal.</u>

How do we actually make this happen?



How do we go from fatigue, disease, brain symptoms, and accelerated aging to health, high energy, resilience, resistance to disease, and longevity?

The Answer is HORMESIS.

Hormesis is the major key to enhanced health, longevity and energy. It's one of the most important, if not the most important, strategy for energy enhancement.

Hormesis is the process by which a mild or acute temporary stressor increases resistance to other stressors and increases the health, resilience and vitality of the organism: the organism, in this case, being you. It can increase resistance to a variety of stresses and stressors, not just the one you were exposed to, and that's a key point—you can be exposed to a temporary dose of one type of stressor, and it can translate into adaptations in your body that make you much more resistant to many other types of stressors.

Another way to think about this is as a transient stressor to the body that stimulates the body to adapt and grow more fit, to be prepared for greater loads of that stressor and any stressor.

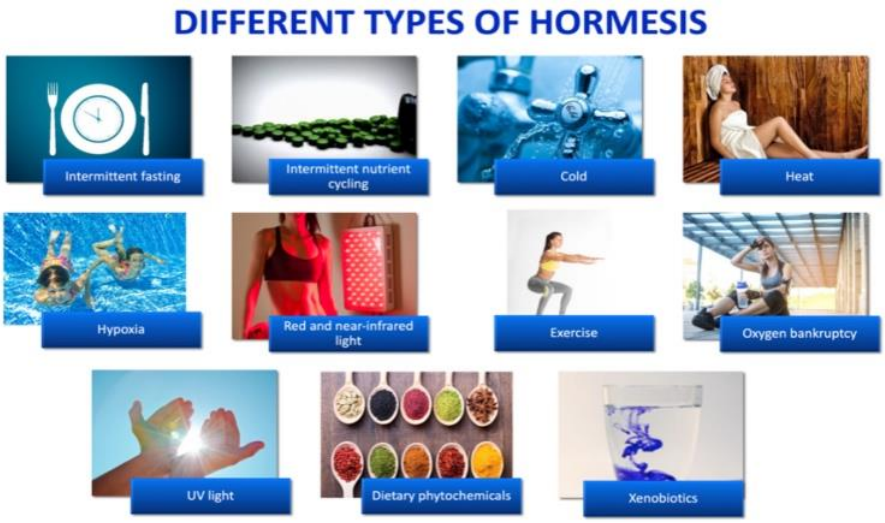
Here's the key point: the more your body has been exposed to hormetic stressors and has had the chance to adapt to them, the more stress tolerant, resilient and energetic your body becomes.

Hormesis is actually more familiar to you than you may realize...

Exercise, plain old physical activity—things like cardio or aerobic exercise, weight training or high intensity interval training—are all forms of hormesis. It's one of many types of hormesis. Exercise is a stress placed on the body that increases resistance to a number of other stressors, not just physical exertion, but also to cardiovascular disease, depression, all sorts of other brain related conditions, neurodegenerative diseases, diabetes and so on.

But exercise is just scratching the surface...

By exposing your body to these forms of hormesis, your body makes adaptations that make it more energetic, more resilient and healthier. Now, here's an important point to understand. It's not just exercise that creates this sort of metabolic stress and these beneficial adaptations—lots of things do.



Here you can see a list of some of the most powerful types of hormesis. There are lots and lots of different kinds of hormetic stressors, and there's a huge amount of research on many of these. Just for example, there are over 5,000 studies on red and near infrared light alone and on the different types of benefits that it can have on the human body (you can read more about the research on red and near infrared therapy in the article I wrote on the topic here).

There's a huge amount of research showing that these are key drivers of health, longevity, resistance to disease and improved mitochondrial health. Importantly, all these different types

of hormetic stressors work by producing a temporary stress on the body and mitochondria which stimulates beneficial adaptations.

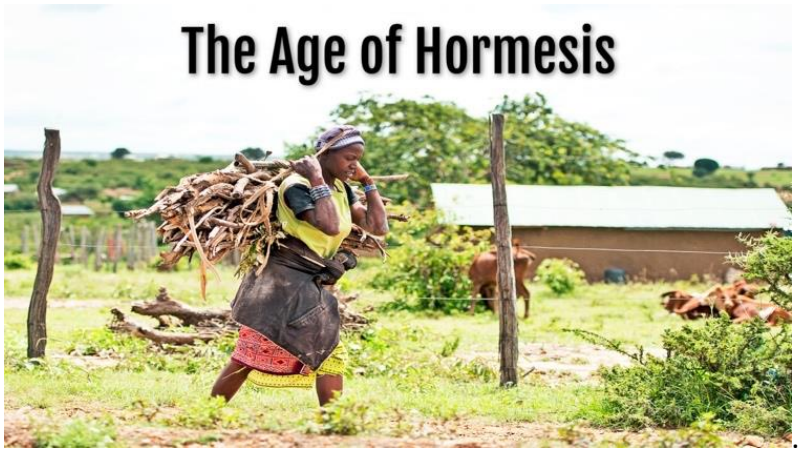
Why these stressors? Why not exposure to air pollution, or chlorine and fluoride in the water supply and exposure to heavy metals? Why not drinking alcohol, smoking cigarettes or undergoing psychological stress? Why are all stressors not created equal?

The answer is that every type of stress sits on a continuum, on a spectrum of the degree to which it has a potential for benefit and the degree to which it has a potential for harm. What we want when looking for an ideal type of hormetic stress is something that has a very big potential for benefit and very low potential for negative side effects. When we look at things like smoking cigarettes, drinking alcohol, or exposure to heavy metals like lead and mercury, these are all things which could potentially have some beneficial effect in minute doses.

But the potential for benefit is so small, and the potential for harm is so great, that these make really bad types of stressors to be exposed to. And so, these types of stressors are overwhelmingly associated with harm whereas others are associated with benefit.

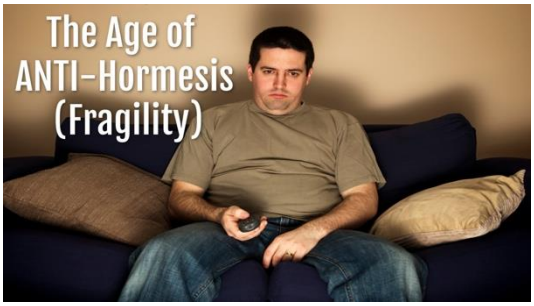
One more key point here is that in order for stress to have beneficial adaptations, we need a balance between exposure to the stressor in a very acute, transient way (temporary stress) on the one hand, and rest, relaxation and cellular regeneration on the other. All these things produce amazing benefits by producing a temporary hormetic stress on the body. By exposing your body to these forms of hormesis, your body makes adaptations that ultimately make it resistant to stress, resistant to disease and more energetic.

Not only are we designed to survive stressors, we're designed to thrive with them, and this is an important concept to understand from an evolutionary and biological perspective. In order to survive and reproduce, our ancestors spent most of their waking hours working to find food either by grazing on plants or by hunting animals. They were regularly exposed to physical activity, occasional fasting due to food scarcity, noxious plants, phytochemicals, heat and cold.



All of these are hormetic stressors that not only don't harm us but have profound health benefits. The failure to expose your body to the right amount of hormetic stress produces poor health and a weak, fragile, diseased and fatigued body. In the past, it was the age of hormesis, and our ancestors lived during a time when hormesis was built into their lives. **We are biologically adapted to these conditions, and any deviation from them is potentially harmful to health.**

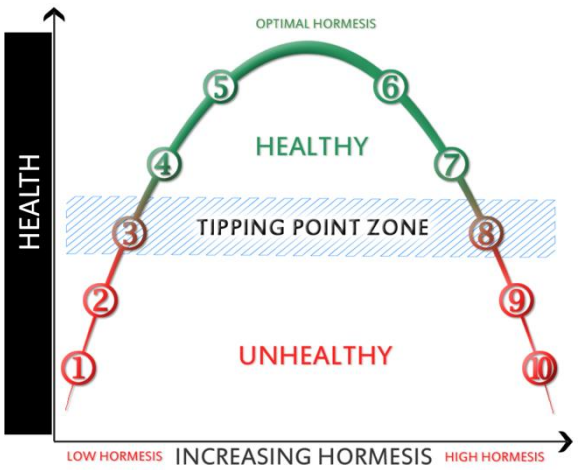
We need these stressors just for our cells and our mitochondria to function normally.



Now we live in an age of **anti-hormesis where exercise is no longer a requirement**, food is available whenever we want it, we don't have to deal with food scarcity or fasting, a junk food diet excluding dietary phytochemicals is the norm for most people, and we live in insulated, climate-controlled environments where we never get too hot or too cold.

It is the absence of all these things that stimulate our mitochondria to be big and strong, the mitochondria atrophy, shrink and shrivel—they literally die off and become weak, fragile and dysfunctional. As a result, we have the fatigue epidemic, diabetes, heart disease, depression, anxiety and all sorts of stress-related diseases. If you want a high energy body, then using hormesis on a regular basis is critical.

This is the paradigm shift around stress. It's that stress is not bad.



The reality is that too little stress is just as unhealthy and toxic to your body as is way too much stress or total stress overload. We want to have these hormetic stressors built into our lives so that we're getting these transient doses of beneficial hormetic stressors while avoiding things like chronic psychological stress or chronic exposure to heavy metals and air pollution: we want transient, brief doses of hormetic stressors, and we want to avoid the pathological chronic stressors. When we have these hormetic stressors built into our lives and have a moderate amount of the right kinds of stressors, that is what creates optimal health resistance to disease and high energy levels. It's time to stop thinking of stressors as bad and instead start thinking of how they work in terms of form.

CANDLE VS. FIRE

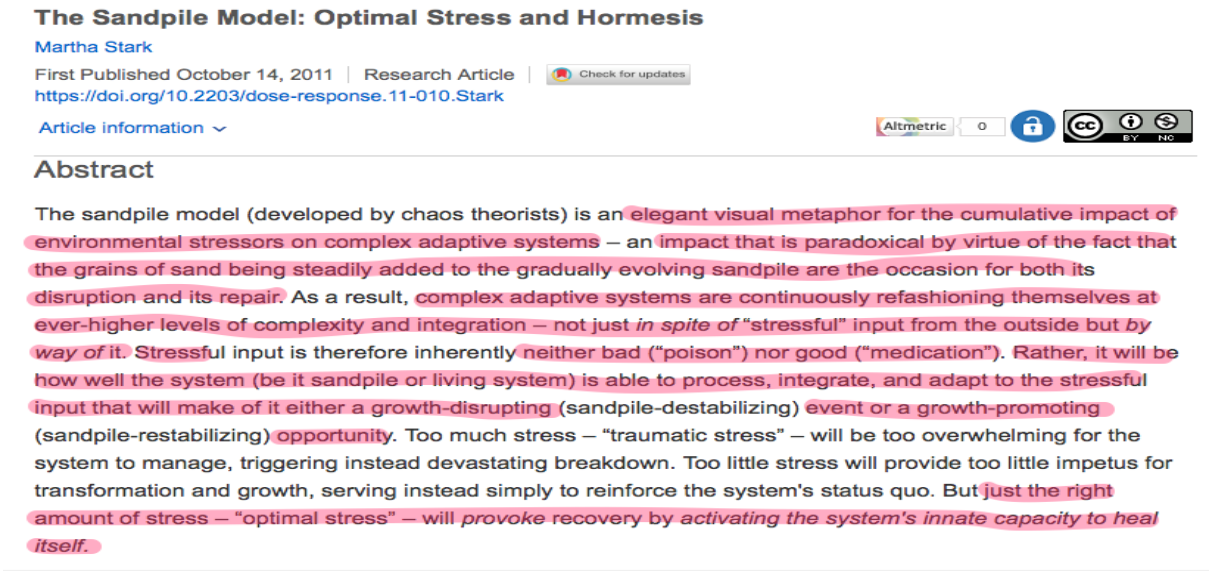
(a metaphor for understanding how hormesis works)

"Wind extinguishes a candle and energizes fire. Likewise with randomness, uncertainty, chaos: you want to use them, not hide from them. You want to be the fire and wish for the wind."

- Nassim Nicholas Taleb

Here's a metaphor for understanding how hormesis works. Wind extinguishes a candle, but that same gust of wind energizes a fire. The key thing here is that we're all being exposed to a gust of stressors in our lives: there's no way of avoiding that. The key is that we want to be the fire and not the candle.

The Sandpile Model



The Sandpile Model: Optimal Stress and Hormesis

Martha Stark

First Published October 14, 2011 | Research Article | Check for updates
https://doi.org/10.2203/dose-response.11-010.Stark

Article information

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Abstract

The sandpile model (developed by chaos theorists) is an elegant visual metaphor for the cumulative impact of environmental stressors on complex adaptive systems – an impact that is paradoxical by virtue of the fact that the grains of sand being steadily added to the gradually evolving sandpile are the occasion for both its disruption and its repair. As a result, complex adaptive systems are continuously refashioning themselves at ever-higher levels of complexity and integration – not just *in spite of* "stressful" input from the outside but *by way of* it. Stressful input is therefore inherently neither bad ("poison") nor good ("medication"). Rather, it will be how well the system (be it sandpile or living system) is able to process, integrate, and adapt to the stressful input that will make of it either a growth-disrupting (sandpile-destabilizing) event or a growth-promoting (sandpile-restabilizing) opportunity. Too much stress – "traumatic stress" – will be too overwhelming for the system to manage, triggering instead devastating breakdown. Too little stress will provide too little impetus for transformation and growth, serving instead simply to reinforce the system's status quo. But just the right amount of stress – "optimal stress" – will *provoke* recovery by *activating the system's innate capacity to heal itself.*

Too much stress—traumatic—stress, will be too overwhelming for the system to manage triggering instead devastating breakdown, fatigue and disease. Too little stress will provide too little impetus for transformation and growth. You can think of that as weakening the resilience threshold, weakening your mitochondria and causing them to atrophy. Too little stress serves instead simply to reinforce the system status quo, but just the right amount of stress—optimal stress or medical stress—will provoke recovery by activating the system's innate capacity to heal itself. Without these brief stressful stimuli, our bodies shrivel and weaken to the point that we lose our resiliency to stress, and we become susceptible to countless diseases.

Hormesis is powerful medicine. It might not be going too far to say that hormesis is the very basis of good health, disease resistance and longevity!

The Mechanisms Behind Hormesis

What are the mechanisms behind what's going on with hormesis? What are these adaptations that we're talking about? There are a number of different studies that illustrate this in different ways, and there are dozens of different mechanisms involved, but the following are some of the key ones.

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Microbial Cell, Vol. 1, No. 5, pp. 150 - 153; doi: 10.15698/mic2014.05.148

When less is more: hormesis against stress and disease

Andreas Zimmermann[1], Maria A. Bauer[1], Guido Kroemer[2-5], Frank Madeo[1] and Didac Carmona-Gutierrez[1]

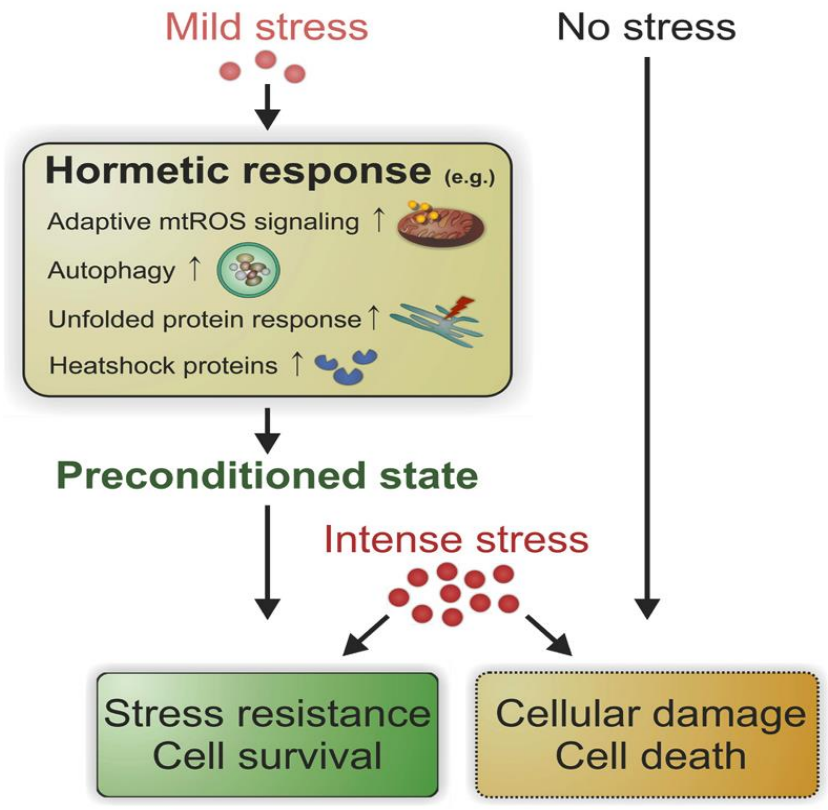
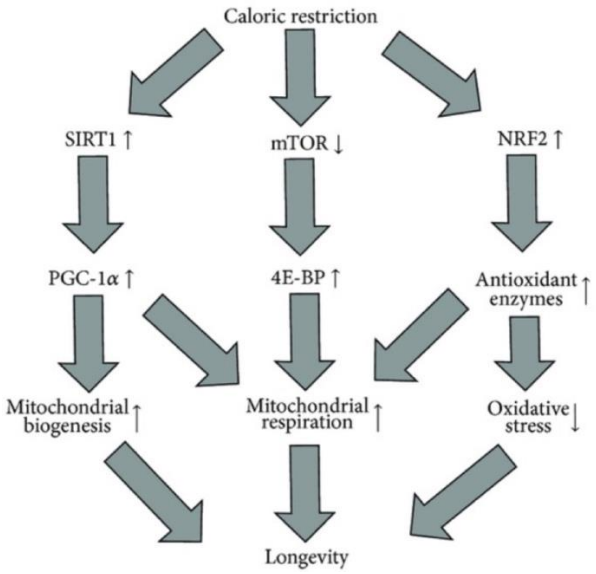


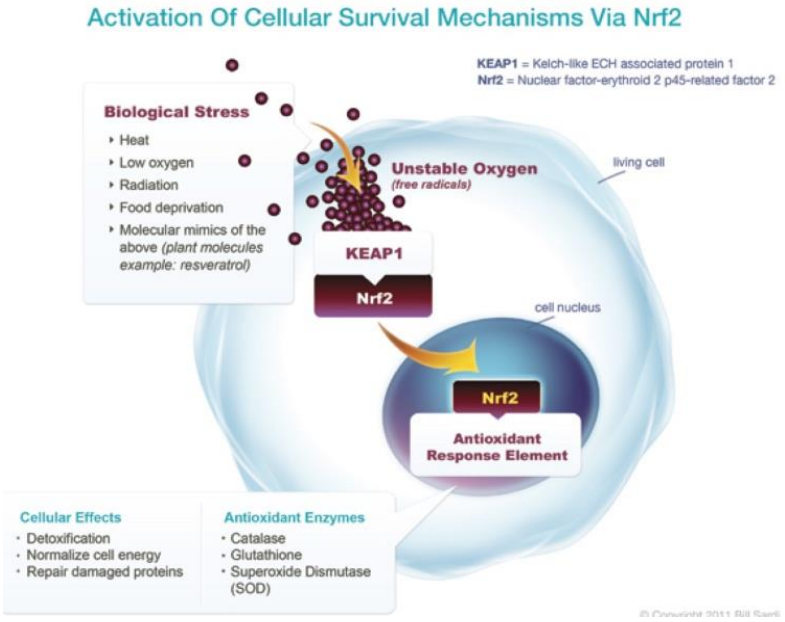
FIGURE 1: Hormesis governs a pleiotropic pro-survival program.

When exposed to mild stress, cells/organisms respond by a variety of adaptive cellular programs that procure a preconditioned state. When an intense stress is applied subsequently, preconditioned but not naïve cells/organisms exhibit stress resistance and eventually improved survival. mtROS, mitochondrial reactive oxygen species.



Open in a separate window

Mechanisms by which caloric restriction may improve mitochondrial function, delay mitochondrial aging, and expend longevity. Caloric restriction (CR) triggers several pathways that may lead to increased longevity via stimulation of mitochondrial function. The first mechanism includes the induction of sirtuin-1 (SIRT1), a protein deacetylase that in turn activates peroxisome proliferator-activated receptor-γ coactivator-α (PGC-1α). PGC-1α is a transcription factor involved in the activation of genes whose products are involved in mitochondrial biogenesis and respiration. CR also inhibits mammalian target of rapamycin (mTOR) signaling associated with an increase in the activity of eukaryotic translation initiation factor 4E binding protein (4E-BP) that stimulates the translation of genes encoding mitochondrial respiratory components. In *C. elegans*, CR activates the nuclear factor-erythroid 2-related factor-2 (NRF2) that regulates expression of several antioxidant genes and therefore may lengthen *C. elegans* lifespan through the reduction of oxidative stress and improving mitochondrial respiration.

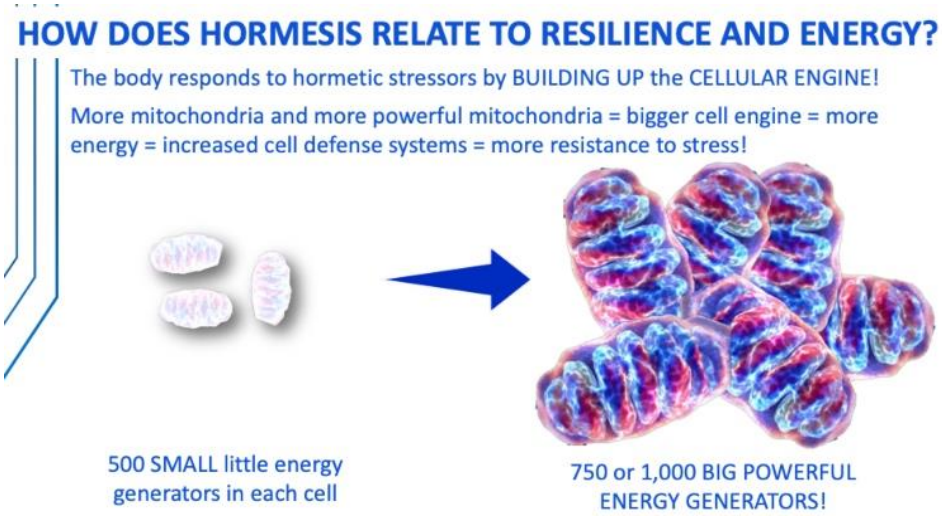


- We get adaptive mitochondrial reactive oxygen species signaling. This simply means that hormetic stress creates a transient burst of reactive oxygen species, and that **actually stimulates our cellular antioxidant defense systems to grow stronger**.

- Autophagy increases, meaning it **stimulates the cells to repair the damaged and dysfunctional parts and to rebuild more robust cell parts and mitochondria parts that can handle greater stress loads**.
- There's also heat shock proteins and a number of other pathways that are stimulated.

In this scenario, you get these hormetic stressors that create hormetic adaptations, and then you get a precondition state which is basically when the body has engaged these adaptations to that mild stress. Then when the body is exposed to intense stressors or a high total body stress load, you have healthy cells as opposed to over here where you were not previously exposed to hormetic stress. The same stressor now creates cellular damage, cell death, and mitochondrial dysfunction.

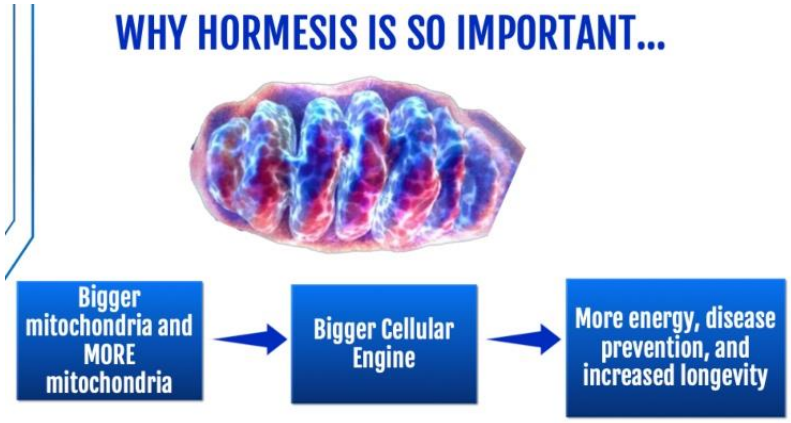
Fundamentally, the key mechanism of how hormesis works is how it affects our mitochondria.



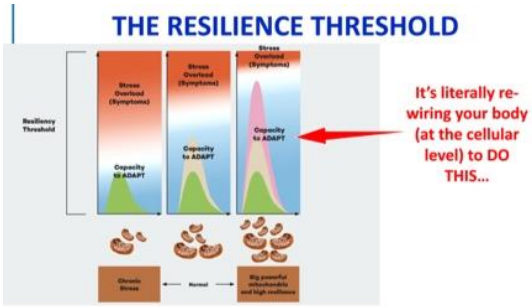
Hormesis revolves around the mitochondria, and this is fundamentally what hormesis does. **It takes small, damaged, weak dysfunctional mitochondria and builds them back up into strong, healthy mitochondria.**

It allows you to go from 500 mitochondria per cell up to 750 or even 1,000.

When you increase the number of mitochondria in your cells and the size and the power of those mitochondria, you can double your energy producing capacity.



Bigger mitochondria and more mitochondria mean a bigger cellular engine, which means disease prevention, increased longevity, increased resilience and more energy. Regular exposure to hormesis is what keeps your mitochondria strong, healthy and in high Energy Mode.



Hormesis is literally rewiring your body at the cellular level.

It's increasing the size and the number of your mitochondria and literally building back up your resilience threshold.

Hormesis may be the single most important strategy to improve your energy levels.

Now, that's a bold statement.

So is there any science to back it up?

YES! As I showed you in the video, **there are DOZENS of studies suggesting that hormesis is likely the single most powerful strategy for not only energy enhancement, but disease prevention and longevity too!**

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When less is more: hormesis against stress and disease

Andreas Zimmermann[1], Maria A. Bauer[1], Guido Kroemer[2-5], Frank Madeo[1] and Didac Carmona-Gutierrez[1]

All living organisms need to adapt to ever changing adverse conditions in order to survive. The phenomenon termed hormesis describes an evolutionarily conserved process by which a cell or an entire organism can be preconditioned, meaning that previous exposure to low doses of an insult protects against a higher, normally harmful or lethal dose of the same stressor. Growing evidence suggests that hormesis is directly linked to an organism's (or cell's) capability to cope with pathological conditions such as aging and age-related diseases. Here, we condense the conceptual and

Hormesis and disease resistance: activation of cellular stress response pathways

Mark P Mattson

First Published February 1, 2008 | Other
https://doi.org/10.1177/0960327107083417

Article information

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Abstract

The survival of all organisms depends upon their ability to overcome stressful conditions, an ability that involves adaptive changes in cells and molecules. Findings from studies of animal models and human populations suggest that hormesis (beneficial effects of low levels of stress) is an effective means of protecting against many different diseases including diabetes, cardiovascular disease, cancers and neurodegenerative disorders. Such stress resistance mechanisms can be bolstered by diverse environmental factors including exercise, dietary restriction, cognitive stimulation and exposure to low levels of toxins. Some commonly used vitamins and dietary supplements may also induce beneficial stress responses. Several interrelated cellular signaling molecules are involved in the process of hormesis. Examples include the gases oxygen, carbon monoxide and nitric oxide, the neurotransmitter glutamate, the calcium ion and tumor necrosis factor. In each case low levels of these signaling molecules are beneficial and protect against disease, whereas high levels can cause the dysfunction and/or death of cells. The cellular and molecular mechanisms of hormesis are being revealed and include activation of growth factor signaling pathways, protein chaperones, cell survival genes and enzymes called sirtuins. Knowledge of hormesis mechanisms is leading to novel approaches for preventing and treating a range of human diseases.

Cellular stress 'resets lifespan profoundly'

By Tim Newman | Published Wednesday 8 November 2017

Fact checked by Jasmin Collier

Surprising results from a recent study show that stressing a cell can reverse signs of cellular aging. The findings might open doors to more successful ways to slow the aging process.

'It's like magic'

These surprising findings fly in the face of the previously held notion that stressing mitochondria has negative effects, as Prof. Morimoto explains. He says, "This has not been seen before."

"People have always known that prolonged mitochondrial stress can be deleterious," he explains. "But we discovered that when you stress mitochondria just a little, the mitochondrial stress signal is actually interpreted by the cell and animal as a survival strategy. It makes the animals completely stress-resistant and doubles their lifespan. It's like magic."

As Prof. Morimoto explains, "I never would have guessed this — a low stress signal resets the organismal lifespan profoundly. What we are learning is that some of these stress signals are interpreted by the organism as a way to reset itself and to live longer. When mitochondria function optimally, the cells and tissue are robust."

Exercise prevents cellular aging by boosting mitochondria

By Tim Newman | Published Wednesday 8 March 2017

It is common knowledge that exercise imparts a smorgasbord of health benefits. What is not yet understood is how physical activity manages to reduce aging on a cellular level. New

"Based on everything we know, there's no substitute for these exercise programs when it comes to delaying the aging process. These things we are seeing cannot be done by any medicine."

— Dr. Sreekumaran Nair

Younger volunteers carrying out interval training showed a 49 percent increase in mitochondrial capacity and, even more impressively, the older group saw a 69 percent increase.

High-intensity biking effectively reversed age-related decline in mitochondrial function.

Int J Mol Sci. 2013 Jul; 14(7): 13109–13128. PMCID: P
Published online 2013 Jun 25. doi: 10.3390/ijms140713109 PMI

Hormesis in Aging and Neurodegeneration—A Prodigy Awaiting Dissection

Lei Mao[1,2,*] and Jacqueline Franke[1]

All living systems have the intrinsic ability to respond and adapt to external and internal sources of disturbance [57]. Although the hazardous damaging effect of ROS is a settled issue, data summarized here support the theory that hormetic effects of ROS in aging and ND are obvious. In this regard, caloric

mediated by increased ROS levels due to enhanced mitochondrial activity. This subsequently induces the organism's adaptive responses and ultimately results in lifespan-extension and health promotion [67].

BELLE Article:

Hormesis and disease resistance: activation of cellular stress response pathways

Mark P Mattson*

Hormesis is a fundamental process in evolution

To survive in the hostile environment of primitive earth, cells had to acquire mechanisms of protecting themselves against free radicals, ultraviolet light and extreme changes in temperature, pH and osmolarity. The fitness of an organism was therefore determined, in large part, by its ability to avoid or resist mild to moderate levels of stress. Many different

Review

Hormesis in aging

Suresh I.S. Rattan *

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biologically amplified effects that are much larger, synergistic and pleiotropic. A consequence of hormetic amplification is an increase in the homeodynamic space of a living system in terms of increased defence capacity and reduced load of damaged macromolecules. Hormetic strengthening of the homeodynamic space provides wider margins for metabolic fluctuation, stress tolerance, adaptation and survival. Hormesis thus counter-balances the progressive shrinkage of the homeodynamic space, which is the ultimate cause of aging, diseases and death. H[illegible]y aging may be achieved by hormesis through mild and periodic, but not

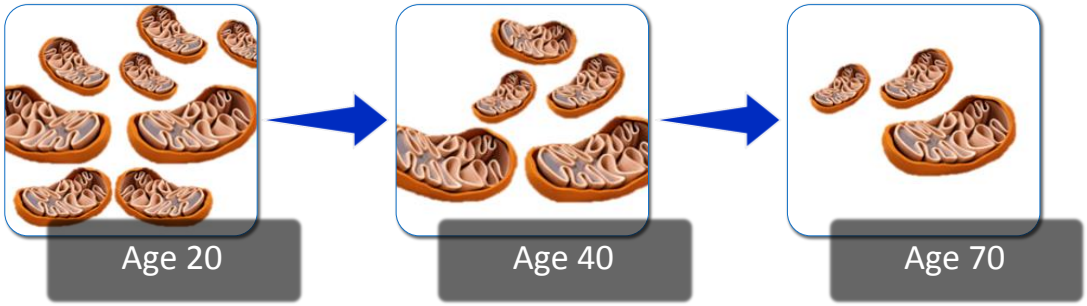
There is lots of more science indicating that hormesis is the key mechanism in our ability to ward off disease, extend longevity and maintain high energy levels.

Key Point: Having MULTIPLE layers of hormesis in your life is a major key to optimal health and energy.

Now, remember how I told you before that aging is one of the key drivers of the loss of mitochondria, mitochondrial damage and dysfunction?

There is research showing that hormesis is the key to maintaining healthy mitochondrial levels, and that it's literally possible to stay with strong, abundant mitochondria as we grow older (instead of losing them), **but only if we are regularly exposing our mitochondria to hormetic stressors.**

Mitochondrial decline doesn't have to happen. This only happens in the modern world in people who are not regularly exposed to hormetic stress.



People who do not regularly engage in hormesis – which is over 90% of the Western world – are pretty much guaranteed to lose roughly half of their potential to produce energy between the ages of 20 to 40, and then again it will be cut in half from the ages of 40 to 70.

Hormesis is the only way to prevent this from happening.

And it may be **the single most important strategy to increase your energy levels and fight disease.**

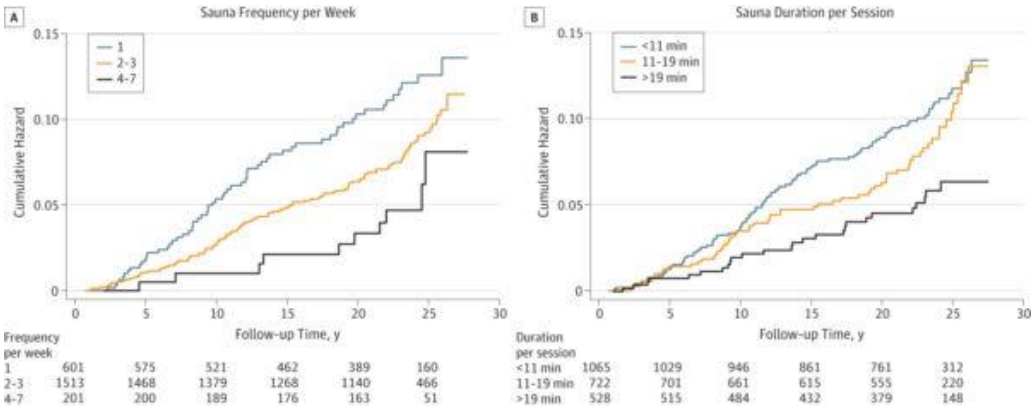
Two Powerful Types of Hormesis to Boost Your Energy

Sauna

First, I've done an extremely comprehensive review of the science on saunas with over 150 scientifc studies referenced. If you're interested in exploring this topic in great depth, I highly recommend reading my article and/or watching my video on it HERE.

Heat hormesis and sauna therapy is simply one of the most powerful medicines known to man...

There was an article titled "Association between Sauna Bathing and Fatal Cardiovascular and All-Cause Mortality Events" that found something absolutely remarkable.



They found massive reductions in cardiovascular disease and even all-cause mortality (the risk of dying from any cause) in direct proportion to the frequency that somebody uses the sauna and the duration that somebody uses a sauna.

In the graph above, you see it's going up, which means a higher risk of dying over this period of time, which is over the span of 30 years, and then as people use the sauna—they go from one time, to two to three times, to four to seven times—the risk of dying goes down dramatically. Huge reductions. Again, the same thing: if you use the sauna for less than 11 minutes per time versus if you use it for greater than 19 minutes shows a direct correlation between the higher the dose, the bigger the benefits and the bigger the reduction in cardiovascular disease and all-cause mortality.

Intern Med. 2015;54(3):333-8. doi: 10.2169/internalmedicine.54.3042.

Effects of Waon therapy on chronic fatigue syndrome: a pilot study.

Soejima Y[1], Munemoto T, Masuda A, Uwatoko Y, Miyata M, Tei C.

Author information

Abstract

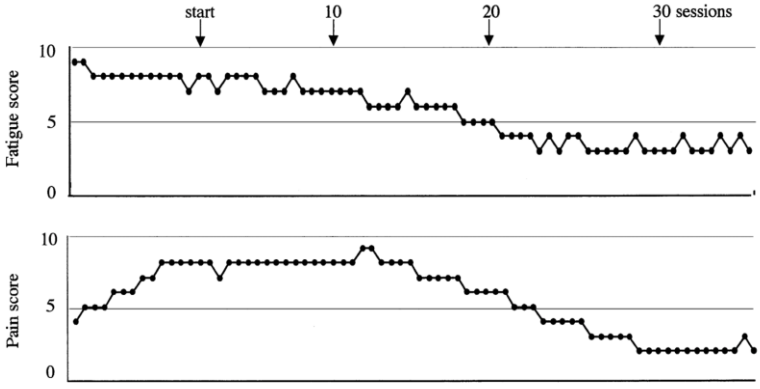
OBJECTIVE: Chronic fatigue syndrome (CFS) is a disabling condition of unknown etiology, and no definitive therapy has been identified to date. We developed Waon therapy, a form of thermal therapy using a far-infrared dry sauna, and in this study herein examined its feasibility and safety in patients with CFS.

METHODS: Ten consecutive inpatients with CFS stayed in a 60°C sauna for 15 minutes and then rested on a bed under a blanket for an additional 30 minutes outside the sauna room. The treatments were performed once a day, five days a week for four weeks. Perceived fatigue, the primary outcome measure, was evaluated using a numerical rating scale before, during (two weeks after the commencement of therapy) and after therapy. The pain level, evaluated using a numerical rating scale, mood, assessed using the Profile of Mood States questionnaire, and performance status, assessed using a scale developed for CFS patients were also examined before and after therapy.

RESULTS: Perceived fatigue significantly decreased after therapy, although no significant reductions were observed during therapy. In addition, a negative mood, including anxiety, depression and fatigue, and the performance status significantly improved after therapy.

CONCLUSION: These findings suggest that Waon therapy may be a useful and safe treatment for CFS.

Here's a study using sauna therapy in people with Chronic Fatigue Syndrome. Waon therapy is infrared saunas (that's what they call it in Japan). **Conclusion: these findings suggest that Waon therapy—sauna therapy—maybe a useful and safe treatment for Chronic Fatigue Syndrome.**

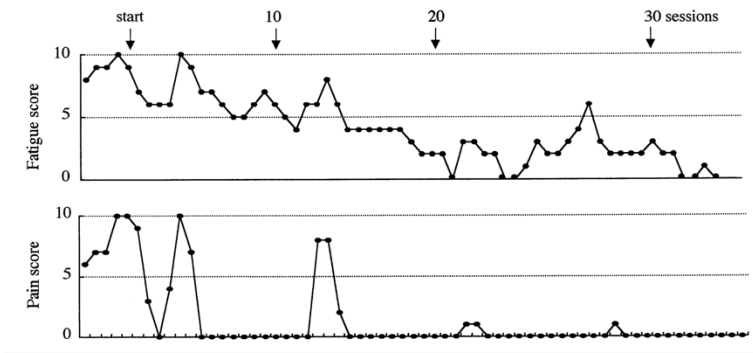


One case reports the fatigue score at the start of the study when they first started a program of 30 sessions of daily Sauna use.

So, they did one sauna session per day over the course of 30 days.

Here's what happened to fatigue for this person… They went from about an **eight (out of 10) average to about a three or a four average**. Their level of fatigue was cut in half.

Over here, they went from a pain score, a level of body aches and pains, that was about an **eight to about a two**.



This other person went from a fatigue score that was somewhere **around 7, and then at the end of 30 sessions they're down at a 2 or a 3**. Then after the sauna is over, they're even hitting some 0's and 1's.

Their pain at the start was up close to **8 or 10 on average, and then halfway into the sauna therapy, their pain is already at a zero and one level**, and then it continues like that throughout the rest. Here are some other specifics from the study.

Table 1
The changes of subjective symptoms and outcomes after repeated thermal therapy

	Case 1					Case 2				
		Thermal therapy		Outcomes[b]			Thermal therapy		Outcomes	
	Baseline[a]	Before	After	6	12	Baseline	Before	After	6	12
CMI										
Physical complaints[c]	51	48	12	15	11	47	44	13	20	12
Mental complaints[d]	16	12	3	2	1	4	1	1	2	1
POMS										
Fatigue[e]	18	17	3	5	3	24	28	5	8	6
Depression[f]	24	16	0	3	2	35	38	0	2	2
Confusion[g]	10	7	1	3	1	23	22	4	5	4
Energy score[h]	−16	−13	17	13	18	−23	−27	8	7	15
Sleep score[i]	8	8	0	1	1	10	9	1	2	2
Nonsedentary activity[j]	2.5	–	–	6.0	7.0	2.5	–	–	7.0	9.0

The changes of subjective complaints and outcomes after repeated thermal therapy.
[a] One month before thermal therapy.
[b] Months.
[c] Range: 0–162.
[d] Range: 0–51.
[e] Range: 0–28.
[f] Range: 0–58.
[g] Range: 0–26.
[h] Energy score was derived by subtracting the POMS fatigue score from the POMS vigor score.
[i] Range: 0–10.

They did scores before and after the sauna bathing on things like fatigue, depression, confusion (brain fog) and sleep.

- **Fatigue went from a 17 to a 3 for the first person, and from 28 to a 5 for the second person.** (Obviously greater numbers mean higher levels of fatigue, so they're going from high levels of fatigue to very little.)
- **Depression went from a 16 to a 0 for the first person, and from a 38 to a 0 for the other person**.
- **Confusion or brain fog went from a 7 to a 1; over here it went from a 22 to a 4.**

- **Their sleep ratings went from an 8 to a 0, and a 9 to a 1 (lower numbers mean better sleep).**

So, massive improvements in energy, in pain scores, reductions in pain, improvements in brain function, improvements in mood, just from this one simple type of hormesis. 30 days of one single type of hormesis can massively improve brain function and energy levels. That's how powerful hormesis is.

Now, you have several options of how you want to integrate this information into your life. You may want to go out and buy a sauna, or you may want to find a local gym or health spa where you can use a sauna there; maybe it's included in your gym membership where you currently work out, or you can find a place nearby where you can use one.

(If you're interested in my recommendations of what saunas are best for home use, check out my article here: https://www.theenergyblueprint.com/benefits-of-saunas/)

But again, if you can't afford that, I suggest joining a nearby gym or recreation center where you can get access to a sauna for $10-$50 a month, along with a gym and other facilities.

In addition to that, I also want to teach you another powerful form of hormesis that doesn't cost ANYTHING…

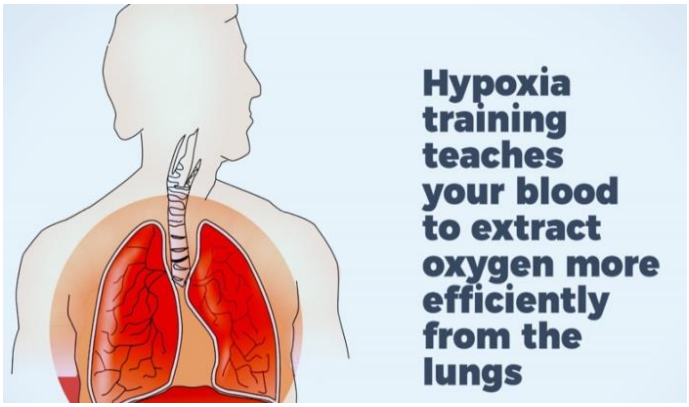
Intermittent Hypoxic Training (IHT)

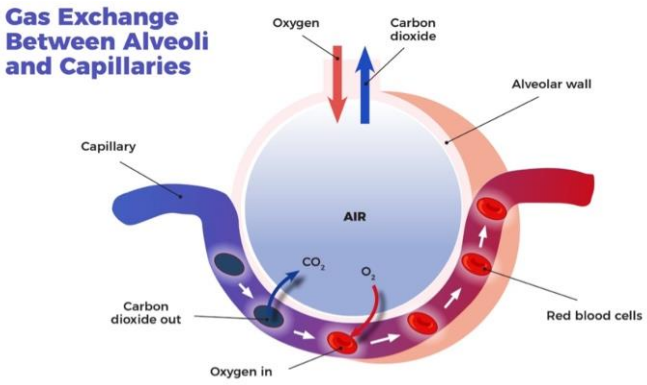
I want to give you something that is free that you can do starting right now. It doesn't require any equipment, just you beginning to practice intermittent hypoxic training. This is something that's little known but is incredibly powerful. And basically, this just means using breathing techniques to induce low oxygen levels in the blood to progressively train the mitochondria to utilize oxygen more effectively and induce a lot of these beneficial, medical adaptations that we've been talking about. There are numerous confirmed scientific benefits to this type of training.

These are some of the benefits from intermittent hypoxic training.

Let's talk about some of the mechanisms of how this actually works.

Intermittent hypoxia training teaches your blood to extract oxygen more efficiently from the lungs.

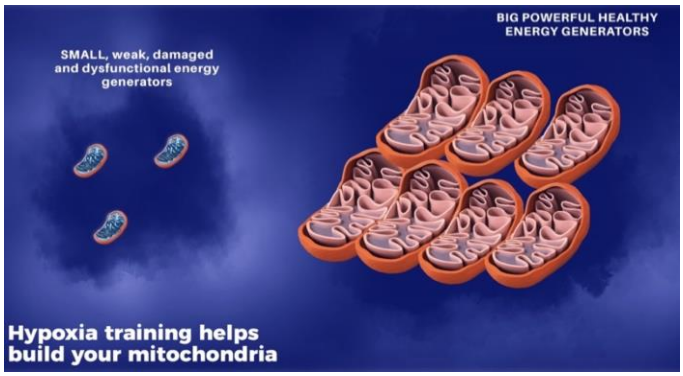




The Alveoli (a little air sac within the lungs at the smallest level) is connected to a capillary, which is a very small blood vessel where blood passes through, drops off carbon dioxide and picks up oxygen. When you do intermittent hypoxic training, it literally remodels this interface between the lungs and the blood to help your blood extract oxygen more efficiently.

It also directly affects your mitochondria and protects them from damage.

It also helps build your mitochondria and size. Mitochondrial biogenesis.



Here's one study where they did a biopsy on the lung and heart tissues of healthy rats to look at how they adapted to intermittent hypoxic training, and they found this change in the structure of mitochondria called “micromitochondria within mitochondria,” and they say that this is an additional adaptive mechanism for intermittent hypoxic training.

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The effect of intermittent hypoxic training on lung and heart tissues of healthy rats.

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Abstract

INTRODUCTION: Recently, particular attention has been focused on the problem of the beneficial influence of intermittent hypoxia (IH) on the human organism. However, knowledge regarding the negative effects of intermittent hypoxic training (IHT) on cellular adaptive mechanisms remains limited. The aim of the present study was to investigate: 1) lung and heart ultrastructural changes under IHT; and 2) the adequateness of morphological and morphometric methods to determine the constructive and destructive displays of hypoxia.

MATERIAL AND METHODS: Adult male Wistar rats underwent IHT every day for 7-28 days. Lung and heart tissues were assessed by morphological and cellular morphometric methods.

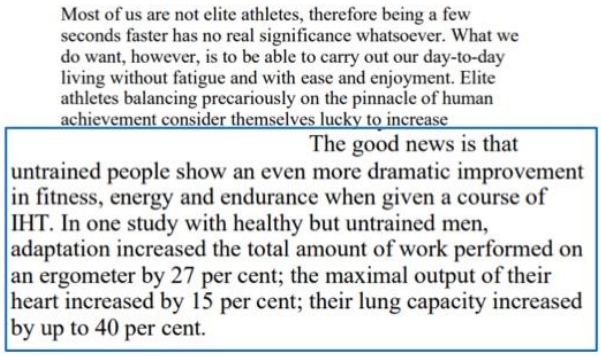
RESULTS: We observed evident ultra structural changes of the lung air-blood barrier (LABB) by the 7-10(th) day of training. Structural damage of LABB was most considerable after 2 weeks of IHT exposure, its ultrastructure partially normalized by the end of the IHT 4-weeks course: there was diminishing of LABB hydration and disappearance of areas of its destruction. The structural changes in the heart blood-tissue barrier (HBTB) were considerably less marked compared with those in LABB during the 1(st) and 2(nd) weeks of training. Heart tissue structural changes increased by the end of the fourth week of IHT. Both tissue cells revealed no significant necrotic damage of mitochondria after IHT, while changes relating to the energy-directed restructuring of mitochondria were observed. We hypothesized that acute moderate hypoxia promotes a specific type of mitosis in lung and heart tissues.

CONCLUSIONS: Ultrastructural changes in the rat lung and heart tissues depend on IHT duration. The phenomenon of "micromitochondria within mitochondria" is an additional adaptive mechanism for IH exposure.

These breath practices which I'm about to teach you literally change the shape and structure of your mitochondria. In Russia, Intermittent hypoxic training has been investigated for more than 30 years, but initially people, including the Russian Ministry of Health, were skeptical. Proponents of intermittent hypoxic training had to show overwhelming evidence of benefits, and in fact this has been studied very extensively in Russia as a result of this.

Clinical trials on more than 300,000 people suffering from various conditions such as neurotic and psychiatric disturbance, heart disease, gynecological diseases, pediatric diseases, and many other conditions were conducted over this time and showed positive results. Yet, most people have never even heard of intermittent hypoxic training.

It's mainly known in the athletic world where it has been successfully used by athletes to improve their fitness and performance for many years. Yet, it is the case that non-athletes may even get more profound benefits from this practice.


Most of us are not elite athletes, therefore being a few seconds faster has no real significance whatsoever. What we do want, however, is to be able to carry out our day-to-day living without fatigue and with ease and enjoyment. Elite athletes balancing precariously on the pinnacle of human achievement consider themselves lucky to increase

The good news is that untrained people show an even more dramatic improvement in fitness, energy and endurance when given a course of IHT. In one study with healthy but untrained men, adaptation increased the total amount of work performed on an ergometer by 27 per cent; the maximal output of their heart increased by 15 per cent; their lung capacity increased by up to 40 per cent.

In one study with healthy men who were not currently doing exercise, adaptation increased the total amount of work performed on a stationary bike by 27%, the maximal output of their heart increased by 15%, and their lung capacity increased by up to 40%, so this is making big adaptations in your body.

Another study on 102 human patients concluded that intermittent hypoxic training may be a bonafide anti-aging treatment because it helps the body clean out damaged and dysfunctional mitochondria and replace them with healthy, bigger, stronger mitochondria among several other anti-aging mechanisms.

Intermittent hypoxic training is a very powerful medicine and a very powerful form of hormesis to strengthen and build your mitochondria. So how do you actually implement this method?

Hypoxia Exercise

Building Your Cellular Engine with Hormesis

If we're trying to overcome fatigue and increase our energy, we're trying to go from weak, fragile mitochondria, not very many of them and a low resilience threshold back up to big, strong, healthy mitochondria, lots of them and a very high resilience threshold. We want a body that is capable of handling the stressors of life while maintaining a high energy state.

Resistance to stress parallels the health of your mitochondria. The health of your mitochondria predicts your resistance to disease, your longevity, resilience and—most importantly—your energy levels. The only way to stop the decline in mitochondrial number, size and capacity as we grow older from happening is through hormesis.

The only way to prevent this scenario of fatigue, brain symptoms, accelerated aging and loss of resilience is through hormesis.

Stay tuned for the next training. It comes out on Thursday, April 11th! (Mark your calendars... you won’t want to miss this!)