How to Make Lifting Weights a Maximum Anti-Aging Workout

A recent study found that high-intensity interval training (HIIT) robustly increased both aerobic capacity and mitochondrial function in both old and young people. The older people saw a greater increase in mitochondrial function, because they had a lower baseline function. This study has been making the rounds, calling HIIT “the best anti-aging exercise”. Here we’ll see how to turn lifting weights into a maximum anti-aging workout.

Decline in mitochondrial function is strongly linked to age and aging. In young people (and other young organisms), mitochondria, the powerhouses of the cell, function perfectly and with high efficiency, but with aging comes a falling off of that function. As mitochondria generate power, the decline literally means a decline in overall energy, the energy you feel. It probably explains a lot about why children have seemingly limitless energy, and why exercise improves the amount of energy you actually feel in everyday life.

Increasing mitochondrial function in older people improves their physiology and makes them much more like a young person.
HIIT vs resistance training

One little hitch for us weightlifters:

Here we report that 12 weeks of high-intensity aerobic interval (HIIT), resistance (RT), and combined exercise training enhanced insulin sensitivity and lean mass, but only HIIT and combined training improved aerobic capacity and skeletal muscle mitochondrial respiration.

The researchers reported no effect of resistance training (weightlifting) on better aerobic capacity and mitochondrial function.

Similarly, HIIT, but not continuous aerobic training, led to increases in PGC-1α, the molecule that upregulates mitochondrial biogenesis, i.e. signals cells to make more mitochondria to enhance energy generation.

Does all this mean that strength training does not improve health, or that we must perform HIIT to improve mitochondrial function and reverse aging?

Not at all.

We know that strength training increases VO2max, the measure of aerobic capacity. While VO2max is a general measure of function, including heart rate, circulation, hemoglobin, and lung function, it also includes mitochondrial function, the ability of the cells to use oxygen to make energy. For a good review, see Resistance Training to Momentary Muscular Failure Improves Cardiovascular Fitness in Humans: A Review of Acute Physiological Responses and Chronic Physiological Adaptations.

So, why didn’t the people who did resistance training in the new study see any improvement in mitochondrial function and aerobic capacity?

Most likely because of the way they trained.

I can speak from experience that most people who train with weights are hardly even trying. How so? They

- do the traditional 3 sets of 10 reps, and rest between each set
- they don’t lift until failure, but stop at a given number of reps
- their between-set breaks are far too long
- they spend a good deal of their gym time socializing or looking at their phones
- they do isolation, not compound, exercises

This isn’t meant to be boasting on my part, just simple observation; in contrast, I

- perform one set of each exercise to failure
- move quickly to the next set
- do compound lifts
rarely socialize and don’t even own a phone, much less take it to the gym

I frequently have to stop after a set to catch my breath, and this is especially obvious when I do big compound exercises, such as squats, deadlifts, T-bar rows, weighted dips, and the like. But I can’t even say when I’ve ever seen another weightlifter in my gym stop to catch his breath. I don’t know, maybe I’m not looking hard enough, but it’s striking.

When the new study put their trainees in resistance training, it’s highly unlikely that they did a high-intensity routine. They most likely did a standard 3 set per exercise protocol, with plenty of rest between sets, 3 days a week, etc.

Most people aren’t psychologically cut out to do high-intensity weightlifting. It’s too demanding. Which explains the general lack of progress seen in most gym-goers.

If your heart and lungs are not working intensely, at least some of the anti-aging benefits of strength training are lost to you.

### How to increase mitochondrial function and VO2max with weightlifting

1. Here’s a good example of high-intensity strength training: Shawn Baker, M.D., deadlifting 405 pounds for 20 reps. Note that toward the end he pauses, and it looks to me like he does this not so much for his muscles, but to catch his breath.

   Trying to do this x 4 years- now on #zerocarb 405lb DL x 20 reps

   50 years old-N0 drugs, hormones, supplements, carbs or belt

   Objectivity!! pic.twitter.com/84aoKjoCq7

   – Shawn Baker MD (@SBakerMD) March 23, 2017

Dr. Baker is 50-years-old, eats zero carb, and is a world-record holder in his age group for 1000 meter rowing.

Compound exercises, like deadlifts, squats, dips, bench, overhead, maximize the use of heart, lungs, and circulation, and will robustly increase mitochondrial function. Isolation exercises like biceps curls and triceps pulldowns are much less effective for this.

Note, this is not Crossfit, which carries a high risk of injury. All exercises must be done with good form and attention to safety.

2. Move quickly to the next set. “Quickly” is subjective of course, but don’t wait minutes or until you feel all rested and ready. Attack your workout.
3. Do an adequate number of repetitions. Lifting at your max weight for low reps (1RM) does little to improve cardiovascular conditioning.

4. Finally, you can always add a set or two of actual HIIT at the end of your strength training. For example, a 20-second all-out bout on the stationary cycle at the end of my workout leaves me gasping for breath. Sometimes I do a set or two of jump rope.

Conclusion

Weightlifting robustly increases VO2max and mitochondrial function, but it must be done right. Since the extent to which strength training improves VO2max depends on initial state of conditioning, someone who is already highly trained but wants to improve VO2max even more should add some HIIT to his strength training.

PS: For more on why strength training is the best anti-aging exercise, you know you want my book, Muscle Up.

PPS: Check out my Supplements Buying Guide for Men.
Control Your Mitochondria or They Will Control You

Mitochondria are small organelles within cells, popularly known as the powerhouses of the cell, since their main function is to burn energy. With a few exceptions, such as red blood cells, every cell in the body contains hundreds or thousands of mitochondria, and they are crucially important in aging. That’s why you must control your mitochondria or they will control you.

Aging mitochondria

Mitochondria are so important to aging that there’s an entire theory called the mitochondrial theory of aging.

As cells age, so do mitochondria, and they decline in capacity to make energy, generating reactive oxygen species (ROS, or free radicals), which cause self-damage as well as damage to the cells within which they reside.

Mitochondrial quality control is crucial to fighting aging.

Mitochondrial quality control

Perhaps the most crucial mitochondrial quality control process is autophagy, the cellular self-cleansing process that rids cells of junk. When mitochondria are subject to this process, it’s known as mitophagy. Mitochondria that are past their expiration date, that are inefficient and generating large amounts of free radicals, are sent through the meat grinder of autophagy, their constituents broken down and sent for recycling, and new mitochondria are built to replace them.

The decline in autophagy is one of the hallmarks of aging. An aging organism can no longer increase autophagy to the extent that it could when young. Autophagy is necessary because of the importance of maintaining clean cells. With aging, cells become cluttered and inefficient, and this is one of the crucial differences between young and old cells. Aging takes place most of
all at the cellular level; aging cells mean an aging body. Maintenance of highly functional mitochondria is a characteristic of youth.

Insulin resistance is a characteristic of aging, and people with it have poorly functioning mitochondria.

Older people have lower exercise capacity and in general a lot less energy than young people. This is due in large part to declining mitochondrial function.

**How to increase mitochondrial function**

As you get older, and if you do nothing to intervene in the aging process, mitochondria decline in function and cause aging. In essence, if you don’t control your mitochondria, they will control you. Fortunately, there are a number of things you can do about this; most of them require some discipline.

**Exercise**

Exercise robustly increases mitochondrial function. A new study found that high-intensity interval training robustly increased the ability of mitochondria to generate energy, 69% greater in older people, and 49% in younger. The older people had a greater deficit in function, hence they had a greater improvement.

Intensity is a crucial component of exercise in every way, but especially so regarding improvement in mitochondria.

The study found that resistance training did not improve mitochondrial function (though it did improve insulin sensitivity), but this is likely because of training that wasn’t intense enough. Other studies have found increases in mitochondrial proteins involved in energy production in resistance training. That’s one reason for strength training I recommend high-intensity training. Nonetheless, if you lift weights, it may be beneficial to add a component of high-intensity interval training.

**Intermittent fasting**

Nothing increases the process of autophagy more than going without food. Intermittent fasting increases the quality of mitochondria, partly through this mechanism.

The cellular and molecular effects of intermittent fasting are similar to those of regular exercise, which suggests that mechanisms are similar.

**Resveratrol and other phytochemicals**

Resveratrol increases lifespan in mice on a diabetes-inducing diet. One of the ways that it works is by increasing mitochondrial quantity and quality.

EGCG, from green tea extract, also improves mitochondrial quality.
Iron

The accumulation of iron causes mitochondria to become dysfunctional, and this is critical in aging. Controlling iron levels is critical to fighting aging.

Control your mitochondria or they will control you

Aging is characterized by a loss of mitochondria quality and quantity, and there’s every reason to think these are critical to the aging process.

A couch-potato life, with no hormetic stressors, leads to poor mitochondria, and subsequent aging and disease.

Therefore you must control your mitochondria or they will control you.

For more on how to control aging, the best few bucks you’ll ever spend are on my book, Stop the Clock.

PS: You can support this site by purchasing through my Supplements Buying Guide for Men.

Chocolate is an exercise mimetic

(--)-Epicatechin enhances fatigue resistance and oxidative capacity in mouse muscle
Abstract  The flavanol (−)-epicatechin, a component of cacao (cocoa), has been shown to have multiple health benefits in humans. Using 1-year-old male mice, we examined the effects of 15 days of (−)-epicatechin treatment and regular exercise on: (1) exercise performance, (2) muscle fatigue, (3) capillarity, and (4) mitochondrial biogenesis in mouse hindlimb and heart muscles. Twenty-five male mice (C57BL/6N) were randomized into four groups: (1) water, (2) water–exercise (W-Ex), (3) (−)-epicatechin (−)-Epi), and (4) (−)-epicatechin–exercise (−)-Epi-Ex). Animals received 1 mg kg−1 of (−)-epicatechin or water (vehicle) via oral gavage (twice daily). Exercise groups underwent 15 days of treadmill exercise. Significant increases in treadmill performance (∼50%) and enhanced in situ muscle fatigue resistance (∼30%) were observed with (−)-epicatechin. Components of oxidative phosphorylation complexes, mitofilin, porin, nNOS, p-nNOS, and Tfam as well as mitochondrial volume and cristae abundance were significantly higher with (−)-epicatechin treatment for hindlimb and cardiac muscles than exercise alone. In addition, there were significant increases in skeletal muscle capillarity. The combination of (−)-epicatechin and exercise resulted in further increases in oxidative phosphorylation-complex proteins, mitofilin, porin and capillarity than (−)-epicatechin alone. These findings indicate that (−)-epicatechin alone or in combination with exercise induces an integrated response that includes structural and metabolic changes in skeletal and cardiac muscles resulting in greater endurance capacity. These results, therefore, warrant the further evaluation of the underlying mechanism of action of (−)-epicatechin and its potential clinical application as an exercise mimetic.

It’s shown here that chocolate functions as an exercise mimetic, i.e. it provides many of the same benefits, such as improved mitochondrial function and increased capillaries in muscle tissue. Also notable from the study above is that the effects of exercise and epicatechin together were additive, so even if you already exercise, chocolate may provide additional health benefits.

Testosterone, fatigue, energy

One of the symptoms of low testosterone (T), also known as hypogonadism, is fatigue or low energy levels. A couple of papers give some insight into how this works, as well as the extent to which replacing T contributes to higher energy.

Voluntary running, skeletal muscle gene expression, and signaling inversely
Declines in skeletal muscle size and strength, often seen with chronic wasting diseases, prolonged or high-dose glucocorticoid therapy, and the natural aging process in mammals, are usually associated with reduced physical activity and testosterone levels. However, it is not clear whether the decline in testosterone and activity are causally related. Using a mouse model, we found that removal of endogenous testosterone by orchidectomy results in an almost complete cessation in voluntary wheel running but only a small decline in muscle mass. Testosterone replacement restored running behavior and muscle mass to normal levels. Orchidectomy also suppressed the IGF-I/Akt pathway, activated the atrophy-inducing E3 ligases MuRF1 and MAFBx, and suppressed several energy metabolism pathways, and all of these effects were reversed by testosterone replacement. The study also delineated a distinct, previously unidentified set of genes that is inversely regulated by orchidectomy and testosterone treatment. These data demonstrate the necessity of testosterone for both speed and endurance of voluntary wheel running in mice and suggest a potential mechanism for declined activity in humans where androgens are deficient.

In this study, castrated mice who had their T replaced engaged in voluntary running at more than three times the amount that untreated mice did.

**Relationship Between Testosterone Levels, Insulin Sensitivity, and Mitochondrial Function in Men.** In this study, low T was associated with insulin resistance and low aerobic capacity, which appears to be related to mitochondrial function.

So overall, it seems that one of the pathways through which T works is improved mitochondrial function. If you’ve read my book (see sidebar), you know that mitochondrial dysfunction is one of the main ways through which fatigue is produced in illness. Higher T levels can help this, perhaps even when other causes of fatigue are at work.

The lesson here is that, if you’re a man and have low energy levels or even outright chronic fatigue, you must ensure that T levels are normal. A doctor can check this.

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**Increasing longevity through mitochondrial signaling**

The NAD+/Sirtuin Pathway Modulates Longevity through Activation of
Mitochondrial UPR and FOXO Signaling

Authors
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Highlights
Enhancing NAD+ availability extends lifespan in C. elegans through sir-2.1
The NAD+/sir-2.1-dependent activation of mitochondrial UPR is crucial for longevity
Higher NAD+ bioavailability protects against ROS by enhancing daf-16 activity
UPRmt is a conserved target of the NAD+/SIRT1 axis in mammalian cells

Summary
NAD+ is an important cofactor regulating metabolic homeostasis and a rate-limiting substrate for sirtuin deacylases. We show that NAD+ levels are reduced in aged mice and Caenorhabditis elegans and that decreasing NAD+ levels results in a further reduction in worm lifespan. Conversely, genetic or pharmacological restoration of NAD+ prevents age-associated metabolic decline and promotes longevity in worms. These effects are dependent upon the protein deacetylase sir-2.1 and involve the induction of mitonuclear protein imbalance as well as activation of stress signaling via the mitochondrial unfolded protein response (UPRmt) and the nuclear translocation and activation of FOXO transcription factor DAF-16. Our data suggest that augmenting mitochondrial stress signaling through the modulation of NAD+ levels may be a target to improve mitochondrial function and prevent or treat age-associated decline.

Chocolate improves mitochondrial function and increases mitochondrial biogenesis

Alterations in skeletal muscle indicators of mitochondrial structure and biogenesis in patients with type 2 diabetes and heart failure: effects of epicatechin rich cocoa.
(-)-Epicatechin (Epi), a flavanol in cacao stimulates mitochondrial volume and cristae density and protein markers of skeletal muscle (SkM) mitochondrial biogenesis in mice. Type 2 diabetes mellitus (DM2) and heart failure (HF) are diseases associated with defects in SkM mitochondrial structure/function. A study was implemented to assess perturbations and to determine the effects of Epi-rich cocoa in SkM mitochondrial structure and mediators of biogenesis. Five patients with DM2 and stage II/III HF consumed dark chocolate and a beverage containing approximately 100 mg of Epi per day for 3 months. We assessed changes in protein and/or activity levels of oxidative phosphorylation proteins, porin, mitofilin, nNOS, nitric oxide, cGMP, SIRT1, PGC1α, Tfam, and mitochondria volume and cristae abundance by electron microscopy from SkM. Apparent major losses in normal mitochondria structure were observed before treatment. Epi-rich cocoa increased protein and/or activity of mediators of biogenesis and cristae abundance while not changing mitochondrial volume density. Epi-rich cocoa treatment improves SkM mitochondrial structure and in an orchestrated manner, increases molecular markers of mitochondrial biogenesis resulting in enhanced cristae density. Future controlled studies are warranted using Epi-rich cocoa (or pure Epi) to translate improved mitochondrial structure into enhanced cardiac and/or SkM muscle function.

Another recent paper found similar effects in mice: (−)-Epicatechin enhances fatigue resistance and oxidative capacity in mouse muscle

Non-technical summary

During exercise, skeletal muscle performance depends in great part on the use of aerobic metabolism to supply the energetic demand of contractions. Endurance training increases the muscle aerobic capacity, which is not only associated with enhanced exercise performance, but also with a decreased risk of cardiovascular and metabolic diseases. Recently, it has been shown that regular use of small doses of dark chocolate may result in similar health benefits to exercise training. We show here that mice fed for 15 days with (−)-epicatechin (present in dark chocolate) had improved exercise performance accompanied by: (1) an increased number of capillaries in the hindlimb muscle; and (2) an increased amount of muscle mitochondria as well as signalling for mitochondrial biogenesis. These results suggest that (−)-epicatechin increases the capacity for muscle aerobic metabolism, thereby delaying the onset of fatigue. These findings may have potential application for clinical populations experiencing muscle fatigue.
Mitochondrial Theory of Aging: Importance to Explain Why Females Live Longer Than Males

Females live longer than males in many species, including humans. This can be explained on the basis of the mitochondrial theory of aging. Mitochondria from females produce significantly less hydrogen peroxide than those from males and have higher levels of mitochondrial reduced glutathione, manganese superoxide dismutase, and glutathione peroxidase than males. Oxidative damage to mitochondrial DNA is also fourfold higher in males than in females. These differences may be explained by estrogens. Ovariectomy abolishes the gender differences between males and females and estrogen replacement rescues the ovariectomy effect. The challenge for the future is to find molecules that have the beneficial effects of estradiol, but without its feminizing effects. Phytoestrogens or phytoestrogen-related molecules may be good candidates to meet this challenge.

Rapamycin does not compromise muscle endurance
Rapamycin inhibits the mTOR pathway, crucial for muscle growth

The following study partly answers something I’ve long wondered about, whether the anti-aging drug rapamycin can compromise muscle endurance or performance: **Rapamycin doses sufficient to extend lifespan do not compromise muscle mitochondrial content or endurance**.

Rapamycin extends lifespan in mice, but can have a number of undesirable effects that may ultimately limit its utility in humans. The canonical target of rapamycin, and the one thought to account for its effects on lifespan, is the mammalian/mechanistic target of rapamycin, complex 1 (mTORC1). We have previously shown that at least some of the detrimental side effects of rapamycin are due to “off target” disruption of mTORC2, suggesting they could be avoided by more specific targeting of mTORC1. However, mTORC1 inhibition per se can reduce the mRNA expression of mitochondrial genes and compromise the function of mitochondria in cultured muscle cells, implying that defects in bioenergetics might be an unavoidable consequence of targeting mTORC1 in vivo. Therefore, we tested whether rapamycin, at the same doses used to extend lifespan, affects mitochondrial function in skeletal muscle. While mitochondrial transcripts were decreased, particularly in the highly oxidative soleus muscle, we found no consistent change in mitochondrial DNA or protein levels. In agreement with the lack of change in mitochondrial components, rapamycin-treated mice had endurance equivalent to that of untreated controls, and isolated, permeabilized muscle fibers displayed similar rates of oxygen consumption. **We conclude that the doses of rapamycin required to extend life do not cause overt mitochondrial dysfunction in skeletal muscle.**
Rapamycin is perhaps the most promising anti-aging drug available, the other candidate being metformin, a diabetes drug. However, this doesn’t answer the question in mind as to whether rapamycin compromises muscle hypertrophy, size, and strength; that is, just because endurance performance and mitochondrial number and function are not compromised, it doesn’t mean that hypertrophy is not affected. There are good grounds for thinking that it may be, since rapamycin works (or appears to) by affecting mTOR (mammalian target of rapamycin), which is the main nutrient sensor that signals growth. It seems possible that rapamycin may leave enough mTOR activity in place so that hypertrophy is not affected, but this remains to be shown, as far as I know.

The fundamental growth-longevity tradeoff is still in place.

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**Glucose restriction and life extension**

*Glucose restriction extends Caenorhabditis elegans life span by inducing mitochondrial respiration and increasing oxidative stress.*

Schulz TJ, Zarse K, Voigt A, Urban N, Birringer M, Ristow M.
Source
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Abstract
Increasing cellular glucose uptake is a fundamental concept in treatment of type 2 diabetes, whereas nutritive calorie restriction increases life expectancy. We show here that increased glucose availability decreases Caenorhabditis elegans life span, while impaired glucose metabolism extends life expectancy by inducing mitochondrial respiration. The histone deacetylase Sir2.1 is found here to be dispensable for this phenotype, whereas disruption of aak-2, a homolog of AMP-dependent kinase (AMPK), abolishes extension of life span due to impaired glycolysis. Reduced glucose availability promotes formation of reactive oxygen species (ROS), induces catalase activity, and increases oxidative stress resistance and survival rates, altogether providing direct evidence for a hitherto hypothetical concept named mitochondrial hormesis or “mitohormesis.” Accordingly, treatment of nematodes with different antioxidants and vitamins prevents extension of life span. In summary, these data indicate that glucose restriction promotes mitochondrial metabolism, causing increased ROS formation and cumulating in horsemetic extension of life span, questioning current treatments of type 2 diabetes as well as the widespread use of antioxidant supplements.
New paper by Ristow group on mitochondrial hormesis

Mitochondrial hormesis links low-dose arsenite exposure to lifespan extension.


Abstract Arsenite is one of the most toxic chemical substances known and is assumed to exert detrimental effects on viability even at lowest concentrations. By contrast and unlike higher concentrations, we here find that exposure to low-dose arsenite promotes growth of cultured mammalian cells. In the nematode C. elegans, low-dose arsenite promotes resistance against thermal and chemical stressors and extends lifespan of this metazoan, whereas higher concentrations reduce longevity. While arsenite causes a transient increase in reactive oxygen species (ROS) levels in C. elegans, co-exposure to ROS scavengers prevents the lifespan-extending capabilities of arsenite, indicating that transiently increased ROS levels act as transducers of arsenite effects on lifespan, a process known as mitohormesis. This requires two transcription factors, namely DAF-16 and SKN-1, which employ the metallothionein MTL-2 as well as the mitochondrial transporter TIN-9.1 to extend lifespan. Taken together, low-dose arsenite extends lifespan, providing evidence for nonlinear dose-response characteristics of toxin-mediated stress resistance and longevity in a multicellular organism.

Mithridates was on to something.
Nutraceutical with leucine and B6 causes fat-burning

Effects of a leucine and pyridoxine-containing nutraceutical on fat oxidation, and oxidative and inflammatory stress in overweight and obese subjects.

Abstract

Leucine stimulates tissue protein synthesis and may also attenuate adiposity by increasing fatty acid oxidation and mitochondrial biogenesis in muscle and adipocytes. Accordingly, the effects of a nutraceutical containing 2.25 g leucine and 30 mg pyridoxine (Vitamin B6) (NuFit active blend) were tested in cell culture and in a clinical trial. 3T3L1 adipocytes were treated with leucine (0.25 mM or 0.5 mM) and/or Pyridoxal Phosphate (PLP) (50 nM or 100 nM) for 48 h. For the clinical trial, twenty overweight or obese subjects received the NuFit active blend or placebo three times/day for 4 weeks without energy restriction. Leucine decreased fatty acid synthase (FAS) expression and triglyceride content in adipocytes, and PLP addition significantly augmented this effect. Administration of NuFit active blend in the clinical trial increased fat oxidation by 33.6 g/day (p < 0.04), decreased respiratory quotient, improved HOMA(IR), reduced oxidative and inflammatory biomarkers (plasma MDA, 8-isoprostane-F(2α), TNF-α, C-reactive protein), and increased the anti-inflammatory marker adiponectin. These data indicate that the NuFit active blend significantly increased fat oxidation and insulin sensitivity, and reduced oxidative and inflammatory stress. Therefore, the NuFit active blend appears to be a useful nutraceutical in the management of obesity and associated co-morbidities.

This would seem to be useful in treating obesity, as well as a useful anti-aging supplement that likely induces mitochondrial biogenesis, hence good for anyone who wants to stay in shape. The beauty here also is that leucine and B6 are readily available elsewhere, so you don’t need to buy an expensive supplement.

Methylen blue enhances memory

Methylen blue is a common and cheap dye used in biology and medicine. Neurometabolic mechanisms for memory enhancement and neuroprotection of...
Rojas JC, Bruchey AK, Gonzalez-Lima F.
Source
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Abstract
This paper provides the first review of the memory-enhancing and neuroprotective metabolic mechanisms of action of methylene blue in vivo. These mechanisms have important implications as a new neurobiological approach to improve normal memory and to treat memory impairment and neurodegeneration associated with mitochondrial dysfunction. Methylene blue’s action is unique because its neurobiological effects are not determined by regular drug-receptor interactions or drug-response paradigms. Methylene blue shows a hormetic dose-response, with opposite effects at low and high doses. At low doses, methylene blue is an electron cycler in the mitochondrial electron transport chain, with unparalleled antioxidant and cell respiration-enhancing properties that affect the function of the nervous system in a versatile manner. A major role of the respiratory enzyme cytochrome oxidase on the memory-enhancing effects of methylene blue is supported by available data. The memory-enhancing effects have been associated with improvement of memory consolidation in a network-specific and use-dependent fashion. In addition, low doses of methylene blue have also been used for neuroprotection against mitochondrial dysfunction in humans and experimental models of disease. The unique auto-oxidizing property of methylene blue and its pleiotropic effects on a number of tissue oxidases explain its potent neuroprotective effects at low doses. The evidence reviewed supports a mechanistic role of low-dose methylene blue as a promising and safe intervention for improving memory and for the treatment of acute and chronic conditions characterized by increased oxidative stress, neurodegeneration and memory impairment.

See also: Protective role of methylene blue in Alzheimer’s disease via mitochondria and cytochrome c oxidase.

Atamna H, Kumar R.
Source
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Abstract
The key cytopathologies in the brains of Alzheimer’s disease (AD) patients include mitochondrial dysfunction and energy
hypometabolism, which are likely caused by the accumulation of toxic species of amyloid-beta (Abeta) peptides. This review discusses two potential approaches to delay the onset of AD. The first approach is use of diaminophenothiazines (e.g., methylene blue; MB) to prevent mitochondrial dysfunction and to attenuate energy hypometabolism. We have shown that MB increases heme synthesis, cytochrome c oxidase (complex IV), and mitochondrial respiration, which are impaired in AD brains. Consistently, MB is one of the most effective agents to delay senescence in normal human cells. **A key action of MB appears to be enhancing mitochondrial function, which is achieved at nM concentrations.** We propose that the cycling of MB between the reduced leuco-methylene blue (MBH2) and the oxidized (MB) forms may explain, in part, the mitochondria-protecting activities of MB. The second approach is use of naturally occurring osmolytes to prevent the formation of toxic forms of Abeta. Osmolytes (e.g., taurine, carnosine) are brain metabolites typically accumulated in tissues at relatively high concentrations following stress conditions. Osmolytes enhance thermodynamic stability of proteins by stabilizing natively-folded protein conformation, thus preventing aggregation, without perturbing other cellular processes. Experimental evidence suggests that the level of carnosine is significantly lower in AD patients. Osmolytes may inhibit the formation of Abeta species in vivo, thus preventing the formation of soluble oligomers. Osmolytes are efficient antioxidants that may also increase neural resistance to Abeta. The potential significance of combining MB and osmolytes to treat AD are discussed.

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**Mitochondrial dysfunction in chronic fatigue**

**Mitochondrial dysfunction and the pathophysiology of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS).**

Abstract

The objectives of this study are to test the hypothesis that the fatigue and accompanying symptoms of Chronic Myalgic Encephalomyelitis/Fatigue Syndrome are in part due to defects in energy provision at the cellular level, and to understand the pathophysiology of the defects so that effective medical intervention can be implemented. We performed an audit of 138 patients (ages 18-65) diagnosed with ME/CFS and attending a private practice. The patients and 53 normal, healthy controls had the ATP
Profile test carried out on neutrophils from a 3-ml venous blood sample. This test yields 6 numerical factors that describe the availability of ATP and the efficiency of oxidative phosphorylation in mitochondria. Other biomedical measurements, including the concentration of cell-free DNA in plasma, were made. The results of the audit are compared with the controls and a previous cohort of 61 patients. **We find that all patients tested have measureable mitochondrial dysfunction which correlates with the severity of the illness.** The patients divide into two main groups differentiated by how cellular metabolism attempts to compensate for the dysfunction. Comparisons with exercise studies suggest that the dysfunction in neutrophils also occurs in other cells. This is confirmed by the cell-free DNA measurements which indicate levels of tissue damage up to 3.5 times the normal reference range. The major immediate causes of the dysfunction are lack of essential substrates and partial blocking of the translocator protein sites in mitochondria. The ATP Profile is a valuable diagnostic tool for the clinical management of ME/CFS.