The Energy Blueprint
The Science of Superhuman Energy

Summary Doc
BONUS: The Mitochondrial Biogenesis Protocol
Mitochondria are the cellular energy generators! We have over 100,000 trillion of these powerhouses in our body working constantly to produce ATP. They use over 90% of the oxygen we breathe. Bigger mitochondria and MORE mitochondria = bigger engine = higher capacity to PRODUCE ENERGY!

Why is Mitochondrial Biogenesis so Important to Increasing Energy Levels?

<table>
<thead>
<tr>
<th>Sedentary Lifestyle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor circadian rhythm</td>
</tr>
<tr>
<td>Aging</td>
</tr>
<tr>
<td>Poor diet</td>
</tr>
<tr>
<td>Minimal exposure to hormetic stressors</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ample exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong circadian rhythm</td>
</tr>
<tr>
<td>Diet rich in phytonutrients</td>
</tr>
<tr>
<td>AMPLE exposure to hormetic stressors</td>
</tr>
</tbody>
</table>

**Poor energy levels**
- Low fitness
- Increased susceptibility to disease
- Decreased longevity

**Increased energy levels**
- Increased fitness
- Resistance to disease
- Increased longevity
Symptoms of Low Mitochondrial Function

If you answer yes to these, then that may indicate low mitochondrial function:

- Do you get tired often?
- Do you have a low metabolism?
- Do you lack energy in the day?
- Do you have a disturbed circadian rhythm? *(sleepy during the day and/or have trouble sleeping at night)*
- Do you have chronic inflammation?

What You Will Find About Improving Mitochondrial Health/Biogenesis if You Look Online...

Here’s what you will find if you look online on this subject...

- Do exercise, because exercise boosts mitochondrial health/biogenesis. *(Fact: Only some types of exercise do, and only when done in certain ways).*
- Go low-carb or keto. *(Fact: Likely only a good approach as an intermittent strategy—NOT as a chronic one, where it can become counterproductive.)*
- Supplement with various compounds: CoQ10, PQQ, Shilajit, alpha lipoic acid, NAC, glutathione, antioxidants, etc. *(Fact: Some of these compounds have evidence to support their use and others don’t. Many of them will actually WORSEN mitochondrial function, in direct contradiction to marketers’ claims.)*

* Not all mitohormetic factors work to increase mitochondrial biogenesis
* Different types/intensities of mitohormetins work or don’t work to stimulate mitochondrial biogenesis (e.g. exercise types—some work and others don’t)
KEY: Different mitohormetins synergize and can be layered together to amplify the increase in mitochondrial biogenesis. This is a major secret to high energy levels.

Remember our Previous Scientific Literature Review on Exercise and Mitochondrial Biogenesis. If you don’t, here it is:

CONCLUSIONS

Untrained subjects
* Continuous and interval exercise have a similar effect on PGC-1α, and other genes regulating mitochondrial biogenesis, if the duration and work done are the same.
* Concurrent resistance and endurance exercise dramatically enhances the signaling pathway of mitochondrial biogenesis (over endurance exercise alone).

Trained subjects
* Sprint interval training is a powerful inducer of PGC-1α, and other genes regulating mitochondrial biogenesis. Likely needs to be done fasted. (Added bonus: Leptin mimetic, which may have powerful implications for increased energy levels and fat loss.) (Note: Does not actually need to be “sprinting”—sprint efforts on a cycle also work.)
* Eight weeks of concurrent strength and endurance training does not enhance mitochondrial content (CS-activity) or performance
* Exercise with low muscle glycogen enhances the expression of PGC-1α, and other genes regulating mitochondrial biogenesis

General finding
* Intracellular glycogen levels during/after exercise might play a pivotal role for the magnitude of the exercise induced increase in mitochondrial biogenesis regardless of exercise mode

Now we’re going to add several new layers on top of this:
Consuming food prior to sprint exercise will block most/all of the mitochondrial biogenesis.

Sodium bicarbonate ingestion augments the increase in PGC-1α mRNA expression during recovery from intense interval exercise in human skeletal muscle.
Curcumin treatment enhances the effect of exercise on mitochondrial biogenesis in skeletal muscle by increasing cAMP levels.
Untrained subjects

* Continuous and interval exercise have a similar effect on PGC-1α, and other genes regulating mitochondrial biogenesis, if the duration and work done are the same.

* Concurrent resistance and endurance exercise dramatically enhances the signaling pathway of mitochondrial biogenesis (over endurance exercise alone).

Trained subjects

* Sprint interval training is a powerful inducer of PGC-1α, and other genes regulating mitochondrial biogenesis. Likely needs to be done fasted. (Added bonus: Leptin mimetic, which may have powerful implications for increased energy levels and fat loss.) (Note: Does not actually need to be “sprinting”—sprint efforts on a cycle also work.)

* Eight weeks of concurrent strength and endurance training does not enhance mitochondrial content (CS-activity) or performance

* Exercise with low muscle glycogen enhances the expression of PGC-1α, and other genes regulating mitochondrial biogenesis

* Pre-loading with baking soda prior to HIIT or SIT will increase PGC-1α expression and increase mitochondrial biogenesis.

* Supplementing with turmeric (with black pepper) or curcumin extract prior and just after SIT.

* Supplementing with resveratrol also boosts the effects of SIT/HIIT on mitochondrial biogenesis.

General finding

* Intracellular glycogen levels during/after exercise might play a pivotal role for the magnitude of the exercise induced increase in mitochondrial biogenesis regardless of exercise mode.

* You want to do SIT or HIIT in a glycogen depleted state, or use the SIT/HIIT session to deplete glycogen.

Summing Up: Exercise and Mitochondrial Biogenesis

Bottom line:

* Are you currently sedentary and untrained?
ANY type of exercise will work to increase mitochondrial biogenesis. But combination exercise of both resistance exercise and endurance or HIIT is most effective. Adding in baking soda and xenohormetins is helpful, but not yet necessary.

- Are you currently a workout warrior who exercise close to everyday (and you’re already in good metabolic health)?
  - You will have to do either HIIT or SIT, and you may probably want to experiment with doing HIIT or SIT workouts after occasional intermittent fasts and/or the nightly fast, and/or a day or two of carb restriction. Adding in baking soda and xenohormetins (specifically, cycling curcumin and cacao) is a smart idea.

The Mitochondrial Biogenesis Protocol
Factor #2: Ample DHA Consumption


- Polyunsaturated fatty acids of marine origin upregulate mitochondrial biogenesis and induce beta-oxidation in white fat.

- AIMS/HYPOTHESIS:

  * Intake of n-3 polyunsaturated fatty acids reduces adipose tissue mass, preferentially in the abdomen. The more pronounced effect of marine-derived eicosapentaenoic (EPA) and
docosahexaenoic (DHA) acids on adiposity, compared with their precursor alpha-linolenic acid, may be mediated by changes in gene expression and metabolism in white fat.

* CONCLUSIONS/INTERPRETATION: The anti-adipogenic effect of EPA/DHA may involve a metabolic switch in adipocytes that includes enhancement of beta-oxidation and upregulation of mitochondrial biogenesis.

What Kind of Seafood Should You Be Consuming?

Unfortunately, due to pollution concerns, I do not recommend any large predatory fish (tuna, swordfish, etc.)
Wild-caught fish is best (especially wild Alaskan).
Low on the food chain is best (sardines rather than tuna).
Shellfish are ideal (mussels, oysters, scallops, shrimp, crab, etc.)
Whole food, not supplements. Most fish oil supplements are oxidized.
If you're vegan or don't like seafood, use algae oil
* STUDY: Cell, Volume 98, Issue 1, 9 July 1999, Pages 115–124

* Mechanisms Controlling Mitochondrial Biogenesis and Respiration through the Thermogenic Coactivator PGC-1

* Mitochondrial number and function are altered in response to external stimuli in eukaryotes. While several transcription/replication factors directly regulate mitochondrial genes, the coordination of these factors into a program responsive to the environment is not understood. **We show here that PGC-1, a cold-inducible coactivator of nuclear receptors, stimulates mitochondrial biogenesis** and respiration in muscle cells through an induction of uncoupling protein 2 (UCP-2) and through regulation of the nuclear respiratory factors (NRFs). PGC-1 stimulates a powerful induction of NRF-1 and NRF-2 gene expression; in addition, PGC-1 binds to and coactivates the transcriptional function of NRF-1 on the promoter for mitochondrial transcription factor A (mtTFA), a direct regulator of mitochondrial DNA replication/transcription. These data elucidate a pathway that directly links external physiological stimuli to the regulation of mitochondrial biogenesis and function.
How To Use Cold and Heat

* Both heat and cold exposure stimulate mitochondrial biogenesis

* You can combine alongside exercise to maximize effects.

  * **Pre-exercise cold exposure** (i.e. cold shower or bath), (Note: if you do it after exercise, you must wait at least 6 hours after exercise to do it—particularly resistance exercise).

  * **Post-exercise heat exposure** (ideally sauna).

  * Both of these will amplify the mitochondrial biogenesis from exercise.

  * If done apart from exercise, cold is generally best done in the morning, and heat is generally best done in the evening 1-3 hours before bed (though it can also be done in the morning).
The Mitochondrial Biogenesis Protocol
Factor #5: PQQ

Compounds reported to stimulate mitochondrial biogenesis are linked to many health benefits such as increased longevity, improved energy utilization, and protection from free radicals. Pyrroloquinoline quinone (PQQ) is a novel vitamin-like compound found in plant foods that is showing a wide range of benefits to brain and body function based upon preclinical studies and initial clinical evaluation. Although PQQ is not currently viewed as a vitamin, it is likely to be considered an essential nutrient in the future.

What exactly does PQQ do?
- PQQ stimulates growth and serves as a cofactor for a special class of enzymes involved in cellular function including cellular growth, development, differentiation, and survival.
- Mice and rats fed diets lacking in pyrroloquinoline quinone (PQQ) have reduced mitochondrial content.
- The creation of new mitochondria by PQQ occurs through the activation of CREB and PGC-1alpha, pathways known to increase mitochondrial biogenesis.
- As a result of activation of the PGC-1alpha pathway, PQQ increased NRF-1 and NRF-2, proteins (transcription factors) that protect us more free radicals by increasing our internal antioxidant production and can protect us from toxins, UV, etc. PGC-1alpha is a “master regulator” that directly stimulates genes that promote mitochondrial and cellular respiration, growth, and proliferation.
- By increasing cellular metabolism it favorably affects blood pressure, cholesterol and triglyceride breakdown, and the onset of obesity.

“What are the clinical uses of PQQ?”

* Given the nutritional importance and tremendous span of physiological effects of PQQ, there are considerable benefits in conditions that revolve around low mitochondrial function including in aging, many brain and neurological disease (e.g., Alzheimer’s and Parkinson’s disease), and many other chronic degenerative disease. Current research has primarily focused on its ability to protect memory and cognition in both aging animals and humans.

* PQQ Decreases Inflammation
  - Healthy humans given 20mg of PQQ (for a 150 pound male) resulted in significant decreases in the levels of plasma C-reactive protein (by 45% after 3 weeks) and IL-6. A lower dosage, didn’t decrease inflammation.
  - Various urinary markers of oxidative stress also improved, which is consistent with enhanced mitochondria-related functions.
  - Lower inflammation = Higher orexin = Higher energy levels

* PQQ Improves Sleep, Mood, Fatigue, Mood
• One human study conducted with 20mg PQQ for 8 weeks in 17 persons with fatigue or sleep impairing disorder noted that PQQ was able to significantly improve sleep quality, with improvements in sleep duration and quality appearing at the first testing period after 4 weeks. It also led to a decrease in the time it took to fall asleep, but required 8 weeks to reach significance. (R)

• This study also noted improved appetite, obsession, and pain ratings that may have been secondary to improved sleep; contentedness with life trended toward significance over 8 weeks but did not reach. (R)

Are there any food sources of PQQ?

* PQQ is found in virtually all plant foods in small amounts. PQQ-rich foods include parsley, green peppers, kiwi fruit, papaya and tofu. These foods contain about 2-3 mcg per 100 grams. Green tea provides about the same amount per 4 oz serving.

* Pure raw cacao powder is the richest source by far!
  * Make hot chocolates using liberal amounts (1-2tbsp+) raw cacao powder
  * Bonus: Cacao also has Flavan-3-ol, and Epicatechin which are other compounds that can stimulate mitochondrial biogenesis

The Mitochondrial Biogenesis Protocol Factor #6: Hydroxytyrosol
Sources of Hydroxytyrosol

Food source: Olives and olive oil
Supplement: Olive leaf extract

The Mitochondrial Biogenesis Protocol Factor #7: Massage and Foam Rolling
There is also now evidence that massage and self-myofascial release can help promote mitochondrial biogenesis—particularly when paired with exercise that also helps stimulate mitochondrial biogenesis.

- “Massage stretches and pulls muscles and, as one might expect, the authors found that mechanosensory sensors focal adhesion kinase–1 and its downstream effectors extracellular signaling kinases 1 and 2 were activated, as revealed by their increased phosphorylation. Several hours after massage, another downstream target of this pathway, PGC-1α, shifted into the nucleus, where it in turn activated transcription of its own targets COX7B and ND1. This set of responses indicated that additional mitochondria were forming.”

The Mitochondrial Biogenesis Protocol
Factor #8: Cloves and Cinnamon

Both of these spices can improve mitochondrial function and a number of important compounds critical to metabolic health and energy levels.
Use them liberally!

Here is some research on the effects of these compounds in stimulating mitochondrial biogenesis:

* The prevalence of metabolic syndrome and type 2 diabetes is increasing worldwide. Herbs and spices have been used for the treatment of diabetes for centuries in folk medicine. Syzygium aromaticum L. (Clove) extracts (SE) have been shown to perform comparably to insulin by significantly reducing blood glucose levels in animal models; however, the mechanisms are not well understood. We investigated the effects of clove on metabolism in C2C12 myocytes and demonstrated that SE significantly increases glucose consumption. The phosphorylation of AMP-activated protein kinase (AMPK), as well as its substrate, acetyl-CoA carboxylase (ACC) was increased by SE treatment. SE also transcriptionally regulates genes involved in metabolism, including sirtuin 1 (SIRT1) and PPARγ coactivator 1α (PGC1α). Nicotinamide, an SIRT1 inhibitor, diminished SE's effects on glucose consumption. Furthermore, treatment with SE dose-dependently increases muscle glycolysis and mitochondrial spare respiratory capacity. Overall, our study suggests that SE has the potential to increase muscle glycolysis and mitochondria function by activating both AMPK and SIRT1 pathways.


* Type 2 diabetes is characterized by insulin resistance and chronic hyperglycemia, and is increasing in incidence and severity. This work explored the effects of trans-cinnamaldehyde (CA) on carbohydrate metabolism, mitochondrial content, and related metabolic gene and protein expression in cultured myotubes treated with various concentrations of CA for up to 24 h. CA treatment increased myotube myocyte enhancer factor 2 (MEF2) along with glucose transporter 4 (GLUT4) content. CA treatment also significantly increased expression of markers of improved oxidative metabolism including 5’ adenosine monophosphate-activated protein kinase (AMPK), peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1α), cytochrome c (CytC), as well as peroxisome proliferator-activated receptor α (PPARα) and PPARβ/δ. …The ability of CA to stimulate mitochondrial biogenesis and GLUT4 expression suggests CA may offer possible benefits for metabolic disease.
Most importantly, Rhodiola Rosea, Reishi, Shilajit, and Gotu Kola are Adaptogens that can be used to support mitochondrial biogenesis. Adaptogens increase your body’s resilience against stress and thereby prevent burnout and exhaustion. Part of how they do this is likely by stimulating mitochondrial biogenesis.
The evidence for adaptogens stimulating mitochondrial biogenesis:

### Rhodiola Rosea

* **Salidroside Stimulates Mitochondrial Biogenesis and Protects against H₂O₂-Induced Endothelial Dysfunction.** Shasha Xing, et al.

Salidroside (SAL) is an active component of *Rhodiola rosea* with documented antioxidative properties. The purpose of this study is to explore the mechanism of the protective effect of SAL on hydrogen peroxide- (H₂O₂-) induced endothelial dysfunction. Pretreatment of the human umbilical vein endothelial cells (HUVECs) with SAL significantly reduced the cytotoxicity brought by H₂O₂. Functional studies on the rat aortas found that SAL rescued the endothelium-dependent relaxation and reduced superoxide anion (O₂−) production induced by H₂O₂. Meanwhile, SAL pretreatment inhibited H₂O₂-induced nitric oxide (NO) production. The underlying mechanisms involve the inhibition of H₂O₂-induced activation of endothelial nitric oxide synthase (eNOS), adenosine monophosphate-activated protein kinase (AMPK), and Akt, as well as the redox sensitive transcription factor, NF-kappa B (NF-κB). SAL also increased mitochondrial mass and upregulated the mitochondrial biogenesis factors, peroxisome proliferator-activated receptor gamma coactivator-1alpha (PGC-1α), and mitochondrial transcription factor A (TFAM) in the endothelial cells.

### Reishi

* **Neuropharmacology.** 2012 Sep;63(4):719-32. doi: 10.1016/j.neuropharm.2012.05.019. Epub 2012 May 24. **Activating mitochondrial regulator PGC-1α expression by astrocytic NGF is a therapeutic strategy for Huntington's disease.**

Mitochondrial dysfunction plays an important role in Huntington's disease (HD). NGF gene delivery in AD patients showed an increase in brain energy metabolism and NGF has been shown neuroprotective effects against mitochondrial toxins. However, the role of NGF in regulating mitochondrial function is unclear. Here, we found that NGF-stimulated mitochondrial biogenesis in PC12 and primary neuron cells. Our results demonstrated that peroxisome proliferator-activated receptor gamma coactivator 1-α...
PGC-1α) is a downstream key target of the NGF signalling pathway. In a 3-nitropropionic acid (3-NP) cell model, NGF treatment rescued the defects in mitochondrial activity and mitochondrial membrane potential. Since NGF cannot freely cross blood-brain barrier, we found an astrocytic NGF inducer, Ganoderma lucidum (GaLu) extract. Its active constituents had potent effects on the induction of NGF in primary astrocytes. Among the identified ingredients, ganoderic acid C₂ was most effective. We further found that GaLu-conditioned media can enhance mitochondrial biogenesis in PC12 cells and preventing NGF signalling using NGF antibody or PGC-1α siRNA blocked these effects. Moreover, GaLu and ganoderic acid C₂-conditioned media treatment attenuated mitochondrial defects in 3-NP cell model. After 3-NP-induced behavioural impairment and striatal degeneration in mice, GaLu treatment therapeutically restored the behaviour score, sensorimotor ability and neuronal loss. We found that striatal NGF, PGC-1α expression level and succinate dehydrogenase activity were recovered in GaLu-fed mice. These results suggest that the NGF-signalling pathway connected to the mitochondrial regulator, PGC-1α, expression. This signalling triggered by astrocytic NGF with small molecule inducers may offer a therapeutic strategy for HD.

Ginseng


* Ginseng has been reported to ameliorate hyperglycemia in experimental and clinical studies; however, its mechanism of action remains unclear. In this study, we investigated the metabolic effects and putative molecular mechanisms of Korean red ginseng (KRG, Panax ginseng) in animal models for type 2 diabetes mellitus (T2DM) and peripheral insulin-responsive cell lines. Korean red ginseng was administered orally at a dose of 200 mg/(kg d) to Otsuka Long-Evans Tokushima fatty rats for 40 weeks. Initially, chronic administration of KRG reduced weight gain and visceral fat mass in the early period without altering food intake. The KRG-treated Otsuka Long-Evans Tokushima fatty rats showed improved insulin sensitivity and significantly preserved glucose tolerance compared with untreated control animals up to 50 weeks of age, implying that KRG attenuated the development of overt diabetes. KRG promoted fatty acid oxidation by the activation of adenosine monophosphate-activated protein kinase (AMPK) and phosphorylation of acetyl-coenzyme A carboxylase in skeletal muscle and cultured C2C12 muscle cells. Increased expression of peroxisome proliferator-activated receptor-gamma coactivator-1alpha, nuclear respiratory factor-1, cytochrome c, cytochrome c oxidase-4, and glucose transporter 4 by KRG treatment indicates that activated AMPK
also enhanced mitochondrial biogenesis and glucose utilization in skeletal muscle. Although these findings suggest that KRG is likely to have beneficial effects on the amelioration of insulin resistance and the prevention of T2DM through the activation of AMPK, further clinical studies are required to evaluate the use of KRG as a supplementary agent for T2DM.

Gotu Kola

- Asiatic acid, a pentacyclic triterpene in *Centella asiatica*, attenuates glutamate-induced cognitive deficits in mice and apoptosis in SH-SY5Y cells
- Aim:
- To investigate whether asiatic acid (AA), a pentacyclic triterpene in *Centella asiatica*, exerted neuroprotective effects *in vitro* and *in vivo*, and to determine the underlying mechanisms.
- Methods:
- Human neuroblastoma SH-SY5Y cells were used for *in vitro* study. Cell viability was determined with the MTT assay. Hoechst 33342 staining and flow cytometry were used to examine the apoptosis. The mitochondrial membrane potential (MMP) and reactive oxygen species (ROS) were measured using fluorescent dye. PGC-1α and Sirt1 levels were examined using Western blotting. Neonatal mice were given monosodium glutamate (2.5 mg/g) subcutaneously at the neck from postnatal day (PD) 7 to 13, and orally administered with AA on PD 14 daily for 30 d. The learning and memory of the mice were evaluated with the Morris water maze test. HE staining was used to analyze the pyramidal layer structure in the CA1 and CA3 regions.
- Results:
- Pretreatment of SH-SY5Y cells with AA (0.1–100 nmol/L) attenuated toxicity induced by 10 mmol/L glutamate in a concentration-dependent manner. AA 10 nmol/L significantly decreased apoptotic cell death and reduced reactive oxygen species (ROS), stabilized the mitochondrial membrane potential (MMP), and promoted the expression of PGC-1α and Sirt1. In the mice models, oral administration of AA (100 mg/kg) significantly attenuated cognitive deficits in the Morris water maze test, and restored lipid peroxidation and glutathione and the activity of SOD in the hippocampus and cortex to the control levels. AA (50 and 100 mg/kg) also attenuated neuronal damage of the pyramidal layer in the CA1 and CA3 regions.
- Conclusion:
- AA attenuates glutamate-induced cognitive deficits of mice and protects SH-SY5Y cells against glutamate-induced apoptosis *in vitro*.

Shilajit
Shilajit attenuates behavioral symptoms of chronic fatigue syndrome by modulating the hypothalamic-pituitary-adrenal axis and mitochondrial bioenergetics in rats.

ETHNOPHARMACOLOGICAL RELEVANCE: Shilajit has been used as a rejuvenator for ages in Indian ancient traditional medicine and has been validated for a number of pharmacological activities.

AIM OF THE STUDY: The effect of processed shilajit which was standardized to dibenzo-α-pyrones (DBPs; 0.43% w/w), DBP-chromoproteins (DCPs; 20.45% w/w) and fulvic acids (56.75% w/w) was evaluated in a rat model of chronic fatigue syndrome (CFS). The mitochondrial bioenergetics and the activity of hypothalamus-pituitary-adrenal (HPA) axis were evaluated for the plausible mechanism of action of shilajit.

RESULTS: Shilajit reversed the CFS-induced increase in immobility period and decrease in climbing behavior as well as attenuated anxiety in the EPM test. Shilajit reversed CFS-induced decrease in plasma corticosterone level and loss of adrenal gland weight indicating modulation of HPA axis. Shilajit prevented CFS-induced mitochondrial dysfunction by stabilizing the complex enzyme activities and the loss of MMP. Shilajit reversed CFS-induced mitochondrial oxidative stress in terms of NO concentration and, LPO, SOD and catalase activities.

CONCLUSION: The results indicate that shilajit mitigates the effects of CFS in this model possibly through the modulation of HPA axis and preservation of mitochondrial function and integrity. The reversal of CFS-induced behavioral symptoms and mitochondrial bioenergetics by shilajit indicates mitochondria as a potential target for treatment of CFS.

Other Supplements and Xenobiotics That Can Boost Mitochondrial Biogenesis

- Rosemary
- Tiliroside (found in raspberries and strawberries and rosehips)
- Aspirin
- Schisandra
- EGCG (tea)
- Quercitin (berries, citrus, sage, grapes)
- ALCAR
- Other adaptogens most likely (Ashwagandha, tulsi, cordyceps, etc.)
Cruciferous veggies are the ONLY place you can get sulforaphane. Sulforaphane is a potent inducer of mitochondrial biogenesis. Bonus: It also INHIBITS mitochondrial function in cancer cells and is one of the most potent anti-cancer foods in existence.

* Consume some kind of cruciferous vegetable EVERY DAY—ideally with breakfast.
* Bonus: They’re also a great source of sulfur, which helps to make cholesterol sulfate.
* Broccoli sprouts can be grown at home very cheaply and are the absolute best source of sulforaphane. I grow them myself in large amounts.
Combine intermittent fasting/ketosis with SIT for maximal mitochondrial biogenesis

* **What happens if your body senses that it cannot fuel his energetic demands with glucose?**

In the presence of borderline hypoglycemic glucose levels, your body would be ill advised to increase glucose uptake. So if this is not an option the only way to make up for the lack of energy are fatty acids. Unfortunately the amount of fatty acids your skeletal muscle can oxidize is strictly rate-limited by your mitochondrial capacity ...

* **So glycogen depletion COMBINED WITH SIT or HIIT in the depleted state will send a powerful signal to increase mitochondrial biogenesis.**

* **In elite cyclists undergoing a glycogen depletion and training protocol, they saw an 800% increase in PGC-1a after training!**

**WARNING:** Doing glycogen depleted HIIT or SIT REGULARLY without glycogen REPLETION is a BAD idea. This strategy should be used OCCASIONALLY—NOT DAILY.
Sample Intermittent Fasting/Ketosis Approaches

SAMPLE #1:
M: HCLF
T: HCLF
W: IF – 1 meal per day combined with exercise to deplete glycogen stores
Th: LCHF (very low carb). Morning SIT should be done before breakfast.
F: HCLF. Morning SIT should be done before breakfast.
S: HCLF
S: HCLF

SAMPLE #2:
M: HCLF
T: HCLF
W: IF – 1 meal per day combined with exercise to deplete glycogen stores
Th: LCHF (very low carb) combined with IF. Morning SIT should be done before breakfast.
F: LCHF. Morning SIT should be done before breakfast.
S: IF – 1 meal per day combined with exercise to deplete glycogen stores
S: LCHF combined with morning SIT.

SAMPLE #3:
Weeks 1-3: HCLF with intermittent fasts 1x/week
Week 4: LCHF all week

WARNING: GO SLOW WITH INTRODUCING THESE. THEY ARE STRESSORS!
Endurance or low intensity exercises: the oxidative capacity of muscle fibers is proportional to its mitochondrial density, since these cellular organelles can completely oxidize energy substrates (glucose, fatty acids and proteins) for ATP synthesis during muscle contraction [2, 4, 5, 9–11]. Endurance or low intensity exercise is a powerful stimulus to promote mitochondrial biogenesis in its own right, favoring aerobic metabolism and reducing muscle fatigue from metabolic origin, as the accumulation of Pi, ADP, H⁺ and lactate in the sarcoplasm [1, 2, 10, 11]. However, when LLLT and/or LEDT is added to the effects of endurance exercise on the mitochondria, the adaptive process can be increased. Giant and more functional mitochondria (higher enzyme activity) can provide high levels of cellular respiration and ATP synthesis [40, 41, 43] during these exercises, which gives increased oxygen consumption [31] and reduced muscle fatigue [33].

Preliminary results showed that the LLLT group had upregulated the genes PPARGC1-α (mitochondrial biogenesis), mTOR (protein synthesis and muscle hypertrophy) and VEGF (angiogenesis). Furthermore, only the LLLT group downregulated MuRF1 (protein degradation and muscle atrophy) and IL-1 β (inflammation).
Mitochondrial biogenesis, protein synthesis and protein breakdown signaling modulated by LLLT associated to exercise. Gray boxes were upregulated by LLLT and black boxes were downregulated by LLLT.

Translating this in practical terms...
- Improved strength and muscle size
- Increased FAT LOSS
- Improved exercise performance
- Lower inflammation
- Reduced fatigue
- Increased muscle mitochondria
- Increased ENERGY levels!

Practical Benefits of Red Light

Nearly DOUBLED muscle size and strength gains!
Cold shower/bath first, then light exposure (either red light or sauna or both).

* Cold exposure increases nitric oxide synthase (NOS) activity in both adipose and epithelial cells, and therefore also increases the amount of Nitric Oxide (NO) in the body if substrate is available.

* This increase in NO has a host of benefits. It is likely the mechanism for stimulation of mitochondrial biogenesis from cold, likely through the feedback-formation of Reactive Nitrogen Species to the cell nucleus, telling it that the mitochondria are bunk and need to be recycled.

* HOWEVER, chronically elevated nitric oxide is clearly bad. NO bound to Cytochrome C Oxidase prevents it from accepting electrons, and thus preventing electron flow through the mitochondrial complexes.

* When this happens, you’re left with 2 choices:
  * (1) Free Cyt C Oxidase from NO through use of Red Light Exposure/Sunlight (or Methylene Blue)
  * (2) Kill the mitochondria and make a new one

* Sick people are oftentimes stuck with option (2), since sun exposure is not regular (due to being indoors) and people aren’t familiar with red light
* Cold Exposure, which likely generates even more NO, is thus not a direct fix for someone who is sick or fatigued. **Restoring high energetic flows to the cells** is the answer, and that usually means restoring mitochondrial electron flow.

* The **COMBINATION** of cold and light (red light or sunlight) after cold exposure allows you to get the benefits of cold (mitochondrial biogenesis and metabolic benefits), while minimizing any stress to your system, and maximizing your energy levels.

* By using red light right after cold exposure, you can amplify the effects of BOTH the cold and the red light!

---

**The Mitochondrial Biogenesis Protocol Summary**

1. Morning cold exposure (cold shower, bath, ice vest, etc.) followed by sun exposure or brief red light exposure.

2. SIT or HIIT after fasting for at least 10 hours. (Done every other day). Can use sprints, weighted sled, bodyweight exercise, or stationary bike.
   - Occasionally after 24-72 hours on LC diet.
   - Pre-load with baking soda.
   - Use cacao, PQQ, curcumin, or sulforaphane before workouts. They can also be used in general with meals. (Cycle these compounds, rather than using them all, or the same few, all the time).
3. Infrared sauna/heat therapy either post-exercise or in the evening.

4. Have ample amounts of some kind of cruciferous vegetable for breakfast for sulforaphane. Broccoli sprouts are ideal.

5. Consume ample DHA in your diet. Whole food rather than fish oil pills.

6. Massage or Self-myofascial release (i.e. foam rolling) post-exercise.

7. Consume PQQ either in supplement form or in the form of ample raw cacao. (Combine with ubiquinol to amplify effect).

8. Consume olives, olive oil as a staple fat source, or use olive leaf extract.

9. Consume liberal amounts of the spices cinnamon and cloves. (Can cycle them).

10. Cycle these adaptogens: Rhodiola Rosea, Reishi, Shilajit, and Gotu Kola

11. Optional: Consider low dose methylene blue and occasional aspirin as xenobiotics to supplement biogenesis.

12. Eat a wide variety of herbs, other adaptogenic substances and the xenohormetins mentioned in the section on xenohormesis. Many of these likely promote mitochondrial biogenesis, even though there isn’t research yet.

13. Do occasional intermittent fasts (one or two days per week, or a few days each month), and cycle in some low carb days to fully deplete glycogen stores (particularly before morning fasted exercise).

14. Red/Near-infrared light therapy either post-exercise, or in the evening before bed (on the muscles that you trained that day, or on whole body). KEY!