

HOW TO FIND YOUR INNER MASTERPIECE?

READERS SUMMARY:

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3. HOW IS A LEAKY GUT, THE LIVER, OBESITY, CHOLESTEROL, BLOOD PRESSURE TIED TOGETHER?
4. HOW IS EXERCISE COUPLED TO THIS COMPLEX WEB?
5. HOW DOES PQQ FIT INTO ALL THIS?
6. HOW DOES LIGHT AND LEPTIN PLAY A ROLE HERE?

Today we are going to hit on a new levee that ties diet to exercise and throws in a bit of leptin. I am going to apologize in advance, because there is going to be some mind bending biochemistry with in it. I think after explaining it to you, it will begin to help you understand how some of my recent blog posts are all tied together and needed for optimization. It also will help show you why low volume HIIT exercise is optimal for health, and endurance exercise is not. The levee under discussion today is number 12. PPAR (peroxisome proliferator-activated receptor) gamma is regarded as the master regulator of the adipocyte and of lipid metabolism in the cell. It is under the direct control of leptin and its receptors and is heavily impacted by the lighting in your environment, as you will see as the blog progresses. Fat cells in humans sit right below our skin surface. In my opinion, *with time, it will be proven surface chemistry of the skin and gut is the most important driver for adipocyte biochemistry for humans.* This is also where omega six pathways enter into to the healthy or inflammatory cascade and determine our ultimate health.

PPAR's form heterodimers with retinoid X receptors (RXRs), and

these heterodimers regulate transcription of various genes involved with our fat cells. RXR receptors link to DHA tissue levels. These genes are up-regulated by both carbohydrates and lipids in our diet. PPAR-gamma activates the PON1 gene, increasing synthesis and release of paraoxanase 1 from the liver, reducing atherosclerosis. It functions as a plasma antioxidant; it prevents the oxidation of LDL found in the plasma. High levels of paraoxanase are also seen with high levels of glutathione in our plasma. They tend to walk hand in hand with one another. Low levels of plasma paraoxanase is tied to the development of atherosclerosis and cardiovascular disease. Both are linked to artificial light and low Vitamin K₂ and D₃ levels. Artificial light lowers the amount of natural UV and IR light people should get on their skin. This lowers glutathione in tissues as well. This is why medical lasers are useless in many skin pigmentation cases caused by altered sun exposures.

Low levels of glutathione are also found when these diseases develop. Low levels of paraoxanase are also tied to Vitamin K₂ depletion in arterial walls. PON1 gene transcription occurs in the hepatocyte. Its coded protein is synthesized in the liver and transported along with HDL in the plasma. Low levels of HDL are associated with vitamin K₂ depletion in arterial walls. A large study of more than 4,800 subjects followed for 7-10 years in the Netherlands demonstrated that people in the highest one-third of vitamin K₂ intake had a 57% reduction in risk of dying from vascular disease, compared to those with the lowest intake. Vitamin K₂ absorbs UV light too. Furthermore, their risk of having severe aortic calcification plummeted by 52%—a clear demonstration of the vitamin's protective effects (Geleijnse, 2004). Another study by the same group showed that higher vitamin K₂ intake was associated with a

20{a7b724a0454d92c70890dedf5ec22a026af4df067c7b55aa6009b4d34d5da3c6} decreased risk of coronary artery calcification (Beulens, 2009).

It appears when your plasma HDL is low, so is your level of paraoxonase. In my clinic, I have noticed that people with low HDL's almost always live a life indoors as well. So HDL is a type of a clinical marker for paraoxanase (and perhaps UV light exposure and Vitamin K₂ levels by extrapolation). This should explain to you why I use HDL as a measure of how leaky our gut is (and why your Vitamin K₂ is likely low too) to endotoxins that then are able to oxidize our LDL molecules. The absolute level of LDL is of little consequence to me in clinical evaluation. The level of oxidation of the plasma, however, is hugely important. So when one has a low HDL, high hs-CRP, and a high ferritin level you have the "trifecta of a highly inflammatory serum plasma" and one that causes all kinds of neolithic diseases. This lowers the exclusion zone in water part of blood plasma to carry energy all over the body.

It is also associated with lower hemoglobin and hematocrit levels. Hemoglobin is loaded with porphyrins that also absorb all frequencies of UV light. This linkage is tied to a higher HDL level in blood plasma and lower LDL in the plasma. Most people who eat a ketogenic diet and have a high LDL do so because they live in artificial light and not natural sunlight. This is why your H/H is a key redox measure. The link to HDL was explained in detail in my VAP and leaky gut posts here.

Paraoxonase serum concentration is influenced directly by these inflammatory changes and the levels of serum oxidized-LDL. Proliferator-activated receptor- γ (PPAR) has a co-activator called (PGC)-1 alpha. PGC-1 alpha is a member of a family of transcription co-activators that plays a central role in the regulation of all cellular energy metabolism. PGC-1 alpha protein may be also involved in controlling blood pressure, regulating cellular cholesterol homoeostasis, and

the development of obesity and T₂D. PGC-1 alpha also helps control mitochondrial number and density within a cell. Mitochondrial numbers are regulated by mitochondrial biogenesis to meet the energy demands of the cell and compensate for cell damage. This process is mediated by peroxisome proliferator-activated receptor γ coactivator 1 α (PGC1 α), which is relevant to mitochondrial dynamics since it is a transcriptional coactivator of the fusion mediator mitofusin-2. Mitofusin-2 is what connects the endoplasmic reticulum to mitochondria and control calcium homeostasis in the cell. Mitochondria- endoplasmic reticulum connectivity is regulated by mitofusin-2 and can create microdomains that facilitate fission.

PGC-1 alpha can interact with, and regulate the activities of, cAMP response element binding protein (CREB) and nuclear respiratory factors (NRF's) that allows us to make new mitochondria to produce more energy. CREB interacts with UV light as well in the brain to stimulate neuron growth. This is likely how exercise links to neocortical growth and repair in neuro-degeneration cases like Alzheimer's disease. PGC-1 alpha is strongly induced by cold exposure. This is why I use ice when I exercise and swim in freezing water; it also links the environmental stimulus to adaptive thermogenesis (think UPC-1 from the leptin series). If one can mix this cold exposure to AM sunlight you really are doing yourself a big help in reversing diseases. The link to cold exposure and UV sunlight on the skin and circulatory system also involves AMPk pathways. The reason for this is how the AMP-activated protein kinase pathway (AMPk) works to these environment stimuli. The AMPk pathway is best described as a fuel sensor for lipid and glucose metabolism. Activated AMPk inhibits PPAR- α and PPAR- γ . Cold exposure on our skin surfaces and face increase fat release from adipocytes. AMPk rises with cold. Ultraviolet radiation and reactive oxygen species from cytochrome 1 (ROS) impair the AMPk signaling axis. This is how AMPk works within a circadian cycle with UV light. Both

leptin (nutrition success) and adiponectin (nutrition deprivation) activate AMPk pathways. Cold and UV light are at opposite ends of the circadian cycles. Metformin mimics cold exposure but it does not work ideally in an artificial lit environment.

The ROS of cytochrome 1 is also linked to light and seasons. Recent studies show that cytochrome b_{c1} complex-linked ROS production is primarily promoted by a *partially oxidized* rather than by a *fully reduced* ubiquinone pool. The difference is felt in the amount of ELF-UV light released from cytochrome 1 and the singlet or triplet state of ROS released. The resulting mechanism of ROS production has offered a straightforward explanation of how the redox state of the ubiquinone pool could play a central role in mitochondrial redox signaling.

The mitochondrial respiratory chain is not only the main source of ATP in eukaryotic cells, but it is also responsible for the production of deleterious reactive oxygen species ROS. ROS have been implicated in apoptosis, cellular injury during ischemia and reperfusion, and the aging process (low NAD^+) as well as in the pathophysiology of several neurodegenerative diseases including Parkinson, Huntington, and Alzheimer diseases.

PGC-1 alpha stimulates mitochondrial biogenesis (new fat burning plants) and this promotes the remodeling of muscle tissue (muscle becomes LS and adapts to burning fat over sugar) to a fiber-type composition that is metabolically more oxidative (fat burning furnace-LS) and less glycolytic (sugar burner-LR) in nature. PGC-1 alpha and PPAR- gamma also effect the AMPk pathways we discussed in the Intermittent fasting blog and helps further explain how we gain muscle mass and change our fiber content over time using IFing. Moreover, PPAR gamma and these co-activators participates in the direct regulation of both carbohydrate and lipid metabolism in all cells. Rub your head now...I know it hurts. Just re read this a

few times and click on the links. You will begin to see how this orchestra of pathways makes beautiful music for our bodies when we are in a natural environment. Modern humans rarely are.

It is highly likely from the multitudes of peer reviewed articles I have read, that PGC-1 alpha is intimately involved in disorders such as obesity, diabetes, and exercise induced cardiomyopathy. We also should say at this point, that PQQ is intimately tied to the activation of the PGC-1 alpha pathway. Remember, I just introduced you PQQ in my last blog. This is why many researchers and clinicians have called PQQ the "exercise pill." I am not a fan of supplementation but food that contains PQQ. **All quinones are UV light absorbers.**

Exercise directly up regulates the PPAR-gamma and PGC-1 alpha pathways. So when one is fit and exercises, we are adapted to burning fats and not sugars. This is what we want when we are leptin sensitive and UV light is present. When we are leptin resistant we cannot do this well. In cold environments, adiponectin predominates and empties fat cells of their fatty acids.

It has also been shown recently that exercise has been shown to help those with severe neurodegenerative disease like Alzheimer's disease. The same is true with cold exposure.

This has shocked many researchers and people until they begin to understand this complex biochemistry. The 2011 publication "The neuroprotective action of pyrroloquinoline quinone against glutamate-induced apoptosis in hippocampal neurons is mediated through the activation of PI3K/Akt pathway" was a seminal paper in this area. It clearly gave us a biochemical link of how PQQ reversed excitotoxic damage at the memory center (hippocampus) of the brain. PQQ is induced by exercise so it stands to reason that memory and cognition can also be improved and expanded by using PQQ as well. We know PQQ is a UV light absorber and it is also a direct agonist of the PGC-1 alpha pathway, so it appears to simulate the exact response we

get from exercise. All cells are known to release ELF-UV light. I think using high dose PQQ is something that should be studied in all neurodegenerative diseases for this reason.

Going out in the AM sun before one does this might also be most wise. This quinone link also should make us realize that artificial light exposure alone may alter singlet and triplet ROS signaling to set the stage for neurodegeneration after diabetes is firmly entrenched.

Moreover, I use PQQ with an exercise to enhance the HIIT routines I recommend with after a successful leptin reset. This is why it is on my top ten paleo supplement list. When you understand this biochemistry, you will understand why I do not recommend cardio much at all. If you happen to be leptin resistant, doing any endurance exercise may cause you to “kill” your mitochondrial biogenesis signals by raising ROS signaling in your sugar burning mitochondria. If you continue to do this exercise while leptin resistant, you are inducing an apoptotic signal in your own mitochondria to force them into apoptosis. This in turn, makes you even more energy inefficient and you feel really bad. In other words, you are killing your own fat burning furnaces! This maneuver, in turn, depletes your stem cell supply. A stem cell supply is your eventual replacement cells. This is why we must make sure our exercise routines are hormetic and not apoptotic! People who over-train often talk about adrenal resistance issues that may develop. The real issue that plagues them is the loss of mitochondria and stem cells. They are killing their mitochondria off instead of stimulating new ones to form and this depletes their adrenal gland and kills their stem cells. I don't believe many people have made this connection. I know Art DeVany has often made this link and I applaud him for doing so.

A key clinical sign of this occurring is when you have excessive pain with exercise and it persists into the next few days. Other signs to pay attention for are having no weight

loss response to exercise at all. Many overweight people face this and few people can tell them why. This biochemistry is precisely why it happens. If you are killing off fat burning mitochondria, you can't lose weight! If you feel terrible after exercise, this is another sign that you may need to back off. Most fit people do not understand this feeling because they get the exact opposite feeling of euphoria or a general sense of well being from most exercise. This is due to the endogenous opioid release that exercise usually causes in people who are leptin sensitive. When this occurs we generally call exercise a hormetic adaptation. This signal is not present in those who are leptin resistant.

These adaptations may not be of consequence to you currently when you are younger, but the lifetime effects of this, will shorten your lifespan at the back end of your life when you are closer to death or your cells Hayflick number is up! When you reach your Hayflick number for a particular cell line the end result is cellular senescence because there are no more left cells to divide. Why? Because your telomeres have become critically shortened. This is why short telomere lengths are associated with aging and degeneration and cancer regardless of chronological age. I have actually tested my own telomere lengths before I started my optimized life program. I have retested it about 6 months ago to see the difference. I went from a biologic age of 55 years 5 years ago to 29 years old today! So we can change change our biology if we know how! Do not give up!

When telomere shortening occurs, you get end stage degenerative conditions. This is why we see so many joint replacements and spine surgery in this country. This is precisely why we see much evidence in the literature of endurance athletes getting sick and dying early from neolithic diseases we would not normally expect. It is because they have exhausted their stem cells supplies. There are no cells left to replace the dying ones. This is why long time marathoners

have signs of cardiac fibrosis in their hearts. It is also why we see many acute changes in runners heart after a marathon. We are placing huge metabolic stresses on our mitochondria in too short a time for proper exercise hormesis. A better way to approach exercise is to use it to hormetically stimulate your cells to make new mitochondria instead of killing them off. Low volume HIIT in sunlight is essentially hormetic and stimulates your cells to make new mitochondria. PQQ is a big time adjuvant to doing just this. This is why it was included in my top ten paleo supplement list. The early data is quite compelling that using supplemental PQQ can often times give the same metabolic stimulus to the PPAR gamma and PGC-1 alpha pathways as real HIIT exercise does! This is why many think PQQ is the exercise helping pill! I think exercising indoors in a gym and not out in nature is a bad idea because of how AM sunlight and PQQ act in unison to increase cell signaling.

Exercise-induced expression of PGC 1 alpha appears to enhance insulin sensitivity too. So does sun exposure because sunlight is a natural calcium channel blocker. This makes sense because many reports link exercise to improvements in insulin sensitivity as well. Thus, it is likely that maintenance of up-regulated levels of PGC-1 alpha and PPAR- gamma are protective against diabetes and neurodegenerative disorders. Right now, I see no reason not to consider it as an adjuvant of a healthy lifestyle and low volume HIIT. I use it myself and have several patients in my Optimized Life practice also using it.

The level of activation of PPAR-gamma affects the amount of leptin released per unit fat mass. So PPAR-gamma is clearly linked to diet and fat mass. It is also linked to AM sunlight.

PPAR-gamma deficiency leads to hyper secretion of leptin from adipocytes; humans become very slender and adipocytes very small because the brain thinks the body is fat. The leptin released from the fat cells is easily signaled to the hypothalamus and the brain is told not stimulate feeding. Hunger is kept at bay in this scenario. So naturally lean

folks tend not to have a lot of PPAR-gamma activation by leptin. They tend to be quite sensitive to leptin as a result. Obese people tend to have a lot of PPAR-gamma activation because their fat cells are loaded with leptin from excessive carbohydrates and lipids in the diet. I find it very interesting that PPAR-gamma activation is not really affected by protein intake.

This is also why I use high protein levels in my leptin reset protocols. PPAR-gamma is not really activated by protein and neither are the neuropeptides that control hunger or satiety in the hypothalamus. I think this is why protein levels are critical to reengineering a human and resetting their hypothalamic thermostat. It is also why high protein meals abolish hunger quickly, in artificial lit environments that we live in today. Fats can do this too, but protein loads tend to demolish hunger and keep us satiated for much longer times. When someone begins to use sunlight more I like them migrating to a higher fat version of the Leptin Rx. Fats contain carotenoids that help us absorb more energy from AM sunlight to quicken a reversal using our skin as a solar panel booster.

Any person who has tried my Leptin Rx will attest to the loss of hunger and to carbohydrate cravings. This is why it occurs! We are effectively resetting their PPAR activation when we use the Leptin Rx protocol. Natural sunlight and cool temperatures can really augment the results. I learned these things from the Amgen trials on synthetic leptin and from the work done by protein researchers over the last 50 years. PPAR-gamma is heavily influenced by diet and its macronutrients. PPAR-gamma agonists have been used in the treatment of dyslipidemia and hyperglycemia seen in humans as well. Interestingly enough, these trials by big pharma have been epic failures. It appears this system is so vital that tinkering with it can cause death. The best way to activate PPAR gamma is not the newer CETP drugs...it is from exercise, inducing PQQ via exercise, supplementing PQQ, and remaining leptin sensitive your entire

life. Peter from Hyperlipid has done some great blogs on the risks of CETP drugs for humans. I fear that once Big Pharma “cooks” the upcoming data on CETP drugs, they will use them to replace statins and people will die in large numbers. I have overheard some cardiologists on Sirius Doctor Radio talking about sub group populations who likely would do quite well on CETP drugs! This is appalling to me and shows me the really don’t understand rudimentary lipid biochemistry. **Medicine applies technical solutions to adaptive challenges today and this is why it is failing.**

It also shows that they do not critically read their own literature. Please read Peter’s blogs if your doctor ever pushes these drugs on you in the future. These drugs are some of the most deadly ever tested so far. Evolution and/or God don’t take too kindly to messing with PPAR-gamma. The moral here is always make exercise a part of your wellness platform but make sure it is the correct exercise Rx for our evolutionary biology and the current environment you inhabit!

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