How Does The Leptin Rx Work?

Readers Summary

1. How does The Leptin Rx Work?
2. Do we have alternative pathways that leptin used to use?
3. Why is leptin and light yoked?
4. Does timing matter more than macro-nutrients in a leptin reset?

Many people have contacted me about “why” the leptin Rx works and “how” does it work. Many people in the blogosphere have made some claims that much of what is in the leptin Rx is a rehash of the work found in some diet books. The leptin Rx works because of gravity and the electromagnetic force’s effect on sunlight. Most people do not realize light bends under both forces to a different degree. This is critical at night when light is the key signal being used in the CNS and PNS. Well, today’s post is being done to show you the science underneath my recommendations were formulated and made. None of the underlying science I will mention to you about neuroplasticity will be found in any diet book mentioned in any blog post that I know of. Most of you know I am a neurosurgeon, and as such, I was dramatically influenced by two world famous neurosurgeons named Wilder Penfield and David Kline. Dr. Penfield was the first neurosurgeon to use electrodes on the brain to map it prior to surgeries to avoid neurologic damage during tumor removal. Dr. Kline was and still is the pre eminent world expert in peripheral nerve surgery. I happened to train with Dr. Kline in New Orleans, and got turned on to his work, Dr. Penfield’s work and the work of Dr. Merzenich in the early 1990’s before leptin was even discovered. Dr. Michael Merzenich work on sectioning the median nerve in the hand and seeing how the brain remapped its sensory territory in the cortex via micro-electrodes was brought to my attention by Dr. Kline while I was a resident.

The Leptin Rx basis was made by a lot of reading by me in the past twenty years in multiple disciplines of science. The biggest contribution to the leptin Rx genesis came from the work of two Nobel Prize winning teams in 1981 (David Hubel and Torsten Wiesel) and in 2000. The Nobel prize in each case was awarded for work on neuroplasticity. I was further influenced in 2009, when the Nobel Prize was given to Elizabeth Blackburn on her work on telomere biology. It was further given even greater meaning by the work of Dr. Michael Merzenich on how dynamic the brain was in his brain mapping experiments after peripheral nerve injuries to the hand. I have also mentioned Dr Luis DeLecea (sleep researcher) and Dr. Myers (world leptin expert) works also many times in my blog about leptin. One could spend close to a decade reading what these scientists have given us in the literature. Their work was the foundational building blocks of the Leptin Rx. The works of these giants showed us that the brain is not hardwired for life, and is in a constant state of flux given the inputs it does receive and can interpret. When we continuously use a brain circuit, it is favored by its overuse and eventually is learned to be relied upon as the defacto center of this function. In this way, as a human ages, certain parts of the cerebral cortex become specialized for certain functions.

For example, if a child learns two languages fluently before the age of six, they will be able to learn not only the language but also the accent of the native tongue. This age of 6 will be really important when we get to speak about myelination and autism. If the child learns two languages later in childhood, they can learn both languages, but the newer language will not be learned with any accent because the dominate language filled that receptive field in the brain that wires for accent already. The same is true for adults who learn a new language in later life. This appears to play a role in how we hardwire our brains and its epigenetic signals for foods as well.

Back in the 1930's, the world believed that the brain had localized areas of eloquent functions that were fixed in position for life. Dr. Penfield's work revealed slowly that the belief of localization of function was not hardwired but dynamic. He never became famous for showing how we could adapt brain functions because this was not his goal as a neurosurgeon. It was to avoid eloquent areas to avoid neurologic damage to a patient during a surgery. The extreme adaptability of the neural pathways was shown by Dr. Merzenich work from the 1960- to current day. His research has allowed us to take deaf people with destroyed cochlea's and allow them to hear again by retraining lesser used auditory cortex to learn via an external micro-electrode array placed upon the brain. 25 years ago this sounded crazy. Today we now have life long deaf people learning to hear for the first time. When I read about his work, I realized that we might be able to do the same thing for obesity, if we could retrain the brain how to account for food without using the newly discovered leptin receptor.

Back in the late 1990's ,I did not have the knowledge of how to use alternative central and peripheral pathways in the nervous system to do this, but in the last 10 years I think I came up with a way to do this using circadian rhythms, light, timing, and the stretch receptors innervated by the vagus nerve in the gut that controls our entire gut plexus.

The vagus nerve is the afferent nerve of the brain gut axis as well. It is critically important in gut dysbiosis and obesity generation as well. Cyberonics is a company that began making vagal nerve stimulators when I was in my residency to treat seizures. I remember Dr. Kline asking me to look at this technology back in my residency and thinking how bizarre it was to place a peripheral nerve stimulator on a cranial nerve could treat seizures and cause weight loss as a side effect.

When Dr. Kline forced me to learn about this stimulator, it made me realize that we did not have to have an external

stimulator to reset or reteach a damage neural circuit, if the afferent arm of the neural circuit was functioning normally. In the case of seizures, the vagal nerve was totally normal in all cases. When I read more deeply about how the stimulator worked, I realized that this could also help people with hypothalamic obesity from surgery or from radiation damage as well. These were conditions were people were losing energy to the environment.

Simultaneous to this, leptin was found in 1994 and research began to pour out about this hormone and receptor in the obesity literature. I also found out that Cyberonics was planning on using their vagal nerve stimulator in obesity trials. Those of you who attended the AHS will remember that I specifically asked Dr. Robert Lustig a question about the vagal nerve stimulator and "his theory" on how leptin fit into the genesis of metabolic syndrome at UCLA this past August.

The Leptin Rx is my version of how to retrain the hypothalamus to account for the electrons and photons from food that are delivered to the mitochondria. I do this without using any electrical stimulator, because the vagus nerve and the patients light perception pathways are intact in most people who I employ this on.

Interestingly, the leptin Rx will not work well in people who have had previous gastric surgery (vagotomies for ulcer surgery) or gastric bypasses that destroy the normal neural connections of the gut innervated by the vagus nerve. People with lap bands, however, it seems not to bother much because the vagus nerve remains mostly intact in these cases. My belief is that those people who had a formal gastric bypass will need deep cold thermogenesis, an external vagal stimulator, and/or synthetic leptin to get to optimal once again. It will work in blind people because the light perception pathway is not 100{a7b724a0454d92c70890dedf5ec22a026af4df067c7b55aa6009b4d34d

5da3c6} visually mediated so circadian timing can be relearned to meal timing. Neither of these things are currently approved treatments, but both are being researched today. That is why I am so anti gastric bypass, in case you were wondering.

I learned empirically, the mitochondrial response of this neural retraining, could be followed and accounted for by the neuro-humeral response of the brain. This means that energy balance is codified in our hormone panel. That means the patients hormone status could be used as a detector to see how the system went awry and how it was responding to retraining over time. This was the most labor intensive time in synthesizing what I had learned about leptin. When I had I thought I had it all worked out in my own mind and in my notes, I became the guinea pig for this thought experiment. I used quarterly labs to test what I had learned by following my own diurnal rhythms. I wrote down a lot of thoughts as time went on. I went back and got extra training on neuro-humoral chemistry and endocrinology when I got lost. I read a lot of papers and books. The entirely of these works also showed that completely damaged parts of the neurologic system can be reconstructed by teaching the brain how to use lesser used or unharmed neural circuits to replace the damaged hardwired circuits the organism was adapted to and relied upon. This is when I began to synthesize the leptin Rx. I have never spoken of how I came up with this, because it is very complicated and drew from many areas of science, especially quantum physics. You asked me to blog about it, so here it is for you to read.

Now, on to the neuro-humoral significance of the Leptin Rx. Why did I choose to use protein and fat to retrain the brain? Because carbohydrates are coded for in the brainstem by a neuropeptide called neuropeptide Y (NPY). Altering NPY is easy via the diet and by timing. It appears our biology is adapted to realizing that excess carbs in our environment tend to show up only when the light cycles are long as well. Carb

intake is also tied to the controller (dopamine) of the releasing hormones of the pituitary and to the light cycle. So the choice was pretty easy considering how the brain accounts for carbs in these two ways. What is the significance of the prolactin control or surge you ask? The significance of the prolactin surge (especially in older people) is made clear if you eat carbs within 4 hours of going to sleep. Prolactin release is yoked to the dark/light conditions in most mammals. If you do not think prolactin is important for a natural sleep cycle watch this 4 minute TED video. It is also tied to NPY and to inflammatory cytokine signals in the brain. If you eat a large amount of carbs after dark it is spikes NPY, IL-6, TNF alpha, and raises sdLDL release at our liver. This has multiple effects on the system. The sdLDL blocks the ability of leptin to enter the hypothalamus at its evolutionary appointed time, 4 hours after you last eat or 4 hours after darkness falls. Il-6 and TNF alpha block the effects of leptin in the brain, liver and at muscles. The more carbs one eats, the higher NPY levels remain in the brain as well and this causes the carbohydrate cravings that most people report when they are leptin resistant.

These findings are all adaptable by the brain as light levels change as well. The evolutionary reason for this is that carbs were not available in most places as winter fell because of growing season changes. This would be more pronounced as one moves from the equator, and less pronounced closer to it. The circadian rhythm of vitamin D levels is also accounted for to judge light levels as well. Those closer to the equator would have much higher levels of Vitamin D and would be able to account for a higher carb level they face. Many current day leptin resistant folks find out their vitamin D levels are low when they finally test for it. We are best adapted to eat carbs in high light conditions and not in low light conditions, and this is why leptin is signaled at low light conditions in the brain. Its not magic its evolution at work. This is also the reason why I want my Leptin Rx patients

supplementing with D3 to optimal levels and limiting carbs when they are trying to lose weight. This input radically causes the hypothalamus to reorganize based upon the new sensory “non leptin” signals and not rely on the newly adapted leptin receptors in the damaged hypothalamus.

It is time to get back to Prolactin secretion, and how our circadian rhythm works side by side with the leptin receptors in the brain. Prolactin plays a huge role in setting the system up via our circadian rhythms. The first step in the process is leptin levels rise slowly for fours after our dinner meal, and the second phase of insulin released is completed and over. This generally occurs by midnight in a normal person. At midnight, leptin then should enter the hypothalamus and bind to its receptor. Once it binds to the leptin receptor two things occur. The first is a second messenger is sent to the thyroid gland to up-regulate the T3 production. Increasing T3 then stimulates the uncoupling protein 3 in muscles to burn fat liberated from our fat cells as we sleep. So we are designed to lose weight as we sleep. This is how the brain regulates calories intake and excess. Leptin raises our metabolic rate during the first two stages of sleep. If one has a sleep disorder, this will not work. This is another way leptin and sleep are coupled. The fats liberated from adipocytes are then burned both as energy producing ATP to drive repair programs in sleep, and they are burned to free heat at UCP1. If one is LR, you cannot do these things. This is why calories don’t really matter when one is leptin sensitive and matter a lot more when one is leptin resistant. Hormones completely control how we account for calories. If you remember reading the Leptin part three blog, fat burning requires leptin sensitivity and proper thyroid function at the muscle level for this to occur.

The second effect is via another second messenger. The leptin molecule and receptor bind, and sends a message to the anterior pituitary gland to release prolactin from 12-2 AM

while we are in the first few stages of sleep. The prolactin release is required for proper control of all 4 sleep stages and this effectively yokes sleep and metabolism at the hypothalamic level. The real benefit is the signal the hypothalamus uses to release growth hormone in a pulsatile fashion from from 2 AM to 5 AM during sleep stages 2-4. Growth hormone release allows the process of autophagy to be at maximal efficiency as we sleep. Recall that autophagy is the process of cellular renewal. In autophagy, we recycle proteins, we hardwire new behaviors and circuits we learned, and retool our brains from yesterdays oxidative damage. To do this well requires good sleep and optimal leptin function. People with sleep apnea have some of the lowest levels of growth hormone measured and this helps partially explain why most of them have body composition issues.

People who have sleep apnea, are generally obese. This is true in 80-90{a7b724a0454d92c70890dedf5ec22a026af4df067c7b55aa6009b4d34d5da3c6} of cases. After reading the science above, it should be clear to you why this happens now. The 10-20 {a7b724a0454d92c70890dedf5ec22a026af4df067c7b55aa6009b4d34d5da3c6} of sleep apnea patients who are not obese get it because of high inflammatory cytokines that occurs from other etiologies. Remember that obesity cause inflammation itself, and this is why one becomes leptin resistance most of the time. This is why I use HS -CRP as a major clinical marker of a person inflammatory status. The underlying cause of sleep apnea is usually due to high levels of IL-6 and TNF alpha. The clinical measures one can use to assess this is a history from the patient of insomnia with daytime sleepiness and a general lack of energy. They also will report significant muscle pain with exercise. Often they have low CO2 on chemistry testing as well. Often when the sleep disturbance is the most prominent physical finding or complaint I will check a DHEA level. DHEA levels correspond very well with high IL-6 levels

(98{a7b724a0454d92c70890dedf5ec22a026af4df067c7b55aa6009b4d34d5da3c6} correlation). Testing for IL-6 is very expensive and therefore is not commonly done. DHEA levels are very commonly done and much cheaper to do so that is why I lean on this test more than a formal cytokine panel.

Leptin resistant patients never get their pulsatile GH release at 12-2 AM, and as a result of this lack of growth hormone release, autophagic repair is poor in them. This means that they cannot recycle and repair their normal cellular damage from the daytime and this further degrades their ability to be energy efficient at their mitochondrial level. When this occurs chronically, poor autophagy can eventually cause neolithic diseases we commonly see in aging. These patients suffer more chronic diseases and age faster because their sleep is uncoupled from their metabolism. This is why sleep is restorative, and why evolution seems to have coupled sleep and energy metabolism. If you remember from the Gnoll's post I spoke about how magnesium is a co-factor in ATP production at the mitochondria. In people who have poor sleep or poor metabolisms (think Sleep Apnea or T2D) they also have other sleep disorders that are also tied to lack of magnesium due to the loss of intracellular water. One great example is the "restless leg syndrome." Restless leg syndrome is on a "disease continuum" with sleep apnea and just represents an earlier symptom of a brewing energy inefficiency problem. When a patient presents with these signs in their history, it is a tip off to the physician that there is a significant underlying metabolic disorder ongoing at the mitochondrial level.

It then follows, when the mitochondria are involved, leptin functioning is also not optimal because both are linked at all physiologic levels of energy production. The most important point is that this energy inefficiency is then directly translated physiologically to our telomeres. Our telomere lengths determine how long our cells live normally, become

senescent, or become diseased and are forced to go through cell suicide (apoptosis) or become oncogenic. This is why metabolic and diseases of aging are linked together. This is why T2D's have more AD, more risk of heart disease, atherosclerosis, stroke, and cancers as they age. The biologic message of inflammation at our mitochondrial means we age faster and die sooner of some neolithic disease. The diseases we get or die from are largely due to a combination of what our epigenetic receptors sense on a daily basis from all of our metabolic pathways that converge on the mitochondria. The key to healthy living is to pay great attention of what lifestyle changes are ideal for your mitochondria. Most people will find the evolutionary life style advocated by books like the Epi-paleo Rx, are generally are ideal to meet these goals. I believe your leptin status is the golden key to unlocking how it all is coupled.

When someone is not responsive to the receptor signaling of leptin in the hypothalamus, they become unable to burn their excess energy off as pure heat so they remain overweight. The reason is simple. They do not have any excess energy to burn as you will find out. They find it very difficult to lose the weight, even when they restrict calories to starvation levels. This will change when they become leptin sensitive once again. Some obese people appear to do tremendous damage to their leptin receptors and need synthetic leptin to continue to lose or maintain their weight loss. We realized this in the results of Amgen leptin trials data. Moreover, some of these people have found that removing adipocytes surgically also helps them maintain their weight better as well. Long term studies need to be done on these people to see if surgical removal of fat is really necessary for long term weight control, or can long term neuroplastic training be done while the hypothalamus undergoes neuroplastic repair over time. In my opinion, I think if we use timing of meals and couple it to the day light cycles as they adjust daily, we can facilitate that neuroplasticity. This is really the

science behind the Leptin Rx. I have read extensively about the work of neurosurgeon and neuroscientists **Penfield, Paul Bach y Rita, and Merzenich** and their experiments have proved that the brain is very plastic, and can be retaught how to work optimally again if we give it a “new way” to perceive a stimulus once damage to another part of the brain has occurred.

We can achieve leptin sensitivity after the hypothalamus is damaged, if we teach the brain how to use our older evolutionary non-leptin neural circuits. Yoking eating to light and day, and making timing to sleep and wakefulness and to the visceral sensations of distention of the gut via the vagus nerve are precisely how the Leptin Rx is designed to work. Taking full advantage of how certain macro-nutirents are tied to light cycle further helps reset hypothalamus in two to three months. The more inflammation that is present, the longer the reset may take. Instead of relying on optimal functioning of the hypothalamic leptin receptor, we can re-teach the hypothalamus to pay attention to the light levels, awakening time, time we sleep and face dark, when our gut is distended and filled with food and when it is not. We can also load the diet with protein and fat at certain times, to take full advantage of the existing working neural circuits in the brainstem and hypothalamus that accounts for carbohydrates, to our advantage in resetting how the brain can more fully perceive our energy status when the leptin receptor is not functioning. This science is precisely how a **cochlear implant** works in a neural deaf patient. It is not opinion, it is merely applying what we know works in one part of the brainstem, and using it another part using the natural circadian rhythms to allow the brain to re learn how to account for macronutrients correctly once again. It is also how neuroscientists have taught blind people to see using their tongue or tactile skin receptors to read (Paul Bach Y Rita work and braille as examples).

When the leptin receptor is not working well ,we can try to bypass it by using other neural pathways that leptin does also monitor but rarely uses any longer. This retraining allows the brain to relearn perception. **The experiments of Dr. Merzenich cutting the median nerve completely and seeing the brain re map its sensory territory opened my eyes to this possibility.**

When we eat meals, the sensation of physically eating is perceived by the vagus nerve. This nerve controls the entire GI tract down to the transverse mesocolon. It also monitors the hypothalamic parotid axis in the mouth that monitors carbohydrate contents in food in the mouth. This signal is an early detection system for the incretin gut hormone (ghrelin, PYY, CCK, agouti, glucagon) system that readies the gut for digestion. If one eats with a **certain regularity** (Leptin Rx) and makes sure it is tied to the sleep wake cycle, we can retrain the brain to account for food using older evolutionary pathways. The leptin receptor in the hypocretin neurons are newly adapted evolutionary speaking compared to the ones that rely on circadian signals. This has been demonstrated in Dr. LeCea's work on sleep and leptin in narcolepsy. Leptin function, however, is found widespread in the animal kingdom, and has been used for long periods of time in evolution. The difference for humans today is how our neural circuitry has evolved to incorporate the leptin receptor for use in our brain to accounts for energy status. It appears we humans still have the "old wiring diagrams" in place, but we don't use it these days because we evolved a "better" mechanism to account for food electrons from macronutrients. Moreover, it appears that today's standard American diet causes a mismatch in how the currently evolved leptin receptor works over time. These new receptors are mismatched to our current diet and can cause our leptin receptor to fail when the signaling is overwhelmed with inflammation.

We are adapted to use the new system because of the positive reinforcement of these tracts from 0-6 years old. This hard

wiring is not set in stone for a lifetime. But we rarely use it past this age. It becomes the preferred neural circuit because it is used chronically while the alternative pathways are not reenforced. It is analogous to how humans code for languages as I mentioned earlier. I think that should help many understand why I mention the age of six as being a huge factor in setting how we partition energy epigenetically. Once the leptin receptor is not able to pick the signal up correctly major intracellular magnesium changes begin in our cells of our pancreas, liver, and our muscles to compensate. Energy status changes protein structure just as it does in the core of a star. When this occurs over years, we eventually wind up seeing the metabolic syndrome and the development of a variety of diseases of aging. Once we re-engineer the hypothalamus, we can then feed it a non inflammatory ancestral diet and get on to the business of optimizing ourselves once again.

We should now get back to discussing the neuro-humeral response of the brain to leptin; **Timing is more critical than any other factor in the Leptin Rx**. The reason for this is we are using multiple circadian cycles to reset the hypothalamus when it is flying blind due to brain inflammation at the receptor site. When we eat our last meal of the day as light levels begin to fall, leptin needs a minimum of four hours to be able to act on its receptor to signal the brain to our current energy status. The reason for this appears to be the biphasic insulin response from our last eaten meal, namely dinner. Any spike of insulin blocks the ability of leptin to enter the hypothalamus to give the brain this signal. This is why I tell you not to snack post dinner at all. Once leptin binds to the receptor, it then blocks dopamine's control over the releasing factors in the pituitary. Pituitary prolactin secretion is regulated by dopamine to act on the dopamine-2 receptors Prolactin cells, causing inhibition of prolactin secretion. Once leptin binds, it blocks this inhibition and allows for prolactin to be released and to act to release

growth hormone. Prolactin is the trigger for growth hormone release in humans. 90{a7b724a0454d92c70890dedf5ec22a026af4df067c7b55aa6009b4d34d5da3c6} of a humans growth hormone is released during sleep, if prolactin is allowed to act. Women in menopause have major prolactin releasing problems, and this is why they have sleep complaints, and why they get more belly fat at this point in their life. GH decreases abdominal fat while simultaneously increasing your lean muscle mass. It does this by increasing protein synthesis for renewal during autophagy. This is the hormone responsible for body composition in large part with the sex steroid hormones.

If you have a bad body composition, you can bet that you have a leptin problem and a quantum sleep issue. This is why the mirror test works in most cases without testing. GH levels fall off a cliff for most women after age 40 (peri-menopause) and for men after age fifty. Any increase in inflammation for any reason generally makes menopause or andropause happen more quickly. When this happens, there is a corresponding drop in the quality of sleep as well the amount of autophagic repair. This is why I always ask a patient about sleep. It is a cardinal sign of a serious metabolic problem at the brain level. This reduction in autophagic repair is why people age and why disease increases as we age too. These biologic facts are widely reported in the literature. This is why older people tend to sleep less than younger people. It is also why babies sleep so long.

Infants are growing, myelinating, and learning, and require more autographic repair as they trim all their newly laid down hard wired tracts. Babies release a ton of GH as they sleep to grow and evolve to get everything working optimally in their brain and in their immune system.

Older circadian rhythms were most important before mammals had the leptin receptor in their brain working as it does now. They used it to adapt as the light/sun changes with seasons.

Light is part of the electromagnetic spectrum. Humans still have this ability, but it goes unused because it is not selected for as we live and grow in today's modern environment. We evolved past these more primitive systems, but they still work within us, if we exercise those circuits. With changing light levels, our pituitary is still capable of controlling energy metabolism if we teach it how to do so. Pituitary secretion has been shown to adapt to light and to new circadian cycles in humans as well. When I learned about these methods and married them to what I new about the vagus nerve control of the gut, I came up with some "exercises" to re train my own hypothalamus.

These biological facts have allowed me to reset many people's hypothalamus over the last 6 years to use alternative pathways to account for the electrons we use to make ATP from food. It helps to restore proper brain signaling when our newer, more adapted systems becomes resistant to normal dietary signaling. As light levels change your diet should too, in my view. In our world, today it does not. Interestingly, exercise is more efficient in cold temps and low light conditions, as well because you activate both UCP1 and 3 if you are LS and thyroid is working well. That is also why I like training in low light conditions prior to bed. It also helps abruptly end the insulin spike of eating and readies the brain to accept leptin into its normal receptor binding area. It also allows for fat burning at the muscle levels to occur far in advance of what will occur when leptin acts on the brain later to do the same thing. This is why so many people report dramatic weight loss from night to day. I still tell people not to scale watch, because it increases your cortisol which slows weight loss down. It appears that exercising also has a circadian leptin Rx. That will be the feature of a later blog in the Quilt.

I hope this explains how the leptin Rx works for humans.

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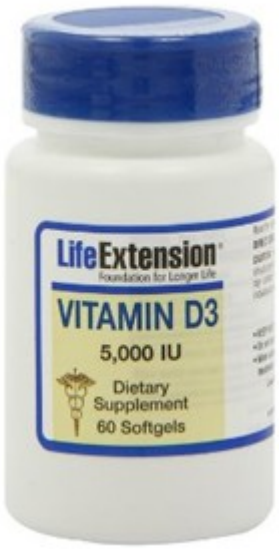

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- View The Epi-Paleo Store

Additional Resources

- My Leptin Prescription /my-leptin-prescription/
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Cites

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