So You Completed The Leptin Rx? What’s Next?

Readers Summary

1. How does The Leptin Rx evolve into the Permanent Epi-paleo Rx Template?
2. Was finding out about ultradian rhythms key to design The Leptin Rx?
3. How important are ultradian rhythms to a developing fetus?
4. How does a fetus handle circadian rhythms when it’s leptin receptor is non functional?
5. What is the postscript for The Leptin Rx?
6. How does one get to optimal living using circadian cycles?

Once you have added the Leptin Rx to your ancestral template and you have successfully experienced all the “small wins” that I mentioned in the Leptin FAQ’s blog, what should you do next? If you recall reading the blog on how the leptin Rx works, it basically is a plan to make your gastrointestinal tract perform visceral exercises that it is not accustomed to performing, in order to cause neuroplastic changes in your hypothalamus’ arcuate nucleus. It uses the vagus nerve as the “stimulator” to send these new messages to the brain. After a period of time, the inflammation will slowly dissipate at the median eminence, and these afferent signals will force expression of certain genes that have been repressed since we were in utero. These genes and pathways are hardwired into our DNA at conception, and used until the child is 12-24 months old. After this time, they are not expressed any longer, because transgenerational epigenetics favors instead the use of the leptin receptor from an evolutionary perspective. This occurs because the leptin receptor in the
arcuate nucleus is far more sensitive and accurate in accounting for electrons from food than was using older circadian and ultradian cycles that we used in uteri during morphogenesis. The human brain learns “what neural circuits” to use by repetitive firing. We have a saying in brain surgery, nerves that fire together wire together. This is the basis of the theory of Hebbian learning.

These exercises I told you about in the Leptin Rx signal hypothalamic neurons to adapt to these visceral responses to food in a new way, to sensitize the leptin receptor in order to account for electrons from food in precisely how it was designed to do by evolution. In essence, we are altering the genetic expression of the genes in our arcuate nucleus. I describe it to my patients as “performing brain surgery on them without using a blade.” The visceral responses to the Leptin Rx are transcribed by the vagus nerve, and this information is sent to the brain. This message is dramatically different than the one the patient is used to giving the leptin receptor, and the new message induces changes to the neuropeptides in the brainstem. After some time, (6-8 weeks for most) changes will be induced. These can be followed by the clinician or the patient. Those clinical signs are outlined in the Leptin FAQ blog post. In doing this, we force the neurons to see neurochemical signals that radically confuse the leptin receptor and the brain. The brain’s response to a signal it does not understand is to revert to an older known pathway or to learn a new way to tackle on old problem. I would suggest you watch How your brain re-learns from 2007 by Dr. VS Ramachandran in a TED talk. He exquisitely explains how this type of learning is stimulated in the brain for phantom limb pain and its treatment. One need not use expensive technology to induce gene expression. It is possible to do without an NIH grant too. It requires some synthesis of thought and experience. When you understand the essence of how the brain works, you just need to design a program and force it upon the
brain to decipher what to do. **That is the essence of the Leptin Rx reset.**

You can force the hypothalamus to once again rely on circadian and ultradian rhythms during the Leptin Rx reset process. Once some clinical markers begin to be reported by the patient, we then have the clinical evidence that the leptin receptor has regained its ability to be yoked again to meal timing and to light cycles. We essentially induced this gene expression by thinking about how to force the change. The overriding factor in the brains organization, is that when it is faced with confounding sensory variables, it becomes to rely on things it knows it can count on. The circadian cycles are among the oldest biologic rhythms found in all life forms on earth. Before we had our current leptin receptor, we only had the circadian cycle to use for macronutrient partitioning. Today, we are going to talk about how one might consider eating and living after the reset is complete. This method is where a paleo or primal person, who is already fit and healthy, may consider starting at as well. It optimizes our biologic clocks and rhythms to lead to optimal performance and optimal body composition when it is performed consistently overtime. These biologic response are already built into our DNA. It is our job to rediscover these ancient truths.

I have said in many blog posts that leptin controls oocyte selection in the mother and directs all placental growth all fetal development. This plays a major role in epigenetics and you will see that when we get to the Energy and Epigenetics series down the road.

Some found this hard to believe initially, but a quick search of the literature will show you this is biologic fact. I will now show you how this process begins during a period when the leptin receptor is not yet functioning in the fetus. Circadian rhythms are paramount to how a baby grows in utero. What I have not told you is how circadian cycle information are transmitted to the fetus by their mother’s hormone system
when they are in the womb. This neuro-humoral transfer of information is how the child “yokes” external light (it can’t see) to metabolic cycles of their mothers feeding before the leptin receptor is even operational in the fetus. This point is critical to understanding how this neural circuit can be rediscovered when the leptin receptor is non functional. It is hardwired into every human alive at some point in their maturation. With time, humans evolved a better accounting system for electrons from food in adult life, but these systems remain silent and latent because these neurons no longer fire together once the leptin receptor becomes function from 12-24 months of age. The Leptin Rx is designed to make those neurons fire once again in unison to restart the older ultradian intra-uterine circadian system. So you must be wondering how does the baby do this?

Circadian variations develop during intrauterine life in many variables that are induced and synchronized from the mother through humoral messengers (hormones) passing through the placenta. Maternal leptin status is the critical hormone that completely controls placental development and it modulates the changes in human placental hemodynamics. This is great news if the mother is in optimal health, and LS, but it can be bad news if she is LR. This information is directly sent to the mitochondria and this help initially set how they will handle electrons and protons from food and water. These signals are first sent to the heart. The heart is the first organ formed and it begins to beat early in embryology, therefore it needs its mitochondria to be earlier adaptors of the information contained in these particles.

This will send a poor humoral response to the child and cause major problems for the developing leptin receptor in the child’s brain regarding the current circadian cycles the mother find herself in. Fetal development is tied to the mother’s circadian cycle for optimal growth. In fact, the fetus is
dependent upon it to live. When I finally realized this, I knew that a adult human could bypass a defective leptin receptor later in life. How to do it, however, took me 5 years of thinking and reading. Circadian and ultradian patterns in fetal movement can be recognized beginning between 24 and 30 weeks of gestation with increasingly prominent peaks during the night hours, especially during REM sleep of the mother. Ultradian rhythms are recurrent periods or cycles repeated throughout a 24-hour circadian day. One ultradian rhythm has been shown to moderate the ‘hemispheric dominance’ within the brain. Although the exact function and interplay of the 2 hemispheres is as yet unknown, we do know that the left hemisphere is more specialized for linear, logical thought, and communication, and the right is more active when we are relaxed, dreaming, and in hypnotic state. But even this can be overridden if a child has an intra uterine stroke that wipes out an entire hemisphere. That child can be born with totally normal neurologic function and yet have one half a brain. The reason it occurs is because the brain relearns that all neural circuits will have to be accounted for on a smaller cortical footprint. This indices epigenetic programs to put all specialized brain function into one hemisphere prior to birth. The brain is extremely neuroplastic and adaptive. This was not well known until the last 50 years of neuroscience developed.

Based upon very new sleep research, it appears that maternal ultradian rhythms seem to set the hypocretin neurons in the arcuate nucleus for both sleep and for metabolism before the leptin receptor is functional. Some of the other common human ultradian rhythms of the body are hormonal release, heart rate, thermoregulation, urination, bowel activity, nostril dilation and appetite. Appetite is critical to growth and development. And we can use this ultradian cycle to reset the leptin receptor. Appetite cycles involve the rhythmic release of Neuropeptide Y (NPY) and Corticotropin-releasing
hormone (CRH). These two peptides are stimulating and inhibiting appetite peptides of the fetal ultradian rhythms. This is the key neural circuit that fired together and wired together in all humans before their leptin receptor was fully developed and functional.

The mother’s sleep cycle is vital to a developing fetus ultradian cycles and helps to preset the leptin receptor in the arcuate nucleus. When the mother’s sleep cycle is off, none of these signals are transported to the fetus optimally. The fetus then reverts to sampling the maternal hormonal levels to determine the light and night cycles. High cortisol levels, with low DHEA levels, high IL-6 levels are all sent to the child’s developing heart first and then to the developing brain (via the circumventricular organs) from the mother’s circulation via the placenta and affects how its own leptin receptor will work later in life. It also appears the fetus can sample serotonin and melatonin levels from the mother as well to distinguish light from dark as well. This original wiring remains intact in every human, but is not expressed unless we force that issue by altering our environmental circadian cycles. Modern man is expert at that.

A rhythm in the “breathing” movements of the fetus is present after 30 weeks of gestation with a peak between 2 AM and 7 AM during maternal sleep, and with a superimposed ultradian rhythm component with a cycle length of 100-500 minutes. The human fetal heart rate shows a trough between 2 AM and 6 AM similar to the maternal rhythm in heart rate. At times, a drop in heart rate is deep enough to raise clinical concern. A circadian rhythm in fetal bladder volume with a trough between midnight and 6 AM indicates circadian rhythmicity in fetal cardiovascular, renal and/or adrenal function (Haus and Smolensky 2004). These rhythms in the mother are teaching the fetal brain how to account for the day night cycle before the child ever sees the sun once. This is precisely how the arcuate nucleus in the hypothalamus learns the circadian cycle
before the leptin receptor even develops in the fetus. It is clear that we have these cycles hard wired into us while we are in the uterus and they are vital to life in utero. These neural circuits become useless to us once we are born because we can then sense the circadian cycles for ourselves and from the feeding times from our mothers behavior. When humans are born, they begin to be able to use the hypothalamic leptin receptor to account for circadian cycles and electrons from food more efficiently. This occurs when we first get leptin from our mothers colostrum during our first feeding cycle. This is initially how the leptin receptor is set in a child. The leptin receptor then is selected for, because it begins to fire with other neurons it is wired to based upon feedings and sleep cycles. This remain true in human life unless the leptin receptor is overwhelmed by inflammation and no longer works from any etiology. This is what we see in obesity and leptin resistance.

The endogenous circadian and maternally induced rhythms of the fetus give rise to circadian differences in the susceptibility to toxic agents and to therapeutic interventions. In animal experiments, the circadian periodicity encountered in the fetus is linked to circadian variations in the susceptibility to teratogenic agents. The type and severity of embryopathies due to fetal toxicity in experimental models is determined by the interaction of both the circadian time and the developmental stage of exposure (Sauerbier 1992). This is critical work, that shows how the developing human fetus responds to circadian rhythms. It has been shown experimentally for cortisol, dexamethasone, hydroxyurea, cyclophosphamide, 5-fluorouracil, cytosine arabinoside and ethanol. These experiments also showed that we can retrain the leptin receptor by using circadian cycles when many different toxicities maybe present. Inflammation being the one we are most interested in for a **Leptin Rx reset**. These experiments helped me realize that humans could lose weight if we could somehow retrain the adult brain how to “remember”
what it learned in utero long ago. At birth, high-frequency ultradian rhythms predominate over normal adult circadian rhythms. The leptin receptor is still not functioning well at this time. The child will not reach adult pattern of circadian rhythmicity before 12-24 months of age. At this point then leptin receptor takes over. These processes are still maintained by the human adult but rarely used. This information was critical in coming up with the Leptin Rx reset. To become an Optimal human, you must live and eat in a biologically congruent fashion to the circadian cycles. Here is how I have done it since my own reset over six years ago.

Once reset on The Leptin Rx, what should I consider doing?

1. Plan on eating a straight forward seasonal template of food made naturally by the photosynthetic webs and not man made machines. If you want to improve performance or longevity I would tell you adding more seafood to that template is a smart move. If you are active, you can add carbohydrates from 10\(\text{a7b724a0454d92c70890dedf5ec22a026af4df067c7b55aa6009b4d34d5da3c6}\) to 20-30\(\text{a7b724a0454d92c70890dedf5ec22a026af4df067c7b55aa6009b4d34d5da3c6}\) of your diet within the proper long light seasons. The diet is still a high fat moderate protein paleo template outlined in my book, _The Epi-Paleo Rx_, The diet should be seasonal tied to you latitude altitude and to the population density and technology use in your local zip code.

2. Upon rising within one hour eat 50\(\text{a7b724a0454d92c70890dedf5ec22a026af4df067c7b55aa6009b4d34d5da3c6}\) of your daily carbs with 25 grams of protein and 20-30 grams of fats.

3. Never miss breakfast because eating it stimulates the circadian rhythms in the brain retina and gut for
gastric acid secretion in adults. Breakfast should be the largest meal of the day while sunlight is out and you should make dinner a tapas like meal before the sun sets. The key is eating when the sun is out and fasting when the sun is absent to retrain your mitochondria and shrink the respiratory proteins in the inner mitochondrial membrane to allow for autophagy which will replace poorly functioning engine in your cells. This will become critical later in the day for body composition optimization. Many will naturally begin to only eat one meal because your redox potential rises. This becomes most easy with a chronic connection to the solar cycles and grounding in your local environment.

Avoid working out prior to breakfast. It is a circadian cycle breaker because it raises cortisol at a time it is already high. Working out is optimized 3-5 PM based upon the circadian cycles for protein synthesis in diurnal animals.

For Optimal results you must get most of your daily activity between 9AM and 4PM when light cycles are strong year round. This is another reason I strongly advocate high vitamin D levels year round. The higher your redox potential the less you will rely on Vitamin D3. We evolved around the equator and equatorial sun has been shown to keep human vitamin D levels 50-150 ng/mL. Avoid sitting at all costs and consider walking to get lunch or a short run during your mid day break. The real goal here is to increase Non-Exercise Activity Thermogenesis (NEAT) during strong light hours. This will help shrink the distances between your respiratory proteins to make electron/proton tunneling more efficient. This has major effects when it is done consistently over time for reversal of disease by improving mitochondrial function and improving CO2 production in mitochondria and decreasing H2O production by mitochondria from oxidative phosphorylation. For example, I run upstairs and avoid
elevators and I park far away from my destinations to increase my NEAT daily. I also carry all my groceries out to the car and never use a shopping cart to make it easier. I look at every aspect of my actions to make sure I am maximizing it for NEAT. NEAT is a cheap form of exercise for us all.

6. For lunch, if you need to eat it, (some won’t eventually) you should consider eating 25{a7b724a0454d92c70890dedf5ec22a026af4df067c7b55aa6009b4d34d5da3c6} of remaining daily carbs. I use this meal as a snack now. Rarely is it a big meal for me any longer and if I am IFing this is the one meal I cut like a bad habit.

7. **Critical point:** The best time to work out biologically occurs when it is least likely to be convenient for you because of our neolithic lives won’t allow it. I retooled my entire schedule as a surgeon to make this work optimally for me to lose weight and change my body. It is that important biologically to get to optimal. 1-5 PM is the ideal workout window. For best results, try to do the exercise in bright sunlight.

8. Dinner should be eaten within 45 minutes to 1 hour of this late afternoon work out while the sun is out. This will vary due to your latitude greatly. During dinner you want to make sure to include a lot of protein (25-75 grams), the remainder of your carb allotment and the balance in fats. The type of fats at dinner are also critical. Try to concentrate on 10-18 carbon fats because these are best at stimulating Cholecystokinin (CCK) that destroys the night time appetite. I use **coconut oil**, ghee, pastured butter, and bacon lard to get this effect in different seasons. I use the fat to cover the carbs and the protein most times in sauces.

9. Try to complete dinner by 7 PM. **This is critical in autumn and winter time to get to optimal results.** 8PM is the outer limit for dinner in spring and summer. I actually alter my meal times very precisely as the light
cycle changes during the year. Many people might find this too regimented. I agree with this but I do it because I had a huge clinical move to make from 44% body fat. Doing this strictly my first year I lost 133 pounds in 11 months. So the details make a huge difference in good vs. Optimal.

10. Sleep by 11PM in spring and summer months. I stay up longer June 10th to July 10th due to summer solstice on June 21. During this time of the year I tend to have higher body fat with longer light cycles. In autumn and winter I am in bed by 10 PM. I am in bed earlier when the clocks are set back on hour in fall and heading toward the winter solstice on Dec 21st. I have found I am leanest during this time of the year. The goal of sleep in any day of the year is an optimal 7.5-8 hours of sleep a night no matter the season. You will know when you are doing well because you will no longer need an alarm clock and your sleep wake cycle will be automatic. I found after one year of using this protocol I no longer needed an alarm clock to wake up for surgery.

What changes should I consider after The Leptin Rx Reset?

1. If you are active, drop all of the top ten paleo supplements I mentioned in that blog. They were only meant for the transition from a sugar burning metabolism to a fat burning furnace as the permanent paleo template takes flight. If you are not active, you could strongly consider remaining on PQQ and vitamin D3. I would not do it that myself. Try to optimize your vitamin D levels to 60-100 ng/mL naturally using sunlight and no supplements.

2. If you decide to Intermittent Fasting do not skip
breakfast ever. It is the key to circadian congruity and optimal body composition. You will see below how this determines body comp and not the amount of exercise one does.

Key Points to keep in mind

1. High protein consumption occurs at night now, not at breakfast as it did in the Leptin Rx reset. The reason is because late afternoon is when the human body is normally programmed to undergo up regulation of protein synthesis biochemically. This is how our biology is designed by Lady Evolution/deity. If you remember back earlier in the post, I told you the key point for breakfast was to use carbs and a small protein load to prime the gastric acid circadian cycle for maximal effect later in the day. This is precisely the reason why. Gastric pH should be highest when we are eating our biggest protein load of the day while simultaneously upregulating protein synthesis maximally in our body. **This maneuver actually influences our body composition more than any exercise could if it was added to the equation at all.** Doing this on time is akin to an orchestra playing in unison. It is a huge point to try to follow daily.

2. Carb macro’s should parallel activity and light cycles. Too often I hear many in the “primal world” talk about carbs and activity. They always forget about the light cycle. If you are real active and work out more than 4 days a week in sunlight, you can handle 30% of your calories from carbs. If not consider 10-20% range. **The closer I get to June 21st the higher my carb amounts tend to go, and the closer I am**
to Dec 21st I am at a zero carb diet. I give this to you as a baseline to work from. It is not meant for you to copy exactly as I do. This is precisely how I ate to lose 135 pounds the first 11 months I came up with this program.

3. Exercise/activity is optimal for us between 9AM and 4PM biologically. I understand this might be hard to fit into your schedule but the payoff is massive. Let me explain why now. Remember that cortisol is highest in the AM to allow us to wake up. If you exercise before breakfast you are risking elevating your cortisol even higher. This will cause a pregnenolone steal syndrome and ruin your hormonal response that controls your lean muscle mass and fat ratios and eventually your body composition. If you continue to do this over time, it will slow your protein synthesis that occurs later in the afternoon and evening, that increases your body comp. Moreover, it will also ruin your sleep cycle (checked by having low DHEA levels) and you risk being in an overtrained situation. I think this is the biggest error I see in the paleo community because they are trying to fit their “neolithic life” into their day best from a time stand point. My advice is don’t even try it.

4. You get the best (optimal) protein synthesis benefit if exercise occurs 1-4PM. Make sure your lifting days occur on the days of the week you can accomplish this. Save sprinting days for days that this wont work for your schedule. Use common sense about building this into your own life. Optimize your schedule to benefit your body composition. If you fight this trend you can still get ripped up but you will exhaust your stem cells in doing so and you will lose years on the back end of your life. Timing is that important.

5. To show you how important meal timing to the light cycles are to us humans, consider these facts regarding
exercise and meal timing. If you are able to yoke your workout to your evening protein dinner meal (within 30-45 minutes) you actually “triple the amount of protein synthesis” that occurs compared to those who do not. This is how a hunter gatherer attained their optimal body comp without having to do huge amounts of exercises. Moreover, if this is also yoked to the light cycle in winter when the temperatures are below 40 degrees, you can increase protein synthesis to \(400\) while inducing uncoupling proteins to burn fat at a tripled rate to baseline. This allows you to increase fat burning to shred body fat further faster while you are increasing lean muscle mass. NASA uses this technology for the astronauts that space walk. They found this data out ironically from the Sherpa’s who help foreigners scale the last 2000 feet of Mount Everest summit. This is also precisely why I am leanest around December 21\(^{st}\). At this time, the light cycle its lowest and the temperature is usually low so exercising in this window is the easiest way I know to shred body fat and gain muscle mass quickly. I went from 44\%BF to 19\%BF in one year doing this. I would also like to point out something here that you might not have ever thought about in order to show you how in-congruent humans really are with this timing issue. When do we see ads in the newspapers for weight loss aids? The answer is around New Years Day in January. Why? Because humans tend to get fat in winter so sports stores place ads when they are most likely to gain revenue. They are in tune to our behavior. Now change your mind set and think about wild animals you have seen on the Discovery channel. When are they leanest during
the year? The answer is in winter, when food is scarce and they have to really forage for food in subzero temperatures. Most humans live a life that is biologically in-congruent to how our biology is designed to live. Once I thought about the leptin receptor biology and how I could reset it using circadian rhythms I went back to my veterinarian friends and to the exercise literature (Frank Booth) to figure how to live the rest of my life optimally and regain my optimal body form and metabolism. This is precisely how I live daily today. Feel free to call my operating room team and ask them when was the last time they ever saw me operating between 2-5 PM? For the last 5 years the answer is never.

6. The high protein and fats we eat at dinner diminish our appetite tremendously and this allows leptin released from your fat cells to enter the hypothalamus from midnight to 2 AM to send second messenger chemicals to the thyroid to allow us to burn excess calories stored in fat to be burned at the uncoupling proteins in muscles as we sleep in stage 3 and 4 sleep. Sleeping is the second critical way in which we increase our body composition. We use sleep to get rid of excess fat and calories, using T3, leptin and uncoupling proteins. During sleep, protein synthesis is also simultaneously occurring during the process of autophagy. This is when we recycle all our proteins that we used during the day cycle. Sleep deprivation leads to increased levels of IL-6 and TNF alpha, which simultaneously lowers our DHEA levels. Decreased sleep also blocks the secretion of growth hormone at night and this leads to increase abdominal fat and eventually decreased lean muscle mass. This is why patients with sleep apnea have terrible body composition as a rule. The lowered growth hormone levels leads to high levels night time cortisol release. This is why so many obese, LR, sleep apnea patients feel the need to get up and eat carbohydrates
at night. Cortisol is supposed to spike at wakefulness not during our sleep. People who awaken with high cortisol levels will also be drawn to eat a lot of carbohydrates at breakfast. If this occurs chronically, it will diminish the gastric acid cycle and destroy our naturally occurring cycle for developing our ideal body composition. Why does this occur? Cortisol directly stimulates gherlin release, which is an incretin hormone, produced by our stomach. Gherlin is an appetite stimulant. This hormone increases our drive to eat at wakefulness. It is usually high when we rise, or it spikes anytime when cortisol is too high. Elevated cortisol is a constant feature of obesity. Cortisol should not be high during sleep ever. When gherlin levels are increased by 30\% from its baseline, it drives carbohydrate hunger while simultaneously decreasing leptin endocytosis into the brain by 50\%. Elevated triglycerides and high inflammatory cytokines further block the action of leptin at the hypothalamus. For leptin to enter the brain, gherlin levels must be low, and this is why 4-5 hours post dinner is the best time for leptin to enter the brain. So if you do shift work you must be a great sleeper and run on a ketogenic paleo diet to have a chance of good body composition. I have met only one person in my life who did this.

That is how I live now and why I do it after the leptin Rx reset. I hope you found this interesting. I will be gone for a brief period because my wife wants to get remarried on a boat near the equator. So I will be optimizing Vitamin D the real way. Leave a comment and I promise to answer them when I get back. Happy Thanksgiving to all out there. Please pay something forward this holiday season. We all can make each
lives better if we just do something to help one another.

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Additional Resources

- My Leptin Prescription /my-leptin-prescription/
- The Leptin Rx: FAQs http://www.jackkruse.com/the-leptin-rx-faqs/
- Leptin Reset http://www.jackkruse.com/easy-start-guide/
- Intermittent Fasting and Leptin /intermittent-fasting-


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