Central Leptin Dominance: Part 3 – King of The Hill

Readers Summary

1. What do the reward tracts do?
2. Why Neurosurgery does not support reward theory
3. Why leptin is King of the Hill with respect to obesity
4. Why leptin is so critical for control of everything dependent of energy
5. What type of diet is best for prevention of neolithic disease or aging

So now that we examined Dr. Lustig's insulin theory of metabolic control we need to take a look at the reward tracts that are located in the human brain. These tracts have been well studied and their neurochemistry is well understood. What appears not to be as well known is how the hypocretin neurons and the leptin receptor control and modulate their activity. The key point here is that the dopaminegic tracts eloquently spoken of Dr. Guyenet's reward series are the "**efferent only**" path that is part of the effector arm of the leptin receptor and the hypocretin neurons. This means, in English, they are playing second fiddle to the leptin receptors and are not the dominant cause of obesity. They clearly play a major role in the neuro-circutry but they do not control obesity. They carry out the action but the orders were given by someone else. One of the reasons I had a major problem with the reward series, is because of my "day job" as a neurosurgeon. I have had the opportunity to operate on many brain tumors in the reward tracts and never have I ever seen either preoperatively or postoperatively one patient develop severe morbid obesity. If these tracts were truly dominant causes this would lead neurosurgeon and neurologists to see many patients with this problem. Well, we do not. That was a big issue for me with the

theory. The second issue I had with it was that when we neurosurgeon's have patients with brain tumors involving the hypothalamus we see tremendous effects on feeding, obesity and on anorexia. This is well documented and I have personally seen this in many cases. Dr. Lustig pointed this out in his AHS 2011 talk when he showed some clinical cases of craniopharyngioma's and of hypothalamic trauma's that resulted in morbid obesity.

Reward Story: We now have to go back to the science.

The reward tracts are best understood if we read the work of Paul Kenny from the Scripp's clinic in Florida. His recent paper from 2010 is a phenomenal work in neuroscience. His paper showed that the development of obesity was coupled (did not cause obesity) with the emergence of a progressively worsening brain reward deficit. He also referenced Dr. Lecea work on the hypocretin neurons and their affects on reward homeostasis on cocaine and on heroin addiction. The neurochemical change underlying obesity in the reward tracts showed striatal (part of the brain) dopamine (D2) receptors were down regulated. This has been found in rodents as well as humans. The lentivirus mediate knockout studies of the striatal D2R rapidly allowed the development of reward deficits and caused addictive behaviors to develop to drugs and to food. So the neuro-biology of these tracts clearly show that over-consumption of drugs or palatable food was able to trigger addiction like neuroadaptive behaviors. No one disputes this.

But here was the rub of the studies and where the dispute arises.

What controls the reward tracts neurochemistry to begin with?

Here we head back to Dr. Myers' lab and the answer, not surprisingly, is the hypocretin neuron groups in the lateral hypothalamic area. These neurons project directly to the dopamine receptors in the ventral segmental areas of the brain. This is the seat of the reward tracts in Dr. Kenny's studies and the ones referenced extensively in Dr. Guyenet's reward series. Dr. Myers work showed using various adenoviral and transgenic systems that the hypocretin neurons directly control the firing and the behavior of the entire reward tract. This means in simple terms that the reward tracts are the outflow of the hypocretin neuron system and they are controlled totally by the leptin receptor. Given this work at the University of Michigan and at the Scripps Lab, I see no way one can say the reward tracts are dominant in causing obesity. The reward tracts clearly do allow for the action of the hypocretin neurons and the leptin receptor. Dr. Myers works shows that the totality of biologic function of leptin and it receptor have to be the summation of its action on the hypocretin neurons. He has tediously worked these pathways out in numerous publications. No where in his works did I find any evidence for insulin to play any control in modulating the biology of the leptin receptor or of the hypocretin neurons. In fact, there is a lot of evidence that leptin affects in the brain receptor modulate insulin effects directly. In simple terms, this means that the leptin receptor and leptin itself modulate control over insulin and the reward tracts at the hypothalamic level of the brain.

In fact, there is no neuro-biologic evidence that the reward tracts can feedback and modulate the hypocretin neurons outflow. This completely explains why I have never seen a brain tumor in the reward bundles cause obesity in a human. Moreover, there is no higher cerebral controls over the leptin

receptor. This means that the cerebral cortex, the basal ganglia or thalamus play any role at all in modulating energy balance in the humans system. The sum of my writing here means that control of all energy balance, feeding, appetite, anorexia and obesity are all controlled by leptin function. This tight control is also then linked to the reward systems to drive behavior and it is also linked to the Parvo-cellular nucleus to control sex steroidogenesis and all endocrine function and fecundity to create a new generation of the species.

Another point I'd also like to make about these finding's of Dr. Myers. In Dr. Lustigs, AHS 2011 lecture he mentioned the Melanocyte concentrating hormone binding receptors (MCH4 to be exact) and their linkage to leptin and insulin in the brain. What he told us about those tracts was certainly true in 2009, but in 2010 Dr. Myers new data showed that MCH4 role has now changed. The new data showed that the leptin receptor neurons in the lateral hypothalamic areas are quite distinct from the adjacent leptin-regulated neurons in the melanin concentrating hormone cluster. These neurons are biologically different and perform different functions and do not appear to be involved in obesity pathways at all. In 2009, this was not worked out. This was another reason why I was not accepting of the theory as it was presented to the AHS group at UCLA.

Dr. Lustig's theory and Dr. Guyenet's reward series have a lot in them that are correct and aid us all in understanding how obesity occurs. There is no doubt about this. But in science when we use the word always or never, or dominant, or non dominant, you can bet that some researcher or clinician somewhere will challenge that assertion with a new hypothesis and experiment. The work of Dr. Myers on leptin receptor biology and control put leptin as the "**King of the Hill**" with regards to obesity development. After studying this work for nearly 7 years as a neurosurgeon I became fully ready to accept its dominant position about three years ago. I did not

write my Quilt document until I had read Dr. Myers work in its entirety. After doing so I put leptin at position two in my Quilt and I think I have laid out here in the last three blogs why I believe this to be true. I think obesity and anorexia are the sum quotient of the outflow of the neurochemical signals from the hypocretin neurons which are controlled directly by the leptin receptors' biology.

Any theory on the dominant control of obesity must explain the neurobiology findings of these researchers work. What we learned here is the seat of control of energy metabolism is clearly delineated by these experiments. What the next step in researchers minds should be is how to clinically affect the leptin's action to help people and disease whose biology is coupled to energy metabolism at its core. Examples of such conditions are anorexia, bulimia, osteoporosis, obesity, diabetes and aging. Dr. Ron Rosedale is one of those early pioneer's and his work should be looked at closely and dissected. I think his theories are quite solid for healthy living, but I have two minor areas where I do not fully accept his thesis for optimal longevity. His book has some negative connotations for saturated fats and for protein intake. He is particularly concerned about the mTOR pathway being unregulated with moderate to high protein diets. This theory really separates himself from the work of his former partners, Dr's. Eades of Protein Power fame.

This protein issue has been linked to shortened lifespans in many articles in the literature. The same is true of high carbohydrate diets that stimulate the IGF-1 pathways. Carbohydrates are broken down into two groups, high and low glycemic. There are two other reasons why I think Rosedale's thought might be superficial on mTOR and IGF 1 signaling. The redox potential of the extracellular matrix is what opens the door to heaven or hell in this pathways, in my opinion. Moreover, the 1930 studies Rosedale touts have never been reproduced in primates and they have not been reproducible in

today’s modern world filled with non native energies that are fully capable of altering the redox potential of the extracellular matrix. To my this is why I cannot get behind Rosedale’s idea’s 100{a7b724a0454d92c70890dedf5ec22a026af4df067c7b55aa6009b4d34d5da3c6}. Both Dr. Rosedale and the “power couple Eades” are sour on both of these pathways. Proteins are also broken into two groups. Those that are insulinogenic are called the branch chain amino acids proteins (BCCA) and the rest are made from unbranched amino acids (AA). Dr’s. Eades do not discriminate on proteins for his diet. Dr. Rosedale is not fan of protein at all in his diet. His diet is a high fat, low carb and low protein diet. The effect of neolithic diseases is directly proportional to aging. Neolithic disease increases as we age in all studies. So the diet we should advocate for humans is critical to us all. It also is clearly tied to this leptin story. An interesting aspect of the role of leptin in mTOR (levee 11) function is that within mature human adipocytes leptin synthesis itself is dependent on mTOR activation. So that biologic fact alone tells me at the very least some protein is very helpful. How much is optimal is unknown. This supports Drs. Eades and the paleolithic diet for health and longevity. I believe the missing piece is DHA. This is why my template allows for natural development of ketosis while naturally restricting calories and increasing redox signaling.

Dr. Rosedale’s concerns are valid no doubt but not yet proven beyond a doubt. My mind on this issue remains very open. On this topic, I won’t be dogmatic. I think telomere biologic studies and redox signaling of NAD+, along with calorie restriction studies will prove who’s theories are correct or not in the future. One thing that we already do know from telomere biology that supports the use of protein in diets for longevity is that telomere lengths are increased when the diet is high in carnosine. The paleolithic diet has the highest level of carnosine in it. Carnosine is found in red meat that is grass fed. On the flip side of this issue is the calorie

restriction data and the data found in lower animals to yeast. This strongly points to limiting protein and calories to extend lifespan. This is why I believe the Epi-paleo Rx template matches our current environment much better for optimal performance and longevity.

Given these contradictions, I cannot in 2011, indict all proteins based upon what we know about leptin and mTor as it stands today. I personally believe that the best paleolithic diet for aging may eliminate the part of the macronutrients of carbs, proteins and fats that all decrease our telomere lengths. Right now this is completely unknown but the diet I eat uses this principle today. I think BCCA maybe the "bad side of protein" for neolithic disease development. But I don't think the remaining AA that make the rest of proteins up are all bad. I think, like carbs, protein have the good and bad qualities. The same is true for fats. Sally Fallon and Dr. Mary Enig have shown this in their work. These are many years away from completion but they are being done now on humans and primates. These minor disagreements today may have huge implications for human aging and longevity recommendations for patients in the future, but I don't believe any dogmatic statements can be made today based upon what we know now.

My quest is for a long healthy lifespan free of the neolithic diseases of aging. The reason should be obvious. I'm aging as I type, as we all are. If there are things we can do with dietary alterations as we age to extend lifespan and simultaneously limit disease we should consider these options. But one thing should be clear to you now. I believe leptin is king of the hill.

Leave a Comment

Your Shopping List for this Post

- View All Recommended Products from The Leptin Rx
- View The Epi-Paleo Store

Additional Resources

- My Very Fresh Initial Thoughts of AHS 2011
- The Quilt
- The Quilt: mTOR
- The Leptin Rx: FAQs
- Leptin Reset

Cites

- See last two blogs for complete list of cites