Central Leptin Dominance: Part 2

Readers Summary

1. Why are men and women really from Mars and Venus regarding leptin?
2. Why having a baby successfully is completely dependent upon leptin
3. How does leptin control fertility?
4. How does leptin status affect epigenetic signaling
5. Why Dr. Lustig's new hypothesis might be leaking some fructose

Continuing on in the Central leptin series we will resume discussing the talk from Orlando, Florida.

In Orlando, Dr. Myers, went on to say, "In addition to examining the molecular details and importance of specific LRb signals, we are dissecting the regulation and function of individual populations of LRb-expressing neurons and examining the role of leptin in the development of neural circuits. By understanding the totality of leptin action in this way we hope to decipher the mechanisms by which leptin regulates the predisposition to diabetes and other aspects of the metabolic syndrome." This statement carries huge implications. He has found that not only is leptin neurons somatotopically organized in the brain, but the leptin receptor also appears to be somatotopically organized into certain regions that wire and select certain neurons in the brain that modulate all parts of the obesity physiologic response. It also appears that this organization is different in men and women at the parvo-cellular nucleus in the hypothalamus. Certain parts of the receptor control total body glycemic control, others body weight and size, and others power the para-mammillary neurons to directly control fecundity, placental growth and oocyte maturation. The receptor even codes for gender differences! Men and women really are from Mars and Venus when it comes to obesity and fat deposition, and this explains why the endocrine response is different in men and women. We have known men and women have different leptin levels as adults but did not know how or why this happens. Now we do. We now are beginning to understand why it is the case as well. It helps explain why we see can see PCOS and stubborn weight gain together and why fat is distributed differently in both sexes.

Leptin Receptor Biology: The real cause of obesity

I mentioned to Dr. Lustig right before his talk at AHS 2011 that any discussion of obesity has to explain the apparent paradox of clinical "leptin resistance" in anorexia and the obese. These are two polar opposite phenotypes that have the same biologic basis and can be measured by high blood reverse T3 levels. This paradox is also seen in rodents. The scientific story began for rodents began in 1994, with the discovery of two independent mutant mouse strains at the Jackson Laboratory. The obese (ob/ob) and diabetic (db/db) strains suffer from an identical set of problems: they are obese, they have type 2 diabetes, and a variety of their endocrine systems are disrupted in a pattern reminiscent of the response to starvation

(anorexia). Leptin was discovered in these experiments and named by Dr. Jeff Friedman at Rockerfeller University in 1994.

Leptin is produced by fat cells. To a reasonable approximation, the more energy (fat) is stored in a fat cell, the more leptin the cell produces and secretes into the circulation. Circulating leptin makes its way to the brain, where it binds to the leptin receptor. Subsequent to the identification of leptin, the cloning of the leptin receptor revealed that this gene was disrupted in db/db mice.

Different parts of the brain mediate distinct functions, and only a few parts of the brain express the leptin receptor. It is found in high levels in the hypothalamus and very sparsely in the motor cortex. The motor cortex controls body movements. Leptin action via leptin receptors in the brain, suppresses appetite and hepatic glucose production (thereby modulating the amount of glucose in the blood). Leptin also signals that the long-term energy stores in fat suffice to permit the utilization of energy on energy-intensive endocrine functions including reproduction. It also controls placental growth and maturation to foster the fetus during pregnancy. The progesterone made by the placenta directly affects neuron development and maturation and synaptic connections. This is done in concert with vitamin D levels in the brain all mediated by brain derived nerve growth factor (BDNF). This mechanism is felt to be disturbed in disease like autism spectrum disorders and in development of dyslexia and other neurologic causes of developmental delay. It is easy to see how leptin functioning can affect epigenetic signaling in this fashion and also the developing fetus synaptic neuronal connections. The epigenetic effects on the receptor seem to follwo Lamarkian inheritance patterns and not classic patterns.

Leptin also controls oocyte selection and maturation in humans. This means fertility is also controlled by leptin in humans. Today infertility is exploding. If there is a leptin problem in the mother it will directly affect her ability to mature and egg suitable for fertilization. This could jeopardize her ability to conceive any pregnancy because of poor egg maturation or poor placental growth to support the fetus. Moreover, this egg is also susceptible to epigenetic signaling due to leptin’s effects at this stage of development. It also appears that leptin may affect chromosomal fragility and the mitotic spindle critical for cell division in a growing fetus and may be the source of chromosomal abnormalities in pregnancies that end in spontaneous abortion due to placental chromosomal abnormalities and in somatic mutations of the fetus. There are all tied to proper microtubule function in the cell. It appears energy metabolism is critical in these physiologic systems and leptin modulates them all. The Leptin receptor is the electron accountant for the brain and monitors energy balance in all systems.

Falling leptin levels mediate the response to fasting. We see this in fasting, anorexia, and in cold exposure. Fasting and cold exposure decreases the amount of energy stored as triglyceride in fat cells, thus decreasing the amount of circulating leptin. This reduction in leptin receptor signaling therefore increases the drive to eat, increases hepatic glucose production (helping to support blood glucose levels during fasting), and diminishes the

permissive action of leptin on endocrine functions.

Genes that have mutations for leptin's receptor show dramatic response's in the animal. In the absence of the leptin receptor signal in db/db mice, for instance, the brain cannot sense the leptin signal at all. This leads to increased appetite. Simultaneously, it also allows the animal to respond by unleashing hepatic glucose formation and these two factors also stimulate feeding behavior that causes weight gain over time. The longer this persists, the animal develops and increased fat mass. The lack of leptin- mediated restraint on hepatic glucose production in db/db mice also predisposes to diabetes. (Hepatic leptin resistance) This excess glucose production leads to chronic surges in insulin and a simultaneous drop of intracellular magnesium. This drop in magnesium is also seen in concert with a loss of free water. This is why diabetics frequently present with the symptom of frequent urination. The distal tubules in the kidney are affected directly by these changes within a cell. Magnesium depletion is always a sign of dehydration. To understand the role of mangnesium and insulin please read the link once again. Once enough time has elapsed, the leptin resistance leads to insulin resistance and results in type 2 diabetes and eventually with more time, elevated cortisol levels. This is not Dr. Lustig's current vision. He presented his view for us at AHS 2011. The talk was great and it was dynamic. His view of how the system works is quite different from mine however.

Dr. Lustig, in his AHS 2011 talk said, "insulin is an endogenous leptin antagonist" @39:13 mark of the video made at AHS. He went on to hypothesize why this happens and says, "because at puberty and/or pregnancy, becoming insulin resistant is beneficial for growth and propagation of the species respectively." When he said this at AHS I was stunned. Why? Here is the rub: Leptin has been "definitively" shown to control all aspects of fecundity, oocyte maturation, and placental growth in humans and insulin has not.

If insulin resistance bolsters pregnancy for propagation of the species, and insulin is an endogenous antagonist of leptin why in God's world of evolutionary biology would leptin control fecundity in humans? In his theory Insulin should control fecundity and oocyte selection and placental growth. That is not what science is telling us. Taking it one step further, using Dr. Lustig's own theory as a base, a diabetic could never have a child because as he says, "insulin always blocks leptin." All diabetics have insulin resistance and high circulating levels and since leptin controls fecundity in humans. Well, we have a big problem with this theory right here. Dr. Lustig's hypothesis has a major gaping hole that can't be easily explained biologically. There are some other issues I have with his theory at the brain level but the one I presented it a big problem for his theory. This is why I said in my post AHS blog I loved that his theory added leptin to the mix but I was not in love with the biology of his theory. The biology works a lot better when you understand that leptin controls the entire process not insulin at the hypothalamus.

So how does leptin signaling work in the brain at a

receptor level?

First, we need to ask a few questions. One, what are the cellular mechanisms of leptin receptor signaling and how do specific leptin receptor signals control energy balance and glucose homeostasis? And two, on what set or sets of neurons in the brain does leptin act to control energy balance and glucose homeostasis?

The leptin receptor operates as a preformed dimer that is integrated into the cellular membrane of the hypocretin neurons. The remanding portion of the receptor sits in the extracellular space where hormones can bind to the receptor. Another interesting finding of the leptin receptor is that it contains no enzymatic activity at all. Most other receptors do. Leptin seems to respond to electron movements within reactions and these seem to impact the amino acids in the leptin recepetor's 3 Dimensional protein confirmation. When the redox potential of the leptin receptor is altered so are the proteins in its 3 D arrangement. The leptin receptor relies on a tyrosine kinase (JaK2) for signaling when leptin binds to it. When leptin binds to it, it activates JaK2 which then activates 3 different tyrosine residues (Think EE 11) on the inside domain of the receptor. These domains have special amino acid patterns that use special co factors at each position to activate and confer a biologic response. **There are 4 inception points that confer a specific biologic response**. These four domains respond to the redox state and to electron transfers. Combined, these four signals mediate all of leptin action on energy balance, glucose homeostasis, and endocrine function. Each specific response was worked out by Dr. Myers lab using gene knock out experiments. They studied 6 types of knock outs. A normal wild type, and a complete knock of the four inception areas and confirmed that the total knock out animals all gained a lot of weight. When the Jak2 knock out was completed it did not show a major weight effect, but did modestly effect blood glucose levels. This might represent the basis of liver leptin resistance I wrote about here.

When the next tyrosine residue (985) was knocked out, it affected two binding co factors (SOCS3 and SHP2). This showed the opposite clinical effect found in the complete knocked out mice. These mice lost weight no matter what they ate. It was as if they were super leptin sensitive and were real lean. This modeled what we see in anorexia or cachexia. As these animals become exquisitely sensitive to leptin, they in effect decrease the receptor sensitivity to leptin to remain quite lean but they all had issues with sex steroid production. This caused major issues with fecundity and reproduction. This is also seen in the human condition of anorexia and starvation as well.

Insulin plays no role in this issue. IR can cause PCOS in women and aromatization in men, but humans with these conditions can reproduce with some difficulty. Humans with leptin problems are seeing fertility doctors because they can not get pregnant because their eggs and placentas can not mature for a successful pregnancy.

The last two tyrosine binding residues were then tested to see which one was the part of the receptor that controlled energy balance and glucose

homeostasis. The first on was Tyr1107 and STAT5. It was found that STAT5 mutants showed modest increases in body fat and increases in feeding behaviors but no change in glucose utilization. The Try1138 residue and STAT3 were then studied. This mutant showed massive effects in body weight and in glucose utilization. It also appears that this effect is independent of insulin signaling. This point was further made crystal clear in Dr. Myers 2010 Orlando talk. This is in stark contrast to what Dr. Lustig presented in his AHS 2011 talk at UCLA. Based upon the leptin receptor findings, it is clear that this was the part of the receptor that caused most (dominant) of the obesity effects seen in the animals for both body weight and {a7b724a0454d92c70890dedf5ec22a026af4df067c7b55aa6009b4d34d5da3c6} body fat (body composition). As they aged, the also showed “marked” glucose intolerance. This part of the receptor seemed to fit the morbid obesity and diabetes phenotype we see in humans. It was clear the receptor inception sites all had different biological effects. It also appears that insulin signaling pathways and the dopamine reward tracts are directly influenced by what happens at the leptin receptor level first in the hypocretin neurons. That is how I interpret the current data on how this system is designed to work.

Given this data we need to wonder how does the receptor control feeding behavior and glucose homeostasis?

To answer this question we really need to look at how the peripheral tissues like fat, muscle, liver and brain differ as organs since the leptin receptor affects these tissues dramatically. For example, the liver is a homogenous gut organ that is made up of hepatocytes. All of its cells are the same. The brain however is an organ whose cells are all specialized by wiring, connections, and even the neurotransmitters they use. Moreover, their functions can be completely flipped to give the opposite clinical effect with presynaptic of postsynaptic modifications or firing of adjacent neurons. It is clear that there is no way to understand the affect of leptin on the brain if one views the brain like one views the liver, muscles or fat cells. The level of complexity at the hypothalamus changes the game substantially to explain leptin’s vast and various affects on both sympathetic and parasympathetic systems and on its endocrine functions controlling fecundity and oocyte maturation and placental growth.

Next up we will begin to dissect the reward tracts and how they play a role in this unraveling leptin saga.

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Cites

- www.ncbi.nlm.nih.gov/pubmed/20029269
- www.ncbi.nlm.nih.gov/pubmed/21303721
- www.ncbi.nlm.nih.gov/pubmed/19849856
- www.ncbi.nlm.nih.gov/pubmed/17895321
- www.reproduction-online.org/content/140/3/347.full
- www.reproduction-online.org/content/140/6/953.abstract
- Feener E, Rosario F, Dunn SL, Stancheva Z and *Myers MG Jr.* Inhibition of Jak2 signaling by tyrosine phosphorylation in the JH2 domain. Mol Cell Biol (2004) 24(11): 4968-78.
- Bates SH, Dundon TA, Seifert M, Maratos-Flier E and *Myers MG Jr.* LRbÃ STAT3 signaling is required for the neuroendocrine regulation of energy expenditure. Diabetes (2004) 53(12): Feedback inhibition of leptin receptor/Jak2 signaling by Tyr1138 of the Leptin receptor and Suppressor of Cytokine Signaling 3. Mol Endo (2005) 19: 925-938.
- Bates SH, Kulkarni RN, Seifert M, and *Myers MG Jr. * Roles for leptin receptor/STAT3-dependent and -independent signaling in the regulation of glucose homeostasis. Cell Metabolism (2005) 1: 169-178.
- Gelling RW, Morton GJ, Morrison CD, Niswender KD, *Myers MG Jr*, Rhodes CJ, and Schwartz MW. Insulin action in the brain contributes to glucose lowering during insulin treatment of diabetes. Cell Metabolism (2006) 3: 67-73.
- Ishida-Takahashi R, Rosario F, Gong Y, Kopp K, Stancheva Z, Chen X, Feener EP, and *Myers MG Jr.* Phosphorylation of Jak2 on Ser523 Inhibits Jak2-dependent Leptin Receptor Signaling. Mol Cell Biol (2006) 26: 4063-73.
- Buettner C, Pocai A, Muse E, Etgen A, *Myers MG Jr*, and Rossetti L. Critical Role of STAT3 in Leptin’s Metabolic Actions. Cell Metabolism (2006) 4:49-60.
- Bodary PF, Shen Y, Ohman M, Bahrou KL, Vargas FB, Cudney SS, Wickenheiser KJ, *Myers MG Jr*, and Eitzman DT. Leptin regulates neointima formation following arterial injury through mechanisms independent of blood pressure and the leptin receptor/STAT3 signaling pathways involved in energy homeostasis. ATVB (2007): 70-76.
- Munzberg H, Jobst EE, Bates SH, Jones JC, Villanueva E, Leshan R, Bjornholm M, Elmquist J, Sleeman M, Cowley MA, and *Myers MG Jr.* Appropriate Inhibition of orexigenic hypothalamic arcuate nucleus neurons independently of leptin receptor/STAT3 signaling. J. Neurosci. (2007) 27: 69-74.
- Bjornholm M, Munzberg H, Leshan R, Villanueva E, Bates SH, Louis GW, Jones JC, Ishida-Takahashi R, Bjorbaek C, and *Myers MG Jr.* Mice

lacking inhibitory leptin receptor signals are lean with normal endocrine function. J. Clin. Invest. (2007) 117:1354-1360.
- Soliman GA, Ishida-Takahashi R, Gong Y, Jones JC, Leshan RL, Saunders TL, Fingar DC, and *Myers MG Jr.* A simple qPCR-based method to detect correct insertion of homologous targeting vectors in murine ES cells. Transgenic Research (2007) In Press.
- Li Z, Zhou Y, Carter-Su C, *Myers MG Jr*, and Rui L. SH2B1 enhances leptin signaling by both Jak2 Y813 phosphorylation-dependent and -independent mechanisms. Mol. Endo (2007), In Press.
- http://med.stanford.edu/profiles/frdActionServlet?choiceId=showPublication&pubid=209184&fid=7308&
- www.slideshare.net/ancestralhealth/ahs-slidesrobert-lustig