

Leptin -- Its Essential Role in Health, Disease, and Aging

By Ron Rosedale

The Ob mouse is a strain of mouse that has a genetic mutation that makes it obese and unhealthy. It has been used for many years as a model of obesity to do research on, though the reason that it was obese had eluded scientists. This changed when, in 1994, Jeffrey Friedman discovered that this mouse lacked a previously unknown hormone called leptin, and when it was injected with leptin it became thin, vibrant, and very healthy within weeks. This made headlines around the world, "the cure for obesity found" and pharmaceutical companies started tripping over themselves with trillion dollar signs in their eyes to be the first to genetically manufacture leptin on a large-scale. This did not last long. When people were tested for leptin, it was found that, unlike the Ob mouse, they did not lack leptin; on the contrary almost all overweight and obese people have excess leptin. These people were "leptin resistant" and giving extra leptin did little good. The financial disappointment was extreme and scientists working for pharmaceutical companies said that leptin wasn't important anymore since they could not find a drug to control it, and therefore the industry couldn't make money on it. To make big money in medicine one needs a patent and this generally means remedies which are not commonly or easily available -- that are not natural. This illustrates two extremely unfortunate principles in modern medicine; only those therapies that will make lots of money (generally for the pharmaceutical industry or hospitals), ever get pursued and then taught to physicians (since most of medical education after medical school takes place by drug reps), and these therapies, almost by definition, will be unnatural. This inhibition of extremely important knowledge is not only unfortunate, it is deadly, and is exemplified by how few people, including doctors, know anything about leptin, though I would consider it to be the most important chemical in your body that will determine your health and lifespan.

Each and every one of us is a combination of lives within lives. We are made up of trillions of individual living cells that each must maintain itself. Even more significantly, the cells must communicate and interact with each other to form a republic of cells that we call our individual self. Our health and life depends on how accurately instructions are conveyed to our cells so that they can act in harmony. It is the communication among the individual cells that will determine our health and our life. The communication takes place by hormones. Arguably therefore, the most important molecules in your body that ultimately will decide your health and life are hormones. Many would say that genes and chromosomes are the most important molecules, however once born your genes pretty much just sit there; hormones tell them what to do. Certainly, the most important message that our cells receive is how and what to do with energy, for metabolism and therefore life cannot take place without that. The two most important hormones that deliver messages about energy and metabolism are insulin and leptin.

Metabolism can roughly be defined as the chemistry that turns food into life, and therefore insulin and leptin are critical to health and disease. Both insulin and leptin work

together to control the quality of one's metabolism (and, to a significant extent, the rate of metabolism). Insulin works mostly at the individual cell level, telling the vast majority of cells whether to burn or store fat or sugar and whether to utilize that energy for maintenance and repair or reproduction. This is extremely important as we shall see, for on an individual cell level turning on maintenance and repair equates to increased longevity, and turning up cellular reproduction can increase the risk of cancer.

Leptin, on the other hand, controls the energy storage and utilization of the entire republic of cells allowing the body to communicate with the brain about how much energy (fat) the republic has stored, and whether it needs more, or should burn some off, and whether it is an advantageous time nutritionally-speaking for the republic --you-- to reproduce or not.

What exactly is leptin? Leptin is a very powerful and influential hormone produced by fat cells that has totally changed the way that science (real science, outside of medicine) looks at fat, nutrition, and metabolism in general. Prior to leptin's discovery, fat was viewed as strictly an ugly energy storage depot that most everyone was trying to get rid of. After it was discovered that fat produced the hormone leptin (and subsequently it was discovered that fat produced other very significant hormones), fat became an endocrine organ like the ovaries, pancreas and pituitary, influencing the rest of the body and, in particular, the brain. Leptin, as far science currently knows, is the most powerful regulator that tells the brain what to do about life's two main biological goals: eating and reproduction. Your fat, by way of leptin, tells your brain whether you should be hungry, eat and make more fat, whether you should reproduce and make babies, or (partly by controlling insulin) whether to "hunker down" and work overtime to maintain and repair yourself. I believe I could now make a very convincing and scientifically accurate statement that that rather than your brain being in control of the rest of your body, your brain is, in fact, subservient to your fat -- and leptin.

In short, leptin is the way that your fat stores speak to your brain to let your brain know how much energy is available and, very importantly, what to do with it. Therefore, leptin may be "on top of the food chain" in metabolic importance and relevance to disease.

It has been known for many years that fat stores are highly regulated. It appeared that when one tried to lose weight the body would try to gain it back. This commonly results in "yo-yo" dieting and in scientific circles one talks about the "set point" of weight. It has long been theorized that there must be a hormone that determines this. Science points now to leptin as being that hormone.

In our ancestral history, it was advantageous to store some fat to call upon during times of famine. However, it was equally disadvantageous to be too fat. For most of our evolutionary history, it was necessary to run, to obtain prey and perhaps most importantly, to avoid being prey. If a lion was chasing a group of people it would most likely catch and eliminate from the gene pool the slowest runner and the one who could not make it up the tree -- the fattest one.

Thus, fat storage had to be highly regulated and this is done, as is any regulation, through hormones, the most significant being leptin. If a person is getting too fat, the extra fat produces more leptin which is supposed to tell the brain that there is too much fat stored, more should not be stored, and the excess should be burned. Signals are

therefore sent to an area of the brain in the hypothalamus (the arcuate nucleus) to stop being hungry, to stop eating, to stop storing fat and to start burning some extra fat off. Controlling hunger is a major (though not the only) way that leptin controls energy storage. Hunger is a very powerful, ancient, and deep-seated drive that, if stimulated long enough, will make you eat and store more energy. Asking somebody to not eat, to voluntarily restrict calories even though they are hungry, is asking the near impossible. The only way to eat less in the long-term is to not be hungry, and the only way to do this is to control the hormones that regulate hunger, the primary one being leptin.

More recently, it has been found that leptin not only changes brain chemistry, but can also "rewire" the very important areas of the brain that control hunger and metabolism. I'm not aware of any other chemical in the body that has been shown to accomplish this "mindbending" event.

This has really caught the attention of the scientific community. Further studies have now shown that leptin, or more correctly the inability of the body to properly hear leptin's signals, in other words leptin resistance, plays significant if not primary roles in heart disease, obesity, diabetes, osteoporosis, autoimmune diseases, reproductive disorders, and perhaps the rate of aging itself. It helps to control the brain areas that regulate thyroid levels and the sympathetic nervous system which also has huge impacts on blood pressure, heart disease, diabetes, osteoporosis and aging. Leptin's stimulatory effect on the sympathetic nervous system also helps determine the adrenal stress response including cortisol levels.

The importance of insulin in health and disease is becoming well-known. Aside from its obvious role in diabetes, it plays a very significant role in hypertension, cardiovascular disease, and cancer. I was one of the first to speak publicly to doctors about insulin's critical role in health well over a decade ago (see the transcribed talk "Insulin and its Metabolic Effects" on many Internet sites) and I am even more convinced now. However leptin may even supersede insulin in importance, for new research is revealing that in the long run glucose and therefore insulin levels may be largely determined by leptin.

It had been previously believed that the insulin sensitivity of muscle and fat tissues were the most important factor in determining whether one would become diabetic or not. Elegant new studies are showing that the brain and liver are most important in regulating a person's blood sugar levels especially in type 2 or insulin resistant diabetes. It should be noted again that leptin plays a vital role in regulating the brain's hypothalamic activity which in turn regulates much of a person's "autonomic" functions; those functions that you don't necessarily think about but which determines much of your life (and health) such as body temperature, heart rate, hunger, the stress response, fat burning or storage, reproductive behavior, and newly discovered roles in bone growth and blood sugar levels. Another very recent study reveals leptin's importance in directly regulating how much sugar that the liver manufactures via gluconeogenesis.

Many chronic diseases are now linked to excess inflammation such as heart disease and diabetes. High leptin levels are very pro-inflammatory, and leptin also helps to mediate the manufacture of other very potent inflammatory chemicals from fat cells that also play a significant role in the progression of heart disease and diabetes. It has long been known that obesity greatly increased risk for many chronic diseases including heart disease and diabetes, but no one really knew why. Leptin appears to be the missing link.

Leptin will not only determine how much fat you have, but also where that fat is put. When you are leptin resistant you put that fat mostly in your belly, your viscera, causing the so-called "apple shape" that is linked to much disease. Some of that fat permeates the liver, impeding the liver's ability to listen to insulin, and further hastening diabetes. Leptin plays a far more important role in your health than, for instance, cholesterol, yet how many doctors measure leptin levels in their patients, know their own level, even know that it can be easily measured, or even what it would mean?

Leptin appears to play a significant role in obesity, heart disease, osteoporosis, autoimmune diseases, inflammatory diseases and cancer. These are the so-called "chronic diseases of aging". Could it perhaps affect the rate of aging itself? Scientists who study the biology of aging are beginning to look at that question. There are two endeavors, two drives that life has been programmed, since its inception, to succeed at and to succumb to. These are to eat and to reproduce. If every one of our ancestors had not succeeded in eating and reproducing we would not be here, and this paper would be moot. All of your morphological characteristics from your hair to your toenails are designed to help you succeed at those two activities. That is what nature wants us to do. Nature's purpose is not necessarily to have *you* live a long and healthy life, but to perpetuate the instructions, the genes that tell how to perpetuate life. Even so-called "paleolithic" diets, though undoubtedly far better than what is generally eaten today, were not necessarily designed by nature to help us live a long and healthy life but, at best, to maximize reproduction. Nature appears to not care much about what happens to us after we have had a sufficient chance to reproduce. That is why we die. But there are clues as to how to live a long and healthy life. And that brings us once again to fat-- and leptin.

It takes energy to make babies; lots of it. Energy was and always will be a coveted commodity. Nature, and evolution hates wasting it. It makes no sense to try and make babies when it appears that there's not enough energy available to successfully accomplish that goal. Instead, it seems that virtually all living forms can "switch gears" and direct energy away from reproduction and towards mechanism that will allow it to "hunker down" for the long haul and thus be able to reproduce at a future more nutritionally opportune time. In other words nature will then let you live longer to accomplish its primary directive of reproduction. It does this by up regulating maintenance and repair genes that increase production of intracellular antioxidant systems, heat shock proteins (that help maintain protein shape), and DNA repair enzymes. This is what happens when you restrict calories (without starvation) in animals, and that has been shown convincingly for 70 years to greatly extend the life span of many dozens of species. Thus, there is a powerful link between reproduction, energy stores, and longevity. Genetic studies in simple organisms have shown that that link is at least partially mediated by insulin (which in simple organisms also functions as growth hormone), and that when insulin signals are kept low, indicating scarce energy availability, maximal lifespan can be extended--- a lot; several hundred percent in worms and flies. Glucose is an ancient fuel used even before there was oxygen in the atmosphere, for life can burn glucose without oxygen; it is an anaerobic fuel. The use of fat as fuel came later, after life in the form of plants soaked the earth in oxygen, for you cannot burn fat without oxygen. The primary source of energy stores in people by far is fat, as many unfortunately are all too aware of. The primary signal that indicates how much fat is stored is leptin, and it is also leptin that allows for reproduction, or not. It has long been known that women with very little body fat, such as marathon runners, stop ovulating. There is not enough leptin being produced to permit it. Paradoxically, the first

pharmaceutical use of leptin was recently approved to give to skinny women to allow them to reproduce. Leptin also is instrumental in regulating body temperature, partly by controlling the rate of metabolism via its regulation of the thyroid. Metabolic rate and temperature has long been connected with longevity. Almost all mechanisms that extend lifespan in many different organisms result in lower temperature. Flowers are refrigerated at the florist to extend their lifespan. Restricting calories in animals also results in lower temperature, reduced thyroid levels, and longer life. It should be noted that reduced thyroid levels in this case are not synonymous with hypothyroidism. Here, the body is choosing to lower thyroid hormones because the increased efficiency of energy use and hormonal signaling (including perhaps thyroid) is allowing this to happen.

Anything will dissolve faster in hot water than cold water. Extra heat will dissolve, disrupt and disorganize. This is not what I try to do to make someone healthy. It is commonly advised to "increase metabolism" and increase "thermogenesis" for health and weight loss. Yet how many of you would put a brand of gasoline in your car that advertised that it would make your engine run hotter? What would that do to the life of your car? It is not an increase in metabolism that I am after; it is **improved metabolic quality**. That will be determined at the quality of your leptin signaling. If it is poor, if you are insulin and leptin resistant, your metabolism is unhealthy and high in what I call "metabolic friction". If you then increase its rate you will likely accelerate your demise. To increase the quality of your metabolism you must be able to properly listen to insulin and especially to leptin. If your fasting blood serum level of leptin is elevated you are likely leptin resistant and you will not be healthy unless you correct it.

How do people become leptin-resistant? This is the subject of much research. I believe people become leptin-resistant by the same general mechanism that people become insulin-resistant; by overexposure to high levels of the hormone. High blood glucose levels cause repeated surges in insulin, and this causes one's cells to become "insulin-resistant" which leads to further high levels of insulin and diabetes. It is much the same as being in a smelly room for a period of time. Soon, you stop being able to smell it, because the signal no longer gets through.

I believe the same happens with leptin. It has been shown that as sugar gets metabolized in fat cells, fat releases surges in leptin, and I believe that those surges result in leptin-resistance just as it results in insulin-resistance.

The only known way to reestablish proper leptin (and insulin) signaling is to prevent those surges, and the only known way to do that is via diet and supplements. As such, these can have a more profound effect on your health than any other known modality of medical treatment. When leptin signaling is restored, your brain can finally hear the message that perhaps should have been delivered decades ago; high leptin levels can now scream to your brain that you have too much fat and that you better start burning some off for your life is in danger. Your brain will finally allow you access into your pantry that you have been storing your fat in. Your cells will be fed the food from that fat and they will be satisfied. They will not know whether that food came from your belly fat or from your mouth; nor will they care. They will be receiving energy that they need and will not have to ask for more. You will not be hungry. This also makes counting calories irrelevant, for the calories that you put into your mouth today are not necessarily what your cells will be eating; that will be determined primarily by leptin. Whether or not you

put food into your mouth, your cells will be eating, and if they cannot eat fat they must eat sugar. Since little sugar is stored, that sugar will be had by making you crave it, or by turning the protein in your muscle and bone into sugar. This contributes in a major way to weakness and osteoporosis. Whether or not this lean tissue wasting happens is determined by your capacity, or incapacity, to burn fat, and that is determined by your ability to listen to leptin.

A strategic diet that emphasizes good fats and avoids blood sugar spikes coupled with targeted supplements (as recommended in my Rosedale Diet), will enhance insulin and leptin sensitivity so that you can once again hear their music, allowing your life to be the symphony it was meant to be.