Leptin and its Role in Obesity

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One of the most taxing issues facing today’s society is the obesity epidemic. Humans across the globe are becoming increasingly unhealthy from excess body fat. Obesity differs from simply being overweight in that obesity deals with having too much body fat rather than simply weighing too much. Prevalence of obesity has more than doubled in the past several decades, and is most notable among American adolescents. While it is not difficult to locate obese individuals because of their excessive body fat obesity is not only a cosmetic concern. The disease brings health risks such as heart disease, diabetes, and high blood pressure. Individuals who accept their larger bodies aesthetically are then also accepting the countless health risks that come with the disease.

More than one-third of the adult population in the United States was classified as obese in 201017. This number is large, more than doubling obesity rates from thirty years ago. Immense disparities exist amongst demographics, geographic location, and socioeconomic status. Obesity is most prevalent in Hispanics and blacks and rates are lowest for Asian-Americans. Extreme obesity is most prevalent amongst women than men, most notably in black women whose rate of extreme obesity doubles that of white and Hispanic women. Although rates of obesity have plateaued in the past several years, they remain excessively high and the disease continues to be an issue that plagues the population.

The consequences to an individual’s health are the gravest part of obesity, but the disease does also have immense costs to society. As obesity rates rise, the economic burden that the disease places on health care system will become increasingly vast. Recently published data suggests that given current trends, 43% of United States adults will be obese by 2030. This translates to a $344 billion increase in disease-related costs. It is currently estimated that obesity costs nearly $190 billion dollars in healthcare costs, covering 21% of annual spending.

It is necessary to find suitable therapies and treatments for the disease. Today, treatment primarily revolves around lifestyle changes including dietary, physical activity, and behavioral alterations. Even small changes including healthier eating and exercise can lead to drastic results. While some individuals choose this path and possess the will power required to make those changes, others resort to medications or weight-loss surgery for help.

The causes of obesity are numerous and highly varied. The best known and most talked about also revolve around lifestyle choices. Sedentary individuals are unable to expend the calories they consume, thus accumulating excess body fat. This becomes an even greater issue when sedentary individuals make poor diet choices. Of course, there are several other contributors to the disease. Heredity plays a role in disease development, although health lifestyle choices are typically sufficient in counteracting its roles. In fact, heredity cannot be solely pinpointed as a cause for obesity. Rather, inherited genes may predispose an individual to increased weight gain as well as other environmental factors that may contribute to the disease.

Western diet receives a great deal of scrutiny as a major contributor to the increase in obesity rates, specifically in the United States. Portion control is difficult and vastly skewed in Western diets, which teaches both adults and children poor eating habits. The Western diet is lacking in many essential nutrients such as whole grains, vegetables, fruits, and nuts. Balanced diets help individuals maintain healthy weights. Lack of sleep has also been shown to alter hormones causing individuals to feel hungrier than they may actually be. While lifestyle choices do contribute greatly to the disease, a new field of research revolving around individual genetics and hormones that regulate body fat has made great strides in obesity studies. Jeffrey M. Friedman and his lab at The Rockefeller University are in the forefront of this work. Friedman studies the molecular mechanisms that regulate food intake and body weight. His detailed genetic study of mice led to the discovery of leptin, a hormone produced by adipose tissue that plays a key role in body fat regulation.

Leptin itself is a 16 kDa hormone that acts mainly on the central nervous system. Leptin receptors are most highly expressed in the hypothalamus but are also located in the brainstem and other brain regions and tissues. When bound, leptin inhibits feeding and stimulates energy expenditure in order to regulate body weight. The receptors themselves belong to the gp130 family of cytokine receptors, meaning they rely on enzymatic activity of additional proteins in order to initiate signal transduction.

Leptin acts as a homeostatic regulator in the body. It is secreted in direct proportion to the amount of adipose tissue an individual carries. An individual with a greater amount of fat will thus secrete more leptin. Under normal conditions, this greater increase in leptin will then cause loss of body fat. These secretions thus moderate food intake, also taking into account energy expenditure. It is then no surprise that defects or malfunction in leptin regulation would then contribute to obesity.

One area that receives much attention, particularly from Friedman is leptin resistance by means of elevated plasma leptin levels. Friedman pursues this avenue because of prior work performed on hormone signaling. As seen in the case of insulin, negative feedback is a typical response to excessive signaling in hormone resistant cases. He thus proposes that hyperleptinemia paired with high-fat diet is a requirement for eventual leptin resistance, targeting these ideas in a large volume of his work.

There are drastic physiological differences between lean and obese individuals. These differences also translate to mouse models used to study obesity. Although scientists are aware of these differences, the exact events that lead to leptin resistance and subsequent obesity remain up to debate because there may also be other contributors. Those who study obesity often use ob/ob mouse models to replicate leptin resistance. These mice serve as important research tools because of the many hypotheses surrounding leptin resistance and the development of obesity. Because elevated plasma levels are believed to play a role in the eventual development of leptin resistance, the ability to have models that replicate actual leptin resistance is an important research tool. These mice produce no leptin due to mutation on the ob gene. Of course, other models have since been implemented. Although the majority of obesity...
rather similar progression, the difference in leptin levels was normal mice did not. Although diet-induced obesity followed differed significantly between groups. Wild-type mice became increased leptin-sensitivity? ob-norm mice maintained on HFD remained sensitive to leptin and showed a marked decrease in food intake in response to leptin treatment. This indicated the only difference between HFD groups was leptin levels, this indicates that hypoleptinemia is, in fact, a requirement for leptin resistance following long-term maintenance on a diet high in fat. Ultimately, Friedman found that a high fat diet is not sufficient to cause leptin resistance. While hypoleptinemia is shown to lead to eventual leptin resistance, it does so by means of downregulating cellular response to leptin.

Recent attention has also focused on the possible role of leptin receptors directly related to the increase in leptin resistance. Friedman proposes that fats may be sufficient to induce leptin resistance by either blocking leptin signaling or initiating a cellular stress response in response to dietary changes. It is important to note that increased food intake is not the primary target for the development of obesity in these models. In fact, in several of the studies performed, it is not the increased energy intake that leads the development of the disease. Since mice fed high-fat diets do not significantly more than those maintained on a normal diet, it is possible that the fats themselves may lead to a resistance pathway related to their composition? Because of the logic behind both proposals, much of Friedman’s work tends to elucidate the molecular mechanism behind leptin resistance and subsequent obesity.

It was essential for Friedman to determine a mechanism for leptin signaling at different physiological levels. Friedman utilized osmotic infusion pumps in order to clamp plasma leptin to maintain those found in lean wild-type animals. These pumps were able to maintain fixed plasma leptin levels indicative of lean wild-type mice in an average rat at a rate of 150 ng/kg leptin levels near 5 ng/ml.

The resulting study had four groups. The first distinction was that the mice were normally fed mice with plasma leptin levels at 5 ng/ml, and a control group given PBS in identical demands. PBS was given either as a high-fat diet (HFD) or low-fat diet (LFD). High-fat diets contained 65% calories from fat while low-fat diets had 15% calories from fat. The HFD was maintained in the same way that the LFD is maintained, but at a rate of 150 ng/kg leptin levels near 5 ng/ml.

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A combination of research tools will be utilized to test this. Specifically, leptin quantification will be performed by ELISA analysis as well as immunohistochemistry. Transgenic scientific methods will be implemented in order to model leptin resistance in an ob/ob mouse model. Due to the implications in its therapeutic value, leptin replacement therapy would then be tested with each of the groups by injecting 800 nmh subcutaneous leptin for two weeks. After these injections, the same metabolic biomarkers would be tested for in order to detect any improvement. It is expected that leptin replacement therapy would reverse some of the negative consequences of obesity by reducing food intake and increasing energy expenditure in mice that become obese. The results from these experiments would elucidate the importance of the lesser known leptin receptors and give potential insight into avenues for therapies and further study.

Since its discovery, scientists have invested a great deal of time and money into leptin research. It is without question that the implications that each study brings give hope to the millions of individuals in the world who struggle with obesity. The discovery of leptin and its role in the disease changes the way scientists look at it, moving obesity from a disease caused by lack of self control to a disease with actual psychobiological processes. Application of this work to human subjects will be beneficial in developing potential therapies. While Friedman continues to work fervently on the topic, others have also joined and have dedicated their time to leptin study as well. There is more to be done but the possibility that a therapy could be developed for obesity is not far off. Friedman’s work is groundbreaking and has opened doors that may not otherwise have existed. He has created an entire field of research where there was not one twenty years ago. The discovery of leptin could prove to be one of the most pivotal and important in the twenty-first century and Friedman deserves continued recognition.

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References

