**Why Do We Care About Fat?**

Obesity emerges from an imbalance between energy expenditure and food consumption, culminating in immoderate accumulation of fat in adipose tissue, muscle, liver, and many other organs included in the process that is metabolism. Simply, calories in exceed calories out, thus equating to weight gain. Obesity has an immense and wide negative effect on health. Each year obesity-related conditions cost over 150 billion dollars and cause an estimated 300,000 premature deaths in the U.S. Obesity increases the probability of one being diagnosed with high-blood pressure, joint problems, sleep apnea and respiratory issues, arthritis, cardiovascular disease, fatty liver, diabetes, cancer, and psychosocial effects; all which may shorten or complicate one’s lifespan. The U.S. Surgeon General has declared that obesity has reached epidemic proportions in the United States. Approximately: 35% of women and 31% of men are considered seriously overweight and 15% of children between the ages of 6 and 19 are overweight. Public health officials warn that the results of poor diet and physical inactivity are catching up to tobacco as a significant threat to health. Knowledge of the neurobiology of intake and energy homeostasis has aided from the revelation of hormones and their binding sites in the hypothalamus (located at the base of the brain, near the pituitary gland). However, eating and body weight are both complex procedures that are dictated not only by conscious decision-making, but are also predisposed to environmental factors such as properties of food, availability, cultural and social norms, behavioral factors, and genetic factors. A deeper comprehension of how brain regions involved in cognition, reward, and executive control of intake can possibly overtake metabolic regulation which can facilitate how we treat and prevent obesity.

In the principality of gene expression, leptin in terms of allele format is a dominant O. Leptin, an amino acid that is an enzyme, is a peptide secreted by adipocytes (fat cells) in proportion to their triglyceride (main constituents of body fat content). It links changes in body energy (fat) to adaptive responses in the central control unit of energy equilibrium (balance). Leptin suppresses appetite and increases metabolism. It acts as a hormone (chemical messenger released in one part of the body that affects another) that requires a specific receptor for binding before an effect is caused. By binding to and activating the long form of its receptor (LEPR-B) in the brain, leptin reduces food intake while increasing energy expenditure. However, if either leptin or its receptor is not operating correctly, it will render leptin and its usage ineffective. An overview of the cascade of leptin:

|  |  |  |
| --- | --- | --- |
| Leptin binds to the leptin receptor stimulating the hypothalamus | The hypothalamus prompts the pituitary gland | The pituitary gland secretes hormones which galvanize the thyroid gland to release thyroxine (raises metabolism) |

This is known as a cascade of events, a hormonal cascade.

**The Rise and Fall of Leptin**

Leptin levels rapidly diminish via response to fasting and elicit large changes in the balance of hormone and energy levels. Relatively low leptin levels evoke over-eating and diminish immunity, thyroid and reproductive hormones, and energy expenditure. Leptin replacement or alternatives revert (turn back) such alterations in immunity, levels of hormones and hypothalamic neuropeptides, and metabolism. Moreover, exogenous (external) leptin decreases feeding and body weight in normal patients and is an important hindrance of energy expenditure in patients not eating. Furthermore, the restoring of individuals lacking fat cells enhances the function of reproductive and reverses atypical (not normal) glucose and lipid metabolism. Such adaptations caused by low leptin levels might have progressed as a protective against the potential of starvation by restricting energy use and improve energy storage in in the form of fat. In the contemporary or modern setting, where food, for the most part, is plentiful and exercise is not fully participated in, this metabolic efficiency is leans toward obesity. An establishment is made that leptin deficiency is a core regulator of neuroendocrine (both neural and endocrine in structure or function) and metabolic responses that is associated by negative energy balance and weight loss. Although, leptin administration decreases food intake in normal individuals, food consumption eventually returns to normal during extended leptin oversight, once body fat units have been notably impacted. In addition, treatment with leptin alone is ineffective as means to reduce food intake and body weight on obese individuals. Nonetheless, elevated circulating leptin levels in obese subjects inspires the notion of “leptin resistance” in typical cases of obesity.

**Assessing Leptin Resistance**

Ultimately, leptin resistance is synonymous with the word obesity. Furthermore, since obesity promotes a multitude of pathways of cellular leptin resistance, compromised leptin mechanisms is evident in obese subjects. To completely understand this model, occurrences of genetic obesity must be analyzed: 1. NPY suppression 2. Alterations in LEPR-B or LEPR-B signaling, 3. Disruption of neural pathways known to participate in leptin action, and 4) A leaky IMM.

* NPY Suppression

NPY suppression of appetite; represses neuropeptide y (NPY) which is an appetite stimulant that results in the loss of appetite. This stimulant causes leptin to bar transcription of mRNA for NPY leading to appetite levels decreasing.

* Alterations in LEPR-B or LEPR-B signaling

Individuals with primary LEPR-B mutations are the simplest to identify as the correlation of the defeat of cellular leptin action is uninhibited to obesity pathogenesis. Reduced leptin action and LEPR-B signaling is connected to such alterations that accommodate LEPR-B trafficking or down the pathway LEPR-B signaling.

* Disruption of neural pathways known to participate in leptin action

Proopiomelanocortin (POMC) neurons in the nucleus of the hypothalamus protrude to downstream targets in the arcuate nucleus of the hypothalamus (ARC) (e.g., the paraventricular hypothalamic nucleus, PVH) where they free POMC-derived peptides, which involves α-MSH, that activate CNS melanocortin receptors to diminish food consumption and enlarges energy disbursement. Many POMC neurons exhibit LEPR-B, and leptin expands the task of the melanocortin system. Interference of melanocortin activity by physical lesions of the ARC or PVH, by pharmacological features, or by a myriad of genetic modifications at the tier of the melanocortin peptide or its receptors, results in obesity and corresponding hyperleptinemia.

* A leaky IMM

Leptin also has the ability to make the inter-mitochondrial membrane (IMM) leaky. By prompting the release of uncoupling protein, the membrane becomes compromised and leaky to protons (H+) caused by leptin. As a consequence, this leads to the rapid release of electrons from the body in the form of heat (thermogenesis); the lack of ATP increases the demand for more electrons from carbohydrates and fats, causing even more carbohydrates and fats to enter the respiratory pathway.

**To conclude:**

While the apparatus or process of cellular leptin resistance is likely to have imperative implications for energy equilibrium (balance), it is noteworthy to discern cellular leptin resistance that is caused by obesity from the often-specific primary processes that foster or lead to obesity in genetic (and as well another, e.g., diet-induced) structures. The merit or basis of obese genetic models is rooted in the recognition of underlying molecular channels that dominate energy balance and, when faulty, can cause or predispose to obesity. To successfully dictate the potential primary effect of a genetic lesion (wound) on leptin action, trials must be performed in subjects that are a normal weight so that we can compare the internal effects of obesity, record the similarities and differences, which can then inform us on just how obesity comes about on a molecular level. Moreover, it would also allow those who would be considered obese to be treated or prescribed methods of preventative and/or limiting risk.

**References**

Ahima R. S. (2008). Revisiting leptin's role in obesity and weight loss. *The Journal of clinical investigation*, *118*(7), 2380-3.

Mantzoros, C. S. (1999). The role of leptin in human obesity and disease: a review of current evidence. *Annals of internal medicine*, *130*(8), 671-680.

Myers, M. G., Leibel, R. L., Seeley, R. J., & Schwartz, M. W. (2010). Obesity and leptin resistance: distinguishing cause from effect. *Trends in endocrinology and metabolism: TEM*, *21*(11), 643-51.

Shalitin, S., & Phillip, M. (2003). Role of obesity and leptin in the pubertal process and pubertal growth—a review. *International journal of obesity*, *27*(8), 869.

https://stanfordhealthcare.org/medical-conditions/healthy-living/obesity.html