

The Chemistry Behind Eating

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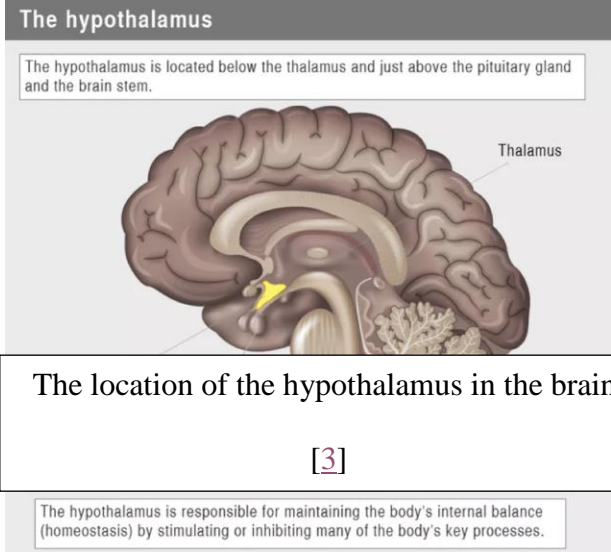
How Does Hunger Work?

Hunger is a physical sensation that is experienced by every human in the world. This sensation is necessary to inform the body to desire to eat food, so the body has the necessary energy to survive. About 800 million people experience severe hunger and undernourishment, while 2.1 billion are overweight. [1] People at either extreme both deal with hunger, but what causes it? The cause of such a pivotal part of everyone's lives goes largely ignored. If people were asked what causes hunger, many would be at a loss of words aside from saying something along the lines of "not eating food" or describing symptoms such as stomach pains or grumbles. This answer is classified as homeostatic hunger, derived by the body's need for energy. Homeostatic hunger is classification most commonly referenced when hunger is discussed. The lesser known and understood type of hunger is hedonic hunger, which is a result of wanting to eat food based on a

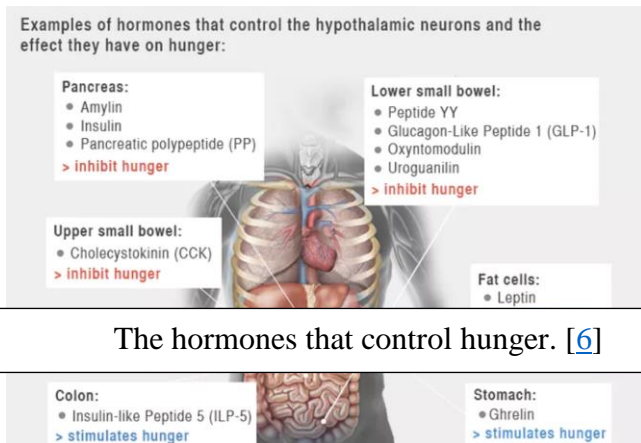
craving. This is most likely rooted from humans wanting to eat delicious-tasting foods, so they eat when they do not actually need to. Hedonic hunger is more mentally-driven than homeostatic hunger, although homeostatic hunger is intertwined with the brain. [2] The feeling of hunger is a complex process regulated by the hypothalamus. The hypothalamus is a region of the brain that connects the nervous system to the endocrine system. These systems are responsible for the body's relaying of information and regulation of bodily functions. Balance in the body's blood pressure, body temperature, immune responses, and hunger are all controlled by the hypothalamus. The nervous system is comprised of neurons to complete electrochemical signaling and the endocrine system is composed of organs that control cell signaling based on hormone production and release. This is achieved by the hypothalamus's secretion of hormones which stimulate or inhibit the brain's neurotransmitters. In the hypothalamus, there are receptors for hunger-signaling chemical messengers. The two main messengers are ghrelin, which signals hunger, and leptin, which signals the feeling of being full (See the sections "[Ghrelin](#)" and "[Leptin](#)"). [4] These messengers are a result of signals from cells in the small intestine and stomach. [1] For example, ghrelin is released from the stomach and small intestine before eating and when fasting, which the timing is influenced by normal meal routines. Ghrelin and leptin levels increase and decrease at opposing times in relation to each other. [5] As a response to the fluctuation of the ghrelin and leptin levels, the hypothalamus in turn produces the proteins neuropeptide Y and agouti-related peptide to stimulate hunger sensations or produces two other proteins, cocaine and amphetamine-regulated transcript and melanocyte-stimulating hormone, to block hunger. [7] The relationship of these proteins to the messenger chemicals can be seen in neuropeptide Y as it causes more food to be consumed

and less physical activity to occur when blood sugar levels drop. Leptin helps prevent production of this messenger. [8]

Ghrelin and leptin are the two most prevalent hormones associated with hunger, but there are more that also have important roles. Insulin and glucagon are two other hormones that can signal hunger. These affect the body's blood glucose level. The blood glucose level rises after food consumption, which is noted by the hypothalamus. This in turn causes the hypothalamus to release hormones to tell the body that it has had enough. [1] Additionally, when insulin enters the brain it also stops hunger by relaying that there is a sufficient amount of energy within the body. Another hunger-preventing mechanism arises from the digestive system. The progress of food in the digestion cycle can also determine hormone production and hunger. When food enters the small bowel and gut, various hunger-suppressing hormones are released, giving the body a full feeling. When the body is full, signals are sent to the hypothalamus to cease ghrelin



production. This results in low levels of ghrelin about thirty to sixty minutes after eating. This time also coincides with a peak in the levels of the hormones that initiate the sense of being full. After three to four hours, the hormones are back at their respective fasting levels. [7]



Ghrelin

What is Ghrelin?

Ghrelin is one of the two ‘hunger hormones’, alongside its pair [leptin](#). A [hormone](#) is a signaling molecule that is produced by glands, and transported through the circulatory system to organs to regulate physiology and behavior. Ghrelin is a hormone that is composed of a 28 amino-acid peptide chain, and is primarily responsible for increasing appetite ([12](#)). It does this by activating receptors in the region of the [hypothalamus](#) responsible for regulating appetite ([9](#)). Ghrelin also has other effects besides increasing appetite, including: reducing blood pressure, reducing inflammation, or [adipogenesis](#) (increasing the production of fat in the body). Ghrelin is secreted by primarily by the stomach in pulses that increase before a meal, and decrease after; however, many other factors affect the rate of ghrelin production, such as: gender, BMI, and age ([12,9](#)).

How is Ghrelin made?

The biological information to produce Ghrelin is located on chromosome 3, and encodes for a 28 amino-acid long peptide chain. This code includes When the ligand that induces ghrelin production binds to the protein receptors of the cell, a chemical signal is sent into the cell’s nucleus in the form of transcription factors. This starts the process of transcription. The transcription factors will bind to certain areas of DNA, in ghrelin’s case, the section of chromosome 3 responsible for ghrelin production. These transcription factors will then ‘recruit’ RNA polymerase to the site, which will read the DNA sequence and produce mRNA. tRNA will then bind to the mRNA strands and transport them outside the nucleus. Once outside the nucleus, the tRNA will take the mRNA to a ribosome, which will read the mRNA and construct an amino acid chain, or a polypeptide. This chain will then fold into a specific shape ([10](#)). The result is the hormone known as ghrelin. This gene and how it becomes ghrelin can also be shown in table 1 below.

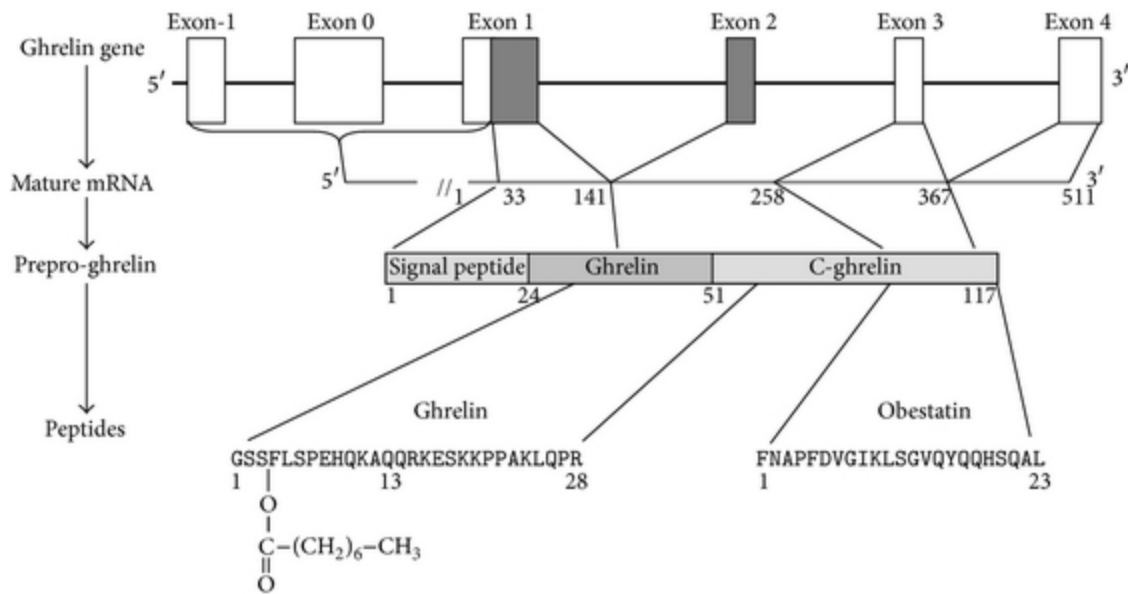


Table 1: The process of Ghrelin transcription and translation. Starts out with the gene for Ghrelin, which is then turned into mRNA, and from there is translated into Ghrelin. [9]

Ghrelin's effects on the body

Ghrelin affects the body in various ways. The primary function of ghrelin is to increase appetite [12]. Ghrelin is also involved in energy homeostasis through long-term body weight regulation, otherwise known as fat production. Ghrelin induces adiposity by reducing the use in energy for digestion, increasing the utilization of carbohydrates while reducing the utilization of fat [12]. The more ghrelin is produced, the more the body produces adipose tissue. Ghrelin also stimulates the production of the secretion of growth hormone. For ghrelin is the ligand for the growth hormone secretagogue receptor, secretagogue being a substance that promotes the secretion of a substance [9]. These three effects, increasing appetite, regulating the production of adipose tissue, and stimulating the production of growth hormone, are the primary effects that Ghrelin has on the body, however, ghrelin still has many other effects.

Ghrelin also affects the production of insulin, inhibiting insulin secretion at low concentrations, and stimulating insulin secretion at high concentrations. Insulin is used to turn glucose, or blood sugar, into energy. Through either stimulating or inhibiting the secretion of

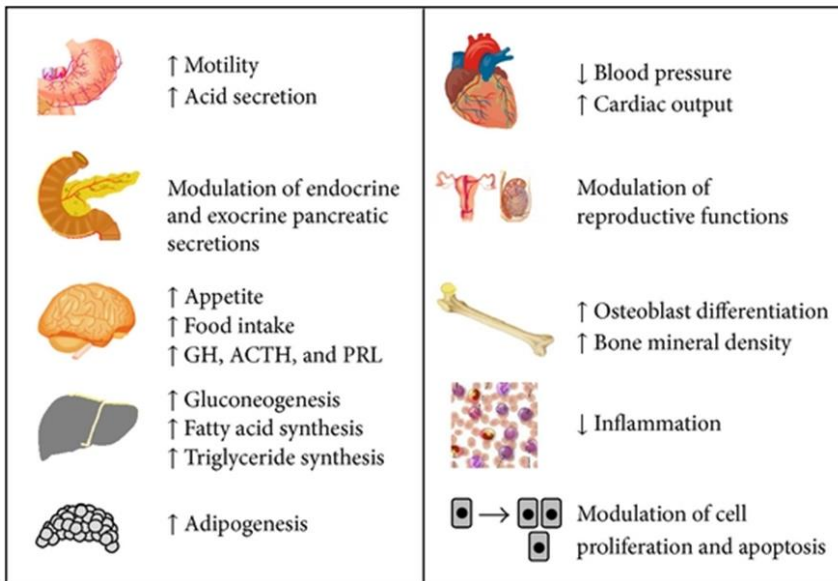


Figure 2: Effects of Ghrelin [10]

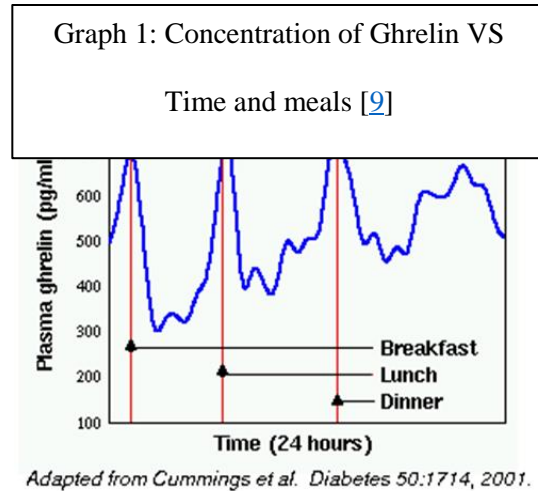
insulin, ghrelin plays a supporting role in glucose homeostasis through the nervous system sensing changes in the levels of glucose, and either increasing or decreasing the production of ghrelin [10]. There are many more effects of glucose, such as increasing the secretion of stomach acid, or lowering blood pressure.

Some of these effects are shown on Table 2 [10].

What affects the production of Ghrelin?

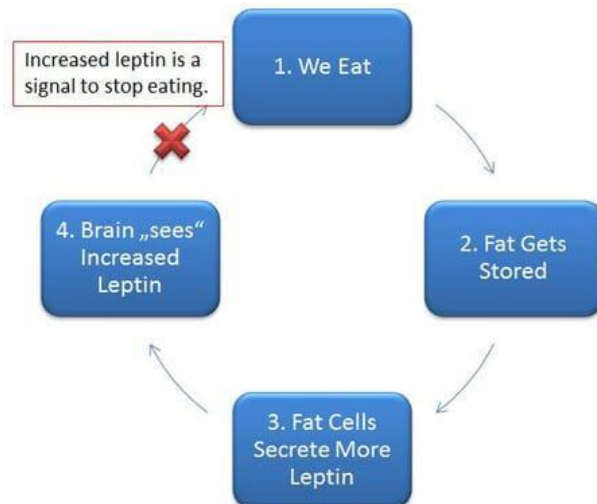
The amount of ghrelin produced, or the circulation of ghrelin has been shown to affect the body in many ways, and the concentration of ghrelin can affect different bodily functions differently depending on the concentration of ghrelin. For example, as noted above, a high concentration of ghrelin will stimulate the production of insulin, thereby increasing the rate at which the body can turn glucose into energy, while a low concentration of ghrelin will inhibit insulin production, decreasing the rate at which the body can turn glucose into energy. The production of ghrelin is controlled by the central nervous system, specifically by the [hypothalamus](#), a region of the brain responsible for the regulation of the [endocrine system](#) through its connection to the [pituitary gland](#). The endocrine system is composed of hormone-releasing glands throughout the body, hormones, and hormone receptors [13]. The pituitary gland regulates the functions of other endocrine glands by either stimulation or inhibition [11]. The central nervous system can detect changes in bodily functions or the concentrations of hormones whose secretion is induced by ghrelin, and send signals through the hypothalamus, to the pituitary gland, which will secrete hormones that will induce the secretion of ghrelin.

The circulation of ghrelin can also be affected by other factors. Glucose, insulin, and growth hormone all inhibit the secretion of ghrelin as to prevent the overproduction of energy from glucose, or the overproduction of growth hormone through ghrelin inducing the secretion of growth hormone. Some outside factors that affect ghrelin circulation include are food intake, age, and gender. Ghrelin levels increase pre-prandially, and decrease post-prandially as shown in graph 1, ghrelin production decreases with age, and females have been shown to have higher concentrations of ghrelin than males [12]. More information on outside factors that affect ghrelin can be found [here](#).

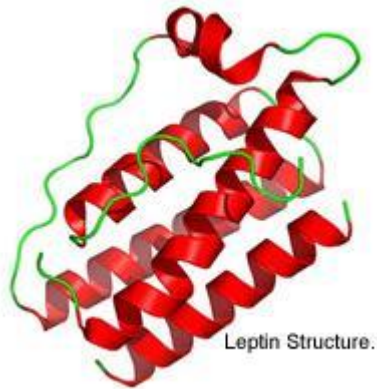


Leptin

Leptin, sometimes known as the “starvation hormone,” was discovered in 1994. [15] This hormone is produced by the body’s fat cells, and it then tells the brain whether to eat though a process known as a negative feedback loop. That is, a stimulus or event causes a decrease in the output of a system. In the case of leptin, when we eat, body fat content increases, which causes leptin production to increase, which results in eating less and burning more calories. On the flip side, if we don’t eat, our body fat content decreases, which causes leptin production to decrease, which results in eating more and burning less calories.



The more you eat the more leptin is produced. [16]



Clearly, leptin has some major effects on day to day life, but what happens if you don't get enough of it? First, you would get hungry due to the negative feedback process. Second, your body would think that it has a shortage of fat and would try to produce more to compensate. In some cases, this has the potential to lead to obesity. In addition, when losing weight, the lower levels of leptin triggers a reaction in the brain that causes more hunger and food cravings. [17]

The structure of the leptin hormone. [22]

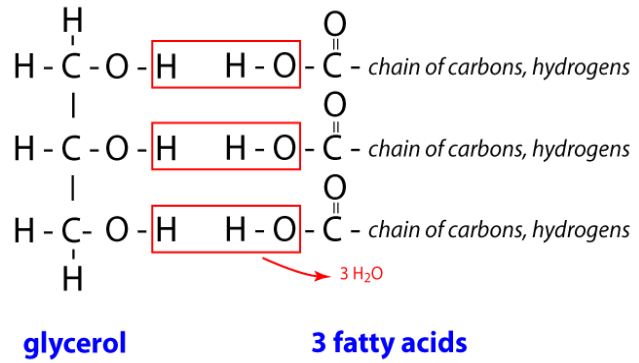
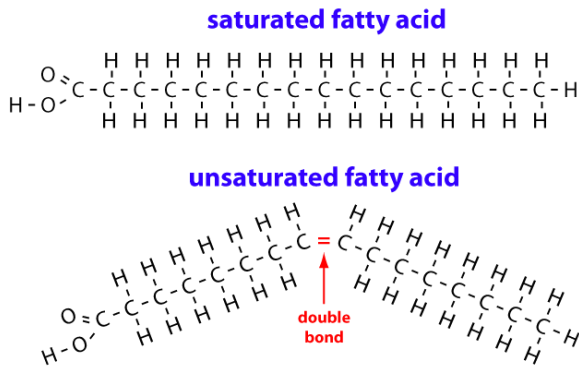
Leptin Resistance

Leptin is directly linked to obesity. Obese people have a lot of fat cells, which produces a lot of leptin. Logically, obese people should not be very hungry due to their elevated leptin levels, however, they may suffer from leptin resistance. Leptin Resistance is an abnormality that causes errors in sending correct signals to the brain. Put simply, someone who suffers from the hormonal defect of leptin resistance would not burn as much energy at rest and would send signals to the brain to eat more food. Unfortunately, even if you know you have leptin resistance, it is almost impossible to overcome it through sheer strength and determination. [16]

Furthermore, taking leptin injections only helps around 5-10% of all obese humans. Fortunately, that means that between 90-95% of the population is not leptin resistant. [18]

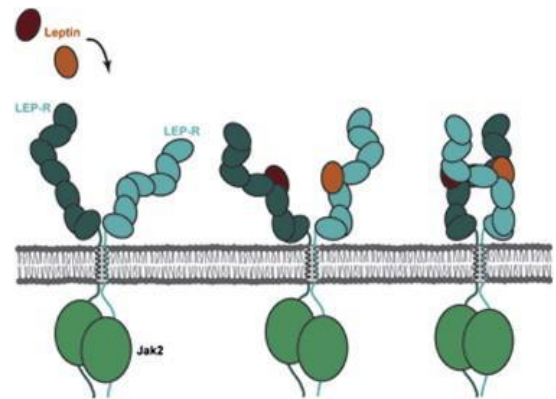
Leptin Resistance is caused by several factors. The first factor is inflammation in the [hypothalamus](#). What happens is that the leptin becomes unable to bind to the leptin receptors in [adipose, liver and muscle tissues](#). If the leptin cannot bind to the receptors, then it cannot transmit the appropriate signals and follow the correct chemical pathways to the brain to stop craving food. [19] One other factor for why the leptin is unable to bind to its receptors is free fatty acids. Both leptin and fatty acids synthesized by increasing the intracellular [lipid](#) concentration, which as a result reduces lipid oxidation. When fatty acids block the enzyme receptor and increase the concentration of intracellular [triglycerides](#), it becomes impossible for the leptin to attach because the fatty acids are in those spots instead. [20] Other possible factors

are still being investigated, but could include stress, immune system disorders, or even having high amounts of leptin, which raises the threshold for what the normal level is.



On the left is an example of fatty acid chains, and on the right is a triglyceride. [23]

Although leptin resistance is not extremely common, there are still ways to mitigate the possibility of becoming susceptible to it or even reverse it. First, avoid highly processed foods. These foods have the fatty acids that will prevent leptin from binding to its receptors, and they can also increase potential inflammation. Instead of eating processed foods, try soluble fiber such as fruits and oatmeal. If you don't have enough fiber, carbohydrates will fill your bloodstream instead, which causes insulin and leptin levels to rise. However, the increased insulin produces triglycerides which prevent the leptin hormones from binding to their receptors. Similarly, lowering the amount of triglycerides by reducing the amount of carbohydrates consumed can help. [21] Another possible way to reduce leptin resistance is to eat more protein. Higher amounts of proteins are correlated with an



The structure of the leptin receptor on cells. [24]

increase in leptin sensitivity since it takes more energy to expend the protein. Finally, sleeping and exercising more could influence leptin resistance, although those factors are still being studied. [16] More information about leptin and weight loss can be found here:

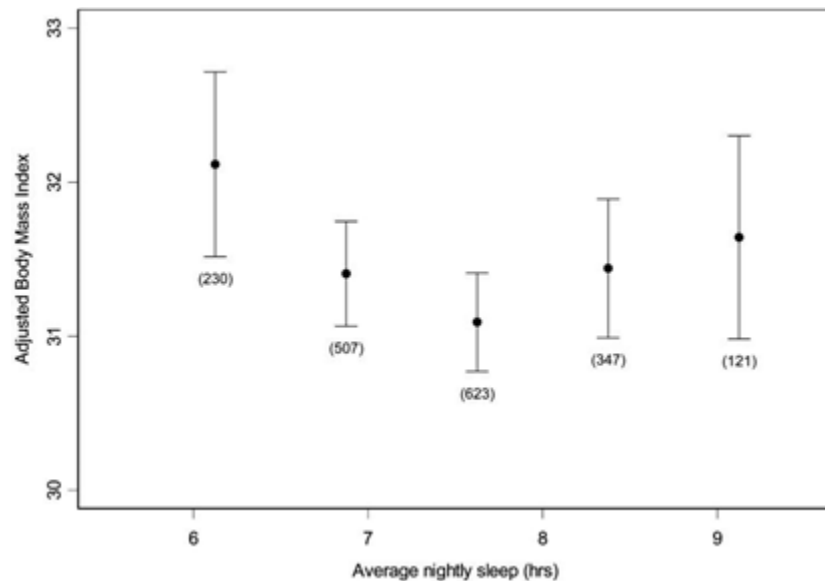
<https://www.webmd.boots.com/diet/guide/the-facts-on-leptin-faq>

Outside Factors and their Effects

Sleep and Ghrelin

The relationship between sleep and Ghrelin has been thoroughly developed by food scientists. [Ghrelin](#), as mentioned above, is an amino acid peptide chain responsible for signaling hunger and inducing psychological and physical responses. This process is controlled by a part in the brain called the [hypothalamus](#). During sleep an individual's ghrelin levels decrease. This phenomenon is due to the relationship between the energy expended and the effect that expenditure has on the rapidity in which ghrelin levels rise (25). A lack of sleep, thus has a direct relationship with an

individual's hunger levels as it causes the brain to perceive that it needs more calories to maintain high energy levels. To document the effect that sleep has on the tendency to overeat, Shahrad Taheri conducted a comprehensive research project. Taheri's finding supported the hypothesized



effect mentioned above and were used to develop a general mathematical relationship between an individual's average daily sleep, and their BMI, which was related to eating patterns and thus ghrelin levels (26). The researchers concluded that for individuals sleeping less than 8 hours there was a very strong, almost linear, relationship between sleep and BMI.

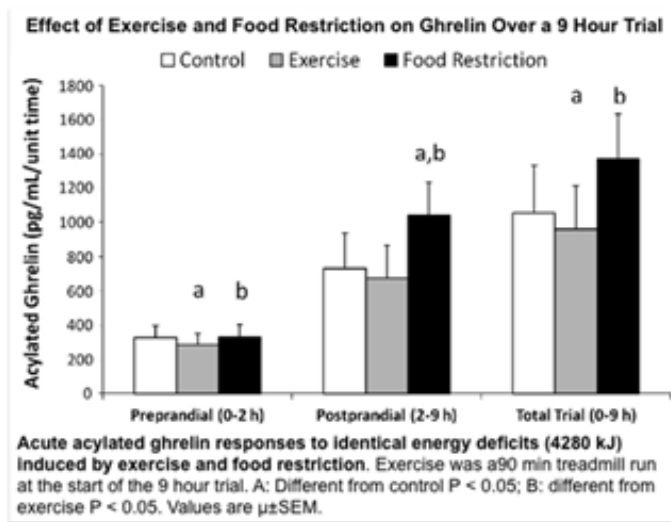
Sleep and Leptin

The effects of sleep on [leptin](#) are the opposite. When an individual is sleeping they require much less energy as the cerebral metabolic rate of glucose is reduced by 44% and the CMR of oxygen is reduced by 25%(27). This means that the amount of energy the brain

perceives it needs to extend, and thus the amount of ATP it needs to intake, is substantially lower. Many researchers have supported the idea that there is an observed relationship between obesity and lack of sleep (26). Companies that conduct weight loss programs often recommend that individuals alter their sleep schedule to reduce the brain's drive to overeat.

Exercise and Ghrelin

Long term exercise patterns have a slightly different impact on the levels of ghrelin present. Long term exercise effects the fluctuation levels of ghrelin in individuals before and after eating. Individuals who do not exercise as frequently have lower sensitivity of ghrelin. The



change in ghrelin levels before and after eating for obese individuals is much lower than the change in levels for healthy and regularly exercised individuals. This means that during times of fasting, individuals who exercise will have higher appetites, but lower appetites after consumption of a meal (28). Figure 2 shows the distribution of ghrelin levels and their differences between exercising and fasting for different periods of time. The study mentioned concluded

that while ghrelin levels may eventually be higher because of a workout (due to lack of energy in an individual's body), the first 30 minutes after a workout are not accompanied by an increase in ghrelin.

Exercise and Leptin

Multiple studies have concluded that there is a relationship between leptin and energy exerted in exercise. While the particularities are still debated within the literature, it has been widely accepted that there is a significant caloric expenditure required in exercise to have a substantial reduction in leptin levels. 800 kcals is the threshold that many researchers in the literature claim is necessary for such effects to be examined (29). Once that level is reached an individual's leptin level drops, because the amount of ATP required to sustain levels of exercise

is higher than the existing amount of ATP being expended which triggers a response from the brain that signals a need for intake of food to replenish ATP (29).

Protein

A high protein diet has been found to have a substantial effect on an individual's appetite. Protein releases leptin at a rate higher than other food types. Protein, therefore, is more "filling" in the sense that it does not require as much intake to make the brain think that it doesn't require much more ATP and therefore eliminates hunger at a higher rate per gram of protein consumed. (30)



Carbohydrates

Foods that are high in carbohydrates have been associated with low levels of satiety and have been thought to be correlated with overeating and obesity. High glycemic carbohydrates (i.e.: potatoes, rice, etc.) have been associated with a "spike" in the amount of insulin produced by the



body. Rather than a gradual increase in the amount of insulin in the blood stream when eating foods with high protein value, eating high glycemic carbohydrates have rapid insulin spikes which can have adverse effects on leptin release, because it acts as a high magnitude delayed reaction (31). It is a common misunderstanding that high carbohydrate diets have no satiety.

While this is untrue, the misunderstanding stems from the fact that the rate of leptin released is much slower in foods with high carbohydrate levels than foods with high protein.

Appendix

Adipose: body fat, fat

Endocrine system: system composed of hormone producing glands, hormones, and hormone receptors.

Hormone: Signaling molecule produced by a gland. Carries a chemical signal to a cell to incite a reaction, such as cell replication, protein synthesis, or hormone synthesis.

Pituitary gland: Gland that secretes hormones that regulate other hormone producing glands, connected to hypothalamus.

Prandial: during/related to lunch or dinner

Adipose, liver, and muscle tissues: These are the main tissues that are associated with leptin. Adipose tissue is just fat cells with the purpose of storing energy. Everyone has fat cells, and although there are different types of fat cells for different parts of the body, such as the neck, liver, or bones, obese people have more of these fat cells than normal. The liver is useful for processes such as protein synthesis, digestion, and hormone production. For those reasons, it is an especially important part in the production of leptin and a damaged liver may have severe consequences for the regulation of leptin and sending those signals to the brain. If the liver is damaged and not able to produce hormones correctly, you might not be hungry when you need to eat. Leptin can also affect the metabolism of bone and muscle tissues by binding to receptors on them.

Lipids: There are many types of lipids, but the ones involved with leptin are the fatty acid ones. These contain carbon chains that can be several carbons in length with different combinations of the same structure called isomers. These chains can also be saturated or unsaturated, with the difference being that saturated fats have single carbon bonds and therefore many more hydrogen atoms, and unsaturated fats do not. While the different types of fatty acids and lipids affect leptin receptors in slightly different ways, they still perform the main function of blocking the receptor.

Triglycerides: Triglycerides are essentially fats in the bloodstream that give you energy. Some come as a product from digestion of food in the liver, others from carbohydrates or other sources of energy. When you are between meals, you are getting your energy from triglycerides that are released by other hormones.

ATP: (Adenosine Triphosphate) is a nucleotide known in biochemistry as the “currency of intracellular energy transfer” as it is able to store and transport chemical energy within cells.

Protein: Large biomolecules consisting of one or more long chains of amino acid residues.

Carbohydrate: Biological molecule consisting of carbon, hydrogen, and oxygen usually containing a 2:1 ratio of hydrogen to oxygen.

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