Worrisome Weight Gain

How Stress Affects Eating Behavior

By Madison Ladd

In the past two decades, childhood obesity rates have seemed to level off. Despite this plateau, obesity in children of low-income families is actually increasing, an alarming phenomenon. Susan Babey, Ph.D. from UCLA Center of Health Policy Research, stated that "when we looked at [obesity] rates broken down by income, we saw that for adolescents whose family incomes are below the poverty line, those rates have gone up, and not just slightly, but rather dramatically." Recent studies show that the environment in which a child grows up can contribute to his or her obesity. Additionally, girls were more likely to be obese if they had experienced stressful experiences such as violence, maternal disconnection, or unstable housing situation.[1]

In the United States alone, individuals who live in the most poverty-dense counties, counties with poverty rates greater than 35%, are the most prone to high rates of obesity. The probability of obesity occurring in poverty-stricken counties is 145% greater than in wealthy counties.[2] As of 2018, 38.1 million Americans lived in poverty, including 13.1 million children.[3,4] Obesity is when there is excessive fat in the body that increases the risk of health issues. Obesity is a growing epidemic in the United States as prevalence rates are trending upwards. Youths from the ages of 2 to 19 in 2018 had an obesity rate of 19.3% while adults, individuals 20 years and older, had an obesity rate of 42.4%.[5]

Poverty is just one example that fits under the umbrella term psychosocial stress: the lack of adequate resources for living such as food, housing, and support. This term can also include other societal and environmental stressors such as a pandemic, famine, gun violence, work environment, loneliness, etc. Most of these we are unable to control; we have to adapt to survive. Such conscious decisions to stay safe are methods to persevere, but how do we save ourselves from changing our biology? Recent research shows that chronic stress wreaks havoc on the biology of our genome. Epigenetics modifies our genome and allows for changes to occur within our genome without changing our DNA sequence, our genetic makeup. With the common assumption that obesity comes from lack of exercise, laziness, and

unhealthy eating, it is time to shine some light on the idea that maybe obesity is not just a lack of healthy eating and exercise, but a deeper modification of our biology: the HPA axis, which contributes to obesity.

What is the HPA Axis?

Stress alters homeostasis, the healthy state of stability or equilibrium within the body, of an individual and causes a chain reaction to occur. The Hypothalamic-Pituitary-Adrenal axis (HPA axis) responds to acute and chronic stressors; however, chronic stress comes with consequences to both mental and physical health. The HPA axis is a feedback loop that involves the brain and the kidneys. Healthy HPA axis function enables the body to respond to stress. The axis will change the levels of hormones within the body to react appropriately. Once the stress level is addressed, the HPA axis will return to homeostasis. However, when an individual is exposed to chronic stress, the HPA axis constantly produces cortisol and does not return to its baseline.

When the HPA axis acknowledges a stressor, the hypothalamus is the first within the brain to recognize it. The hypothalamus is responsible for what some people call the 'four F's': fighting, fleeing, feeding, and reproduction. Therefore, when the hypothalamus detects a stressor, it releases a hormone called corticotropin-releasing hormone (CRH), which then notifies the pituitary gland. This gland in the brain is responsible for controlling the hormones for many different processes in the body. In this specific process of reacting to stressors, the pituitary gland releases a hormone called adrenocorticotropic hormone (ACTH) to the adrenal glands of the kidneys. The adrenal glands produce the stress hormone cortisol. In a healthy HPA axis, cortisol would then act as negative feedback to decrease activity throughout the HPA axis. However, when an individual is exposed to chronic stress, the HPA axis cannot decrease activity, causing constant production of hormones from the HPA axis (Figure 1).[6,7]

Changing our Biology through Epigenetics

Some of these changes within the HPA axis may be due to epigenetics. The study of epigenetics is a relatively new field. To get a better understanding of how changes to our biology contribute to obesity, we need to understand how epigenetics works. Epigenetics are modifications to one's genome that are not changes to the DNA sequence. Additionally, epigenetics can be helpful within an individual and among a population. Within an individual, epigenetics is responsible for cellular differentiation and phenotype maintenance. Within the population, epimutations can allow members of the population to adapt to the environment; this adaptability increases the chances

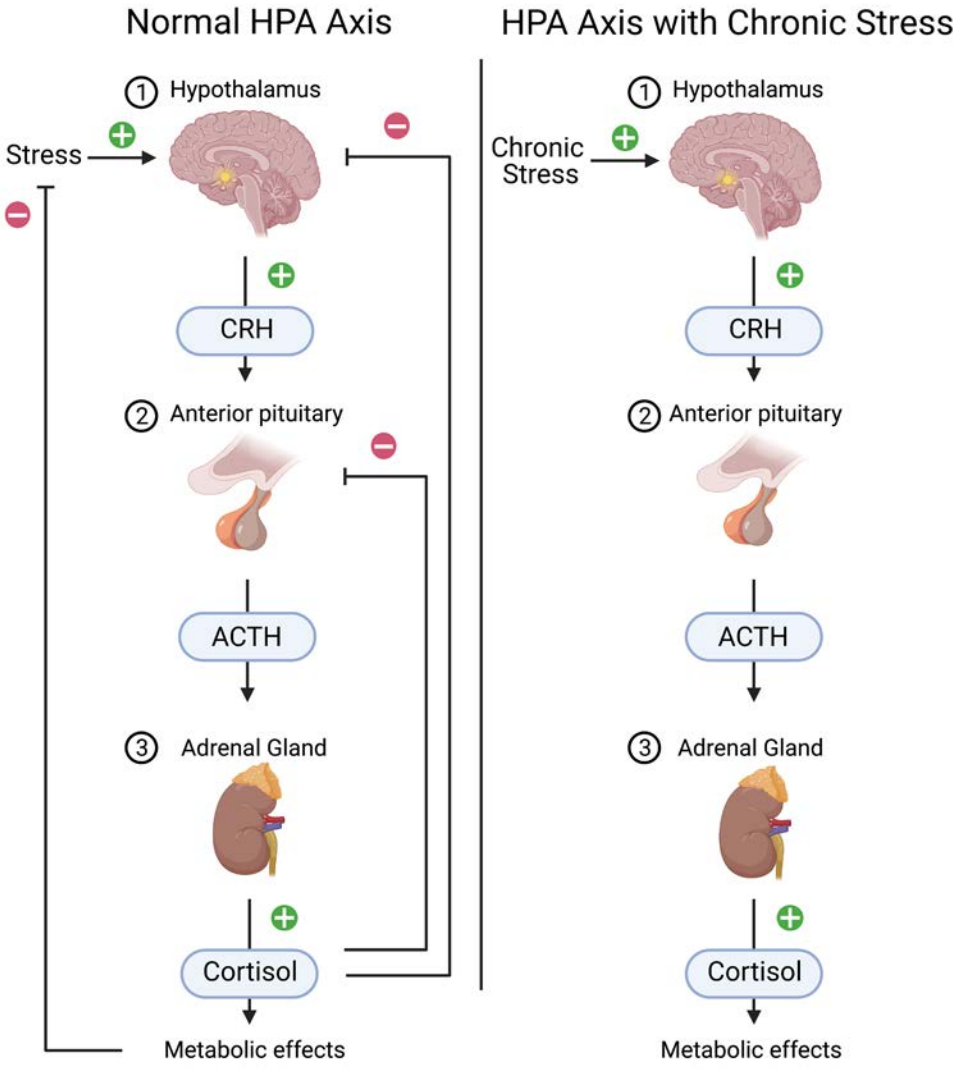

Figure 1. The HPA axis. Adapted by Madison Ladd from Camilla Maria Fontana, PhD student, University of Padova. Created in BioRender.

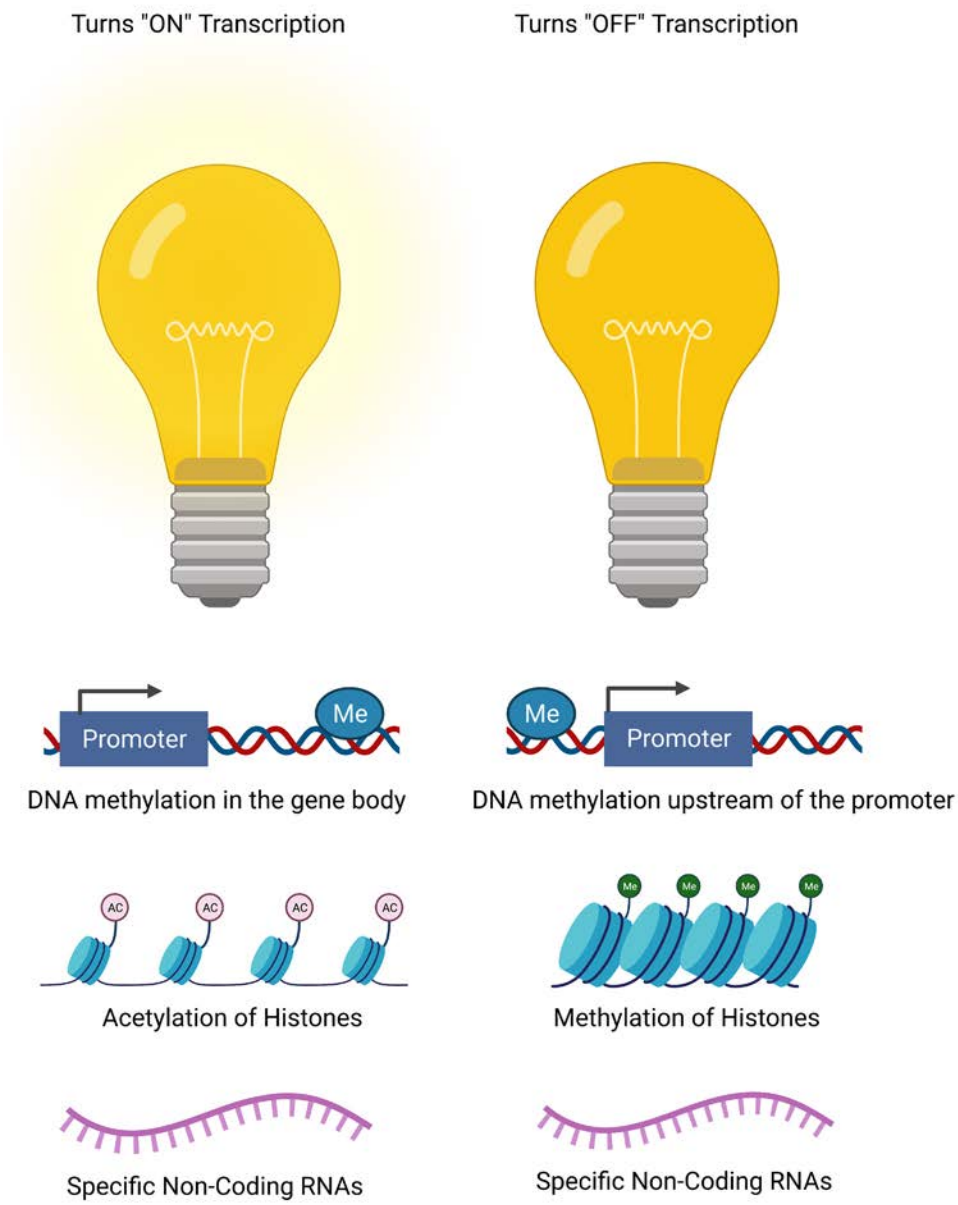

Figure 2. How epigenetics can alter gene expression. Original figure by Madison Ladd. Created in BioRender

of survival.[8] These changes occur when an individual is exposed to different everyday stimuli. Think of these changes as a light switch: with the light turned on, light is produced, and activity happens. Just like when a specific epigenetic change occurs, it allows the opportunity to turn "on" a gene, allowing for the gene to be expressed. When the light is turned off, no light is produced, and nothing usually happens. When a specific epigenetic change turns "off" a gene, the gene is not produced, and nothing occurs (Figure 2). These changes in gene expression can be passed down from generation to generation. Such modifications include methylation, histone modifications, and non-coding RNA.

Methylation is the addition of a methyl group (CH3 group) to a cytosine. Within DNA, methylation controls access to transcription, which is the reading of DNA; this methylation can modify cytosine, a base pair within DNA. When methylation occurs to a CpG pair, which is an area within the DNA where a cytosine is followed by a guanine nucleotide in the sequence, upstream of a gene in the promoter region, this process can silence or decrease transcription activity. Stopping the binding of active proteins, such as transcription factors, and recruiting repressive proteins, such as MeCP2, will decrease transcription activity. If methylation occurs within a gene, then it can activate or increase transcription activity because there is no inhibitor to stop the binding of RNA polymerase.[9] Enzymes known as DNA methyltransferases (DNMT) will add these methylation marks. DNMT falls into two categories: maintenance and de novo (new). Maintenance DNMTs on the opposite strand of the double helix are "writing" in the methylation after DNA replication. De novo (new) DNMTs "write" new methylation marks according to any given environmental stressor.[10]

In a cell, DNA wraps around histone protein complexes to allow DNA to be compacted. These DNA-wrapped histones are called nucleosomes. Within these cells, there is always a constant motion of DNA unwrapping and rewrapping around the histones. This constant motion of DNA can allow changes to occur if needed. Histones can be modified. A histone can be modified through acetylation and methylation. Generally, acetylation is the unwrapping of DNA or "opening up" of the DNA from the histone, enabling transcription, while methylation is the wrapping or "closing" of DNA, silencing transcription. Acetylation inhibits the connection between the wrapped-up DNA and the histone itself because it reduces the number of positive interacting spots with which the negatively charged DNA can interact. Methylation of a histone causes the DNA to wrap tighter around the histone, which prevents transcription from occurring in this DNA.[11]

Protein coding regions make up about 2% of the human genomic real estate. Much of this real estate is transcribed into non-coding RNA, meaning they don't become proteins. Non-coding RNAs have a lot of different functions: they can inhibit protein-coding for mRNA, act as transcription decoys to keep RNA polymerase distracted, or as scaffolding to have genes transcribed together, and they can pass from cell to cell like neurotransmitters. Non-coding RNAs that are environmentally responsive develop when they are needed, but they are not permanent.[12] They can move to daughter cells, but they do not maintain cellular memory. Non-coding RNA can only add to cellular memory through DNA methylation.[13] Epigenetics can cause general modifications to cells all over the body. However, when epigenetic changes occur in the brain, these modifications can generate dysregulation in different systems that uphold homeostasis.

The Biology Behind Obesity

Obesity is the imbalance of energy intake and expenditure and abnormal adipose tissue. Adipose tissue, also known as fat tissue, serves many functions: it stores energy, interacts with hormones, and helps regulate metabolic homeostasis. There are two types of adipose tissue, which are white and brown. The body uses white adipose tissue for energy storage, while brown adipose tissue removes energy from the body.[14] The hypothalamus plays an important role in energy homeostasis. However, factors such as stress, diet, and other hormones can impact how the hypothalamus controls an individual's appetite and energy balance (Figure 3).

Not only can stress impact psychological wellbeing, but it can also cause epigenetic changes within the HPA axis. DNA methylation is one of the most intensely studied epigenetic mechanisms. In a 2010 study by Murgatroyd et al., the researchers looked into the effects of early life stress on DNA methylation in mice. They found that when mice were exposed to maternal separation, they experienced a decrease in methylation at the arginine vasopressin (Avp) promoter. This reduction in methylation causes a decrease in MeCP2 binding. Typically, methyl residues allow for the binding of MeCP2 and stop the transcription of the Avp gene, which helps regulate the HPA axis. The reduction in methylation leads to an increase in Avp expression and the production of proopiomelanocortin (POMC) and cortisol, ultimately increasing stress and causing a hyperactive stress response.[15]

Typically, appetite suppression is useful for moving the path of energy away from looking for food and eating to consciously dealing with the stress that is at hand. But with long-term stress, the energy is turned to coping mechanisms instead of actively dealing with the

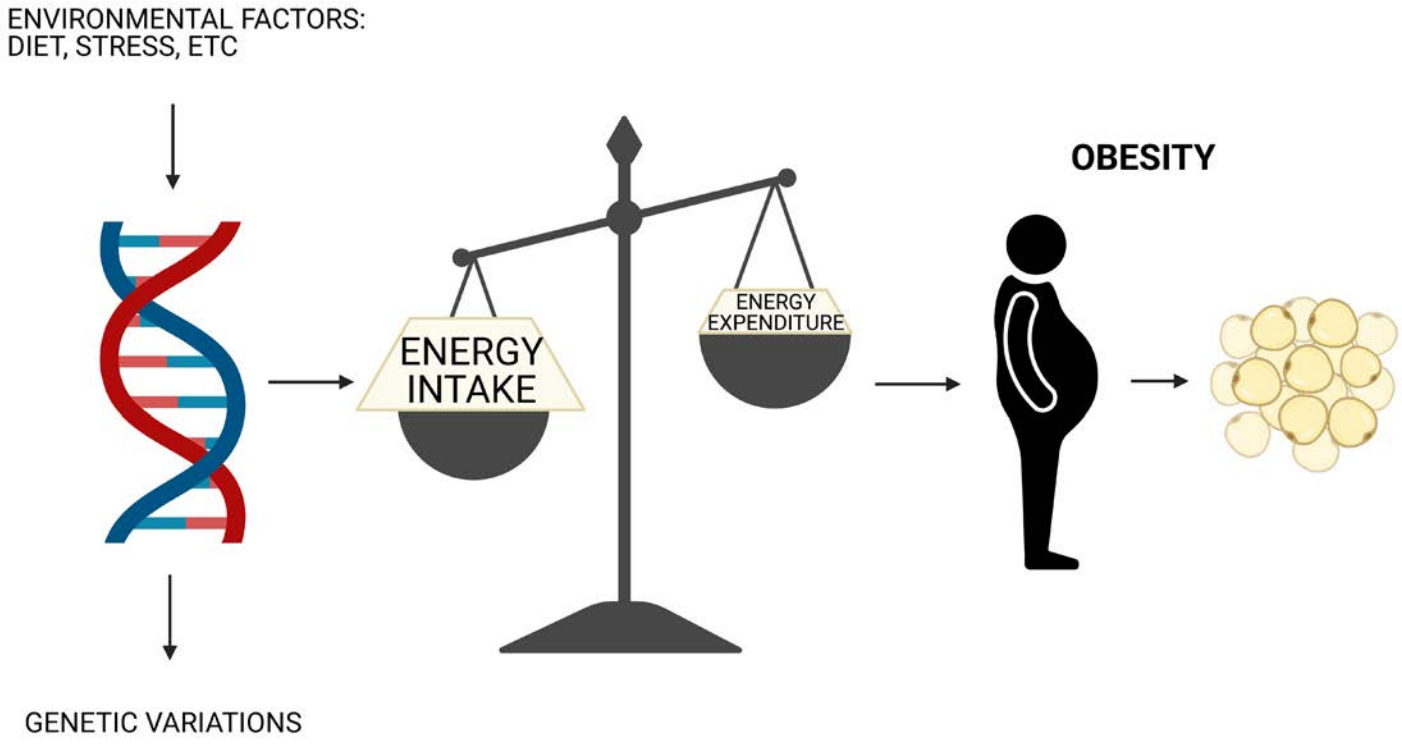

Figure 3. Environmental factors can cause genetic variation, leading to increased energy intake and lower energy expenditure. This can lead to obesity. Original figure by Madison Ladd. Created in BioRender.

stress. Stressful events will enhance the activity of glucocorticoids, hormones like cortisol, within adipose tissue and will lead to an increase in fat storage, especially visceral fat. As a result, these chronically elevated glucocorticoids constantly contribute to an increase in fat tissue. These same glucocorticoids also impact feeding behavior by stimulating food intake by signaling an increase in Agouti-related protein (AgRP) expression in the Arcuate Nucleus (ARC). Such increased glucocorticoid activation also results in insulin resistance. Overall, excessive glucocorticoids can lead to an increase in appetite, weight gain, and insulin resistance.[16]

The ARC is a part of the hypothalamus that receives input through the blood-brain barrier. This location of the ARC allows for the ability to sense the levels of nutrients and hormones that are circulating throughout the body. Within the ARC, the AgRP plays an important role in the function of appetite and energy expenditure. Additionally, POMC neurons of the paraventricular nucleus (PVN) of the hypothalamus produce the suppression of food intake. Ghrelin is a hormone that acts on the AgRP leading to the blocking of POMC neurons and creates the feeling of hunger. But Leptin, another hormone, blocks the Ghrelin neurons, which allows POMC neurons to produce the feeling of satiety.[16,17,18]

The Agouti gene is responsible for skin color, disease, and obesity in several types of animals, including humans. This gene is located throughout the body, but a very similar protein that has the same effect is the AgRP. When DNA methylation occurs to these genes, this process creates differing results. In mouse studies, when the gene is methylated, the mice tend to have good outcomes, such as being thin and healthy. When the gene is unmethylated, it tends to have bad outcomes, such as producing obese mice who are prone to cancer and diabetes. They found that this methylation pattern was passed down to the next generation if it was associated with the mother. If the mother has a poor diet, specific diets that lead to a decrease in methylation, it can lead to overfeeding and obesity in both the mother and the offspring.[17,19]

"I think more and more, there's an awareness that you can't just tell someone, 'Eat healthy'"

- Shakira Suglia, Sc.D

What You Can Do:

Ultimately, there is strong evidence that supports the idea that changes in our biology impact obesity. Even with this evidence, biological changes due to chronic stress are not the sole reason individuals may become obese or overweight. There is also research that shows that epigenetic changes can also cause adverse eating behaviors in the opposite direction. Changes in our biology not only can cause obesity, but they can also cause weight loss and even lead to eating disorders. Since epigenetics is still a relatively new field, more research needs to go into studying how these modifications impact our lives. A lot is still unknown when it comes to epigenetics but if we can fully understand how it impacts our bodies and our lives it will be easier to address the consequences it can create. Overall, it is easy to tie connections of chronic stress through epigenetics to obesity. One of the connecting links is the HPA axis. With the hypothalamus contributing to so many important functions, dysfunction of the HPA axis can wreak havoc on other functions that coexist within it.

Poverty is just one example of an inexhaustible list of stressors that can create chronic stress. In the United States, poverty is a stressor that a multitude of people endure. With poverty, individuals have to adapt and worry about many different aspects of their lives that are necessities of everyday life. Even chronic stress that is not as extreme as poverty can create these imbalances. Stressful job environments, relationship conflicts, and even living through a pandemic can stimulate chronic stress. As humans, we do what is best and we adapt and try to face every problem we can. But with this intention comes consequences and sometimes those consequences aren't visible. But thankfully, they can be reversed. Changes in lifestyles can allow for the "undoing" of epigenetics by allowing a series of reactions to occur that permit our biology to go back to normal.

But how do we get back to normal? It is important to allow yourself to do what makes you happy. Allow yourself to be at peace. If this state includes exercising, make sure to schedule parts of your week to exercise in a place where you can erase your stress. If it is music, you can sing, dance, or move in a way that relieves stress. If it is sleeping, schedule a nap. Not only can this bring you happiness, but it can also help regulate your HPA axis and allows it to "calm" down. These steps can help reverse possible epigenetic changes that have occurred throughout your life. ■

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