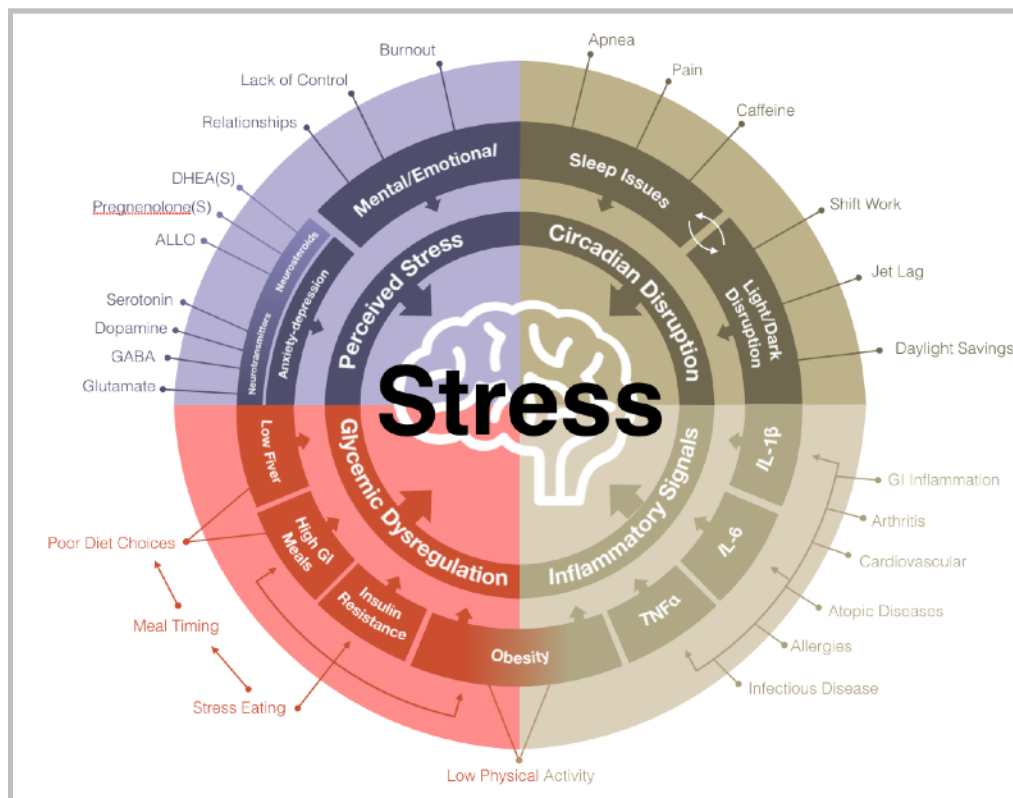


HPA-D Etiology Review

HPA axis dysfunction can be caused by several aspects of the modern lifestyle.

Below is a chart by Dr. Guilliams, which refers to four categories of stressors that lead to chronic HPA axis dysregulation.



The first category is perceived stress. This is what most people think about when they think about stress. There are four key factors that determine the magnitude of the HPA axis response to perceived stress, and thus the relevance of a stressor. The mnemonic for them is NUTS:

1. **Novelty** of the event
2. **Unpredictable** nature of an event
3. Perceived **threat** to body or ego
4. **Sense** of loss of control.

Stressors that fall into this category include relationship difficulties, financial trouble, public speaking, work stress, chronic illness, illness of a family member, or any event perceived as harmful and uncontrollable. Within this category, we would also consider internal stress perception caused by neurotransmitter imbalances, which can often manifest as mood disorders such as depression

or anxiety, and these neurotransmitter imbalances can also affect the HPA axis by modulating the central nervous system sensitivity to stress or through cortisol feedback inhibition.

Control is a key factor in protecting an animal or a human being from stress-induced disease. This is one reason that psychological stressors can actually be more harmful to us than physical stressors. We generally have more control over, or at least the ability to respond to, physical stressors. In most cases, psychological and emotional stressors tend to last much longer than physical stressors, and, therefore, they are more likely to cause illness and disease.

In the face of psychological stressors that are more common in our modern life, however, we don't often discharge the buildup of stress hormones and neurotransmitters that are flowing through our body to get us ready for fight or flight. The chemicals that produce the stress response continue to flow through our body, and we end up in a chronic state of hyperarousal. This overstimulation of our sympathetic nervous system is a major causative factor of stress-related disease, including high blood pressure, arrhythmias, digestive problems, chronic headaches, backaches, sleep disorders, and chronic anxiety.

The difference is that while our ancestors' bodies were specifically adapted to handle the physical stressors they were likely to encounter, our bodies are poorly adapted for dealing with the chronic psychological and emotional stressors that have become a normal part of modern life.

It is important to note that when we ask a patient if they're under stress, many will say yes, but others will say no, and you really cannot trust patients' reports on their subjective interpretation of their experience of stress.

CIRCADIAN DISRUPTION

- The HPA axis is intertwined with mechanisms that control the circadian rhythm.
- It is affected by the 24-hour light-dark cycle.
- Sleep deprivation is probably the most significant issue for most people.
- Sleep loss negatively affects mood and emotional processing and leads to significantly higher subjective experiences of stress.
- It has also been shown to increase cortisol levels.

EXPOSURE TO LIGHT HAS A PROFOUND INFLUENCE ON THE HPA AXIS

- Environmental light is the strongest influence on the circadian system.
- Light exposure has been shown to shift the natural human biological clock.
- For example, exposure to artificial light in the evening or night hours can delay sleep onset, and light exposure during the day affects sleep quality and duration at night.

- A new type of light-sensitive cell in the retina was recently discovered that doesn't contribute to vision at all. Instead, it has multiple effects on biological function, most notably on the secretion of melatonin by the pineal gland.
- Short-wavelength or blue light is the most melatonin-suppressive and is typically emitted by devices such as televisions, computer screens, cell phones, and tablets. This means that products like tablets, smartphones, and other devices are major sources for suppressing melatonin at night, which reduces sleep duration and disrupts sleep.
- Along with blue light emitted from electronic devices, research has shown that even being exposed to normal levels of room lighting can have a similar negative impact on melatonin and the HPA axis.
- In addition, most people in the modern world are not getting enough exposure to light during the day.
- Bright light exposure during the day helps to regulate cortisol levels and balance the HPA axis, and this anchor light, as it's referred to, anchors your circadian rhythm, causing it to be less fragile so that light at night has less of an ability to shift your rhythm.
- The first 30 to 60 minutes of outdoor light exposure creates about 80 percent of that anchoring effect, so just going outside for about half an hour at lunchtime or in the morning can provide you with the majority of anchoring light you need to maintain a healthy circadian rhythm.

JET LAG

- Alters the natural circadian clock.
- Chronic jet lag has been shown to decrease sleep quality, reduce cognitive function, raise cortisol levels and even increase the risk of cancer due to disturbances of melatonin levels.

SHIFT WORK

- Also alters the circadian clock.
- Alternating shift work causes the most disruption.

CASE STUDY

I often tell my patients that you can't eat or supplement your way out of HPA axis dysfunction. For example, I had a patient, a 32-year-old male, who worked as an air traffic controller in alternating shifts. He had extremely high cortisol. He also had severe ulcerative colitis and kept having flare-ups because of the high cortisol, and he would end up in the hospital with these flares. We did everything we could in terms of diet, supplementation, addressing all of the underlying gut pathologies, and he did have some improvement with those changes, but he was only able to go into full remission and stop having these flares after he quit his job.

CAFFEINE

- Can disrupt the HPA axis and sleep.
- This is particularly true for the 50 percent of the population that has a variant in the CYP1B2 gene that leads to slow metabolism or processing of caffeine.
- Timing of intake, when coffee is consumed, also matters. A study in *Science Translational Medicine* found that caffeine consumed three hours before bed delayed the circadian clock by about 40 minutes.
- One study found that 90 percent of Americans who drink caffeine drink it in the afternoon, and almost 70 percent drink it after 6 p.m., so you really have to talk to your patients about this.

GLYCEMIC DYSREGULATION

- Cortisol is known as a glucocorticoid.
- HPA axis dysregulation causes glycemic dysregulation.
- For example, elevated cortisol levels increase visceral and abdominal fat, and visceral or abdominal fat produces inflammatory mediators like interleukin-1B, interleukin-6, and TNF alpha, all of which activate the HPA axis and trigger further cortisol production.
- Hypoglycemia, or low blood sugar, is a powerful HPA axis activator.
- An insulin tolerance test, which causes hypoglycemia, is considered one of the most reliable measures of HPA axis responsiveness or function.
- The hypothalamus is especially sensitive to falling glucose levels since glucose is the main fuel for the brain.
- Impaired glucose sensing in the hypothalamus is a key factor in metabolic problems related to HPA axis dysfunction.

The HPA axis is also involved in mechanisms that manage overall energy balance, insulin sensitivity, metabolic function, food selection, and satiety. This is why we crave comfort foods when we're stressed out, and this has been shown not only in humans but also in animals.

These relationships should be considered when you're treating patients because they can affect treatment plans. For example, aggressive weight loss is an HPA axis stressor, and studies have shown that high perceived stress before and during weight loss is a major inhibiting factor in reaching weight loss goals.

On the other hand, you won't get very far with the HPA axis if you don't address their underlying metabolic dysfunction, since that contributes to HPA axis dysfunction, so it is important to address both in order to achieve a successful outcome.

INFLAMMATION

- Cortisol is a powerful anti-inflammatory substance. Both acute and chronic inflammation trigger the HPA axis and increase cortisol in order to resolve the inflammatory response.
- Chronic elevations of cortisol in chronic stress eventually downregulate the HPA axis and reduce cortisol production, which creates a vicious cycle where the body can't turn off the inflammatory response.

The takeaway here is that any source of inflammation is a chronic stressor.

SPECIFIC EXAMPLES OF THINGS THAT AFFECT THE HPA AXIS:

1. Physical activity, both too much and too little.
 - a. Exercise causes inflammation, and that stimulates the HPA axis, which has a lot of benefits when adequate time is allowed for recovery.
 - b. Overtraining, which is characterized by not enough time for recovery, can dysregulate the HPA axis.
 - c. Physical inactivity is also associated with sleep apnea and other sleep disorders that can disrupt the HPA axis
2. Social isolation
 - a. A landmark study found that social support was a stronger predictor of survival than physical activity, body mass index, hypertension, air pollution, alcohol consumption, and even smoking 15 cigarettes a day.
 - b. Try giving your patients some ideas and support for how they can reach out and create more social connection in their lives. Ideas include things such as joining classes, activities, volunteering, and getting a pet or an emotional service animal.
3. Gut issues can also dysregulate the HPA axis.
 - a. Gut pathogens such as E. coli can provoke intestinal permeability and activate the HPA axis, causing repeated stress response.
 - b. Beneficial microbiota might play a role in regulating the HPA axis.
4. Food intolerances can also activate the HPA axis.
 - a. They induce intestinal permeability. Antigens cross the gut barrier and provoke immune response and inflammation, leading to an altered composition of the gut microbiota, which activates the HPA axis.
 - b. Chronic infections also affect the HPA axis, primarily via inflammation.
5. Environmental toxins can play a significant role in disrupting the HPA axis.

- a. In animals, fetal exposure to environmental endocrine-disrupting chemicals (EDCs) such as bisphenol-A, BPA, and phthalates lead to altered HPA axis signaling and cortisol dysregulation.
 - b. EDCs have also been shown to alter DNA methylation.
 - c. Inflammation is probably a key mechanism governing the effect of toxins on the HPA axis. For example, higher mercury levels increase proinflammatory cytokine activity.
6. Thyroid function
- a. Higher TSH levels are correlated with higher cortisol.
 - b. Hypothyroidism has been shown to cause increases in cortisol by reducing the metabolism or disposal of free cortisol.
7. Certain drugs and substances affect the HPA axis.
- a. SSRIs
 - i. Reduce morning cortisol levels and responsiveness of the HPA axis.
 - ii. Cortisol levels are often high in major depressive disorder. This may explain some of the benefits of SSRIs.
 - iii. In people who are depressed or who have normal or low cortisol, these effects of SSRIs could be undesirable.
 - b. Corticosteroids have the biggest impact on HPA axis (for example, prednisone and hydrocortisone)
 - i. They are more powerful than endogenous cortisol, and both target tissue signaling and HPA axis feedback inhibition. They downregulate ACTH secretion and cause atrophy in the zona fasciculata, which is where cortisol is produced, and this is a condition that can actually become permanent over time and lead to dependence on hydrocortisone therapy.
 - ii. The most common cause of true adrenal insufficiency is ongoing corticosteroid therapy.

ADRENAL INSUFFICIENCY IN PATIENTS ON CORTICOSTEROID THERAPY



DOSE-RESPONSE RELATIONSHIP

The amount of time that patients have taken the corticosteroids makes a difference. If you are prescribing corticosteroids, consider testing patients when they discontinue corticosteroid therapy for adrenal insufficiency.

The takeaway from this is you cannot supplement your way out of HPA axis dysfunction. You have to address behavior, lifestyle, and underlying pathologies such as gut issues, chronic infection, toxic exposure, hypothyroidism, and things that lead to glycemic dysregulation, inflammation, and you have to address circadian disruption along with perceived stress.