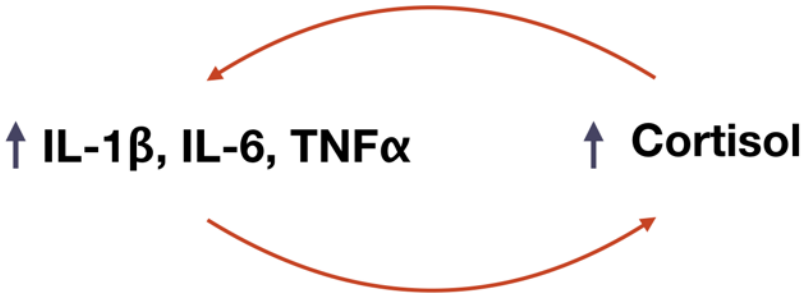
HPA-D: Etiology – Part 3

It's crucial to discuss light exposure with your patients, as I was referring to to some degree in the last slide on alternating shift work. A lot of patients have no idea how these kinds of things affect the HPA axis, because it's just seen as being normal now to use electronic devices all the way up until bed, even in bed, or to sleep with your phone next to your bed. If you fail to address those factors, the treatment will definitely not be as successful as it can be. I often tell my patients that you can't eat or supplement your way out of HPA axis dysfunction. You absolutely have to address the lifestyle and the behavior piece, and in many cases, it's the most important element of addressing the HPA axis. As an example, I had a patient, a 32-year-old male, he worked as an air traffic controller in alternating shifts, and as you might expect given what we've talked about so far, 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, they were very serious. The most recent flare he had, he'd developed an inflammatory condition in his lungs that became life-threatening and required pretty severe immunosuppressive therapy in order to deal with that. 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 didn't go into full remission and stop having these flares and wasn't able to resume a normal life until he quit his job. This wasn't easy, it took years for him to manage, but in the end he decided that his health was more important, and he was finally able to make the transition. And once he did, he was able to have a more normal schedule; a lot of the things that we had done in the past that had only had a minimal effect started to have a really profound effect, and he's now in remission and living a normal life, so obviously, changing jobs isn't as easy as taking supplements or eating a different diet, but sometimes it may be necessary.

Caffeine has a major impact on the HPA axis and sleep, not surprisingly. Americans drink 400 million cups of coffee a day—yes, you heard that correctly—and we spend $30 billion on it every year. The good news is that there's a lot of research that links coffee consumption with health benefits, including lower risk of cancer, Parkinson's disease, obesity, diabetes, metabolic syndrome, and heart disease. The bad news is that coffee and other sources of caffeine have also been shown to disrupt the HPA axis and sleep. This is particularly true for the 50 percent of the population that has a variant in the CYP182 gene that leads to slow metabolism or processing of caffeine. But the 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, which is an effect equal to three hours of additional daylight exposure. The problem is, this behavior is extremely common. Coffee drinkers consume an average of three nine-ounce cups of coffee per day, and one study found that 90 percent of Americans who drink caffeine drink it in the afternoon, and 69 percent, almost 70 percent, drink it after 6 p.m. So you really have to talk to your patients about this. You might think it's obvious and everyone is aware of this and paying attention to it, but they're not.

The next category to talk about in terms of disruption of the HPA axis is glycemic dysregulation. So far, we've talked about perceived stress, we've talked about circadian disruption, now we're moving on to the third category, which is glycemic dysregulation. One of the cardinal features of the stress response is to make more energy available for a life-saving fight-or-flight response. Cortisol, after all, is known as a glucocorticoid. The very name of it refers to its crucial function for regulation of blood sugar. There's a bidirectional relationship between the HPA axis and metabolic functions; all of the factors that cause glycemic dysregulation, like poor diet, lack of sleep, lack of exercise, will also dysregulate the HPA axis. HPA axis dysregulation, in turn, causes glycemic dysregulation, and this leads to a vicious cycle where glycemic dysregulation leads to HPA axis dysfunction, which leads to further glycemic dysregulation.



A classic example of this is the relationship between visceral fat tissue and cortisol. 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, and this is why it can be hard to tease out cause and effect in studies of the relationship between inflammation and cortisol. It is likely bidirectional and it's really difficult to determine which comes first in the research.

Given that one of cortisol's primary functions is to increase glucose, it's no surprise that hypoglycemia, or low blood sugar, is a powerful HPA axis activator. It's so predictable that the 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. Studies have shown that impaired glucose sensing in the hypothalamus, which is observed in type 2 diabetes and metabolic syndrome, is a key factor in metabolic problems related to HPA axis dysfunction. Reactive hypoglycemia is defined as recurrent episodes of hypoglycemia occurring within four hours of a meal in people without diabetes, and there may be a bidirectional relationship here as well. Some researchers suggest that people with reactive hypoglycemia may be more sensitive to the body's normal release of the hormone epinephrine, which is an abnormal SAS, or sympatho-adrenal medullary system response, rather than an abnormal HPA axis response. So as you can see on the slide, I've put the term "hangry," which actually can appear in the dictionary now in some cases. So, a patient that is irritable as a result of feeling hungry, or a blend of hungry and angry, this is a kind of classic symptom of HPA axis or SAS dysregulation.

The HPA axis is also involved in mechanisms that manage overall energy balance, insulin sensitivity, metabolic function, food selection, and satiety, and this explains why we crave comfort foods when we're stressed out, and this has been shown not only in humans but also in animals. You need to be aware of all these relationships 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, so if you have a patient that's extremely stressed out, that's going to really impair their weight loss efforts, and you may need to address their HPA axis before they can be successful with

weight loss. On the other hand, doing super-aggressive diet plans can cause stress, which can then paradoxically make it less likely that they'll achieve their longer-term weight loss goals. Likewise, if a patient is obese or diabetic, 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 there are all of these interacting feedback loops that have to be addressed in a treatment, which is why in this ADAPT level one course, we are including HPA axis and metabolic dysfunction and the gut all together; they so often have to be addressed in order to achieve a successful outcome.