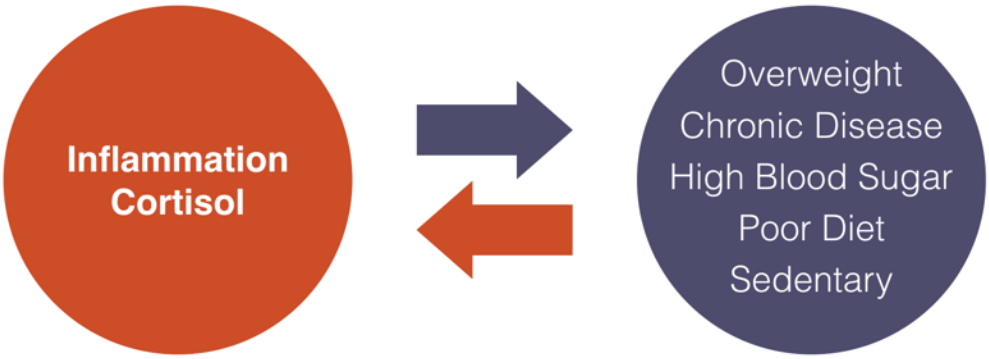
KRESSER INSTITUTE
FOR FUNCTIONAL AND EVOLUTIONARY MEDICINE

# HPA-D: Etiology – Part 4




The last of the four categories of HPA axis disruption that we're going to talk about is 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. The increase in cortisol downregulates inflammatory pathways within tissues and immune cells through genomic and non-genomic signaling. This suppresses most other immune functions, which explains so many of the side effects of prednisone and other steroid drugs. Impaired HPA axis function has been shown in animal and human inflammatory and autoimmune conditions, including rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, asthma, and eczema. Not surprisingly, 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, which leads to more inflammation, which leads to even less cortisol and less ability to resolve the inflammatory response, and it just stays stuck in this vicious cycle. Another way the body protects itself from chronically elevated cortisol is via cortisol receptor site resistance or downregulated expression of glucocorticoid receptors, which we talked about before. This will also have the side effect of blunting the anti-inflammatory effects of cortisol.


The takeaway here is that any source of inflammation is a chronic stressor. I’m going to say that again: any source of inflammation is a chronic stressor. It’s so crucial to understand, on the very first slide of this presentation I showed a picture of a person sitting on a beach chair in a tropical location and I said that even if perceived stress is low, and the person has no cares in the world, if they have an inflammatory condition, they are under stress, and that’s absolutely … I’m just going to keep saying that because it’s so important to understand and so important to get across to your patients. On this slide, I’m showing a young woman with a skin condition, rosacea, and even if she has no subjective experience of perceived stress, when you see a condition like that, you know that the body is under stress because that’s an inflammatory condition, so given that inflammation is involved in virtually all chronic and modern disease, it’s safe to say that all of your chronic disease patients have some degree of HPA axis dysregulation. And you’re going to have to discuss this with your patients, especially the ones that tell you that they’re not stressed out and resist the idea of doing any testing for HPA axis dysfunction, or implementing any lifestyle or behavioral changes for HPA axis modification. If they have SIBO or other gut issues, cardiovascular disease, diabetes, arthritis, eczema or any skin condition, or any inflammatory condition, which is to say pretty much any chronic modern disease, it means number one they are under stress, and it may not be psychological stress, it may be inflammation activating the HPA axis, it may be blood sugar dysregulation, it may be circadian disruption, or it may be some combination of all of those three things, and they do need to focus on HPA axis modification in order to get well.

Let’s look at some specific examples of things that affect the HPA axis, and the effects of these often span some or all of the four categories that we’ve discussed. One is physical activity, both

too much and too little. Exercise is a hormetic stressor. That means it causes a positive adaptation, typically; it causes inflammation and that stimulates the HPA axis, and that's not a problem and of course has a lot of benefits when adequate time is allowed for recovery—that's very important. Studies have shown that overtraining, which is characterized by not enough time for recovery, can dysregulate the HPA axis, which initially could lead to high cortisol levels but over time could lead to low cortisol. On the other hand, physical inactivity and too much sedentary time are also associated with sleep apnea and other sleep disorders that can disrupt the HPA axis, and just physical inactivity on its own irregardless of how it impacts sleep can disrupt the HPA axis.

Social isolation is another major factor that affects HPA axis function and overall health. A landmark study involving over 300,000 participants 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. Another study of adults aged 60 to 64 found that those widowed within the last three years had a 36 percent higher nighttime cortisol than those who were currently married. Those newly living alone also had higher nighttime cortisol and flatter diurnal slope than those living with others. And a study of 238 middle-aged adults found larger cortisol awakening responses and greater cortisol output over the day in both men and women. Again, it's not the easiest thing for your patients to change. Most people who are isolated and alone aren't necessarily that way by choice, but it's crucial to discuss this with them and highlight the importance of it and maybe give them some ideas and support for how they can reach out and create more social connection in their lives. It could include things like joining classes, activities, there a lot of centers, if your patient is elderly, there are a lot of opportunities for that in most cities. Volunteering is a fantastic option because it not only increases social support and allows people to meet others of like mind, but it provides a sense of purpose, which is also very important to health and well-being. There's a lot of research on that. Getting a pet or an emotional service animal; there are a lot of things that can be done to improve this, and it's really important to discuss and focus on in the treatment.

Gut issues, as we've talked about extensively, can also dysregulate the HPA axis. Gut pathogens like E. coli can provoke intestinal permeability and activate the HPA axis, causing repeated stress response. Studies in germ-free mice that have no gut bacteria have shown exaggerated HPA axis response to stress, which suggests that beneficial microbiota might play a role in regulating the HPA axis. Stress reduces the intestinal permeability of the gut, allowing bacteria and bacterial antigens to cross the epithelial barrier and induce a mucosal immune response, which in turn alters the composition of the microbiome and leads to enhanced HPA axis activity, which causes a vicious cycle. Increasing data from patients with irritable bowel syndrome and major depression indicate that in these syndromes, alteration of the HPA axis may be induced by increased gut permeability, and numerous studies on the gut-brain axis indicate that the status of the gut, conditions like SIBO, the gut microbiome, the gut barrier integrity affect the brain and the HPA axis in numerous ways.

Food intolerances can also activate the HPA axis via similar mechanisms. 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, as we just discussed, activates the

HPA axis. Gluten is of course a major consideration, but there are many others that we covered in the gut unit that can be identified with Array 3, 4, and 10 from Cyrex Labs.

Chronic infections also affect the HPA axis, primarily via inflammation. These include gut infections, as well as viral infections, tick-borne infections like Lyme disease, Borrelia burgdorferi or Bobesia or Bartonella, intercellular pathogens like Chlamydophila pneumoniae or mycoplasma.

Environmental toxins can play a significant role in disrupting the HPA axis. In animals, fetal exposure to environmental endocrine-disrupting chemicals such as bisphenol-A, BPA, and phthalates lead to altered hypothalamic-pituitary-adrenal axis signaling and cortisol dysregulation. Cortisol dysregulation means inappropriate diurnal production: too high when it should be low, and too low when it should be high, and this can be pathological even when absolute levels of cortisol are normal. And these environmental endocrine-disrupting chemicals, or EDCs, as well as many of the other triggers we've discussed, can cause pathological changes to cortisol metabolism, which leads to low levels of free cortisol and higher levels of metabolized cortisol, which is exactly the pattern that we see in obesity, and I'm sure that's no coincidence, because some of these toxins also contribute to obesity. EDCs have also been shown to alter DNA methylation, which is a potential mechanism of HPA axis programming. DNA methylation regulates the glucocorticoid receptor via genomic signaling, which we talked briefly about, and is sensitive to environmental influences, so this is an area of study that's relatively new, and I imagine as it progresses we're going to find that more and more environmental toxins have an adverse effect via disrupting the HPA axis.

Inflammation is probably a key mechanism governing the effect of toxins on the HPA axis. For example, in one study, kids containing mercury-containing fish not surprisingly had higher levels of mercury than kids not eating seafood, but they also had higher levels of pro-inflammatory cytokines as well as a blunted diurnal cortisol response. The authors of this study speculated that higher mercury levels increase pro-inflammatory cytokine activity, which in turn then increased acute-phase protein; acute-phase proteins are involved in the inflammatory response, which then blunted the cortisol response, but it's also possible that mercury-induced high cortisol levels led to cortisol resistance in the cells, which then caused inflammation because cortisol's needed to turn off inflammation, and even though the cortisol levels were high here, if the cells are resistant to it, inflammation will continue unchecked. And that would then lead to an increased production of acute-phase proteins and further blunting of the cortisol response. So there are multiple mechanisms, and again, the relationship could be bidirectional, could be either one of these mechanisms or both, and this suggests that inflammation regardless of the cause, as I mentioned throughout this presentation, can adversely affect the HPA axis.