

HPA-D: Pathology – Part 2

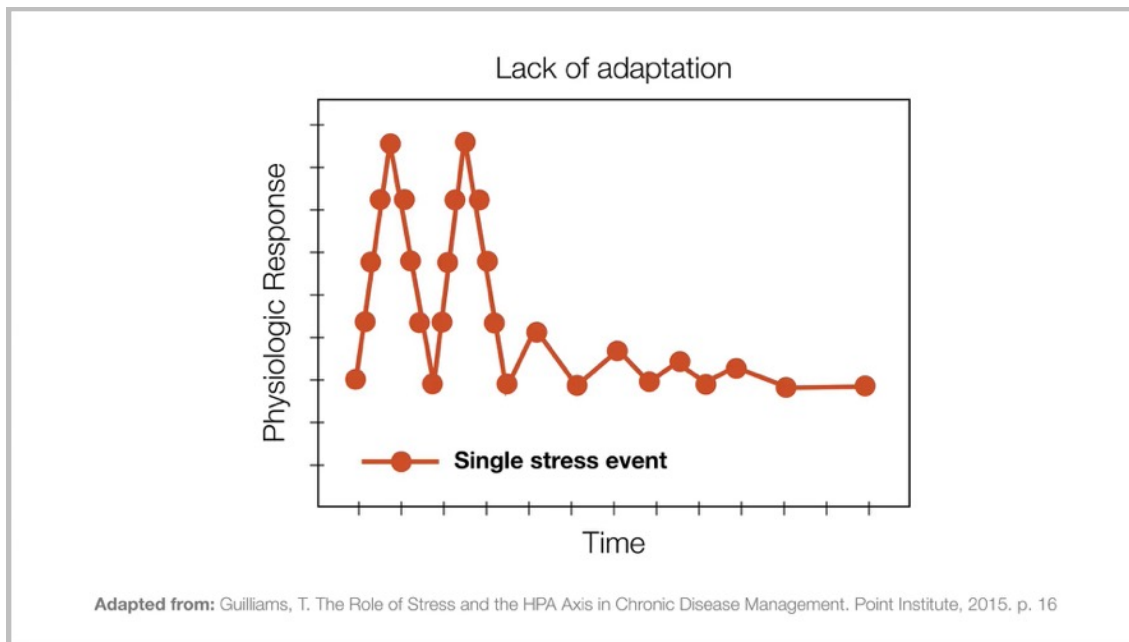
Here's another important thing for you and your patients to understand: only one of these systems can be activated at once, meaning the parasympathetic or sympathetic system. Our stress response system is somewhat crude and relatively binary; cells, tissues and organs used to respond to stress are the very same ones used to maintain normal physiology. So if we go back to an analogy Dr. Williams used in his book: if there's an emergency, the roads that are also typically used for just general commuting and getting around are the very same roads that are used for fire trucks, police cars, etc. So during an emergency, normal traffic and normal function of the roads will come to a halt and can't really start up again until the emergency passes. So this is really important to explain to your patients, if their fight-or-flight system is activated because of stress—perceived stress or circadian disruption or glycemic dysregulation or inflammation—then they cannot also simultaneously be in a parasympathetic rest-and-digest response. So this is one of the main reasons why chronic stress and active stress response can be so insidious.

Which really brings us to exactly why the stress of modern life is so harmful: our binary on-and-off stress response served us well in an environment where threats were more immediate and distinct. So for example, if we encounter a lion or other predator while we're on a hunt, or a confrontation with someone from another tribe, that's a relatively distinct, an intense but distinct period of being under stress, which has a beginning, a middle, and an end. But in the modern environment, we face nearly constant stressors: traffic, circadian disruption as I said, poor diet, sleep loss, financial stress, relationship stress; these are not as life-threatening or as intense in many cases as being chased by a lion or fighting with a rival tribe's person, but the stress response system responds in a similar way, albeit at reduced intensity.

It's not just perceived stress that's an issue, it's mental or emotional stressors that have increased in the modern world. The three other categories that we've discussed—glycemic dysregulation, circadian disruption, and inflammation—are also far bigger players today than they were for our ancestors. Our ancestors ate nutrient-dense real-food diets. When we look at studies of traditional hunter-gatherers, they didn't have blood sugar issues, things like diabetes or cardiovascular disease. They lived in sync with natural rhythms of light and dark, they didn't travel across time zones, they weren't doing shift work, and they didn't use electronic media. They ate an anti-inflammatory diet, so they weren't dealing with as much inflammation, they got plenty of physical activity, and they got plenty of sleep.

Now, contrast this with those of us living in the modern world, where again, the kind of mirror image of that, where many of us are eating inflammatory diets; insulin resistance and leptin resistance and blood sugar dysregulation are extremely common; the incidence of diabetes is growing at an alarming rate, obesity, cardiovascular disease; autoimmune disease, which now is expected to affect one in four women and one in six men in their lifetimes; arthritis, asthma, allergies, all kinds of inflammatory conditions. We have many people who are sleep-deprived, more than a third of Americans get fewer than six hours of sleep, so chronic sleep deprivation is

epidemic. We have people who do shift work, working especially rotating shift work is harmful, people who are traveling across time zones on a regular basis, so all of this is stress, these are all the four primary drivers of HPA axis dysfunction, and this perpetual exposure to stress leads to constant activation of the HPA axis and allostatic load. Allostatic load then stretches physiological resilience and depletes metabolic reserve in nearly every tissue in the body, and the depletion of metabolic reserve is the cost of surviving repeated stressful events.



But that's not the only impact that chronic stress has. The repeated activation of the HPA axis eventually leads to downregulated response to new stressors. This is the body's attempt to protect itself from chronically elevated cortisol levels. These mechanisms might include reduced ACTH secretion, decreases in glucocorticoid receptor expression and sensitivity, and changes to HPA axis feedback sensitivity. While these adaptations are necessary and smart in the short term to protect the tissues from catabolic effects of cortisol, they have the unintended long-term effect of further reducing resilience and metabolic reserve. As you can see in the figure on the slide, what happens is that the body is unable to continue to mount a successful response to stress over time.

This leads to an ongoing semi-permanent catabolic state where breakdown and wear and tear are happening faster than the body can rebuild itself. And I would argue that virtually all patients with chronic illness are likely in this state. A significant percentage of people living in the modern world, even without obvious chronic illness, are in this state, which explains the continued increase in inflammatory diseases, particularly as we age, all of the diseases that are associated with aging like Alzheimer's. Which particular disease people get is a function of genetics, genomics, epigenetics, and other environmental factors, but I have come to believe that allostatic load, the loss of resilience and depletion of metabolic reserve, is at the root of the modern disease epidemic, and at the risk of sounding like a broken record, it's why HPA axis modification must be part of every treatment that you do.

Another important thing to be aware of is that most of the stress-induced changes in physiological function are mediated by alterations in gene regulation triggered by glucocorticoids. These are influenced by genetics but much more strongly modified by environmental factors that affect cellular changes influenced by cortisol. As an example from Dr. Guilliam's book, different glucocorticoid receptor isoforms have been shown to alter the effect of cortisol on gene transcription.

Likewise, while genomics describes how gene transcription is altered by a substance like cortisol, epigenetics refers to how those changes lead to non-sequenced alterations in the genome itself. The two primary forms of epigenetic modification are DNA methylation and histone modification. It shouldn't come as a surprise that a large body of evidence shows that HPA axis stressors induce strong epigenetic modification to the genome via DNA methylation and histone modification. These changes manifest as alteration in metabolism, circadian control, and brain function in particular.

For example, it's well-established that early life exposure to high levels of glucocorticoids due to stress can reprogram the HPA axis and create an imprint that lasts for the rest of that individual's life. Epigenetics along with genetics probably explains why both acute and chronic stress manifest differently in different people, as I mentioned on the last slide, i.e., why it triggers rheumatoid arthritis in one person but obesity and diabetes in another. The significance of this is that complete correction of the HPA axis in cases of trauma, chronic stress, or fetal HPA axis programming may not be possible. These patients will unfortunately need long-term support, though proper treatment can still make a profound difference in their lives.

Conditions related to HPA axis hyperfunction

Depression

Anorexia nervosa

Obsessive-compulsive disorder

Panic disorder

Excessive exercise

Alcoholism

Diabetes

Central obesity

PTSD in children

Hyperthyroidism

All of what we've talked about so far explains why stress and HPA axis dysfunction are associated with such a wide array of conditions. This slide here lists conditions that are typically associated with increased activity of the HPA axis, and these are just examples, there are many more. They include depression, anorexia nervosa, OCD, panic disorder, excessive exercise, alcoholism, diabetes, central obesity, PTSD, and hyperthyroidism.

Conditions related to HPA axis hypofunction

Atypical/seasonal depression	Nicotine withdrawal
Postpartum depression	Rheumatoid arthritis
Chronic fatigue syndrome	Asthma
Fibromyalgia	Eczema
Premenstrual tension syndrome	Hypothyroidism

And this slide lists conditions that may be associated with decreased activity of the HPA axis, and again, this is only a partial list. They include atypical or seasonal depression, postpartum depression, chronic fatigue syndrome, fibromyalgia, premenstrual tension syndrome, nicotine withdrawal, rheumatoid arthritis, asthma, eczema, and hypothyroidism. Okay, that's it for now, see you next time.