KRESSER INSTITUTE FOR FUNCTIONAL AND EVOLUTIONARY MEDICINE

HPA-D: Etiology – Part 5

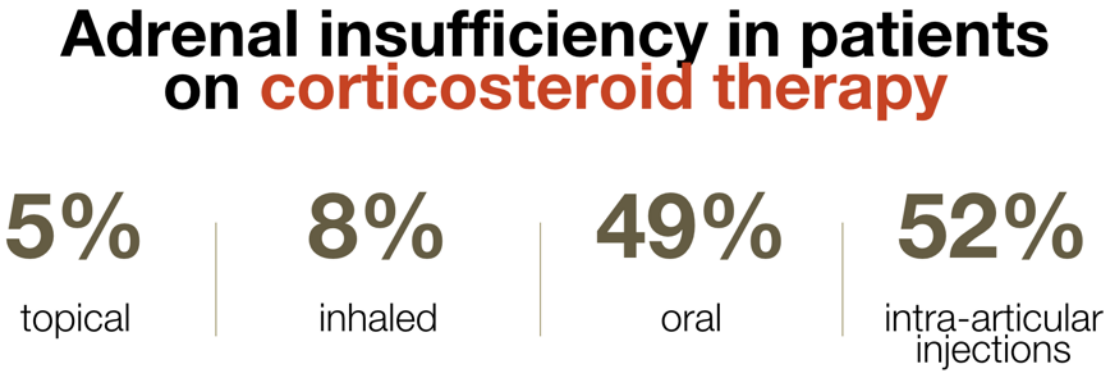
Talking more about mercury, animal and human studies have shown that mercury blunts cortisol output in the stress response, possibly leading to chronic inflammation since cortisol's involved in the resolution of the inflammatory response. A study of pregnant women in Mexico City found that women above the median for mercury and psychosocial stress exposure experienced a blunted morning cortisol response compared to women exposed to higher stress but lower mercury levels. Another study found that kids that consumed seafood with mercury had cortisol levels 25 percent lower than kids with the lowest mercury levels. They also had elevated levels of acute-phase proteins, suggestive of chronic inflammation, despite having better blood lipid profiles. Similar results have been found for lead and other heavy metals, not surprisingly.

Thyroid function also influences the HPA axis, and of course is influenced by the HPA axis. In fact, a more complete description of the hormone-producing axis would be "HPGTA axis," so that's hypothalamus, pituitary, thyroid, gonadal, adrenal axis. One study of young healthy adults without known thyroid disease found a positive association between TSH, or thyroid-stimulating hormone, and cortisol. The higher the TSH levels, the higher the cortisol, and that was true even within the lab reference range for TSH, which goes up to 4.5 in most labs. Hypothyroidism has been shown to cause increases in cortisol by reducing the metabolism or disposal of free cortisol and blunting the feedback of cortisol on the hypothalamic pituitary adrenal axis. Later on, when we look at the DUTCH test, you'll see a pattern where free cortisol is high but metabolized cortisol is low, and one of the causes of that pattern is hypothyroidism. It doesn't have to be frank hypothyroidism, though, with TSH significantly out of the reference range. This can happen even with high-normal TSH, as TSH starts to climb above 2.0, and that's one reason why I will argue in the blood chemistry unit that the TSH range should be lower and more narrow than it is on conventional labs.

Finally, there are certain drugs and substances that affect the HPA axis. We've already talked about caffeine, but antidepressants, particularly SSRIs, are another class of drugs that have been shown to modulate the HPA axis. Several studies have shown that SSRIs reduce morning cortisol levels, cortisol under the curve, and the responsiveness of the HPA axis. And since cortisol levels are often high in major depressive disorder, these effects are understood to be one of the possible mechanisms explaining the benefits of SSRIs, when they do have benefits. But in people that are depressed who have normal or low cortisol, these effects of SSRIs could be undesirable, and it may explain the variable effect of SSRIs, why they work in some people and not in others.

The class of drugs that has the biggest impact on the HPA axis though, of course is corticosteroids. These include drugs like prednisone, used for inflammatory bowel disease and other autoimmune inflammatory conditions; hydrocortisone, which is used for a wide range of issues, including hemorrhoids, dermatitis, anal fissure and IBD; and butycinide, which is a steroid inhaler for asthma. So 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 festiculata, 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. We've talked about how so-called adrenal fatigue due to low output by the adrenal glands is pretty rare, but common use of corticosteroid therapy for things like organ transplant or rheumatic and skin disorders, IBD, asthma, sinusitis, and rhinitis is the most common cause of true adrenal insufficiency, so when you actually do see low cortisol output, one of the major causes of that is ongoing corticosteroid therapy. Unfortunately, few physicians or patients are aware of these risks, and cortisol levels aren't typically monitored, amazingly, when a patient is on corticosteroid therapy.



According to a meta-analysis of 40 years of corticosteroid therapy, adrenal insufficiency occurs in about 40 percent of patients after they discontinue taking corticosteroids. If you stratified the results by route of administration, 5 percent of subjects taking topical steroids developed adrenal insufficiency, 8 percent of those taking inhaled therapy developed it, 49 percent using oral therapy and 52 percent taking intra-articular injections experienced adrenal insufficiency. In asthma patients using inhalers, 2 percent who were taking a low dose, 9 percent who were taking a medium dose, or 22 percent who were taking a high dose developed adrenal insufficiency, so there's obviously a dose-response relationship here. And then the amount of time that patients have taken the corticosteroids makes a difference too, as you might expect. So, only 1 percent of patients on short-term corticosteroid therapy develop resistance; 12 percent of those patients using corticosteroids for medium term developed it; and 27 percent of patients using long-term therapy developed it. So this is a conclusion from the paper: there is no administration form, dosing, treatment duration, or underlying disease for which adrenal insufficiency can be excluded with certainty, although higher dose and longer use give the highest risk. The threshold to test corticosteroid users for adrenal insufficiency should be low in clinical practice, especially for those patients with non-specific symptoms after cessation. In other words, pretty much everyone who is

prescribing corticosteroids should be thinking about this, and should be testing patients when they discontinue corticosteroid therapy for adrenal insufficiency.

There are certainly other factors that affect the HPA axis that we haven't had a chance to cover in this presentation, but I focused on the most significant players and the ones that you will have the biggest impact on as a clinician. Takeaway from this presentation should be that diet, lifestyle, behavior, and health status collectively determine the status of the HPA axis. It's absolutely essential to focus on all these in order to successfully address the HPA axis issues you'll see in your practice. As I hope I've made clear, you cannot supplement or even eat your way out of HPA axis dysfunction. You have to address behavior, lifestyle, and underlying pathologies like gut issues, chronic infection, toxic exposure, hypothyroidism, things that lead to glycemic dysregulation, inflammation, and you have to address circadian disruption along with perceived stress.

Okay, that's it for this presentation. Before we move on to the specific pathologies of the HPA axis, I need to debunk some myths about so-called adrenal fatigue, including the three-stage model of adrenal fatigue that's become so popular in the integrative functional medicine world, and also talk to you about how to discuss HPA axis dysfunction with your patients and other clinicians in a way that makes sense to them and is in alignment with current scientific evidence. Okay, talk to you then.