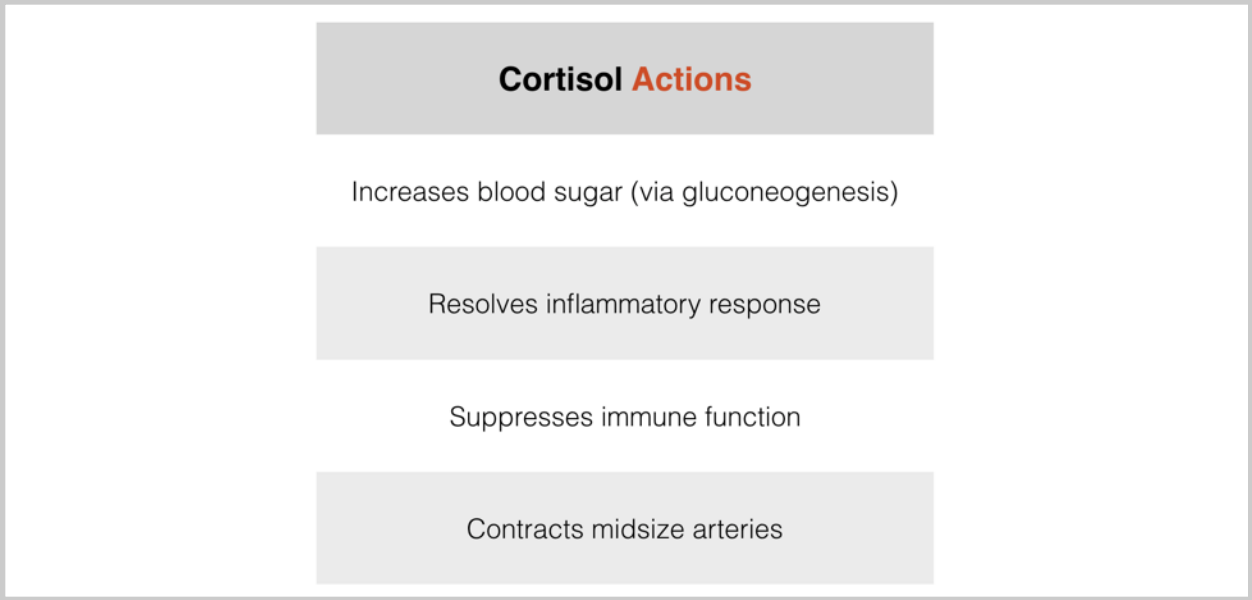
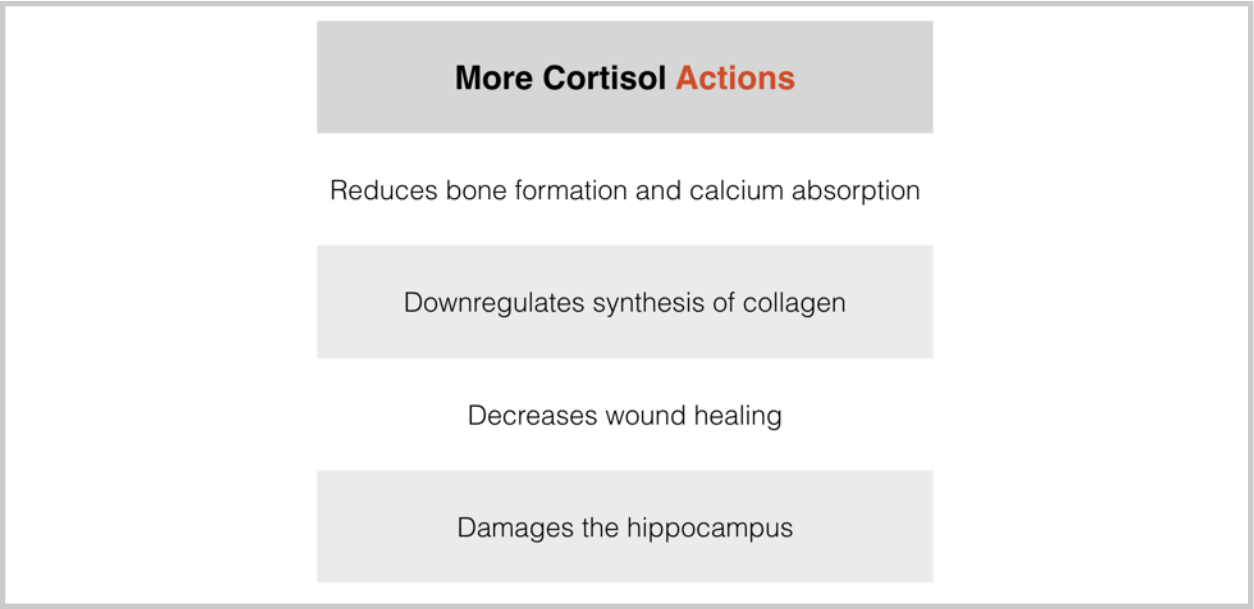
KRESSER INSTITUTE
FOR FUNCTIONAL AND EVOLUTIONARY MEDICINE

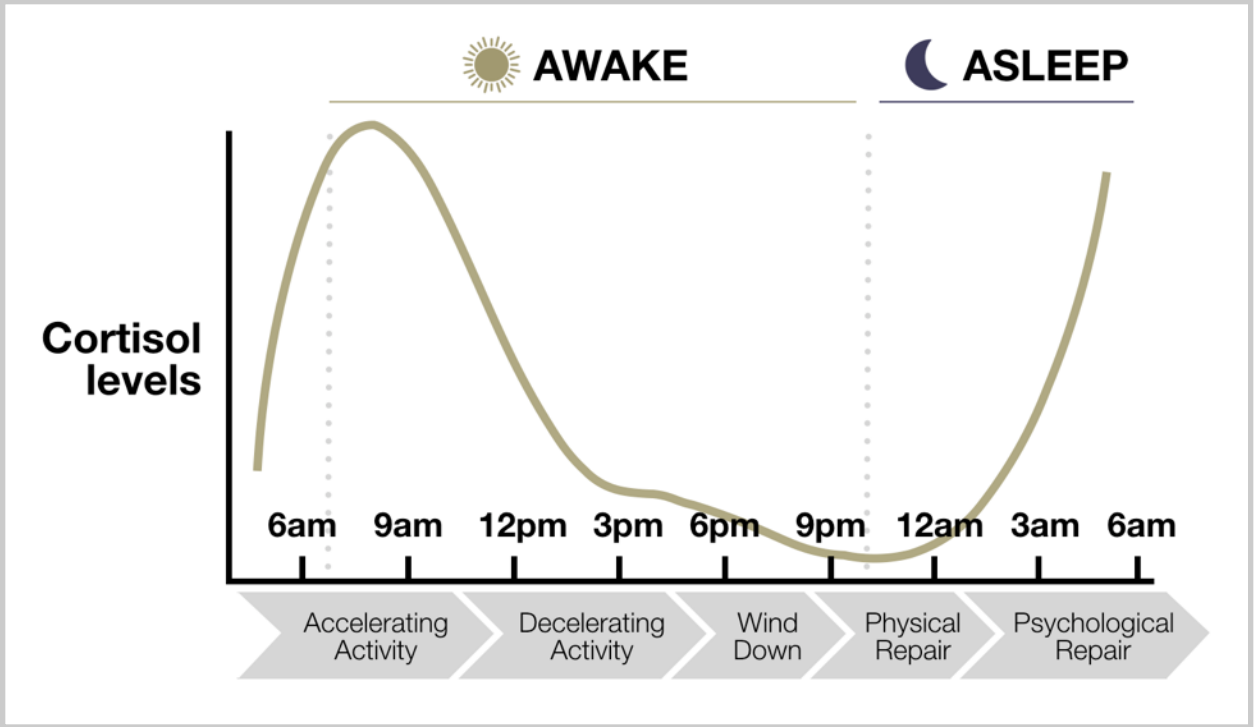
HPA-D: HPA Basic Physiology - Part 3



All right, let's talk more about cortisol, a major player here in the stress response. It's a glucocorticoid produced in the adrenal cortex, and it is the primary stress hormone released in response to stressors, but also to low blood sugar. It's important to remember that about cortisol; it is after all a glucocorticoid. It has several functions, and they include increasing blood sugar through gluconeogenesis, so when blood sugar drops, cortisol works in tandem with insulin to provide adequate glucose to cells for energy. It's anti-inflammatory—after an injury, the body initiates the inflammatory cascade, swelling and redness, which are part of the healing response, and cortisol is involved with resolution of that response. So if patient does have very low cortisol, they won't be able to turn off that inflammatory cascade, and that can lead to chronic inflammation, which is why HPA axis dysfunction is associated with so many inflammatory conditions, one of the reasons. Cortisol also leads to immune suppression. High cortisol weakens immune function; in particular, it shifts to a TH2 response rather than general immunosuppression, which explains the connection between stress and colds and flus and infections, which require a TH1 response to fight off. Vasoconstriction—cortisol contracts the mid-size arteries, which explains the connection between low cortisol and hypotension.



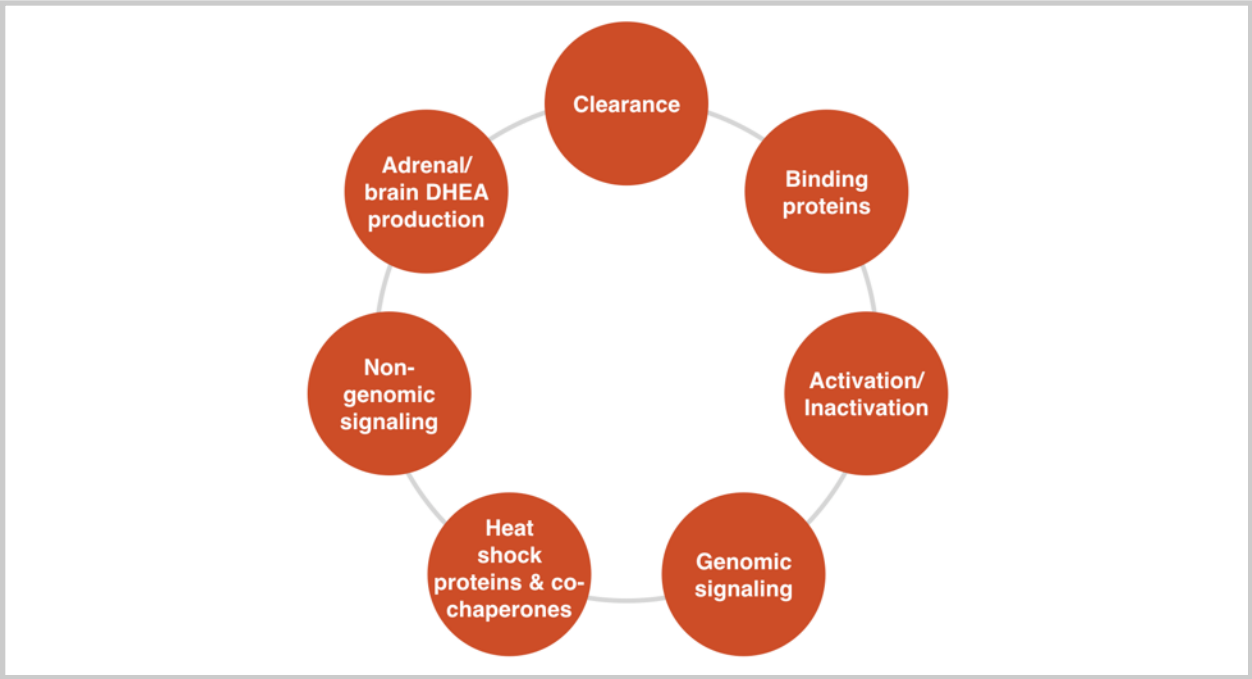
Cortisol reduces bone formation and calcium absorption in the intestine, which explains the connection between high cortisol and stress and osteoporosis. It downregulates the synthesis of collagen, an important component of muscles, tendons and joints, which explains why high-cortisol states are associated with muscle wasting. Cortisol decreases wound healing, probably because of the effects it has on the immune system and collagen. Cortisol acts as a diuretic, it increases sodium retention and potassium excretion, which is another reason why low cortisol is associated with hypotension and high cortisol with hypertension, and why managing stress is absolutely crucial for blood pressure management. And cortisol damages the hippocampus, which impairs learning and inhibits retrieval of stored memories, which explains the connection between stress and cognitive disorders.



As I'm sure you know by now, cortisol is not secreted in a uniform amount throughout the day. It's secreted in a diurnal fashion, so the highest levels of cortisol would be produced around 8 a.m., and then you'll see a gradual decline throughout the day until it's at its nadir between midnight and 4 a.m., and then it starts to rise again quickly, resulting in peak output just as we're waking up. The production of cortisol is regulated by information about the light–dark cycle that's transmitted from the retina to the paired superchiasmatic nuclei in the hypothalamus. This explains why controlling exposure to light is such an important part of HPA axis dysfunction treatment, along with what we discussed before in relation to the superchiasmatic nucleus. We're going to talk extensively about regulation of light exposure in the treatment section.

Like many hormones, cortisol production is regulated by a negative feedback cycle. Under stress, the hypothalamus produces corticotropin-releasing hormone, which again acts on the pituitary to produce ACTH, and then ACTH acts on the adrenals to produce cholesterol. Cholesterol is manufactured into pregnenolone, which is eventually converted into cortisol and released in the bloodstream. Cortisol circulates in the bloodstream and travels through the circulatory system, where eventually it reaches the hypothalamus. The hypothalamus detects higher levels of cortisol, downregulates CRH and ACTH production, so that's your standard negative feedback hormone regulation cycle. And this ensures that the body turns off the stress response and stops secreting stress hormones when they aren't needed anymore. Interestingly enough, epinephrine is a positive feedback loop, so more epinephrine in the blood acts on CRH to secrete yet more epinephrine, and this is intentional; this ensures that the body's primed and ready to deal with acute stress and has enough energy available to fight to flee or do whatever is necessary to survive. That positive loop,

though, is interrupted by cortisol signaling, and that's what prevents constant secretion of epinephrine and being in a continual fight-or-flight response.



As you'll see when we talk about the myth of adrenal fatigue later on in this section, it's crucial to understand that the regulation of cortisol production by the adrenal glands, by negative feedback as we just talked about on the last slide, is only one of the numerous mechanisms by which the body controls the bioavailability of cortisol at the tissue level, and that is really what ultimately determines cortisol's effects on human physiology. So for example, if the adrenals are pumping out tons of cortisol, but the cells are resistant to cortisol, then you could actually see low cortisol effects because, even though the adrenals are making a lot of it, the bioavailability is low. That's just one example, but it turns out that there are at least seven primary mechanisms that determine the tissue-specific regulation of cortisol, and I'm going to briefly mention them on this slide, and then we're going to talk about them in more detail in the slides that follow. So the first would be metabolic clearance of cortisol, the second is binding proteins that carry cortisol through the body, the third would be activation or inactivation of cortisol to cortisone and back, then genomic signaling, heat shock proteins and co-chaperones, non-genomic signaling, and adrenal brain DHEA production.

Okay, let's start with cortisol metabolism rate. The clearance and detoxification of cortisol will alter its effects on target tissues. Clearance of cortisol is reduced in critical illness, poor liver function, and hypothyroidism, and it's increased in obesity, insulin resistance, and hyperthyroidism.

Binding proteins

Reduced CBG	Increased CBG
Infection	Estrogen (HRT, BCP, pregnancy)
Sepsis	Hypothyroidism
Severe burns	Hepatitis
Starvation	PTSD
Malnutrition	
Heart attack	
Liver disease	
Obesity and insulin resistance	
Hyperthyroidism	

Binding proteins: 95 to 97 percent of cortisol is either bound to cortisol-binding globulin, about 80 percent of it is bound to cortisol-binding globulin, or to albumen, which would be the remaining 15 to 17 percent. Only free cortisol has cell-signaling effects, so like other hormones, when cortisol is bound to a protein carrier, it doesn't have any cell-signaling effects. Low cortisol-binding globulin, or CBG, is seen in infection, sepsis, severe burns, starvation, malnutrition, heart attack, liver disease, and other states of inflammation, and some but not all studies have shown that CBG is low in obesity and insulin resistance, which leads to higher levels of free cortisol at the tissue level. On the other hand, cortisol-binding globulin is elevated by estrogen, including hormone replacement therapy, birth control pills, and pregnancy, and that's one of the main causes of elevated CBG that you'll see in your practice. It's also increased by hepatitis, certain forms of liver disease, hypothyroidism, and PTSD. In that case, the increase in cortisol-binding globulin is likely an adaptive mechanism to try to protect the body against the effects of excess cortisol production over an extended period of time. We're going to talk about how all of this manifests in clinical diagnosis and treatment more later in the unit.

Activation / Inactivation

More cortisol	More cortisone
Genetic polymorphisms	Genetic polymorphisms
Hypothyroidism	Hyperthyroidism
Inflammation	Human growth hormone
Visceral obesity	Estradiol
Insulin resistance	Testosterone
Excess sodium	Quality sleep
Licorice	Magnolia, Scutellaria, Zizyphus, Citrus peel
Obesity and insulin resistance	Ketoconazole

Next mechanism is activation or inactivation. So the enzymes 11-beta-hydroxysteroid dehydrogenase 1 and 2 control the interconversion of cortisol, which is the active form of the hormone, to cortisone, which is the inactive form. 11β-HSD1 converts cortisol into cortisone, though it can do the opposite under some circumstances, while 11β-HSD2 converts cortisone into cortisol. Polymorphisms, expression, activation, and inhibition of these enzymes affect the relative balance of active and inactive cortisol. Hypothyroidism, licorice root, inflammation, visceral obesity, insulin resistance, and excess sodium favor more cortisol, while hyperthyroidism, human growth hormone, estradiol, testosterone, quality sleep, magnolia, scutellaria, ziziphus, citrus peel extract, and ketoconazole favor less cortisol. 11β-HSD is upregulated at the tissue level in metabolic syndrome, obesity, diabetes, cardiovascular disease, cognitive disorders, bone disorders, and inflammation. For example, while obese subjects don't always present with high free serum or saliva cortisol, their fat tissue has three to fourfold higher 11β-HSD activity compared to lean subjects, and drugs that reduce 11β-HSD activity in fat tissue are being investigated as treatments for obesity, diabetes, and a wide range of other metabolic and rheumatic conditions.