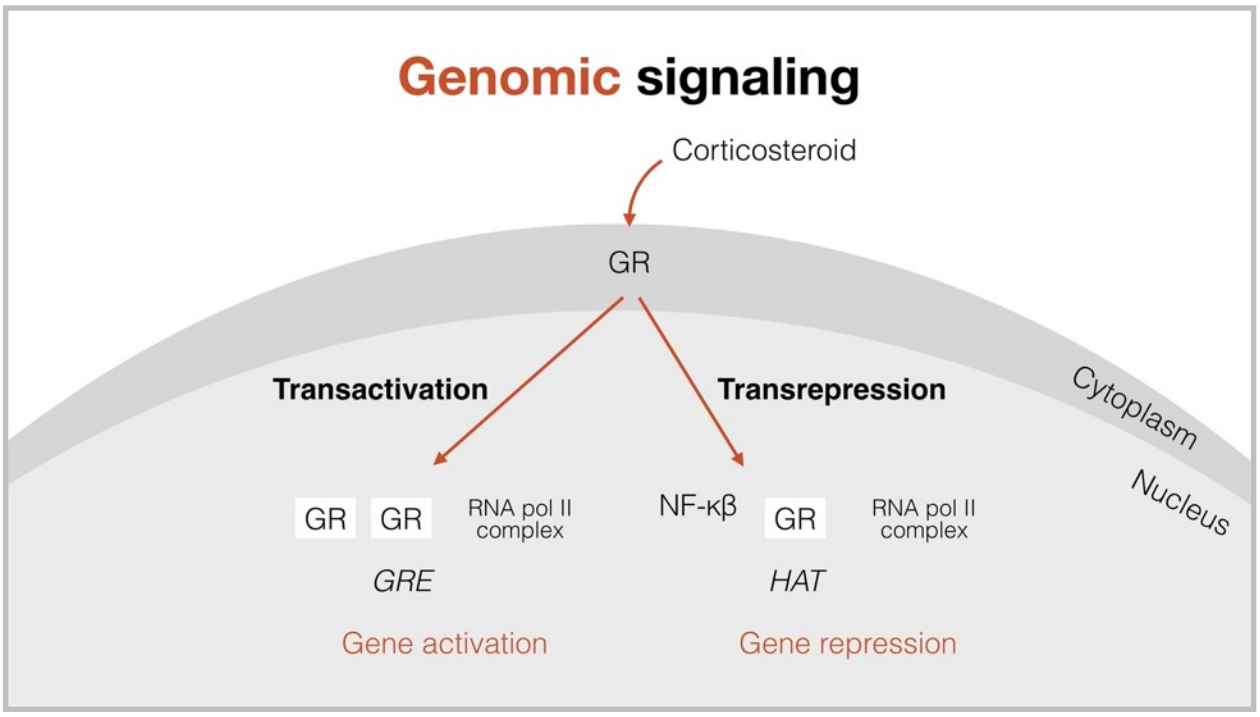
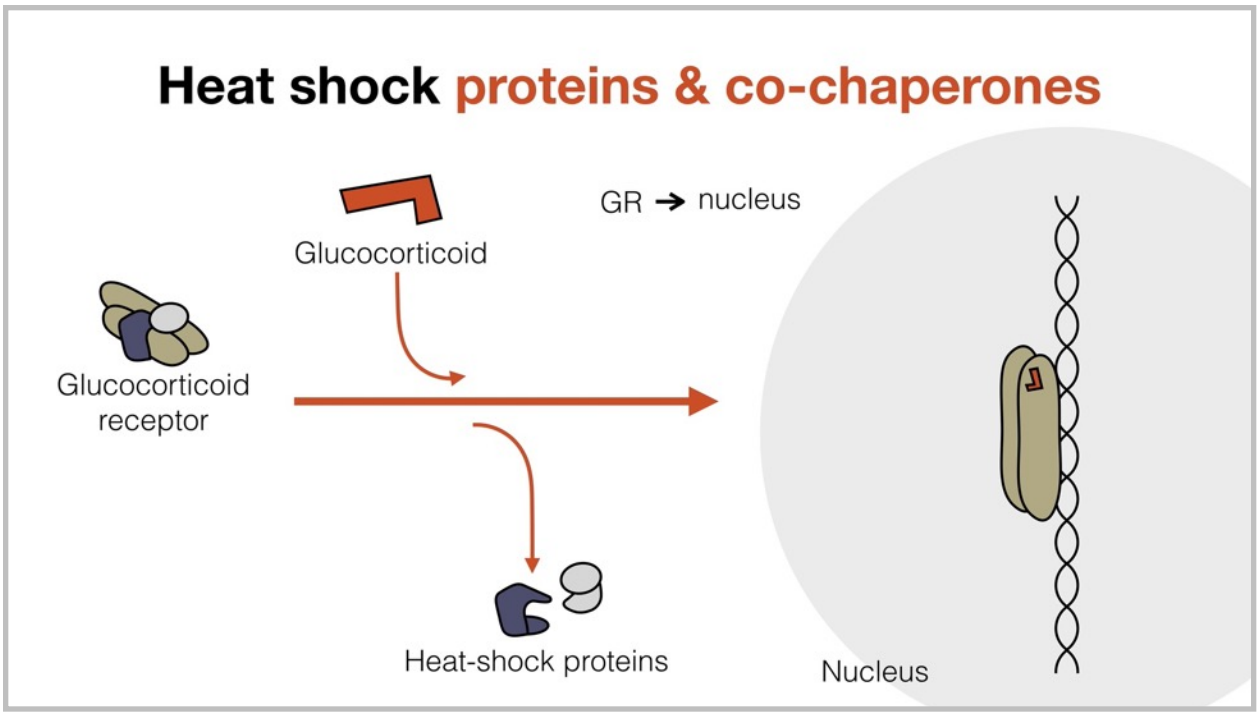
KRESSER INSTITUTE FOR FUNCTIONAL AND EVOLUTIONARY MEDICINE

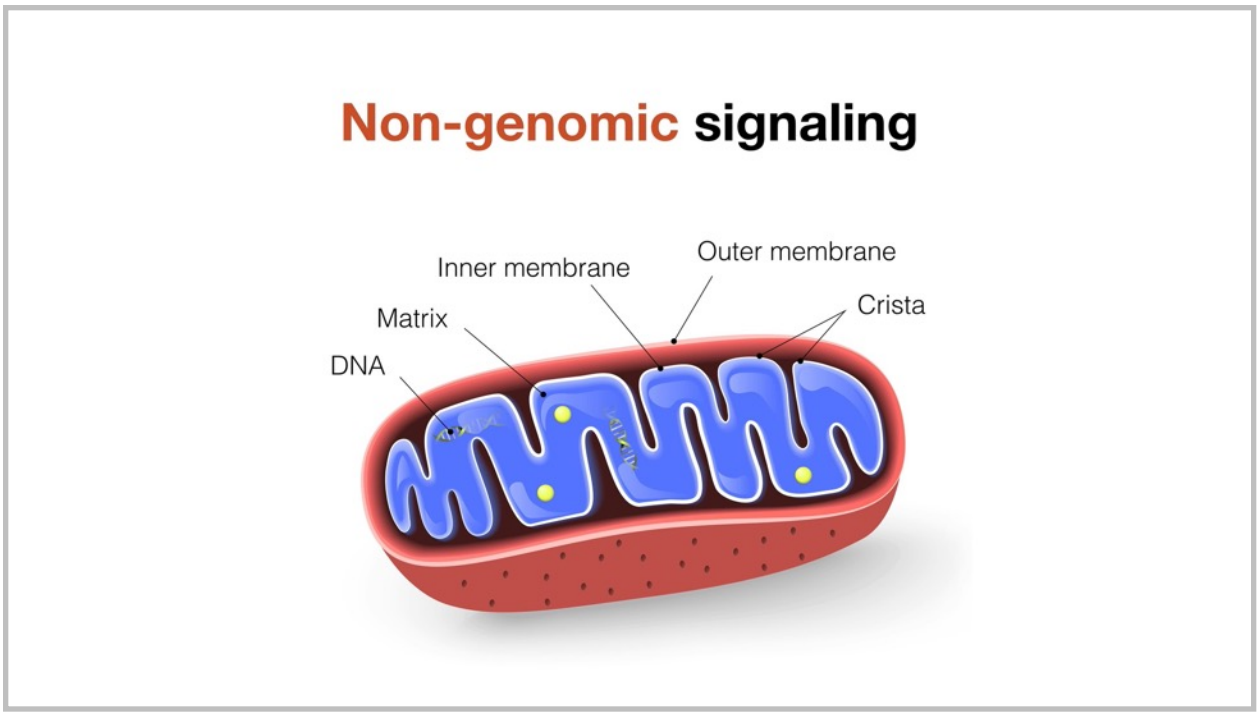
HPA-D: HPA Basic Physiology - Part 4



Genomic signaling: so the genomic effects of cortisol are mediated primarily through glucocorticoid receptors. Most of the known effects of cortisol are mediated through this type of genomic signaling. Nuclear glucocorticoid receptors are expressed in nearly every cell in the body and are involved in modulating up to 25 percent of the human genome in a tissue-specific and developmental pattern. So the genomic signaling of cortisol on glucocorticoid receptor function is absolutely vital to determining cortisol activity in the body, and it's something that's completely ignored and left out of the so-called adrenal fatigue model.



Let's talk a little bit about heat shock proteins and co-chaperones. Cortisol receptors are sequestered within the cell cytoplasm, and then there is a group of chaperone proteins called heat shock proteins that influence binding affinity and signaling effects of cortisol, and their expression is modulated by stress, exercise, and other factors. As an interesting side note, adaptogenic herbs are thought to work by regulating heat shock protein expression. The studies have shown that dysfunctional chaperone proteins may be involved in seasonal affective disorder, anxiety, psychosis, and other neurological and behavioral conditions. So here we have a number of factors that affect cortisol action that are actually inside of the cell, so again, this is not something that's typically acknowledged or dealt with in the adrenal fatigue model, but it's very important in terms of cortisol's ultimate action in the cell, which again is what is the most important factor.



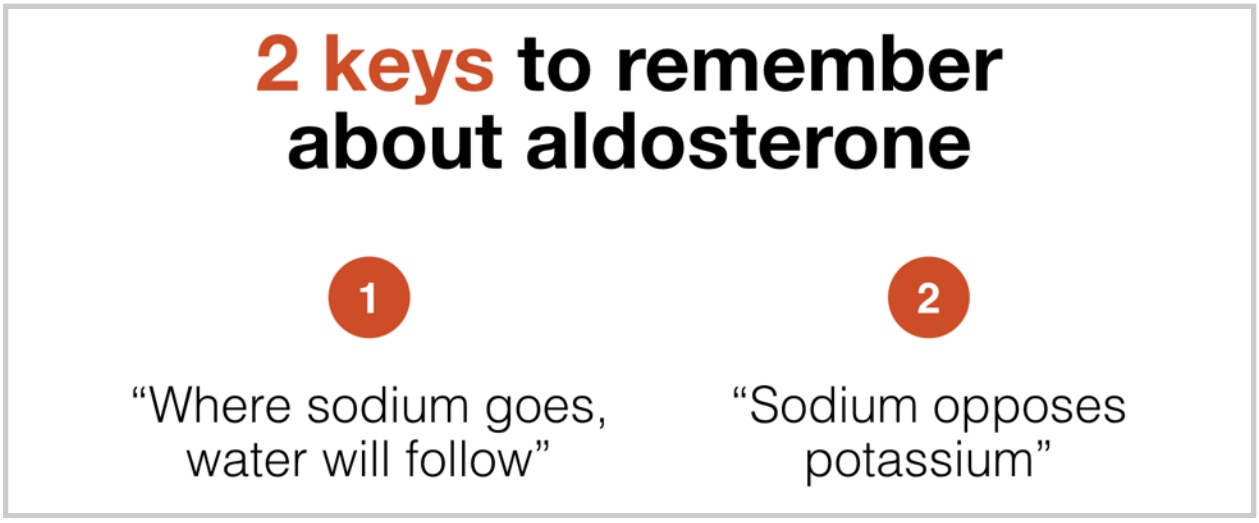
Non-genomic signaling effects: the bioavailability of cortisol is also mediated by membrane-bound receptors or directly through cytoplasmic signal transduction pathways. The mechanisms here include glucocorticoid alterations in membrane fluidity, direct binding to membrane-bound glucocorticoid receptors, non-genomic glucocorticoid receptor-mediated outcomes, heat shock protein signals, which we just talked about, and changes in mitochondrial membrane fluidity or mitochondrial activity.

Now finally, we have the adrenal and brain production of DHEA. DHEA functions as an anabolic counter-regulatory hormone to the catabolic effects of cortisol. Low DHEA and high or even high-normal cortisol, if DHEA is low enough, lead to unopposed actions of cortisol, which creates an ongoing catabolic state. We now understand that DHEA is also produced in the brain as a neurosteroid, as we talked about before. Levels of DHEA, for example, are six to eight times higher in the central nervous system than they are in the serum, because DHEA protects sensitive central nervous system tissues from the catabolic effects of cortisol. The tissue-specific effects of DHEA include improved insulin sensitivity, positive immune modulation including attenuation of information, improved cardiovascular and endothelial function, improved bone metabolism, protecting brain structure and function, and positive effects on sexual function. DHEA crosses the blood-brain barrier, which may be why some studies have shown that supplemental DHEA positively affects cognitive function and mood.

So each of these mechanisms that we've just discussed affects the bioavailability of cortisol on local tissues, and thus how the body physiologically responds to stress. Because these are tissue-specific responses and not systemic, many, though not all of them, can't be easily tested for outside of a research setting. This means that the effects of these mechanisms won't necessarily show up in lab test results, no matter what method you use, whether you're using saliva or serum or urine or hair. So for example, high cortisol in saliva or serum may be compensated for by cortisol receptor site resistance in specific tissues. On the other hand, low cortisol could be compensated for by

hypersensitivity to cortisol in specific tissues. Now, there are a few really important takeaways from this; the first is that the physiology governing cortisol bioavailability is extremely complicated, far more complicated than the adrenal fatigue model has led on. If your head is spinning a little bit after going through all of the mechanisms that we just covered, that's not unusual or surprising because this stuff is very complex. It's acknowledged to be very complex within the field and the people that study it, and there's still a lot that we have to learn, so one of the problems with the adrenal fatigue model is that it's based on a vastly oversimplified and just frankly insufficient understanding of how cortisol is regulated in the body. The second thing that I want you to take away from this is that sometimes we may need to treat empirically for HPA axis dysfunction, rather than relying solely on test results because as I mentioned, there are effects that govern cortisol's function and bioavailability in the body that won't necessarily show up on the test results that we have available to us. So if you see someone, a patient with multiple signs and symptoms of HPA axis dysregulation, and you're convinced that that's what's going on and it's playing a role in their condition, but their test results keep coming back relatively normal, it may be wise to do a therapeutic trial in that situation because the test results don't always tell us the full story.

Okay, let's move on to talking about aldosterone. This is a mineralocorticoid produced in the adrenal cortex under the direction of ACTH. It's secreted in a diurnal rhythm that's similar to cortisol, so it peaks at 8 a.m. and has a low point of 12 to 4 a.m. It plays a central role in regulating blood pressure by increasing reabsorption of ions in water in the kidney and causing the conversion of sodium and secretion of potassium, increasing water retention, and increasing blood volume. Stress increases the release of aldosterone, raises blood pressure, and therefore increases the risk of cardiovascular disease and kidney disease. Hypertension, of course, is the number one single risk factor for cardiovascular disease, so that explains the connection there. It's not a simple relationship, though, because as HPA axis dysfunction progresses, blood pressure can actually end up being low rather than high for some of the reasons that we've already discussed, like the local tissue regulation of cortisol. Blood pressure drugs like Lisinopril lower blood pressure by blocking the angiotensin-converting enzyme ACE inhibitors, leading to lower aldosterone secretion.



There are two things that are helpful to keep in mind about aldosterone from a clinical perspective. The first is "where sodium goes, water will follow," and the second is that "sodium opposes

potassium." So as aldosterone goes up, due to stress for example, the concentration of sodium and water rises, potassium drops, fluid is retained, and blood pressure rises, so this is why stress can have such a significant effect on hypertension. Excessive aldosterone then leads to high sodium, high blood pressure, and low potassium. On the other hand, low aldosterone can lead to low blood pressure, high pulse rate, postural hypotension, getting dizzy when standing up quickly, salt cravings, palpitations, and in severe cases may lead to hyperkalemia and hyponatremia. Aldosterone doesn't have a negative feedback loop like cortisol does, so if it's too high, the only way the body can protect itself is to downregulate receptor sites' production and the sensitivity of aldosterone receptors. The effects of stress on blood pressure are compounded because the adrenal glands produce epinephrine and norepinephrine in the stress response as part of the sympathoadrenal medullary system, the SAS, that we've talked about, and this would be expected to constrict blood vessels and increase blood pressure. And as we discussed, cortisol contracts the mid-sized blood vessels, which would also increase blood pressure, though with less potency than epinephrine.