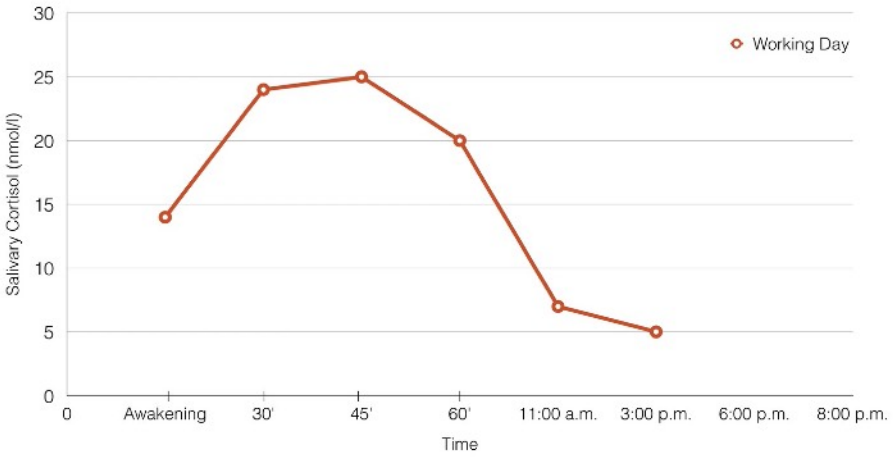
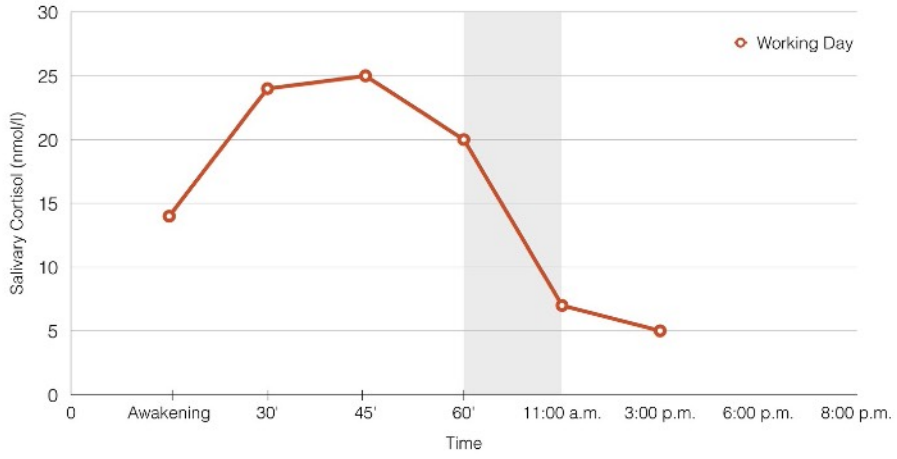
KRESSER INSTITUTE
FOR FUNCTIONAL AND EVOLUTIONARY MEDICINE

HPA-D or Adrenal Fatigue? Part 2



Yet another reason for the perpetuation of the adrenal fatigue idea is that saliva cortisol testing often returns falsely low values, especially in the morning. To understand why, we need to dive into a little more detail on the dynamics of diurnal cortisol production. Several hours before we wake up, the normal HPA axis activity leads to rising cortisol levels. Then, about 30 to 45 minutes after we wake up, light activation of the superchiasmatic nucleus leads to an additional, more dramatic increase of up to 50 percent in cortisol secretion. And this is called the cortisol awakening response, or CAR, and it's pictured here on the figure in the slide. A crucial point is that the cortisol that's produced during the CAR within the first 30 to 45 minutes of awakening accounts for more than half of the total cortisol reported on a full day's saliva test.



This means that the timing of the first sample collected is absolutely crucial to getting accurate results, because when you do an adrenal stress index on a patient, they take four readings and they estimate the total cortisol production for the whole day based on those four readings. They're not actually measuring the total amount of cortisol produced in a day; in order to do that you'd need a 24-hour urine test. With the saliva test, they're estimating based on these four time points. So if the morning sample is taken 60 minutes after waking rather than 30 to 45 as shown here on this slide, the CAR, the cortisol awakening response, will be missed, and since that accounts for over 50 percent of the cortisol produced in the day, that will lead to overdiagnosis of low cortisol or a flattened cortisol curve.

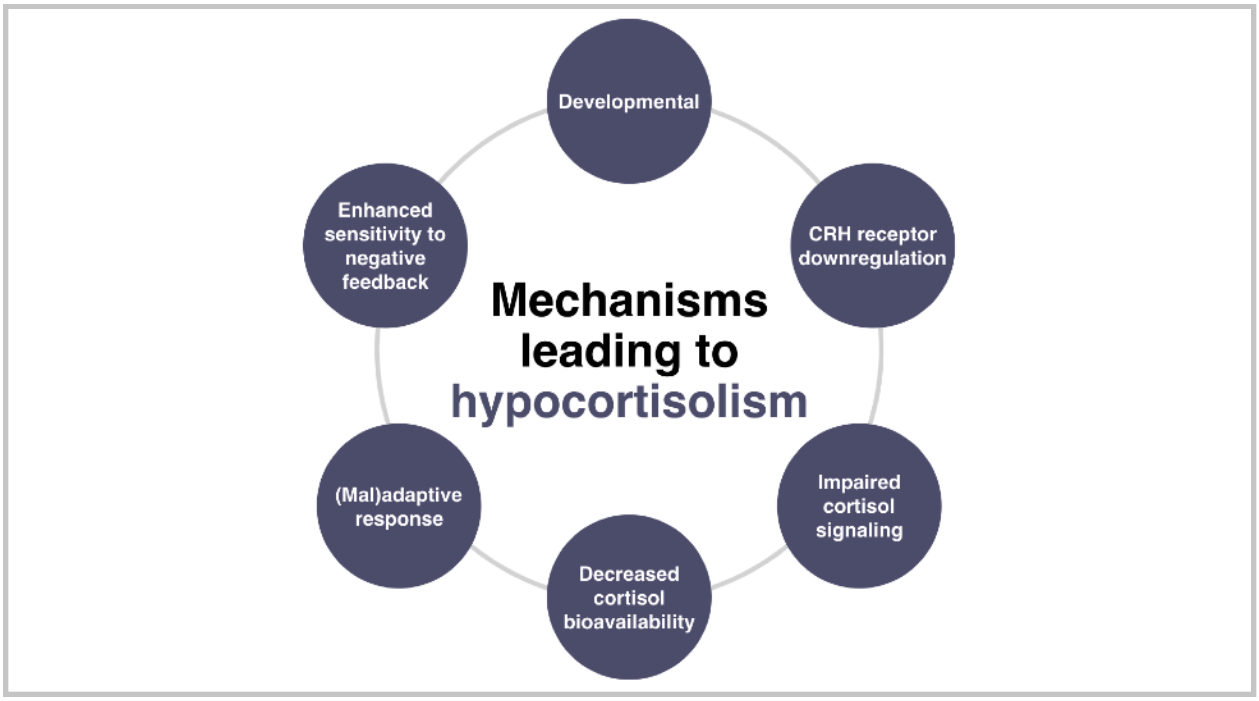
And this is a huge problem, because many of the labs doing saliva testing only suggest doing the waking sample during a window of time, for example between six to eight a.m. with no regard for waking time. For example, say a patient wakes up at 6:15 in the morning but doesn't take the sample until close to 8 a.m.; not only would the CAR be missed in that case, but cortisol production would be falling substantially by then. If you look at the figure on the slide, you could see that there would be a five nanomoles per liter difference in values between 7 a.m., the peak cortisol awakening response would be somewhere between 6:45 and 7:00 if the patient awakes at 6:15, and even 15 minutes later at 7:15 a.m., and likely over a 10 nanomoles per liter difference between 7 a.m. and when the patient actually sampled in this hypothetical example at 8 a.m. This could certainly be a difference between the patient being diagnosed with low cortisol versus having normal cortisol, both in the morning and as a total estimate for the day, since the morning value is used to estimate the total, and in fact is the majority of the total,

based on what I've told you earlier about the morning reading should be 50 percent or more of the total cortisol produced during the day.

If you look in the scientific literature, you'll see thousands of studies detailing the effects of stress on human physiology via dysregulation of the HPA axis, but it's things like high cortisol, cortisol resistance, or disruption of the diurnal rhythm that are far more common than low cortisol as a mechanism. The term "adrenal fatigue" is virtually absent from the scientific literature. If you search for it as a phrase in PubMed as of the time of this recording, you'll see a whopping 10 results, and they're not the highest-quality results, either. Certainly, there are known conditions like Addison's disease that present with low cortisol levels, but Addison's is rare, only about 200,000 cases in the US per year, and it's not caused by stress, at least not exclusively. It's an autoimmune disease, it's caused by certain infections and other rare causes. And the levels of cortisol observed in Addison's are orders of magnitude than those observed when cortisol is low in so-called adrenal fatigue.

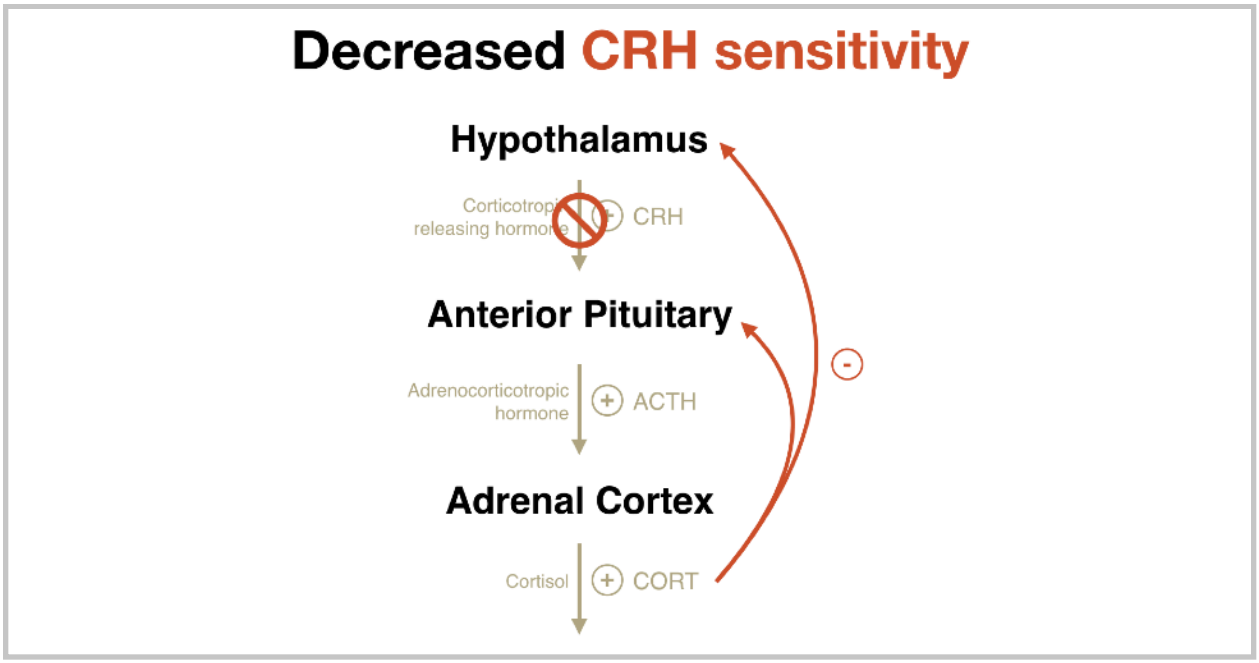
There are some studies in the literature linking low cortisol that's not related to Addison's disease to various disease states. For example, a few studies have found low cortisol in the evening and a blunted cortisol awakening response in chronic fatigue syndrome patients. But in many of these studies, only free cortisol was measured; for example, Jerjes et al. measured both free cortisol and urinary cortisol metabolites, which are, as we've discussed, a better marker for total cortisol production in chronic fatigue syndrome patients, and he found that free cortisol and free cortisone were indeed lower in chronic fatigue syndrome patients than in controls, which is consistent with previous research, but there was no difference in cortisol metabolites between chronic fatigue patients and controls.

However, even if cortisol is low in some patients, it's rarely because the adrenals are fatigued or exhausted and unable to produce it. Instead, the control mechanisms for cortisol are mostly found in the brain and the central nervous system, as well as in local tissues. The HPA axis governs the adrenal production of cortisol through circadian and stress signals in the brain, and negative feedback inhibition. However, the production of cortisol is only the tip of the iceberg when it comes to determining how the HPA axis controls the stress response in local tissues, which is ultimately what is most important in terms of how stress influences health and disease. Since cortisol is such a potent steroid hormone, the body has several and sometimes redundant mechanisms for modulating and buffering its effects on local tissues.

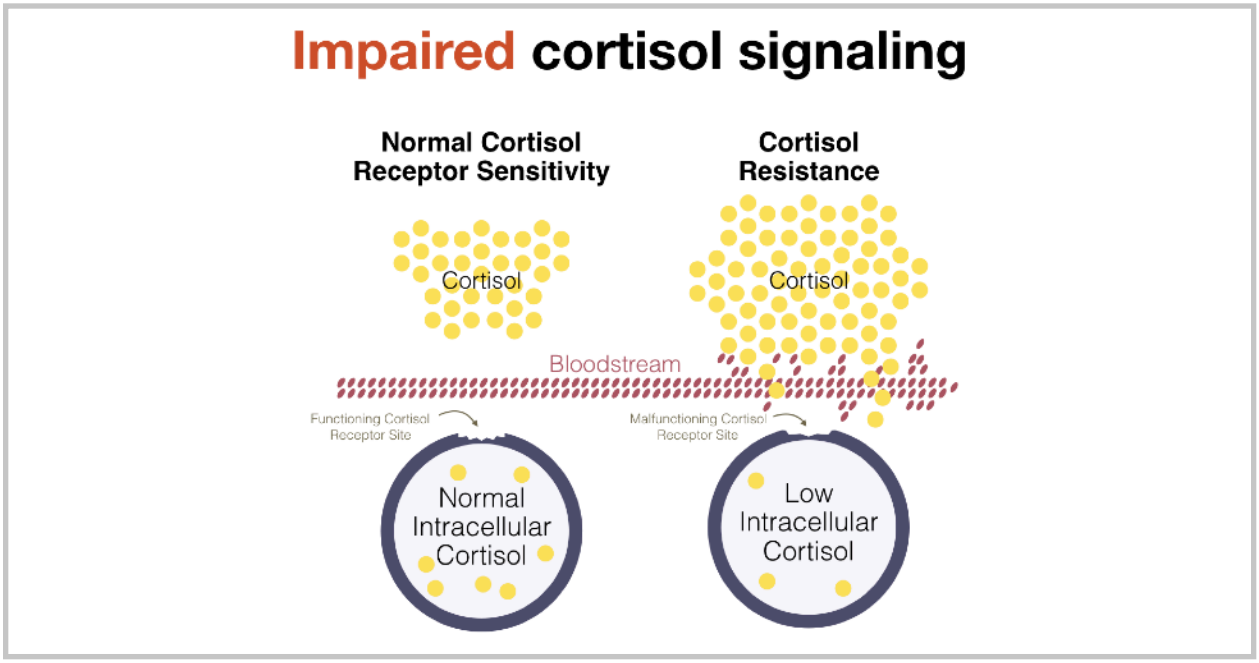


Dr. Lena Edwards reviewed several mechanisms that lead to low cortisol in her paper on hypocortisolism in *Journal of Integrative Medicine*. These include developmental factors, CRH receptor downregulation, impaired cortisol signaling, decreased cortisol bioavailability, maladaptive response, and enhanced sensitivity to negative feedback. So let's talk about each of these in a little more detail.

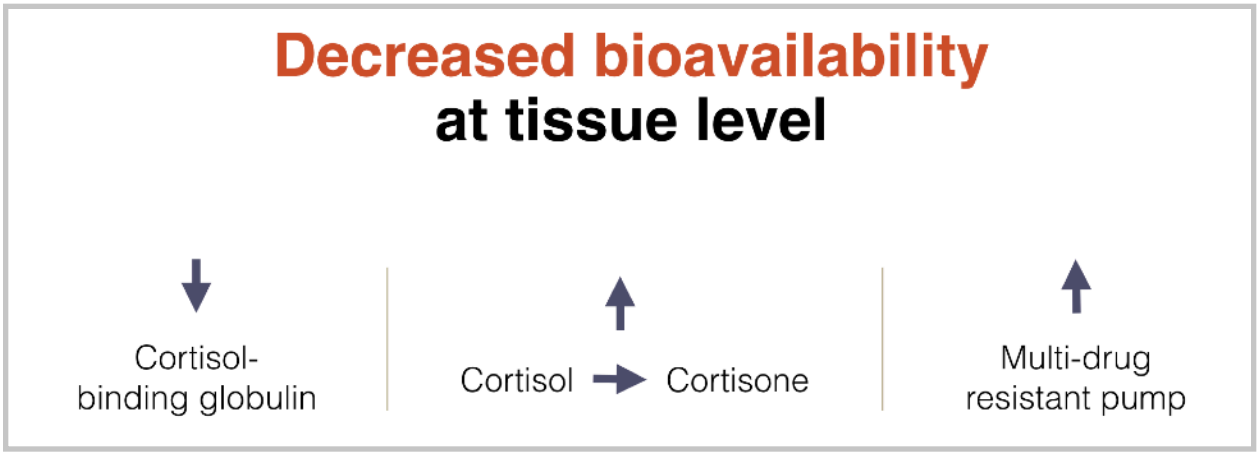
Research has shown that the HPA axis can be permanently programmed by events that happened early in life. Early life stress produces an initial period of HPA axis hyperactivity and hypercortisolism, but this is followed by a downregulation of the HPA axis and reduced cortisol secretion. The speculation is that this is a maladaptive response; cortisol is a catabolic hormone, it breaks things down, so in the body's wisdom, it's trying to protect itself from that, so it downregulates the entire HPA axis, which does protect itself from the effects of excess cortisol, but unfortunately it also leads to a decreased ability to produce cortisol in response to stress later in life, and so that can lead to a kind of chronic low cortisol state later in life that came out of this early life traumatic event.



Next mechanism is decreased CRH, or corticotropin-releasing hormone, receptor sensitivity. Animal studies have shown a decrease in CRH receptor sensitivity in the pituitary gland after prolonged exposure to stress. Other studies have shown that an increase in the sensitivity to HPA axis to cortisol during periods of stress leads to downregulation of further release of cortisol. Again, this is another way that the body attempts to protect itself from the effects of excess cortisol, but unfortunately it overcompensates by producing less cortisol when faced with future stress.



Impaired cortisol signaling refers to a group of related dysfunctions, chronically high cortisol levels will lead to cortisol resistance, and this is a very similar phenomenon to insulin resistance. It can be caused by a decrease in cortisol receptor sensitivity and/or a decrease in glucocorticoid receptor expression. Cortisol receptor dysfunction may also be caused by decreased cortisol binding affinity, decreased receptor DNA binding, and impaired translocation of the receptor into the nucleus.



Another mechanism is decreased bioavailability of cortisol at the tissue level, and this has several causes. One is increased levels of cortisol-binding globulin, which is the primary protein that carries cortisol through the blood. About 80 percent of cortisol is carried by cortisol-binding globulin and the other 15 percent of cortisol that's bound is carried by albumen. Since only free cortisol has cell signaling effects, an increase in cortisol-binding globulin will decrease the overall amount of bioavailable cortisol. Another cause is the increase of the conversion of cortisol, which is the more active form, into cortisone, which is the less active form, and this can be observed in several different disease states, as well as with certain drugs, medications, and finally, activation of the multi-drug resistant pump can cause cortisol exit from the cell, and then when cortisol is not in the cell, it can't have the cellular transcription effects.

Low cortisol may also occur as an adaptive mechanism to promote a more vigorous response to infection or inflammation. Cortisol is a potent anti-inflammatory substance, so during a period of acute illness, we actually want inflammation, inflammation is the healing response. It gets a bad rap, when we're usually talking about inflammation in a negative context, it's chronic inflammation. Of course, if we didn't have the ability to mount an acute inflammatory response to injury or infection, we would die, we wouldn't be able to survive without it, so when we have an acute illness, we don't want high cortisol in that moment because we want to be able to mount that inflammatory response. But then the body will secrete cortisol to suppress and resolve the inflammatory response. In people suffering from recurrent or chronic infections, though, or in chronic inflammation, the body may reduce cortisol production or signaling in an

attempt to deal with the infection. It's essentially prioritizing its defense against a pathogen, or again, serious inflammation which it views as short-term threats, over mechanisms that support long-term health, and this has been documented in cases of both acute and chronic infection.