The Role of Stress and the HPA Axis in Chronic Disease Management

Principles and Protocols for Healthcare Professionals

The Stress Response: Function and Dysfunction • How Stress Depletes Metabolic Reserve
Is it Really Adrenal Fatigue? • Genomics and Epigenetics of Stress • Modulating Cortisol Signaling
Neurosteroids and Neurotransmitters • Understanding Adrenal Hormone Testing
Avoiding Common Testing Errors • The Three-Stage Model of Stress Progression
Sample Patterns of Diurnal Cortisol and DHEA(S) • Addressing the Key Reversible Stressors
Nutrient Support Protocols • Adaptogens • And much more...

THE STANDARD
ROAD MAP SERIES

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The Role of Stress on the Human Condition

Though the details of the stress response system will be covered in later sections, it is important, first, to lay a broad foundation and biological reason for having such a system in the first place. Knowing *why* something is happening often helps in our perspective, especially when it comes to managing a patient through the web of physical, emotional and spiritual complexities related to being human in the modern world.

Humans, like all living things, must respond and adapt to a wide-range of threats to their life and health. Therefore, our bodies are equipped with a complex repertoire of metabolic functions specifically designed to keep us healthy, or at least to survive the immediate crisis with a chance to regain our health in the near future. This process is closely related to the phenomenon known generally as "homeostasis," a physiologic state of balance that is susceptible to a range of stressors, both intrinsic and extrinsic (real or perceived).

The term "stress" is now commonly used to describe a "state of threatened homeostasis or disharmony," a condition that triggers a specific biological phenomenon, the "adaptive stress response."[1] Excessive, prolonged or inadequate regulation of the stress response systems will invariably cause individuals to suffer adverse health consequences. The challenge for today's clinician is in assessing the status of an individual's stress response system and relating that status to the individual's clinical presentation. Ultimately, the goal is to discover the root cause(s) of the imbalance related to the stress response, helping patients regain their physiological balance, while slowing or reversing the chronic manifestations caused by stress.

The Goal of the Stress Response

Ancient philosophers and healers clearly understood the notion of "stress" as a disrupter of the "harmony" of health and a cause of "dis-ease," but the detailed understanding of the intricate pathophysiology of the stress response has come to light only over the past century or so.[2] Standing on the shoulders of many before them, both Walter Cannon (1871-1945) and Hans Selye (1907-1982) popularized the notions of homeostasis and stress as they relate to health outcomes. Cannon coined the term "Fight or Flight" and Selye defined the General Adaptation Syndrome and discovered glucocorticoid function.[3,4] It has been said that Cannon described the actions controlled by the adrenal medulla (driven by epinephrine and norepinephrine) and Selye described those of the cortex (driven by glucocorticoids). Today, thousands of researchers in many different disciplines can trace their lineage to the work of these men, extending their research to reveal how the stress-response affects (and is affected by) nearly every biological and medical phenomenon.

As with any growing field, additional nomenclature was created to define the nuances of the stress response. Because the concept of "homeostasis" was inadequate to fully describe a system that normally functions through rhythmic fluctuations, the term "allostasis" was adopted to describe "stability through change." McEwen and Stellar then coined the term "allostatic load" to describe both the load of stressors upon the biological system, as well as the metabolic cost to the stress response mechanisms as a consequence of adapting to various stressors.[5,6] In this model (See Figure 4), there are three basic ways allostatic load leads to a maladapted stress response, and then to further biological consequences: 1) frequent stressful events that reduce the ability to adapt (made worse by higher magnitude and frequency, and sometimes referred to as "repeated hits"); 2) a stress response that does not resolve or turn off; 3) an inadequate or failure to respond to a stressor. In other words, the stress response can be compromised by repeated use, by dysfunctional regulation and resolution, or by lacking the appropriate capacity to respond. These ideas will be expanded upon throughout this guidebook.

Reassessing the Nomenclature of HPA axis Dysfunction

Is it *Adrenal Fatigue*?

Sometimes when we endeavor to understand and describe complicated medical topics there is a temptation to find a simple explanation to cut through that complexity. Oftentimes, these explanations can help bridge the knowledge gap for a while, but as our knowledge grows, those explanations lose some of their original usefulness (i.e., "good" and "bad" cholesterol). In some cases, those over-simplified explanations actually become a hindrance to helping clinicians and patients understand the important mechanisms and solutions related to their chronic conditions. The use of terms like "adrenal fatigue," and "adrenal exhaustion" to summarize the complex dysfunctions related to the stress response is one such explanation. Though these terms have helped dispel the notion that only extreme issues related to adrenal function (Addison's or Cushing's disease) are of clinical importance, and have become surrogate descriptions for stress-related outcomes, they should now be replaced by more accurate and medically appropriate terms (i.e., HPA axis dysfunction, adrenal insufficiency, hypocortisolism, etc.).

While it is true that the most common laboratory method to assess the function of the HPA axis is through the measurement of hormones secreted by the adrenal glands, primarily cortisol and DHEA(S), the mechanisms that control the level of these hormones reside mostly outside of the adrenal gland (primarily in the CNS). Low cortisol and DHEA levels may indeed be related to chronic stress, most likely they reflect HPA axis adaptation (down-regulation) to protect tissues from excess cortisol; and have little to do with the capacity of the adrenal gland to produce these hormones. So while many clinicians (and laboratories) refer to this as "testing the adrenals," it is much more accurate to say that such testing is assessing the status of the HPA axis using adrenal hormone measurements as surrogate markers. So why does this nomenclature reassessment matter?

First of all, using descriptive and accurate terms helps clinicians and patients have a better understanding of the pathophysiology caused by stress and the stress response system. In most cases, issues related to perceived stress, glycemic control, circadian rhythm, cortisol feedback sensitivity (in the hypothalamus and/or pituitary), inflammatory signaling or tissue-specific glucocorticoid effects will have much more to do with a treatment protocol than support for adrenal function.[1] Related to this is the ability of the clinician to interface appropriately with the vast amount of literature that describes patient outcomes related to stress and HPA axis function. The term "adrenal fatigue" is virtually absent from the peer-reviewed literature and has even caused the Endocrine Society to warn the public against the diagnostic "myth" of adrenal fatigue and to cast suspicion upon clinicians using such terms.[2]

As this guidebook clearly shows, there is an increasing body of research linking a variety of chronic dysfunctions with specific patterns of adrenal hormone output (basal or provoked). By avoiding the use of oversimplified (and incorrect) terminology to describe these relationships and, instead, choosing more appropriate descriptive terms, the clinician will enhance the credibility of this important phenomenon and be better equipped to incorporate therapies that address the complexity of the whole stress response system.

Ironically, the Endocrine Society- first called the American Association for the Study of Internal Secretions when it was founded in 1916- was embroiled in a similar heated debate during its early years about the concept of *hypoadrenia*, what some called a mild form of Addison's disease. The societies' first president (1917), Charles Eucharist de Medicis Sajous, was a powerful advocate for establishing adrenal-related dysfunctions in the pathology of a multitude of "*distressing diseases of mankind"* and proposed three clinical "forms" of hypoadrenia: functional, progressive and terminal. Much of the early debates focused on the fundamental differences (and necessity) between the medulla and the cortex and the role of adrenaline and various adrenal extracts in treating Addison's disease. An excellent historical review of these early discussions has been written by RB Tattersall for those interested in such history.[3]

More Appropriate Terms

HPA Axis Dysfunction (or Maladaption): This term is much more appropriate to describe any of the many consequences that link stress (allostasis) with the myriad of measurable negative consequences related to the stress response; the majority of which can be linked in some manner to processes controlled by the HPA axis. Alternatively, some refer to these as "disorders of the stress-system" or the consequences of the maladaption to stress.

Hypocortisolism: This is the most descriptive term to use when measured cortisol is well below the laboratory reference range, though it is a relative term and does not necessarily implicate dysfunction or "fatigue" of the adrenal gland. Extreme hypocortisolism is associated with Addison's disease and other forms of primary and secondary adrenal insufficiency; though reduced HPA axis function resulting in low cortisol levels is common in PTSD, fibromyalgia, chronic fatigue syndrome, certain affective disorders, and individuals with high "burnout." Additional specific terms for other HPA axis phenomena include hypercortisolism, blunted or elevated cortisol awakening response, loss of circadian rhythm, low DHEA or DHEA-S (these and others are covered throughout this guidebook).

Adrenal Insufficiency: This is a clinical manifestation that results in a deficient production or action of glucocorticoids, a condition that has potential life-threatening consequences. Primary adrenal insufficiency (i.e., Addison's disease) describes diseases intrinsic to the adrenal cortex and is primarily caused by autoimmune adrenalitis; secondary adrenal insufficiency relates to insufficient pituitary ACTH or intrinsic defects in the adrenal responsiveness to ACTH; and tertiary adrenal insufficiency results from impaired synthesis of hypothalamic CRH or AVP. The most common cause of tertiary adrenal insufficiency is chronic use of exogenous glucocorticoids (pharmacotherapy), leading to the suppression of hypothalamic secretions of CRH. True adrenal insufficiency will almost always require hydrocortisone replacement therapy (often life-long). For a complete review of the etiology, pathophysiology, clinical presentation, diagnosis and treatment approaches to adrenal insufficiency, see Charmandari et al.[4]

References

1. It should be noted that many adaptogenic herbs and nutrients that were thought to function primarily by supporting adrenal function, have been shown to have mechanisms that modulate other aspects of HPA axis or glucocorticoid signaling functions.
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The Stress Response System

In order to provide health care professionals with the appropriate context and detail, this chapter will start with a basic overview of the stress response system, followed by a progressive unfolding of the details in subsequent sections. This will allow the reader to start by understanding a broad overview of the anatomy and physiology of the stress response system, followed by an increasingly more detailed look at the organs, glands, hormones, receptors, and signaling processes that control the outcome of the stress response. Our attempt is to strike a balance between oversimplification for the sake of brevity and overwhelming the reader with unnecessary minutia. Our goal is to focus on the portions that are likely to be of interest to healthcare providers and helpful in their application to clinically relevant situations, but also to point out new areas of research that are likely to have a relevant clinical impact in the near future. Readers who would like to explore these topics in more detail are encouraged to read the cited references, which focus on recent reviews of these topics or specific details covered only briefly here.

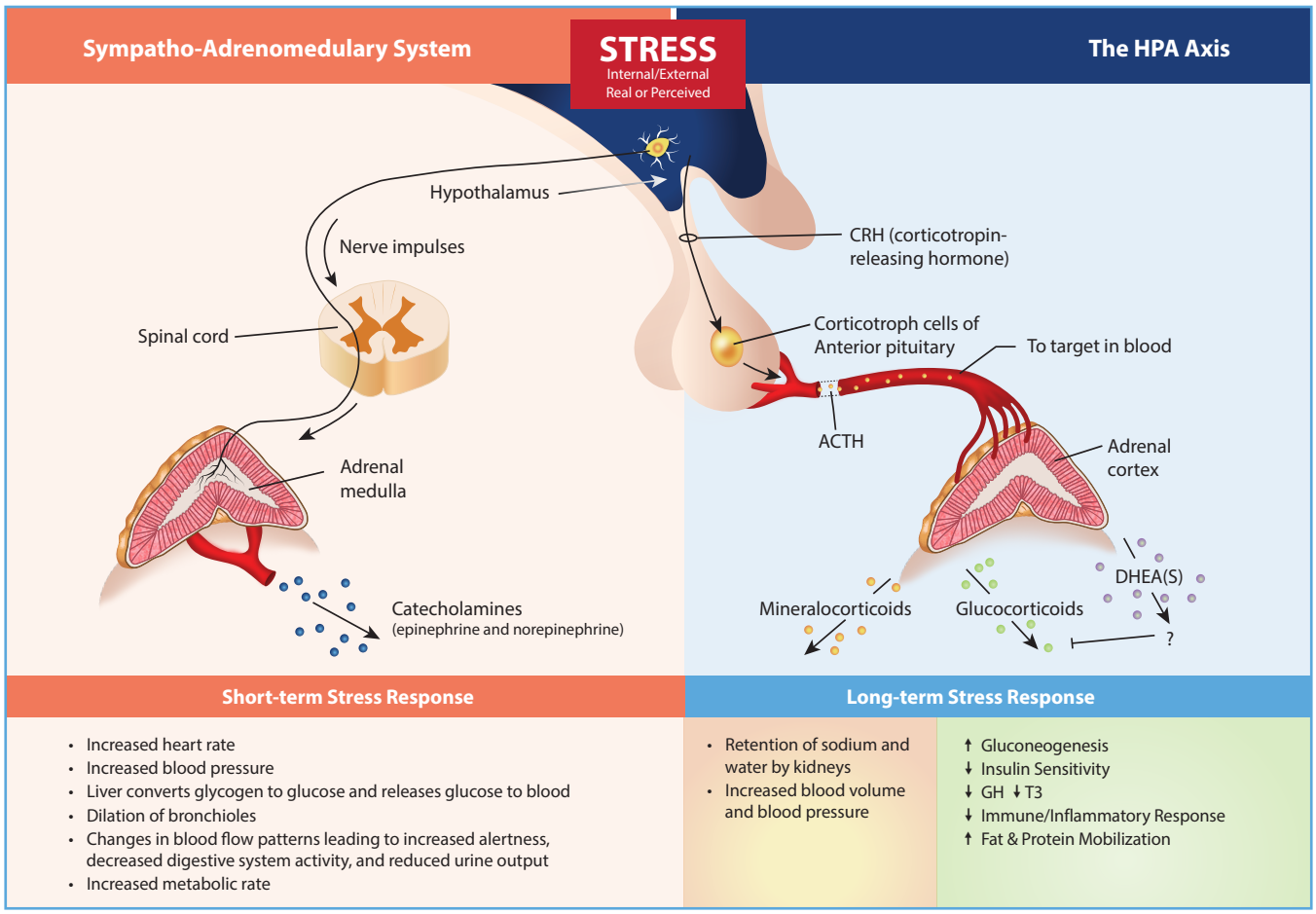


Figure 5: The Stress Response System(s). Beginning in the brain, stress signals are communicated by direct innervation to the adrenal medulla to cause a nearly immediate release of catecholamines (the fight-or-flight response) and through neuro-hormone signals within the HPA axis that influence the release of mineralocorticoids (aldosterone), glucocorticoids (cortisol) and DHEA(S).

Reassessing the Notion of "Pregnenolone Steal"

When clinicians measure salivary cortisol and DHEA(S) to assess HPA axis function, it is common to find DHEA(S) levels below the reference range in a wide-range of individuals. A common explanation for the depletion of DHEA(S) and other hormones (e.g., progesterone, testosterone) due to chronic stress is the phenomenon known as "pregnenolone steal." This notion basically states that since all steroid hormones use pregnenolone (derived from cholesterol) as a precursor, the elevated secretion of cortisol caused by acute or chronic stress will inevitably result in less available pregnenolone to serve as a precursor for the production of DHEA and other down-stream hormones. In other words, according to this theory, the need for cortisol synthesis "steals" pregnenolone away from other hormone pathways, reducing the potential synthesis and secretion of other necessary hormones, resulting in some of the pathophysiological changes related to stress.

While a rise in cortisol levels and a concomitant drop in DHEA(S) is one of the clinical characteristics of early and mid-stage stress progression, this phenomenon is not caused by diminished adrenal pregnenolone availability or "pregnenolone steal." (See page 66 for the three-stage model of stress adaptation). The most obvious reason is the fact that the conversion of cholesterol to pregnenolone occurs in the mitochondria of each respective cell type (See Figure 13). Simply put, there is no known adrenal pool of pregnenolone for one cell to steal away from another, and no known mechanism has been described that could facilitate the transfer of pregnenolone between the mitochondria of different cells (in this case, from the mitochondria of cells within the zona reticularis to those within the zona fasciculata). Unfortunately, the most common figures used to teach steroidogenesis show a common pathway and typically do not specify the differential regulation of available enzymes between different steroidogenic tissues. This leads many to incorrectly assume there is a single "pool" of pregnenolone available for all steroid hormone synthesis within the different adrenal cortex zones.

In addition, the *ACTH-driven* adrenal synthesis of cortisol is orders of magnitude higher than that of DHEA(S), and fluctuates radically within a 24-hour period. If there were an adrenal "pregnenolone pool" that contained enough pregnenolone precursors for elevated cortisol production in the morning (or during stress), this "pool" would then also be available for the much smaller amount of needed DHEA(S) production when cortisol synthesis drops even a little. Finally, as decades of steroidogenesis research has shown, the control of adrenal hormone output is regulated mostly by cell-specific enzyme concentrations and external signals coming from outside the adrenal gland (See main text for specifics).

What, then, does this mean in relation to cortisol and DHEA(S) output which, when measured, appears to confirm this phenomenon? What about the role of oral pregnenolone therapy for supporting adrenal DHEA(S) production? As we will continue to reinforce throughout this guidebook, the HPA axis in general and the production of cortisol and DHEA(S) in particular, have a complex interrelationship. While HPA axis stress and subsequent cortisol synthesis and secretion may coincide with the acceleration of reduced DHEA(S) production (i.e., a stress-induced down-regulation of DHEA(S)), this relationship is facilitated by regulatory processes (e.g., feedback inhibitions, receptor signaling, genomic regulation of enzymes, etc.), not an intra-adrenal depletion of pregnenolone as a precursor to downstream hormones. For instance, experimentally-induced hyperglycemia and hyperinsulinemia has been shown to affect DHEA and androstenedione production in human subjects.[24,25] In one study of poorly-controlled type 2 diabetic subjects with elevated cortisol and low DHEA levels, the enzyme necessary for DHEA formation in the zona reticularis (17,20 lyase) was shown to limit the production of DHEA. The enzyme activity was corrected (along with near normalization of cortisol, DHEA and DHEA-S levels) after six months of diet or pharmacotherapy to improve blood glucose control.[26] Additionally, cell-culture studies suggest that under inflammatory stress (IL-4 and other cytokines), the zona reticularis will down-regulate DHEA production when ACTH is present.[27,28] These and many other factors (e.g., aging) are likely the driving influenced affecting the dynamic relationship between cortisol (activated by the HPA axis) and measured DHEA and/or DHEA-S levels.

As we will review later, the use of oral pregnenolone supplementation as part of a broader strategy to improve patient DHEA(S) levels (accompanied by many anecdotal reports of clinical benefits) is common. However, there is limited published data related to oral pregnenolone therapy and changes in adrenal DHEA output or in measures of serum or salivary DHEA or DHEA-S. There is, however, some limited data on the use of oral pregnenolone with apparent neurosteroid outcomes, which is covered on page 114.

By reassessing the specific mechanisms that drive the stress-related changes in adrenal hormone output, and moving away from older and incorrect explanations, we are able to seek (and perhaps address) the various signals that are actually responsible for modulating adrenal hormone secretion during the progression of chronic stress (For a reassessment of the nomenclature of "Adrenal Fatigue," see page 21; for more information about the function and regulation of DHEA, see page 45).

Hormones of the Adrenal Medulla

The adrenal medulla is fundamentally an extension of the central nervous system and functions primarily to secrete two important catecholamines: epinephrine and norepinephrine. Acetylcholine signals from sympathetic neurons trigger the release of epinephrine and norepinephrine, almost instantaneously upon encountering a stressor, up to 10 minutes faster than the HPA axis can elicit a cortisol response.

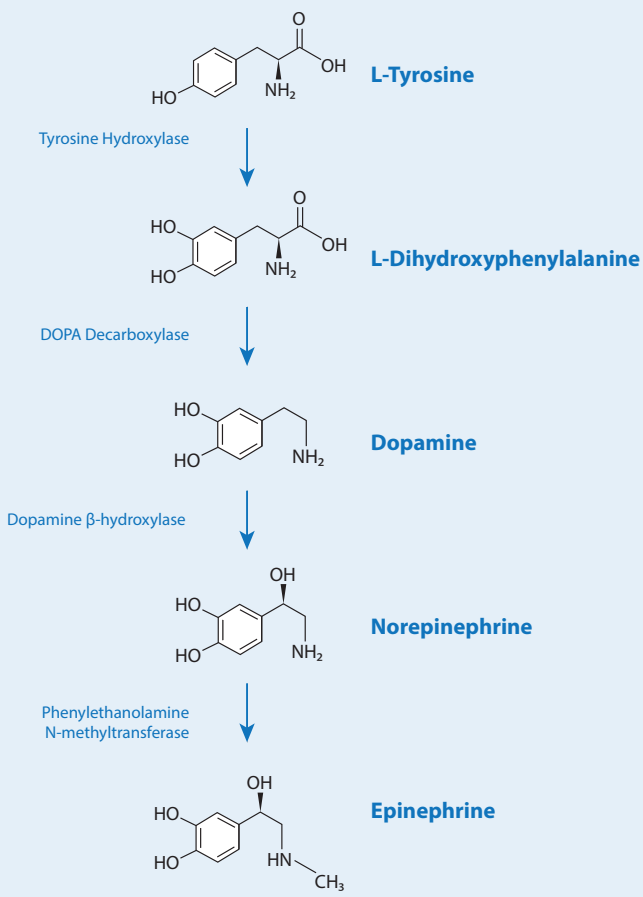
The biosynthesis of norepinephrine from tyrosine is the same as that used by other adrenergic neurons (e.g., LC/NE). However, the adrenal medulla expresses an additional enzyme not found in other adrenergic neurons, phenylethanolamine-N-methyltransferase (PNMT), that uniquely allows it to produce epinephrine (a.k.a. adrenaline). Epinephrine and norepinephrine are pre-synthesized and stored at very high concentrations in the chromaffin granules of the adrenal medulla, which are completely released when triggered by acetylcholine (Of the two catecholamines secreted, 80% is epinephrine and 20% is norepinephrine). The physiological effects of these catecholamines are mediated by two sub-types of adrenergic receptor: α and β. The α adrenergic receptors bind both catecholamines, while the β adrenergic receptors function primarily as receptors for epinephrine.

The effects of these hormones prepares the body (and brain) for immediate physical intervention (fight-or-flight response), which includes increased cardiac output, heart rate, blood pressure, and respiration (epinephrine is a powerful bronchodilator). They also stimulate blood flow to the skeletal muscles, while decreasing the splanchnic and renal blood flow. Adrenal catecholamines, along with norepinephrine made in the brain (See page 24), increase alertness and vigilance.

The two catecholamines have a half-life of a few minutes when circulating in the blood. They can be degraded either by methylation via catechol-O-methyltransferases (COMT) or by deamination via monoamine oxidases (MAO).

Biosynthesis of Catecholamines

- A catecholamine (CA) has a catechol (benzene with two hydroxyl side groups) and a side-chain amine.



Cortisol Signaling: Modulating Target Tissue Responses

Up to this point, we have described the HPA axis primarily as a way to regulate the adrenal production of cortisol through a complex set of positive signals and feedback inhibition loops controlled by circadian and "stress" signals consolidated in the brain. The synthesis and circulation of cortisol is, however, just the beginning of understanding how the HPA axis controls target tissue responses. Since cortisol is a very potent steroid hormone, there are several ways to buffer and modulate its effects on different target tissues. In the next sections, we will discuss the variety of mechanisms used to modulate the cellular actions of cortisol. Understanding these mechanisms can allow the clinician to leverage specific therapeutic interventions that may mitigate the damage of, or improve the adaptation to, cortisol production and chronic stress. Figure 14 shows a schematic diagram of several specific mechanisms that affect the cortisol signaling process. Each will be described briefly here and unpacked further in each of the next sections.

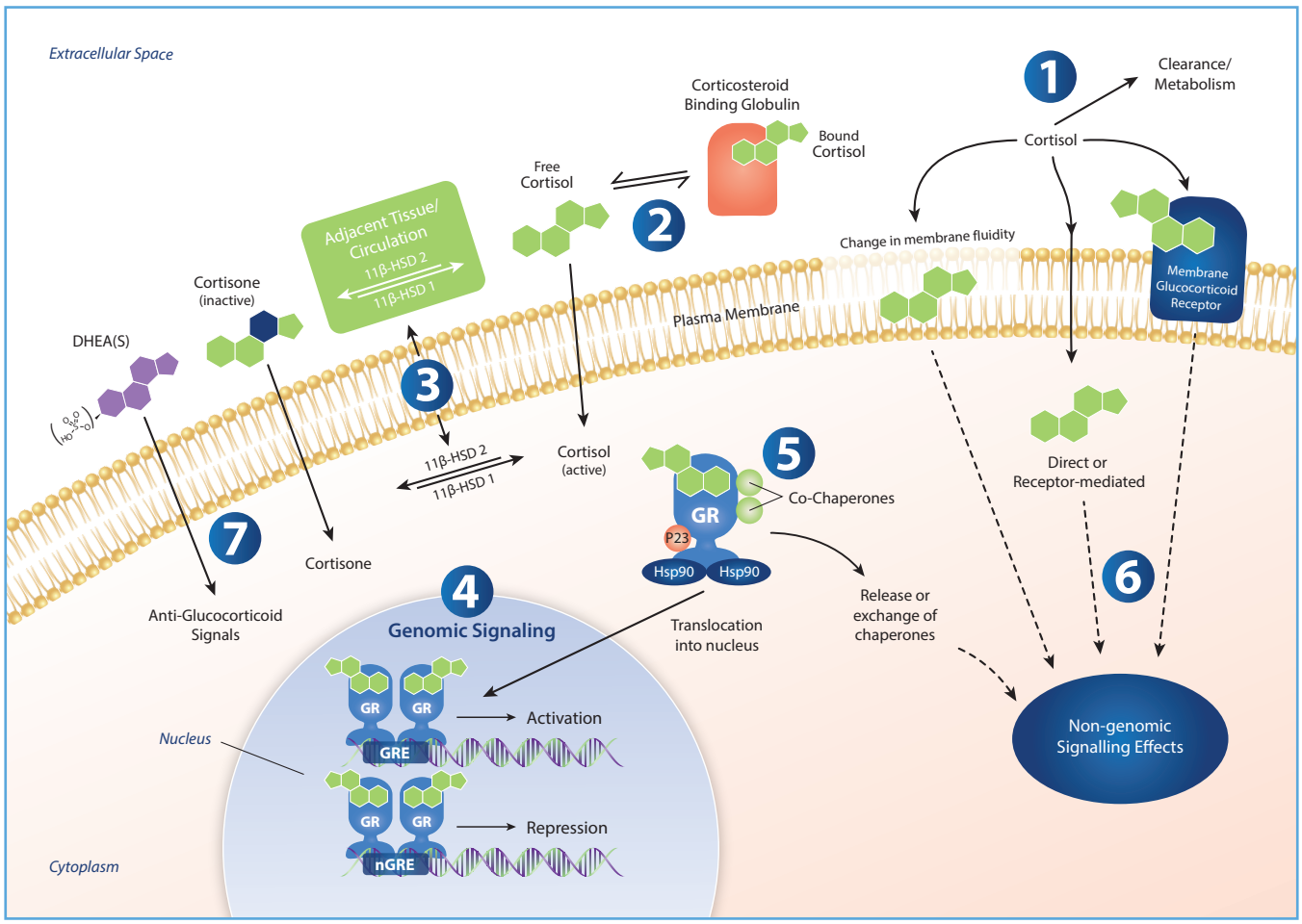


Figure 14: Cortisol Signaling Modulation. This figure depicts the major ways in which the cortisol effects on target cells can be modulated. See text on the adjacent page and following sections for details and context for each of these mechanisms.

Salivary Cortisol: The Preferred Method for Clinical Evaluation

The use of saliva as a biological fluid for measuring cortisol is now common amongst both stress research and clinical practice. As a reliable surrogate marker for serum free cortisol, it can act as a non-invasive, non-stress inducing, time-specific measure of the "active" cortisol available to target tissues.[16] Cortisol concentrations within the saliva are generally lower than the serum free cortisol due to parotid activity of 11β-HSD2, which converts cortisol to cortisone. Nonetheless, there is a linear relationship between serum free cortisol and salivary cortisol measurements.[17,18] Salivary cortisol levels are unaffected by salivary flow rate and are relatively resistant to degradation from enzymes or freeze-thaw cycles. The use of midnight salivary cortisol is now considered reliable as a tool for accurately diagnosing Cushing's syndromes (See sidebar on page 59).

The greatest benefit for the use of salivary cortisol is the ability for self-sampling at specific times throughout the day or night (diurnal rhythm) and during laboratory induced psychosocial stress tests (See page 78). This is especially helpful to discern important changes that occur over a short period of time, such as the cortisol awakening response or before, during and after a specific stressor, where repeated urine or blood sampling would not work. Samples can be collected by passive drool using tubes or special collecting swabs designed to be chewed or held in the mouth. Cortisol in saliva is relatively stable and can be routinely measured with many analytical techniques, though different methods may result in different absolute values.[19] Due to the passive transfer of cortisol from the blood into saliva, the free cortisol measurements in saliva are delayed by about 10 minutes, as compared to serum levels.[20]

Diurnal Salivary Cortisol

One of the most important features of the HPA axis is its circadian rhythm, resulting in a predictable diurnal cortisol secretion pattern. A general pattern of *daytime* salivary cortisol measurements, assuming a waking time in the morning, along with typical laboratory reference ranges for timed saliva samples is seen in Figure 21. The most common diurnal cortisol test available to functional medicine clinicians is usually performed using four saliva collection time-points. Depending on the instructions given for the collection of saliva and how those instructions are followed, some of the important features related to the diurnal secretion of cortisol might be missed using this standard test.

In addition, some labs report what is often referred to as "total cortisol" or "cortisol sum," which is a simple summation of the cortisol measured at each of the four time points. This "total" may give the clinician some clue as to the patient's HPA axis function, but it is highly dependent on the timing of the first morning saliva sample (which may account for more than half of this total) and limited by the number of samples collected. Clinicians should be careful not to over-interpret the findings of a single-day, four-point cortisol test. As we will show, the most important measurements are the first morning cortisol (when sampled correctly) and the last sample prior to bedtime.

Significant elevations in salivary cortisol follows moderate to intense exercise, peaking near the end of a session and resolving over the following one to two hours. Timed samples collected just before an exercise session or more than one hour after the exercise session will likely miss the inclusion of these elevations within the total cortisol value; while collection of saliva just after

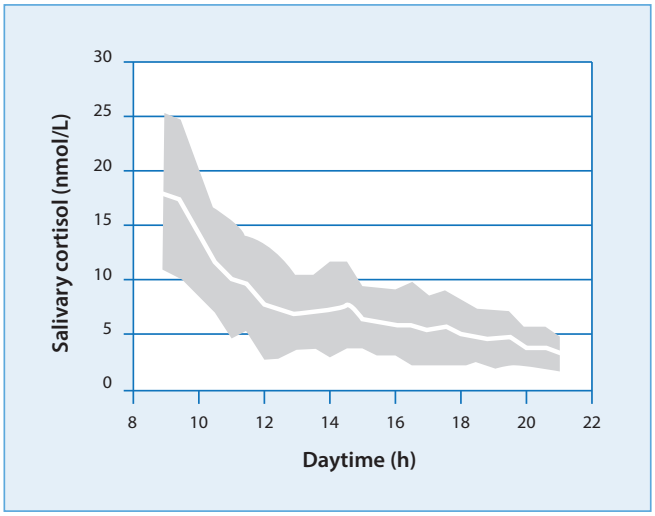


Figure 21: Daytime Salivary Cortisol Pattern. Range of salivary cortisol measurements in an average day in nmol/L. Note that, like most laboratory instructions, the early morning CAR is not captured in these ranges. Absolute levels of salivary cortisol cannot be compared between laboratories due to method variations, but similar magnitude of changes should be reflected by laboratory ranges from morning to evening. Salivary cortisol is similar in men and women.

an exercise session will likely result in an elevation in the total cortisol, the magnitude of which is dependent on exercise duration and intensity. Depending on the purpose for which clinicians are testing HPA axis function, they may choose to ask patients to refrain from all exercise on the day of testing, ask them to record the timing and intensity of their exercise on the day of the test, or intentionally sample at the end of their exercise sessions to record HPA axis response to their routine exercise sessions. Note that this last option, while it gives the clinician an uncontrolled HPA axis provocation and may add interpretive value, may be interpreted by the laboratory report inappropriately as "hypercortisolism" or a diurnal dysrhythmia.

Cortisol Awakening Response (CAR)

One of the most distinctive features of the 24-hour circadian rhythm of cortisol secretion is missed by nearly all laboratory cortisol tests designed to detect circadian function of the HPA axis. This is the predictable increase of cortisol that occurs in the morning, just after awakening, called the cortisol awakening response (CAR). This feature is a result of two phenomena: the first is the momentum of rising cortisol levels that begins several hours before awakening due to normal circadian HPA axis activities (ACTH); the second, a transient (30 to 45 minute) additional increase of up to 50% in cortisol secretion due to light activation of the suprachiasmatic nucleus (there is no similar rise when waking from a nap).[21] The CAR has been used significantly more than the overall diurnal salivary cortisol in the clinical literature to define specific stress-related HPA axis abnormalities that affect cortisol output.[22,23]

CAR is influenced by overall HPA reactivity as well as a person's anticipation of stress. In other words, waking acts as a mini "stress test" for the HPA axis. For instance, a lower cortisol response to awakening is seen in subjects with a high amount of psychosocial burnout, chronic fatigue and PTSD, while it is higher in subjects with ongoing job-related and perceived stress.[24] Also, in subjects experiencing high work stress, the CAR is significantly higher on workdays than weekends, suggesting that daily CAR is partly dependent on the anticipation of stress.[25] While general depression disorders often result in a higher CAR, individuals with seasonally affected disorders have a lower CAR, though only during the winter months.[26,27] Finally, CAR is significantly elevated during ovulation, as compared to the other phases of the menstrual cycle.[28]

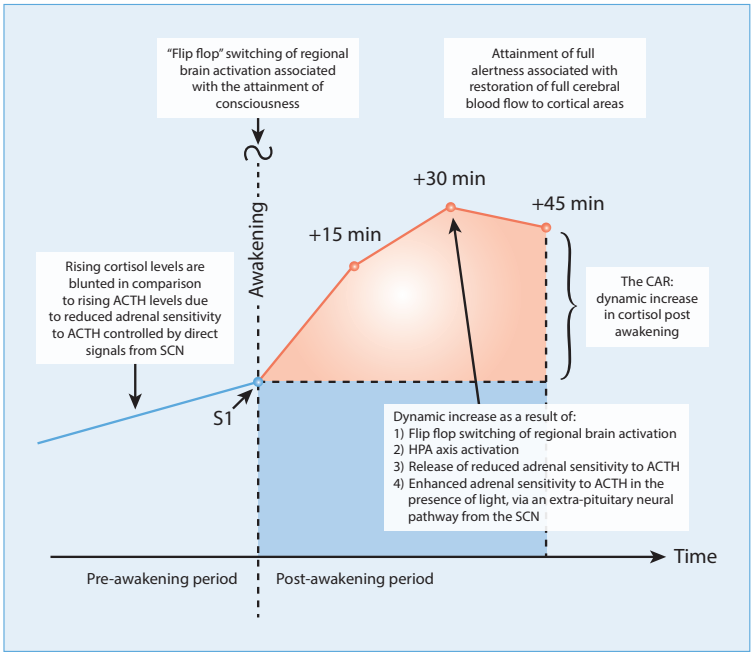


Figure 22: The Mechanisms of the Cortisol Awakening Response (CAR). The dynamic changes of cortisol through the awakening response (+45 min) are shown. See text for more details.

It is difficult to capture the CAR when following the current saliva collection instructions provided by most laboratories. Many only suggest a window of time (e.g., 6 a.m. to 8 a.m.) with no regard to waking time. Others suggest a time after awakening that is much too late to sample the CAR (e.g., >60 minutes after awakening), while some suggest that the first sample be taken upon awakening (before the cortisol reaches its peak). Since the morning cortisol sample is likely to account for more than half of the total cortisol measured using a standard four time-point "diurnal" cortisol test, failing to capture the CAR within the first morning sample can result in over-diagnosis of either hypocortisolism or a flattened circadian profile (See page 74). In individuals working the nightshift for long periods of time, testing should commence upon awakening, as the CAR is shifted to the evening (though usually blunted in most nightshift subjects).[29]

Clinicians can use a standard four time-point cortisol collection strategy to obtain a

The Three-Stage Model of Stress Adaptation (HPA Axis Dysfunction)

Many theories exist to explain how normal HPA axis function progresses to various stages of stress-related HPA axis dysfunction. Within the functional and integrative medicine communities, the three-stage model is often cited to explain this progression. It describes three progressive stages based on adrenal hormone output measured in saliva. This model is loosely based on Hans Selye's GAS theory of chronic stress in animal models (See page 18).

As Figure 26 shows, this model suggests that early in the progression of HPA axis dysfunction, stressors will usually result in elevated levels of cortisol (Stage 1), while DHEA(S) levels remain normal or start to decline. Like the "repeated hits" described by McEwen (See page 16), this acute stress is driven by elevated ACTH production. The type of stress and the age of the individual will dictate whether DHEA(S) levels will be lower than expected based on laboratory reference ranges. Depending on the intensity and frequency of the stressor, we see a slow "adaptation" beginning to occur in Stage 1. This may be an adaptation to the stressor itself (e.g., to a perceived threat) a down-regulation of the HPA axis due to chronic activation of feedback inhibition mechanisms, or both.

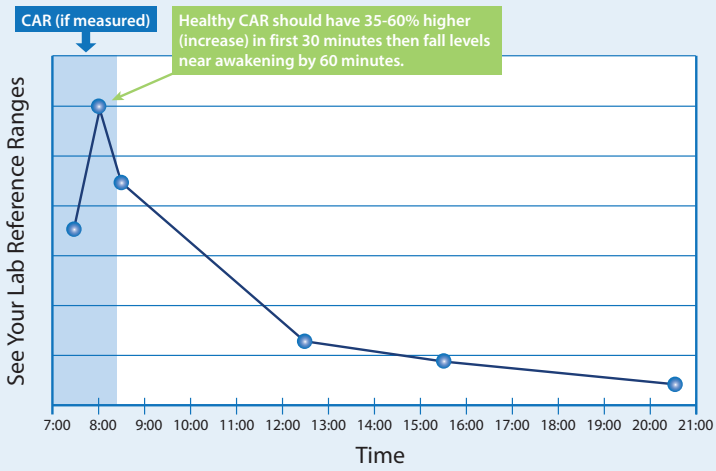
In this three-stage model, chronic stress progresses to a more permanent down-regulation of cortisol production (Stage 2), often resulting in daily cortisol output within the laboratory reference range. This is distinguished from "normal" by a lower-than-expected DHEA(S) level, a history of chronic stress and its consequences, and perhaps, subtle abnormalities within the diurnal rhythm of cortisol. This is often dubbed "adrenal fatigue" by those who assume that the adrenal glands are slowly "fatiguing" in their ability to produce cortisol while ACTH is still elevated. Since ACTH measurements are rarely taken, there is no evidence to suggest the zona fasciculata becomes insensitive to ACTH or fails to respond over time. These lower cortisol levels, if they are indeed low (See page 74), are likely a result of reduced ACTH levels caused by HPA axis down-regulation, a normal adaptation to repeated bouts of elevated cortisol (or exogenous glucocorticoids). It may also be a result of an increase in cortisol-binding globulin (CBG), whereby salivary (free) cortisol levels are lower while total serum cortisol may remain elevated (Figure 29 on page 85). Again, this appears to be an adaptation to chronic stress designed to reduce cortisol burden on the tissue and limit the need for long-term down-regulation of ACTH. Furthermore, years of chronic stress activation (Stage 1) followed by declining ACTH secretion (late Stage 2) and aging results in even lower DHEA(S). Metabolically, we might deem this stage "cortisol dominant" because even while cortisol production is not elevated beyond normal laboratory ranges, there is limited DHEA(S) to oppose the actions of cortisol within the tissues. Even

Models Explain, They Cannot Diagnose

This three-stage model has become a common way to explain stress history and HPA axis progression using two biomarkers: salivary cortisol (sum) and salivary DHEA(S) (sum or single time-point) taken on a single day. Several labs that offer such tests will "diagnose" or categorize patients in one particular stage based on their test results. However, such explanations are based on a number of untested or disproven suppositions from animal models or assumptions based on biochemical pathways. Clinicians should rely upon all of their diagnostic and history-taking skills, in addition to laboratory findings, to assess the status and function of the HPA axis. With a few notable exceptions, the core therapies designed to improve HPA axis function will be fundamentally similar in most patients and independent of their "stage" of HPA axis progression. See pages 68-76 for laboratory findings that may suggest patterns corresponding to specific abnormalities.

Diurnal Salivary Cortisol and DHEA(S) Sample Pattern

Ideal



Note: Diurnal Rhythm Information only represents the day of sampling and is highly dependent on appropriate sampling techniques and timing (especially in the morning). Clinicians should always correlate salivary cortisol information with other factors known to influence HPA axis function before using diurnal cortisol (or DHEA(S)) to diagnose or treat any suspected HPA axis dysfunction.

Subject Type: "Ideal" healthy young subject with low perceived stress, no history of trauma, sleeping 7-8 hours regularly, BMI <25 and taking no medications that influence HPA axis.

Cortisol: Diurnal pattern (after awakening) will show a dramatic difference between morning and evening (greater than 5-fold), mostly dropping in the first 3 hours after awakening. Each time-point measurement should be at the lower end of the laboratory reference range. Older subjects will have higher cortisol at each time point.

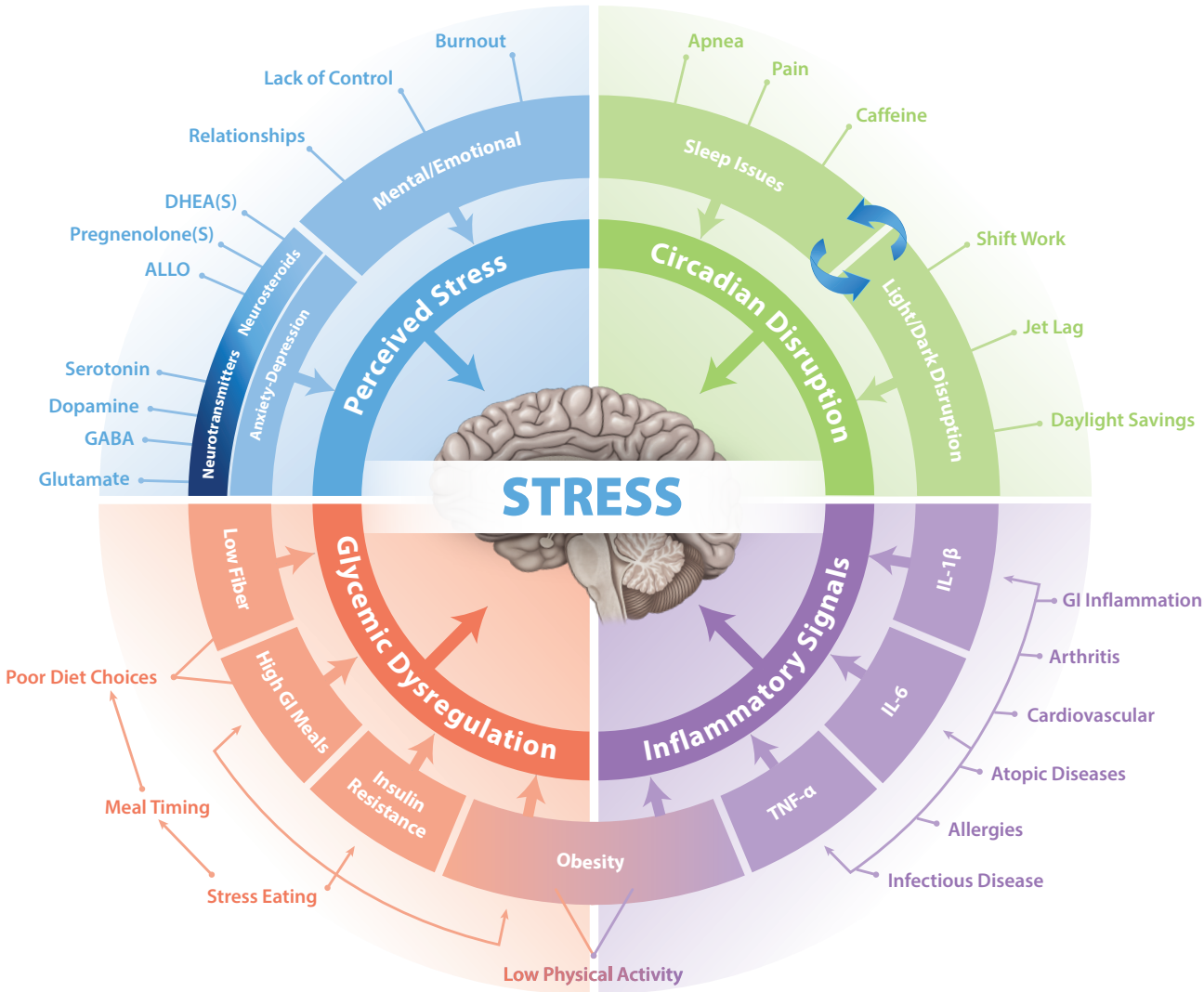
CAR (if measured): Salivary cortisol should increase roughly 35-60% between the time of awakening and 30 minutes post-awakening. Noticeable drop in cortisol should occur by 60 minutes post-awakening (if time-point is included) (See page 56).

DHEA or DHEA(S): Morning DHEA or DHEA-S levels are higher than bedtime levels, but this is highly dependent upon when the first morning sample is collected. The closer to time of waking, the higher the morning sample will be compared to bedtime sample (50-100% higher).

Cortisol:DHEA(S) ratio: Molar ratios (nmol/L:nmol/L) of cortisol to DHEA or DHEA(S), measured using the morning saliva samples, are lower in young healthy subjects (See page 63). Ideal ratios are difficult to define but depending on collection time should be near 10:1 (Cortisol:DHEA) or 4:1 (Cortisol:DHEA-S). Most clinicians will need to calculate their own Cortisol:DHEA(S) levels as most labs do not report this information, or do so using weight:weight ratios or molar:weight ratios. Some laboratories do not report the time-point(s) used to measure the reported DHEA(S) value, making it difficult for the clinician to calculate this value. See chart on page 54 to convert weight measures to molar measures.

Modifiable Categories of HPA Axis Stress

Assessing the status or function of an individual's HPA axis is not the same thing as identifying those unique stressor(s) that have contributed to that status or function. Thankfully, while there are hundreds of internal and external signals that affect the HPA axis, most of them can be collected into just a few simple categories. In most subjects with chronic HPA axis dysfunction, creating strategies to modify the stress-signals coming from one or more of these categories will result in great improvement within the stress response system and, ultimately, overall chronic disease progression.



Perceived Stress

The HPA axis is easily triggered by non-physical signals from outside the body, events which the brain perceives as threatening. These are called "perceived" stressors in that the ability of these events to affect HPA axis function are largely dependent on how the person perceives the event, rather than the event's intrinsic capacity to harm the person (e.g., public speaking). Ultimately, those events which are perceived as both "harmful" and "uncontrollable" are the most stressful. Within this category, we also consider internal stress perception caused by neurotransmitter imbalances, which often manifest as mood disorders (e.g., depression, anxiety, etc.). Neurotransmitter imbalances can impact the HPA axis by modulating the CNS sensitivity to stressors, CRH, norepinephrine, or through alterations in cortisol feedback inhibition (See page 82).

Circadian Disruption

The HPA axis is intimately tied to the mechanisms controlling circadian rhythm. These rhythms are constantly entrained by the light and dark cycles of day and night. Unfortunately, most humans living in the world today have the ability to ignore these important cues when choosing their work, entertainment, social and sleeping schedules. The consequence is often HPA axis dysfunction, as well as an assortment of metabolic dysfunctions that are regulated by the HPA axis (e.g., insulin resistance, obesity, neurotransmitter dysregulation, etc.). Of course, sleep is one of the greatest "reset buttons" for the HPA axis, and one of the most important ways to rebuild our metabolic reserve. Helping patients understand how to manage their daytime activities to ensure the proper quantity and quality of regular sleep they experience, is one of the most power "therapies" available for reducing HPA axis dysfunction (See page 91).

Glycemic Dysregulation

The stress response system is designed to release energy stores, making them available for important life-saving functions. Clinician's often forget that cortisol is a glucocorticoid, a hormone that, by its very name, is fundamental for the regulation of glucose (in stressful and non-stressful situations). The rising epidemic of insulin resistance, obesity, and their related metabolic disorders has a complex cause-and-effect relationship with the growing phenomena of stress-related disorders. Subjects that maintain a healthy balanced lifestyle, choosing diets designed to limit their glycemic impact and maintaining adequate physical activity to ensure proper glucose disposal will be rewarded with good overall metabolic health and, as a bonus, limit the glucose-controlling burden on their HPA axis (See page 95).

Inflammatory Signaling

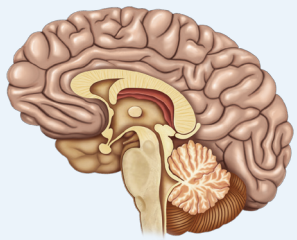
Like its pharmaceutical analogs, cortisol is a powerful endogenous anti-inflammatory steroid. Not surprisingly, acute or chronic inflammatory signals trigger the HPA axis with a purpose to increase cortisol availability within inflamed tissues. These actions result in a suppression of most other immune functions as well, a common and problematic side-effect with corticosteroid therapy. Clinicians should consider inflammation anywhere, to be an HPA axis stressor. This might include inflammation in the gastrointestinal tract (e.g., food allergies or IBD), chronic low level inflammation (e.g., obesity, cardiovascular), or traditional inflammatory conditions (i.e., rheumatic diseases). Assessing and treating the cause of a patient's inflammation (especially when chronic) can profoundly reduce the allostatic load on their HPA axis (See page 98).

Natural Therapeutic Strategies to Support HPA Axis Function

Supporting the HPA axis is a critical component to chronic disease management, but it involves organizing therapies around known processes within the brain, the adrenal gland and the way in which cortisol signaling functions within target tissue. This section will summarize some basic protocols that can be used in most patients with HPA axis dysfunctions giving nuanced applications based on measured cortisol levels (See also pages 66-76). This will be followed by summaries of the key nutrients, herbs or dietary supplement ingredients that have the potential to improve HPA axis outcomes.

It is important to always remember the big picture when addressing stress and HPA axis support protocols. Fundamental to uncoupling the chronic disease consequences of stress, even without discovering or removing a known stressor, is to build the metabolic reserve of all tissues through proper diet and lifestyle inputs. Obviously, removing known stressors that lead to HPA axis dysfunction/maladaption is also profoundly beneficial. In both of these strategies, building metabolic reserve and reducing known HPA axis stressors, there is a wide range of non-pharmacological options available to the clinician.

Strategies for Supporting HPA Axis Function

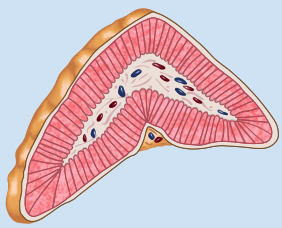


CNS Support

Maintain Appropriate Hypothalamus Response to Stressors
- ↓ Glycemic Dysregulation
- ↓ Perceived Stressors
- ↓ Inflammatory Signals
- ↑ Circadian Signals
  - Sleep Therapy
  - Light/Dark Entrainment
  - Meal Timing

Balance Neurotransmitters/ Neurosteroids
- Consider Supplementing Precursors and Cofactors for Neurotransmitter Synthesis
- Consider Supplemental DHEA & Pregnenolone

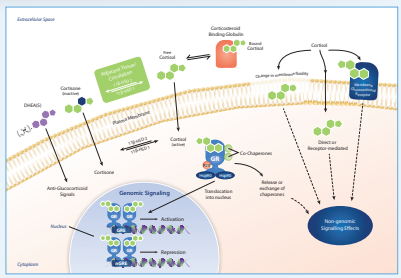
Balance Cortisol Feedback Mechanisms
- Consider Phosphotidyl Serine
- Consider Adaptogens



Adrenal Support

Protect Zone Reticularis
- Antioxidants
- Adaptogens (?)

Nutrient Support for Adrenal Steroidogenesis
- Vitamin C
- B-Vitamin (general)
  - Pantothenic Acid
  - Niacin
- Minerals (general)
  - Magnesium/Zinc
- Glandulars (Adrenal)



Target-tissue Cortisol Modulation

↓ 11β-HSD1 Activity
- Reduce Inflammation
- Reduce Insulin Resistance/Insulin
- Reduce Central Adiposity
- Consider Physical Activity (not intense)

↑ HSP Modulation of GR
- Consider Adaptogens
- Consider Physical Activity (not intense)

↑ DHEA's Anti-Glucocorticoid Activity
- Consider Suplemental DHEA

Physical Activity, Stress and the HPA Axis

Numerous observational and intervention studies have shown the many health benefits of regular physical activity (vs. sedentary behavior). These benefits are wide-ranging, and affect nearly every major category of chronic disease, including cardiovascular, dementia and other cognitive impairments, most musculoskeletal degenerative disorders, diabetes, depression, and most autoimmune and metabolic diseases. Not surprisingly, regular physical activity has been shown to improve mental and emotional function, while strengthening resilience to stress.[1] Many lines of research now suggest that one of the key mechanisms facilitating the benefits of exercise is the direct modulation of the stress response.

As discussed earlier in this text, the stress response is designed to liberate adequate metabolic resources in order to help the organism survive a stressful event, a situation that is usually resolved quickly with physical activity of some kind (fight or flight). Ironically, many of today's mental and emotional stressors (i.e., perceived stress) do not generally require increased metabolic demand, and they are not often quickly resolved. In some cases, like insulin resistance and obesity-driven inflammatory signaling, the mechanisms that permit the liberation of "energy" actually exacerbate the metabolic condition. By creating a limited, energy-requiring stress activation, regular exercise may function to build the metabolic reserve of the stress response system.

Physical activity elicits a stress response but, with the exception of extreme exertion, is considered a beneficial allostatic load. There are many theories to explain how the positive stress (i.e., eustress) of exercise can act to build the resilience to future physical and psychological stressors. One such theory known as the "cross-stressor adaptation hypothesis" postulates that repeated physical exertion will result in positive adaptations within the SNS and HPA axis, buffering the effects of similar or other types of stressors.[2] It appears that such an adaptation process does occur, although the specific mechanisms are still being elucidated. Nonetheless, it is now well-established that, compared to sedentary subjects, individuals partaking in regular exercise have lower amounts of anxiety, depression and perceived stress.[3,4,5] Ironically, high levels of perceived stress often lead to decreased desire for frequent physical activity, a troublesome reality in the task of motivating stressed patients to exercise.[6]

Regular moderate physical activity, especially in the form of routine exercise, improves many of the metabolic signals that drive the HPA axis, primarily by promoting tighter control on blood glucose levels and reducing inflammatory signaling. In fact, modulation of inflammation is considered one of the key mechanisms connecting moderate exercise with reduced risk of certain auto-inflammatory conditions.[7] One particular study showed that 30 minutes of aerobic exercise can blunt the cortisol response to a subsequent psychosocial stressor, correlating the stress-buffering outcomes to both modulations in feedback inhibition and improvements in measures of CNS activity signaling increased positive affect.[8] Trained elite sportsmen have a lower stress response to the Trier Social Stress Test (TSST) compared to healthy, but untrained, young men.[9] Another study shows that postmenopausal women who score higher on rumination/brooding scales (self-critical emotions) had a statistically reduced response to the TSST when they engaged in regular physical activity compared to similar, but sedentary, controls.[10] These studies are consistent in showing that relative physical fitness in young or old, males or females, appears to buffer the HPA axis from non-physical perceived stressors.

It should be emphasized that these benefits are derived by regular (i.e., daily) exercise that would be deemed moderate. While it is true that fit individuals may gain more long-term physiological benefits from exercise compared to unfit individuals engaging in

A Balanced and Evidence-Based Approach

Few clinicians today would dispute that stress has a detrimental impact on human health. However, beyond that admission, most would find it difficult to define exactly how stress influences chronic disease and how to measure that influence in specific patients. Research over the past few decades has greatly increased our understanding of the role the HPA axis plays in metabolic and circadian regulation, and how acute and chronic stressors can create discrete patterns of HPA axis dysfunction. Unfortunately, much of that knowledge is either unknown or unleveraged within most healthcare settings today. Though clinicians trained in integrative and functional medicine paradigms are often more aware of these details, in many cases they are using out-of-date nomenclature or oversimplified explanations that need updating or correcting.

The Role of Stress and the HPA Axis in Chronic Disease Management is designed to bridge the gap between the growing clinical research in the area of stress and HPA axis function and the growing clinical burden of diagnosing and treating stress-related dysfunctions. Thoughtfully written and richly illustrated, this guide is intended as a teaching tool and reference guide for any healthcare provider who cares for patients experiencing stress or its consequences. This guide also provides practical discussions on available laboratory testing options and a critical evaluation of the evidence supporting nutrients and supplemental interventions for stress management.

This guide is intended to be an indispensable resource for anyone making lifestyle, nutritional or dietary supplement recommendations within a healthcare setting:

- Clinicians
- Pharmacists
- Nutritionists
- Dietitians
- Nurses/Nurse Practitioners
- Medical Technicians
- Nutritional Researchers and Educators
- Health Coaches
- Medical/Health Journalist and Writers
- Students of Health Professions
- Manufacturers/ Distributors of Food and Dietary Supplements

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Thomas G. Guilliams Ph.D. earned his doctorate from the Medical College of Wisconsin (Milwaukee), where he studied molecular immunology in the Microbiology Department. Since 1996, he has spent his time studying the mechanisms and actions of natural-based therapies, and is an expert in the therapeutic uses of nutritional supplements. As the Vice President of Scientific Affairs at Ortho Molecular Products, he has worked with thousands of integrative and functional medicine clinicians, and has developed a wide array of products and programs that allow clinicians to use nutritional supplements and lifestyle interventions as safe, evidence-based and effective tools for a variety of patients. Tom teaches at the University of Wisconsin- Madison School of Pharmacy, where he holds an appointment as a clinical instructor, and at the University of Minnesota School of Pharmacy. He is a faculty member of the Metabolic Medicine Institute (formerly Fellowship in Anti-aging Regenerative and Functional Medicine). He lives outside of Stevens Point, Wisconsin with his wife and children.

Dr. Guilliams' other writings can be found at The Point Institute at www.pointinstitute.org

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