

THE STANDARD

Volume 9, No. 2

2010



CHRONIC STRESS AND THE HPA AXIS: CLINICAL ASSESSMENT AND THERAPEUTIC CONSIDERATIONS

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Today's clinician is keenly aware of the role that stress plays in patient health and the challenges that come with assessing, identifying and managing stress. And even though the effects of stress can be linked with most chronic illnesses, only a small percentage of clinicians understand how dysfunction within the stress management system (HPA axis) alters pathophysiology. Nearly a century of research on stress and its physiologic and metabolic complications has provided invaluable insight and increased our understanding. However, the clinical consequences of stress in chronic disease management is still a great challenge. This review explores how current research, spanning from epidemiology to epigenetics, is beginning to reveal specific patterns and pathways in the stress management system, allowing clinicians to effectively identify and treat many stress-related chronic illnesses.

INTRODUCTION

Humans have been designed with a complex repertoire of metabolic machinery intended to maintain normal homeostasis. This physiologic state of balance is susceptible to various perturbations by intrinsic and extrinsic events, whether actual or perceived.¹ The term "stress" has been coined to describe a "state of threatened homeostasis or disharmony" that must then be counteracted by an "adaptive stress response," a complex array of physiologic and behavioral responses intended to re-establish homeostasis.²

Much of the popular and clinical attention related to stress has spotlighted the adrenal gland and the production of cortisol. Thus, "Adrenal Fatigue" has now become a popular term to describe the physiological maladaptation to stress, especially hypocortisolism. While this term has helped to dispel the notion that adrenal-related dysfunction is defined only by extreme phenomena (Cushing's Disease or Addison's Disease), it does not adequately describe the complexity of the cascade of events involved in the stress response. As this review will show, the key components of the "stress system" are the *hypothalamic-pituitary-adrenal (HPA) axis* and the *sympathetic nervous system (SNS)*. The relative actions of these key regulatory centers and their respective hormones are influenced by a myriad of genetic, environmental and developmental factors.⁴ Excessive, prolonged or inadequate regulation of the stress response systems will invariably cause individuals to suffer adverse health consequences. The challenge for the clinician is in assessing the status of an individual's stress response system, relating that status

to the clinical presentation, discovering the root cause(s) of the imbalance, and helping the patient move closer to homeostasis while slowing or reversing the effects of stress-related chronic illness.

After briefly reviewing the historical background of this topic, a discussion of the complexity of factors contributing to the progression and propagation of HPA axis dysfunction and abnormal cortisol states will be provided. In addition, special attention will be given to the proposed mechanisms through which abnormal cortisol release patterns, particularly hypocortisolism, arise. The metabolic and clinical consequences of abnormal cortisol states, accurate diagnostic methods and appropriate treatment modalities will also be reviewed.

THE STRESS RESPONSE SYSTEM

A vast amount of research has been conducted to understand the intricate cascade of events that occur once the brain detects a disruption in homeostasis* (a stressor) and the hormonal responses driven by these systems.^{7,8} The key components of the "stress system" are the *hypothalamic-pituitary-adrenal (HPA) axis* and the *sympathetic nervous system (SNS)*. When the hypothalamus is triggered by a stressor, corticotropin-releasing hormone (CRH)—aka

*Other nomenclature systems include the term "allostasis" to define the process by which the body maintains homeostasis through change. Additionally, "allostatic load or overload" refers to the consequences of this stress on the HPA system, which leads to alterations in the ability to maintain homeostasis.⁵

CRF, corticotropin-releasing factor) and arginine vasopressin (AVP) are secreted, eliciting both the production of adrenocorticotropin hormone (ACTH) from the posterior pituitary and the activation of the noradrenergic neurons of the locus caeruleus/norepinephrine (LC/NE) system in the brain. The LC/NE system is primarily responsible for the immediate "fight or flight" response driven by epinephrine and norepinephrine, while ACTH drives the production of cortisol from the adrenal cortex. Under normal conditions, the production of CRH and ACTH fluctuate in a predictable circadian cycle and are inhibited by high levels of blood cortisol via a well-described negative feedback loop (see Figure 1). It is the predictable rhythm and responses of the HPA axis that lends itself to both experimental and clinical evaluation.

While many metabolites within the HPA axis can be monitored, cortisol is the hormone that usually gets the most attention in clinical research and practice. Cortisol, a glucocorticoid hormone, is a pleiotropic modulator of cellular activity through intracellular glucocorticoid receptors (GR) found in most tissues. Like the stress response in general, cortisol is intended to shunt cellular processes away from long-term metabolic processes and toward those that function primarily on immediate survival and homeostasis. Thus, the negative feedback loop of cortisol on its own secretion is designed to limit long-term exposure of tissues to these short-term catabolic and immunosuppressive actions. Chronic and repeated stressors

can lead to one or more forms of HPA axis dysregulation, altering appropriate cortisol secretion and affecting end-organ function (see sections on Hypercortisolism and Hypocortisolism for mechanisms and therapeutic considerations).

The hormone dehydroepiandrosterone (DHEA) is also produced in the adrenal cortex; and while its secretion is affected by pituitary ACTH secretion, additional regulatory activities and aging result in an almost complete loss of the diurnal rhythm in elderly subjects.^{13,15,12,14} DHEA, a glucocorticoid antagonist, serves not only to prevent excessive systemic inflammation, but also to protect the neurologic machinery, particularly the hippocampus, from the damaging effects of cortisol;^{16,17,18} a phenomenon that may also be true of its neurosteroid precursor pregnenolone.¹⁹ Exposure to chronic stress leads to a substantial reduction in circulating levels of DHEA-S and DHEA and further damage to underlying metabolic processes. Suboptimal levels of DHEA have been demonstrated in patients with numerous chronic disease states, including chronic inflammatory diseases (IBD, RA), mood disorders and chronic pain syndromes (CFS, fibromyalgia).^{20,21} DHEA has also been shown to reverse the classic stress-induced physiological responses in animal models.²² The role of DHEA and pregnenolone as diagnostic and therapeutic agents will be discussed below.

Conditions Related to HPA Axis Dysfunction²³

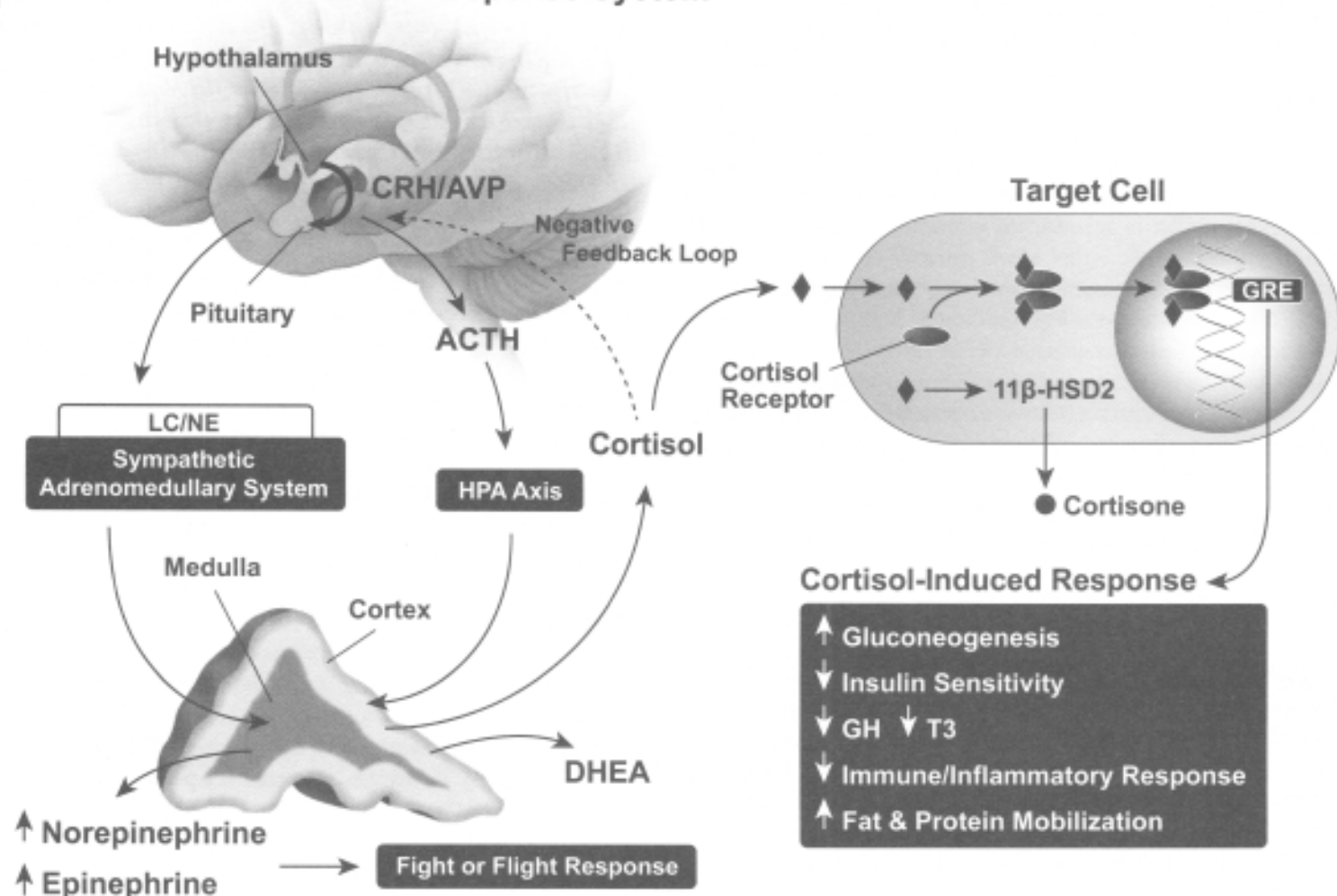
Increased activity of the HPA axis

- Cushing's syndrome
- Chronic stress
- Melancholic depression
- Anorexia nervosa
- Obsessive-compulsive disorder
- Panic disorder
- Excessive exercise (obligate athleticism)
- Chronic, active alcoholism
- Alcohol and narcotic withdrawal
- Diabetes mellitus
- Central obesity (metabolic syndrome)
- Post-traumatic stress disorder in children
- Hyperthyroidism
- Pregnancy

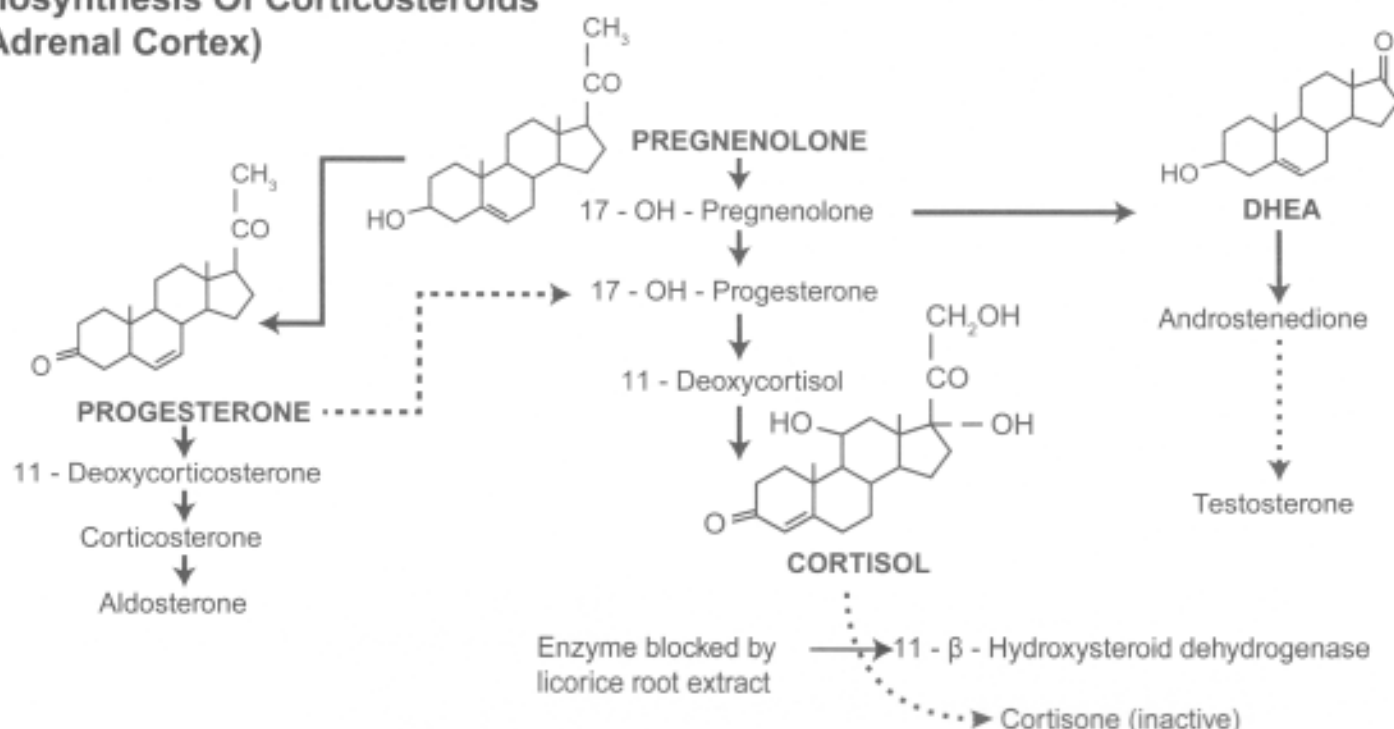
Decreased activity of the HPA axis

- Adrenal Insufficiency
- Atypical/seasonal depression
- Chronic fatigue syndrome
- Fibromyalgia
- Premenstrual tension syndrome
- Climacteric depression
- Nicotine withdrawal
- Following cessation of glucocorticoid therapy
- Following Cushing's syndrome cure
- Following chronic stress
- Postpartum period
- Adult post-traumatic stress disorder
- Hyperthyroidism
- Rheumatoid arthritis
- Asthma, eczema

Figure 1
The HPA Axis and Stress Response System



Biosynthesis Of Corticosteroids (Adrenal Cortex)



CORTISOL:DHEA RATIO

The ratio of the production of cortisol to DHEA/DHEAS can be an important factor in determining how an individual's HPA axis is functioning. Oftentimes absolute cortisol levels will fail to distinguish a patient's HPA axis dysfunction, while cortisol:DHEA ratios will. In a recent report comparing healthy caregivers (for Alzheimer's patients) to non-caregivers, researchers discovered that cortisol levels were similar in age-matched individuals despite the fact that caregivers had much higher stress, anxiety, depression and HPA dysfunction than the controls. However, when cortisol:DHEA ratios were compared, caregivers had significantly higher values—most of which was attributed to reduced DHEA levels.²³ Other researchers consider elevated cortisol:DHEA ratios to contribute to immune senescence,²⁴ to predicting treatment resistant depression,²⁵ and even to determining relapse to smoking cessation.²⁶ While there is certainly more published data comparing chronic stress and cortisol output, clinicians concerned about HPA axis dysfunction should consider evaluating a patient's cortisol:DHEA ratio. The growing body of literature suggests the ratio will help identify HPA axis dysfunctions and refine therapeutic decisions.

STRESSORS AND THE HPA AXIS

While others recognized the relationship between inadequate adrenal output and chronic health outcomes, most modern research on the stress response system can be traced back to the research and writings of Hans Selye. His description of the "General Adaptation Syndrome" (G.A.S.), with its three-stage process of alarm reaction, adaptation stage and exhaustion stage, was a result of years of research in animal models. He was able to show that irrespective of the diverse stressors he placed upon the animals, a similar physiological response ensued.

Chronic exposure to a stressor leads to a recurring set of physiological outcomes (hypertrophy of the adrenal gland, atrophy of the lymphatic organs, and ulcers in the stomach). Epidemiological data suggests that acute, intense episodic or chronic exposure to HPA axis stressors in humans is related to the same phenomena. While numerous advances in our understanding of the stress response have been published in the past 50 years, the simple observation that the same stress response mechanisms are elicited by virtually all stressors has remained unchanged.

There are many events that alter homeostasis, at least as determined by the hypothalamus. These stressors may be physical, chemical or emotional; perceived or real. Sources of acute stress are usually fairly obvious, but it is vital for the clinician to help patients identify their unique source(s) of chronic stress when treating any chronic health condition. There are four general categories of chronic HPA-axis stress that clinicians should evaluate in each patient: mental/emotional stress, sleep disorders, metabolic/glycemic dysregulation and chronic inflammation.

Mental & Emotional

The physiochemical responses of the HPA axis are easily triggered by non-physical events. Grief, excitement, fear, anxiety, guilt, embarrassment—all can trigger a robust HPA axis response. Also, events such as public speaking, performance evaluations, sky diving or clinical appointments (to name but a few) will drive up ACTH and cortisol in most individuals. Research has shown that the magnitude of the response and recovery to these stressors is based on the individual's perception rather than the stressors themselves. The four key factors that determine the magnitude of the HPA axis response to a mental/emotional stressor are its 1) novelty to the individual, 2) unpredictable nature, 3) threat to their person or ego, 4) sense of loss of control.^{27,28} Individual characteristics of the patient are also profoundly influential. Innate qualities such as age, gender (female preponderance) and hereditary predisposition, coupled with personality characteristics (i.e. introversion and low self-esteem) and prenatal and early childhood experiences, serve to further individualize and amplify each patient's unique stress response.

Sleep Disorders

During slow-wave sleep, cortisol release is normally suppressed by a decrease in CRH and a rise in growth hormone (GH) secretion. Exposure to chronic stressors results in abnormal HPA axis and SNS activation and disruption of the normal diurnal pattern of GH, CRH and ACTH release. The result is a paradoxical rise in cortisol levels in the evening hours and initial phases of sleep. A vicious cycle ensues whereby nocturnal hypercortisolism causes sleep fragmentation, raising cortisol levels even further. Insomnia and melancholic depression are frequently observed consequences. The increasingly common Obstructive Sleep Apnea syndrome (OSA) has also been recognized as a key cause of HPA axis dysfunction. The hypoxemia induced by recurrent obstruction to airflow causes pulsatile release of cortisol and sleep fragmentation. It is believed that the OSA-induced disruptions in the release of cortisol and other adrenal hormones promotes the development of secondary metabolic syndrome, hypertension, and inflammatory diseases invariably seen in these patients.²⁹

Metabolic/Glycemic Dysregulation

Under stressful conditions, maintaining adequate levels of glucose for brain and muscle use is imperative. Cortisol secretion helps maintain these levels by stimulating gluconeogenesis and causing peripheral and adipose insulin resistance. While these effects are intended to allow for short-term "fight or flight" benefits, they can lead to disastrous consequences if maintained for more than acute episodes. Individuals who regularly consume high glycemic foods and/or are insulin resistant will often induce a hypoglycemic "crash" after a meal, triggering the cortisol response. Since cortisol itself can drive insulin resistance, this is a

cycle that is difficult to control. Patients with central adiposity or insulin resistance should be evaluated for HPA axis dysfunction and be educated about lifestyle modification and diets that improve glycemic control.^{30,31,32,33,34,35}

Inflammation

Cortisol, like its corticosteroid analogues, is a powerful anti-inflammatory agent. Any acute or chronic inflammatory condition will signal cortisol release through normal inflammatory signaling and the HPA axis. Undiagnosed inflammation in the GI (IBD, food allergies), chronic inflammatory conditions (joints, cardiovascular) or obesity (central adiposity) will drive HPA axis dysfunction if not corrected. Furthermore some pharmacologic agents commonly used to treat the symptoms of chronic inflammatory diseases can further exacerbate HPA axis dysfunction.^{36,37,38}

THE PROGRESSION OF HPA AXIS DYSFUNCTION

Many theories exist to describe how an individual with a normal functioning HPA axis progresses to a stress-induced HPA axis dysfunction, whether presenting as hypercortisolism, hypocortisolism or some form of diurnal dysrhythmia.^{39,40} Many of these models follow Selye's G.A.S. model, suggesting that acute or chronic stressors will eventually cause the HPA axis to move from an over-responsive system to one that becomes under-responsive or non-responsive (hence the popular terms "adrenal fatigue"/"exhaustion"). These models would predict general levels of cortisol, DHEA and pregnenolone (precursor to both DHEA and cortisol) in the manner depicted in the figure below.

These models suggest that under stressful situations, ACTH will drive elevated levels of cortisol and begin to deplete DHEA production (through what is often termed "pregnenolone steal"). This high-cortisol phase may last years (as intermittent

stressors) or reflect intense stressful situations (combat stress) and may lead to an adaptation within the HPA axis, resulting in reduced cortisol production and, eventually, hypocortisolism. While the terms adrenal fatigue/exhaustion may serve to point out reduced adrenal production of cortisol and DHEA, the adaptive changes are most often initiated within and propagated by the hypothalamus and pituitary.

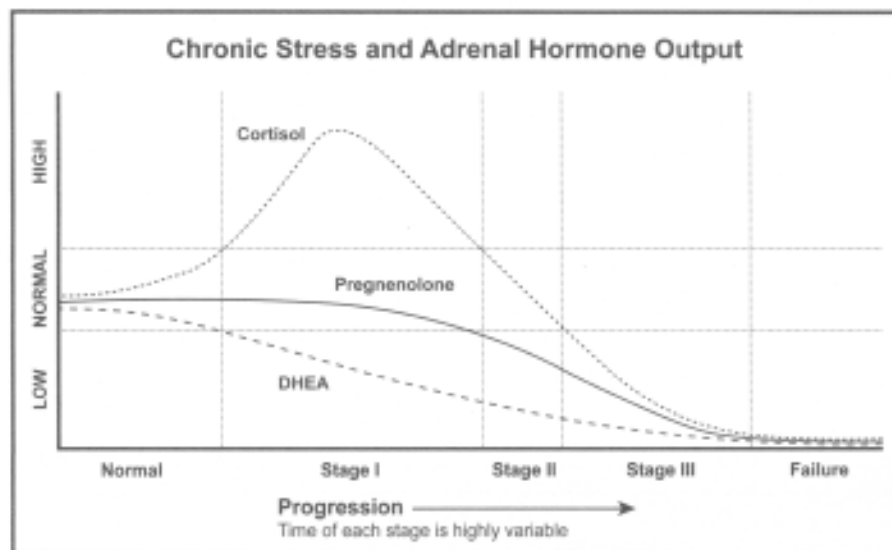
In fact, some researchers believe that the adaptation by the HPA axis is a protective device to ensure long-term survival by preventing chronically high cortisol levels from suppressing immune function and increasing catabolic pathways.^{41,42} This adaptation or habituation to stress, they suggest, functions both at the brain and periphery via reduced glucocorticoid signaling and alterations in the negative feedback loop. However, the consequence of protecting the immune system by blunting cortisol production is not without consequence on other pathophysiological systems (see hypocortisolism section). When using these models, along with patient history, lifestyle assessment and laboratory testing, clinicians can reliably predict the progression or "stage" of a patient's adaptation to chronic stress.

LABORATORY HORMONE ASSESSMENT

Much of the research relating HPA axis function to pathophysiology has come from laboratory assessment of the adrenal hormones cortisol and DHEA (or DHEA-S), although vastly more information is available about cortisol assessment.⁴³ Cortisol can be measured using serum, saliva, urine and even hair samples.⁴⁴ Until recently, many clinicians relied upon 24-hour urine collection to gauge a single day's cortisol output, however, salivary sampling has now become the most common and reliable way to measure adrenal hormone output.

Only three to five percent of the total plasma cortisol is unbound (free) and able to passively diffuse into cells. The vast majority of this steroid hormone is bound to corticosteroid binding globulin (CBG), or albumin. Therefore the amount of the bioactive (free) fraction of cortisol (the portion used to measure HPA axis status) is determined both by adrenal cortisol production and CBG concentration. Since salivary cortisol is not bound to CBG, it correlates very closely to the bioactive free-fraction serum cortisol and has now become the clinical standard for assessing the HPA axis^{45,46} (see Salivary Testing: Clinical Suggestions, page six).

The key laboratory findings that help a clinician evaluate the HPA axis status in an individual are total cortisol output, cortisol awakening response (CAR; see page six), cortisol diurnal rhythm, total DHEA-S and cortisol:DHEA ratio. Since salivary cortisol is non-invasive and can be done conveniently throughout the day, it is the only practical sampling method that can provide all of these measurements in four to five samples.



SALIVARY TESTING: CLINICAL SUGGESTIONS

Over the past two decades, the use of saliva, rather than blood or urine, to determine various adrenal hormone values has gained increasing acceptance and is the method of choice for current stress research. The advantages of using salivary measurements are many. They include non-invasive sample collection, anytime and anywhere (this is especially good for measuring circadian fluctuations); sample collection does not induce cortisol/stress (as with venipuncture); and more consistent responses to suppression tests (dexamethasone) or stimulation tests (ACTH, CRF, etc.).

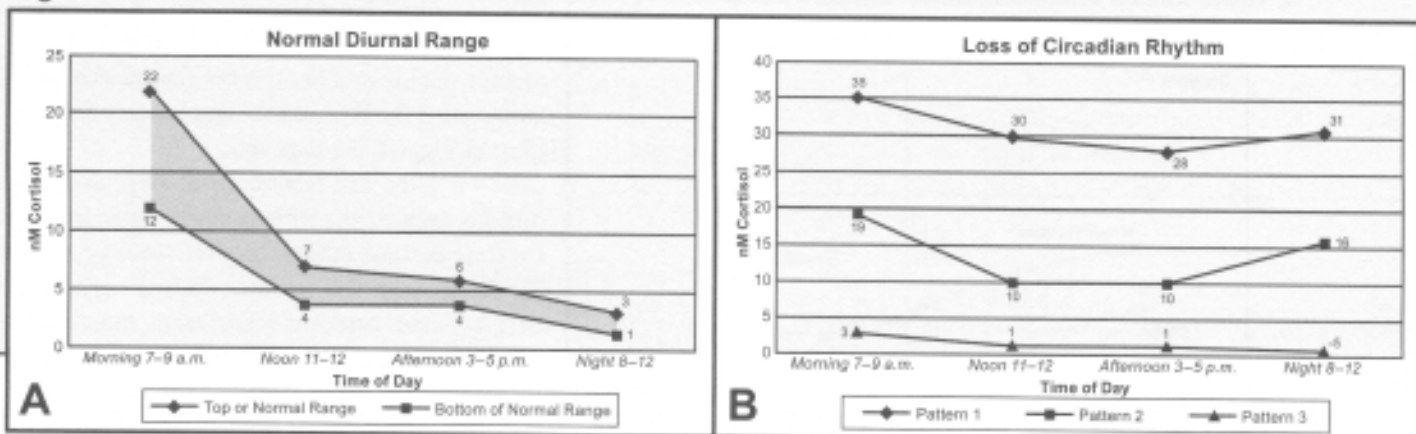
Cortisol enters the acinar cells lining the saliva glands via passive diffusion, and is not affected by the saliva flow rate. This passive transport prevents proteins or protein-bound molecules from entering the saliva. This means that the cortisol measured in the saliva is the active "free" fraction. When serum levels are measured, free cortisol must be measured in the milieu of large amounts of "bound" cortisol (inactivated); and the available literature clearly suggests that saliva cortisol is more closely correlated with the free cortisol fraction in serum compared to total serum cortisol.² Furthermore, salivary cortisol levels are stable at room temperature and through the mail, making this method ideal for out-of-office sampling and shipment to labs for measurements.³

Figure 2A shows the normal diurnal range one would expect from measuring salivary cortisol. Cortisol is highest in the morning; levels drop gradually until about noon and stay steady throughout the afternoon, then drop again in the late evening before midnight.¹ One note of caution: a comparison of absolute hormone concentrations between laboratories is sometimes difficult depending on the assay system for measurement being used. It is important for each clinician to become well-acquainted with the "normal" ranges used in the laboratories they are using.

Figure 2B represents three frequent variations to the normal diurnal pattern. Pattern 1 represents one potential hypercortisol curve where the secretion of cortisol does not shut down throughout the day. This may be due to an ongoing acute stressor or a resistance to cortisol feedback by the hypothalamus and pituitary. Pattern 3 represents a hypocortisol curve. There might be a slight diurnal nature to the curve, but the overall production of cortisol is so low that it is of little consequence. The HPA axis is unable to respond adequately during the sleep cycle and is not triggered by awakening. Patients with Addison's disease would be near zero for each measurement. Pattern 2 represents one of a number of odd diurnal patterns that may cause disturbance in sleep patterns (this person probably has trouble getting to sleep at night or finds sleep less than restful) or depression. One study found that when diurnal salivary cortisol of individuals with major depression were compared with controls, evening cortisol levels were significantly increased.⁶

While the primary understanding of the HPA axis can be gained by taking three or four salivary cortisol measurements throughout the day, the morning measurement may be the most informative and critical since it provides the largest value to the cortisol sum. Put simply, awakening stimulates the HPA axis and acts like a miniature HPA axis stress test every day. Earlier studies have shown that the HPA axis activity (as measured by salivary cortisol levels) increases 50 to 75 percent within the first 30 minutes after awakening, analogous to other HPA axis challenges.^{9,10} The morning surge of cortisol has been termed the Cortisol Awakening Response (CAR) and is considered in many research models to be a key determinant for HPA axis evaluation.^{12,13,14} Clinicians should ensure that patients take the first morning cortisol sample 30 minutes after awakening, the time it takes for the peak serum CAR to reach the saliva. It is also critical to ensure that the test is taken on a day that the patient predicts will be as typical (stress-wise) as possible to avoid measuring anomalies caused by sudden or anticipated physical or emotional stress.

Figure 2



CONSEQUENCES OF HYPERCORTISOLISM

Although the initial stages of the stress response are intended to promote survival, chronic exposure to stressors may lead to periods of elevated cortisol levels that are not reduced appropriately by negative feedback inhibition, creating further HPA axis abnormalities.^{47,48} Since every organ system is adversely affected, the body eventually succumbs to stress-induced physiological and behavioral impairments.

The immune system is one of the primary systems affected by hypercortisolism. The overall actions of glucocorticoids are immunosuppressive, particularly on cellular immunity. Impaired cytokine production and function, loss of tissues important in immune cell production (lymphoid, thymic and splenic tissue), and impaired leukocyte trafficking contribute to increased susceptibility to infection and neoplasm. Additionally, HPA axis dysfunction and prolonged cortisol elevation may actually be the cause, rather than the consequence, of development or perpetuation of autoimmune diseases.^{49,50,51} CRH, through its effects on corticosteroids and catecholamines, further suppresses systemic inflammatory reactions while directly stimulating local inflammatory tissue responses.⁵¹

Prolonged stress also inhibits the non-essential functions of growth and reproduction. Both CRH and cortisol inhibit the release of GH, TRH, TSH and GnRH, which are required for the production of the anabolic steroid hormones. Since these hormones antagonize the effects of cortisol, their absence further potentiates the actions of the now-unopposed catabolic corticosteroids, further impairing growth, repair and reproductive functions.⁴⁸ Furthermore, even if present in small amounts, the anabolic hormones IGF-1, DHEA and testosterone are unable to exert their physiologic effect because of target tissue insensitivity.^{51,48} Stress-induced GnRH deficiencies have been shown to cause delayed puberty, anovulation and spontaneous abortion in women; and decreased testosterone levels, impaired spermatogenesis and decreased libido in men.⁵² Growth and reproduction are also influenced by thyroid hormone function, which is adversely affected not only through CRH-induced inhibition of TRH release, but also by impaired peripheral conversion of the relatively inactive tetraiodothyronine (T4) into active triiodothyronine (T3).⁵¹

CRH and corticosteroids also affect insulin release and glucose regulation. Cortisol increases insulin levels; and the co-elevation of these two hormones, as well as a reduction in the levels of androgens, promotes visceral adipose deposition.⁵³ Visceral fat has abundant glucocorticoid receptors and is very sensitive to the effects of cortisol and insulin. Fat deposition is further promoted by increased and prolonged levels of the enzyme lipoprotein lipase.^{54,55} This vicious cycle of events inevitably plays a role in the development of such diseases as insulin resistance, hyperlipidemia, cardiovascular disease and hypertension.^{56,59} In fact, stress-induced hypercortisolism and its cardiovascular effects—visceral adiposity and other adverse sequelae—increase the all-cause mortality risk of patients two to three times and decrease life expectancy by several years.⁵⁷

Increases in cortisol-induced abdominal fat thickness are associated with an increase in both total oxidative stress and in the number of inflammatory cytokines.⁵⁸ Oxidative stress is further amplified by the absence of protective hormones. Within the central nervous system, for example, stress-induced elevations of cortisol and reductions in the neuroprotective hormones DHEA and estrogen causes enhanced oxidative stress and increased neuronal cell death.^{16,18}

Other conditions in which hypercortisolism and prolonged activation of the HPA axis have been demonstrated include anorexia nervosa, obsessive-compulsive disorder, panic disorder, chronic alcoholism, excessive exercising, childhood sexual abuse, pregnancy and hyperthyroidism, and melancholic depression.^{47,51} Therapeutic approaches that help uncover these causes should be considered in subjects with hypercortisolism along with those that improve HPA axis feedback, immune support and insulin sensitivity.

HYPOCORTISOLISM

Hypocortisolism describes any condition in which paradoxically low cortisol, flattened daytime production patterns and blunted cortisol release to stressors are observed. Evidence suggests that hypocortisolism may be a common, yet underappreciated, consequence of exposure to severe acute stress and chronic intermittent stress. Studies have confirmed states of hypocortisolism in patients chronically exposed to stressful environments, those with unpredictable schedules and in those with traumatic early life experiences.^{42,59}

Given the complexity of the stress response system, delineation of the process through which hypocortisolism arises has been a daunting task. However, since the integrity of HPA axis function and normal diurnal patterns of cortisol release are essential for maintaining internal homeostasis, much of the available research on chronic stress and disease have implicated disruptions in these aspects to be causative. Intrinsic dysfunction of the adrenal glands secondary to chronic stress has not been reliably demonstrated.

Within the context of HPA axis dysfunction, several mechanisms have been proposed to account for the evolution of low cortisol states. One model suggests that under the influence of chronic stress, the initial adaptive hypercortisolism response transforms over time into a self-preserving hypocortisolism state in order to protect the metabolic machinery, and most importantly, the brain.^{39,60} Other potential mechanisms of centrally induced states of hypocortisolism include down-regulation of pituitary CRF receptors in response to elevations of CRH and hypercortisolism-induced negative central nervous system feedback on further release of stimulating hormones.^{61,62,63,64}

"Relative" states of hypocortisolism, or cortisol resistance, may also occur despite the presence of normal or even elevated cortisol levels. Inadequate glucocorticoid signaling, decreased levels of bioavailable cortisol, and failure of cortisol action at the level of the receptor have all been proposed.^{65,66,67} Low cortisol states may also result from

recurrent infectious processes as the body attempts to promote a more vigorous immune response, something typically precluded by cortisol. Left unchecked, levels of pro-inflammatory cytokines increase fueling what has been termed the "sickness response." Patients with hypocortisolism typically suffer from fatigue, impaired cognition, sleep disturbances, anorexia and depressed mood; symptoms are also seen in patients with the sickness response.^{68,61}

Immune system up-regulation is a key component of the metabolic dysregulation seen in hypocortisolism. Since cortisol is profoundly influential in maintaining homeostasis within the immune system, a decrease in baseline levels or a suboptimal stress induced rise in its levels may lead to maladaptive immune system dysfunction. Cortisol selectively suppresses cellular immunity thereby preventing tissue damage from excessive inflammation. Low cortisol states permissively allow up-regulation of cellular immunity resulting in increased production of pro-inflammatory cytokines such as tumor necrosis alpha (TNF- α), interleukin-6 (IL-6) and interleukin-12 (IL-12). The lack of cortisol suppression on sympathetic tone and catecholamine levels potentiate this process by further increasing the levels of pro-inflammatory cytokines. These cytokines cause immune over-activation not only by suppressing production of anti-inflammatory humoral cytokines (IL-4 and IL-10) and stimulating other inflammatory mediators (such as nitric oxide), but also by suppressing lymphocyte function and disrupting T-cell signaling.⁶⁹

The result is amplification of numerous inflammatory pathways and increased susceptibility to developing inflammatory diseases, including autoimmune diseases, mood disorders, atopy, malignancy, chronic fatigue syndrome, chronic pain syndromes, obesity, glucose dysregulation and fibromyalgia.^{70,71,62,59,72,73} Furthermore, due to down-regulation of humoral immunity, hypocortisol patients become more vulnerable to assaults by infectious and environmental pathogens such as parasites, allergens, certain bacteria and toxins.⁶⁹

Since the onset of hypocortisolism is often insidious, many of the signs and symptoms are overlooked or attributed to other causes. Patients may complain of low-grade fever, easy fatigability, myalgias, weight loss and muscular weakness. Abdominal pain, nausea and vomiting, postural hypotension and hypoglycemia may also be seen. It is perhaps because of the remarkable overlap in symptomatology (Table 1) between hypocortisolism and Addison's disease that the terms "sub-clinical Addison's disease" and "adrenal fatigue" have evolved. Many of these are also the symptoms seen in critically ill, glucocorticoid-deficient patients.^{74,75}

Fries, Heim and others have identified high-stress sensitivity, chronic fatigue and chronic pain as the most common presenting symptoms of low cortisol states, labeling this the "hypocortisolemic symptom triad."^{76,79} Reportedly 20 to 25 percent of patients with stress-related bodily disorders present with these and other symptoms of functional bowel disturbances, PTSD, chronic pelvic pain, fibromyalgia, chronic fatigue syndrome, low back pain, "burn out" and atypical depression.^{78,79,76,77,78} Blunted morning cortisol levels and flattened daytime cortisol curves have also been found to be associated with less successful development and a diminished sense of well-being.⁷⁹

Table 1 Signs and Symptoms of Hypocortisolism

General: Fatigue, fever, weakness, myalgia, arthralgia, sore throat, headaches, dizziness upon standing, chronic pain
Gastrointestinal: Anorexia, nausea, vomiting, diarrhea, abdominal or flank pain
Psychiatric: Depression, apathy, irritability, sleep disturbances, difficulty concentrating, difficulty with memory, confusion, stress sensitivity
Cardiovascular: Increased heart rate, postural hypotension, orthostatic tachycardia, hypovolemia, depressed myocardial contractility
Laboratory: Hypoglycemia, hyponatremia, hyperkalemia, hypercalcemia, neutropenia, eosinophilia, hyperprolactinemia, hypothyroidism, leukocytosis, lymphocytosis

NATURAL THERAPEUTIC OPTIONS

While our understanding of the HPA axis dysfunction continues to expand, the management of these conditions, while straightforward, has less published literature. The approach involves reducing HPA axis stressors, enhancing HPA axis signal-sensitivity and supporting systems that are damaged by the catabolic effects of a high-cortisol and reduced-DHEA output. Since many of these therapies fall into "lifestyle management" categories, patient understanding and participation is vital to successful HPA axis management.

Taking control of known stressors

Stress analysis (via questionnaire) and management tools are an obvious start for those whose lifestyle includes avoidable stress. Job stress is directly related to cortisol:DHEA ratios and should be evaluated (including shift-work) and, perhaps, considered avoidable if significant enough.⁸⁰ Regular sleep, work and eating patterns should be considered in order to avoid increasing stress, and regular daily, weekly and yearly patterns of relaxation should be maintained for optimal health. Moderate, non-competitive exercise can be a valuable stress reducer that provides numerous other health benefits.

When it comes to unavoidable stressors, patient response becomes the key. If anger, fear, anxiety and depression are typical responses to unavoidable situations, adrenal stress is sure to follow. Learning to perceive and respond to stressful situations in ways that do not stimulate the HPA axis is one of the keys to preventing HPA dysfunction.

Glycemic control

The interrelationship between stress and glycemic dysregulation is perhaps one of the most overlooked contributors to metabolic abnormalities. When we think of stress, we often think of major life events—those often found on a life-stress inventory (divorce, death of spouse, major health concern). While these episodic stressors have negative consequences, the most common stressors are ones that often go unrecognized, operating chronically at low levels, resulting in profound negative clinical outcomes. One of these common, unrecognized stressors is glycemic dysregulation. This should come as no surprise, since one of the main functions of cortisol is related to

glucose regulation during stress. When we add to this the fact that visceral adipose tissue (a consequence of chronic overproduction of cortisol and insulin) produces increasing levels of inflammatory mediators (IL-1 β , IL-6, TNF- α) that drive HPA-cortisol production, we can see why it is so difficult to determine which is the cause and which is the effect.^{81,82,83,84} The key, however, is to break the cortisol-insulin-adiposity-inflammation-stress cycle; preferably *without* pharmaceutical intervention. Here are some of the methods that should be considered.

1. Reduce glycemic impact of the diet.

The glycemic impact of the diet is vitally important to maintain appropriate insulin and cortisol levels. Both hyperglycemia and hypoglycemia are stressors that signal HPA axis production of cortisol. Chronic glycemic dysregulation results in chronic high cortisol levels, placing the individual in an ongoing catabolic state. This is exacerbated when obesity and insulin resistance have already set in.

Most people are familiar with the glycemic index (GI); a number that reflects the glycemic effect of *available carbohydrates* in food relative to the effects of an equal amount of glucose. Glycemic Load (GL) is defined as the amount of carbohydrate exposure over a certain length of time. It is calculated by taking the GI/100 and multiplying this by the weight of the food and the percent of available carbohydrates in the food. Both the GI and GL are based on relative units, not correlating easily to grams of total carbohydrates or calories consumed. So while they may be helpful in the controlled environment of a clinical trial or for making general diet recommendations, what is needed is a number that helps an individual know the true glycemic impact of the meal they will consume.⁸⁵ This requires understanding the impact of all the other macronutrients (proteins, fats, non-digestible carbohydrates, fermentable fibers) and micronutrients (vitamins, minerals, phytonutrients) that impact glucose disposal and insulin secretion.

Soluble fibers and fermentable fibers (carbohydrates that can be fermented into short-chain fatty acids by gut micro-flora) seem to have an especially profound effect, not only on the glycemic response of the initial meal consumed, but on subsequent meals consumed. Researchers at Lund University in Sweden have recently published data showing that a single breakfast meal consisting of high amounts of soluble and fermentable fibers will decrease the glycemic impact of the subsequent lunch and dinner meals.⁸⁴ This effect was also noted for fibers consumed in the evening—impacting the glycemic response of the breakfast meal.^{85,86} When added to the data from a landmark two-year study published in the NEJM showing that low-carbohydrate and Mediterranean-style diets improve glycemic control and lipid parameters, it is clear that dietary changes play a primary role in improving long-term chronic health outcomes.⁸⁷

Dietary patterns that should be encouraged:

- Model the basic diet after the Mediterranean where possible.⁸⁸ (Read: *Eat, Drink and be Healthy* by Walter C. Willett)
- Reduce glycemic impact by reducing refined carbohydrates, soft drinks and other sweetened beverages, and increase the use of whole grains.
- Do not skip breakfast. This meal sets the foundation for glycemic control for the entire day and helps ensure the normal transition from high morning cortisol production.

- Supplement the diet, if necessary, with soluble and fermentable fibers (FOS, inulin etc.)
- Increase phytonutrients: use brightly colored vegetables, spices and herbs to improve insulin sensitivity.

2. Measure insulin sensitivity early.

Fasting serum tests (especially fasting serum glucose) are ineffective ways to discover insulin sensitivity impairments in at-risk populations. Impaired glucose tolerance often begins years before changes in fasting glucose levels will suggest a problem. Use of oral glucose tolerance tests or other post-prandial tests will identify at-risk patients earlier and allow lifestyle approaches to have the greatest impact. In fact, getting baseline insulin sensitivity for all patients where there is a family history of diabetes, obesity or heart disease would be advisable. Advanced lipoprotein analysis will also reveal signs of insulin resistance. Insulin-resistant patients will most often have an elevated triglyceride:HDL-C ratio⁸⁹ (suspect insulin resistance when ratio is above 3.5), elevated small-density LDL particles, elevated large triglyceride-rich VLDL particles, smaller HDL particles and increased C-reactive protein levels. All of these measurements are routinely available through numerous laboratories at reasonable (and often reimbursable) rates.

3. Measure cortisol/DHEA levels in all obese patients regardless of age.

Measuring cortisol and DHEA levels by saliva sampling is the best way to monitor the diurnal nature of the HPA axis. All stressors, regardless of origin, will result in episodic or chronic elevations in cortisol. Chronic HPA axis stimulation by stress directly impairs insulin function and stimulates caloric intake (especially of comfort foods).^{34,35} Assessing HPA function using salivary cortisol and DHEA enables the patient to begin assessing other potential stressors that may be driving cortisol output. These may be related to chronic inflammatory conditions (allergies, food allergies, GI inflammation, injury, etc.), relationships, work stress, financial worries, chronic illnesses or glycemic dysregulation. Without adequate management of stress-signaling over time, an individual will begin showing signs of HPA axis dysregulation, where the output of cortisol is no longer elevated or well below normal (even though the pituitary output of ACTH still remains high). These individuals will likely have depressed levels of DHEA, leading to an abnormally high cortisol:DHEA ratio.

Once assessment of the HPA axis is accomplished through testing and symptom evaluation, improvements can be suggested for lifestyle, diet and natural therapies. Recall that obesity itself, through inflammatory signaling, will drive the HPA signal for cortisol. Weight loss of any amount will help balance the HPA axis, improve insulin sensitivity and improve self-image.

4. Maintain an adequate sleeping pattern.

Over the past few decades, sleep time (primarily less sleep before midnight) and regularity (weekday vs. weekend) has been reduced in both children and adults. Poor sleep quality and quantity is directly related to visceral adiposity and HPA axis dysfunction.⁹⁰ In fact, sleep deprivation is often used in laboratory studies to invoke HPA axis stress.⁹¹ Additionally, obese patients have elevated risk for sleep apnea, which often goes undiagnosed, adding to an already burdened physiology. Patients (as well as those with whom they sleep) should be questioned about sleeping patterns, duration and symptoms of sleep apnea. Maintaining regular patterns of sleep for at least seven hours per night should be recommended.

5. Set realistic improvements in lifestyle measurements.

Lifestyle management programs often fail due to diminishing adherence over time. Most studies show weight loss will maximize six months into a program, then subjects begin to creep back to their starting weight. Even so, these individuals still have improved metabolic parameters over those who never lost the weight in the first place. It should be emphasized to patients that even small decreases in their weight or increases in their physical activity can have tremendous benefits. Emphasis should be placed upon improving insulin sensitivity and decreasing inflammation, which is less personal than specific weight or BMI targets.

Vitamins and Minerals

The synthesis and secretion of cortisol is dependent on adequate supplies of various vitamins. Vitamin C, needed for steroid biosynthesis, is depleted from the adrenal cortex upon high cortisol secretion.⁹² Niacin derivatives are also necessary cofactors for steroid biosynthesis. Pantothenic acid and folic acid are vital to maintain steroid secretion from the adrenal cortex. The effects of pantothenic acid deficiency have been specifically linked to decreased adrenal function in both animals and humans.^{93,94,95,96} Likewise, adrenocortical insufficiency has also been noted during biotin deficiency.

The relationship between the adrenal cortex and minerals is complex. Aldosterone (a mineralocorticoid), made by the adrenal cortex, has a profound effect on the regulation of minerals. Both aldosterone and cortisol are stimulated by stress (ACTH) and increase the amount of potassium released. Under stress, calcium may be depleted in adrenal tissues, as it is required for the secretion of both hormones. Serum levels of potassium, zinc, iron and copper are reduced under cortisol secretion. A balanced vitamin and mineral supplement regimen is critical when addressing adrenal function and HPA axis dysfunction.

Phosphatidylserine

Phosphatidylserine (PS) is a naturally occurring phospholipid, essential for the membranes of all cells, particularly brain cells. Among the many therapeutic uses for PS are promising effects in HPA modulation. Early studies from Italy have shown that PS is able to blunt the ACTH and cortisol response to stressors.^{97,98} This suggests that individuals whose HPA is overstimulated (high salivary cortisol, no diurnal drop) may be able to take oral PS to reduce this response. These results were confirmed using the Trier Social Stress Test (TSST), a laboratory stress test that can test the response of humans to a socially stressful public speaking situation. After three weeks of a combined blend of phosphatidic acids (400 mg total, 100 mg PS), they saw a marked statistical reduction in ACTH production as well as serum/salivary cortisol production upon stress.⁹⁹ Much higher levels of PS (600 mg) have been used to blunt the HPA axis stimulation effects of intensive exercise.¹⁰⁰

Pregnenolone and DHEA

The use of oral, sublingual or topical doses of DHEA and/or pregnenolone are used by many clinicians in patients with HPA axis dysfunction. Pregnenolone is a precursor to all of the adrenal corticosteroids (See Figure 1) and is considered by some clinicians to be helpful in both hypercortisolism as well as hypocortisolism. When levels of cortisol are high and DHEA levels are normal or low, pregnenolone is often shunted to the cortisol pathway.

While little has been published in peer-reviewed literature evaluating the use of pregnenolone in "healthy" human subjects with HPA axis abnormalities, research has focused on intervention for patients with mood disorders and schizophrenia.¹⁰¹ A recent study showed that 50 mg/day (PO) of pregnenolone had modest benefits on depression and mania in depressed and bipolar subjects with a history of substance abuse.¹⁰² Previous studies showed lower doses (15 mg/day followed by 30 mg/day) had no effect on mood in normal subjects, although pregnenolone pre-treatment resulted in less sedative response to diazepam in these subjects.¹⁰³ In both studies these doses were well tolerated, although both were short-term trials (eight or four weeks respectively). The four week trial did report one patient as experiencing palpitations, a side effect reported by other clinicians (author's personal communications).

Physiological (rather than pharmacological) doses of 25–50 mg oral (5–10 mg/day, sublingual) of pregnenolone is also popular among some physicians and are currently available as dietary supplements in the U.S. (products labeled as "sublingual" are regulated as drugs in the U.S., regardless of ingredient). This approach to supporting HPA axis and/or adrenal dysfunction has not been evaluated or published in the peer-reviewed literature as far as we know.

The use of supplemental DHEA (dehydroepiandrosterone) in humans has been studied extensively with mixed results. The evaluation of these studies is made difficult by the wide-range of patients included, outcomes studies and doses used. The use of DHEA for benefitting well-being and sexual dysfunction in women was recently reviewed with the conclusion that the most consistent benefits seen in clinical trials (typical dose 50 mg/day, oral) are with women described with adrenal insufficiencies.¹⁰⁴

Additionally, menopausal women consuming 25 mg/day of DHEA for one year had improved adrenal enzymatic activity while reducing their cortisol:DHEA ratio, effectively reversing some of the age-related decline in adrenal activities.¹⁰⁵ Several studies have shown oral DHEA therapy in post-menopausal women to also statistically improve bone mineral density, although no benefit was seen in men.^{106,107} These studies suggest that increasing DHEA levels by supplementing physiological doses of DHEA in patients with reduced DHEA levels or increased cortisol:DHEA ratios may help blunt the catabolic affects of cortisol without affecting absolute cortisol production.

Licorice Root Extract

Licorice (*Glycyrrhiza glabra* L.) root was once used to make the candy of the same name, but has since been replaced by anise and corn syrup. Glycyrrhizin, one of the major components of licorice root, has a structure similar to corticosteroids. These compounds have been shown to block 11- β -hydroxysteroid dehydrogenase, the enzyme responsible for the conversion of cortisol to the inactive cortisone.^{108,109,110,111} The result is increased cortisol levels. Chronic high levels of licorice have been known to raise blood pressure by causing increased cortisol binding to the mineralocorticoid receptors in the kidneys, increasing water retention and blood volume. When taken in smaller targeted doses, licorice root extracts can be used to maintain cortisol levels. Therapeutic use of licorice root extract should be reserved for patients determined to have hypocortisolism. Severe hypocortisolism may require three or four separate doses throughout the day. Based on the in vivo and clinical evidence, a suggested acceptable daily intake of 0.015–0.229 mg glycyrrhizin/kg body weight/day is recommended.¹¹² This means that a 75 kg (165 lbs) individual should consume no more than 17 mg of glycyrrhizin daily. Individuals with hypertension (especially salt-sensitive hypertensives), should be monitored for water-retention when given licorice root extract.

Glandular

Using animal glands and organs as supplemental ingredients may be new to some, but the concept is ancient. Dietary use of organ meat for therapeutic functions has been going on in many cultures for centuries. In fact in 1896, at least three pharmaceutical companies (Chaix and Raimy, Paris; Oppenheimer Son and Co., London; and Burrough's Wellcome and Co., London) were producing adrenal gland extracts,¹¹³ which had become the most common therapy for depleted adrenals in the late 19th century.

The concept of glandular therapy is simple: similar organ extracts from animals will support the same organ within the human. Historical evidence suggests that ingesting organ products similar to those in our own system (bovine, porcine, etc.) can stimulate the activity of these organs.¹¹⁴ Today, this is still the active principal in some thyroid medications. While adrenal glandular therapy may be beneficial in the event of reduced activity (hypocortisolism), inadvertent over-stimulation is possible in cases of hypercortisolism. It should be noted that while glandular therapy is quite commonly (and safely) used within clinics throughout the world, the efficacy of these extracts has not been confirmed using current scientific research methods.

Adaptogenic Herbs

An adaptogenic herb is defined as a substance that increases the body's ability to resist stress and exerts a balancing effect on various systems of the body (immune, central nervous, cardiovascular, etc.). Early research focused on the ability of adaptogenic herbs to

increase animal and human performance under physical stress and fatigue-related performance evaluations.¹¹⁵

Numerous botanicals have been listed as "adaptogens" under this general definition including: *Eleutherococcus senticosus* (Siberian Ginseng), *Panax Ginseng*, *Rhodiola rosea*, *Schisandra chinensis*, *Withania somnifera* (Ashwaghandha), *Astragalus membranaceus*, *Scutellaria baicalensis* and others. Current research suggests that adaptogenic herbs work by inducing specific heat-shock proteins within cells, which protects both cells and organs during stress-induced changes in homeostasis.^{116,117} While numerous clinical trials have been performed with single ingredient or combination herbal products,¹¹⁶ a wide variety of doses, subject criteria and primary endpoints make it difficult to give specific recommendations. The effect of adaptogens in combination with vitamins and minerals has been shown to be additive and beneficial in relieving HPA axis dysfunction,^{118,119} and most commercially available products (capsules, tablets, teas) provide a blend of adaptogenic agents.

CONCLUSIONS

There is absolutely no dispute within the medical literature, which spans almost 80 years, of the effects of both acute and chronic stress on aging, disease formation and early mortality. Yet, despite the extensive research that exists substantiating the effects of stressors/chronic stress on human health and disease, there has been little recognition within the "traditional" medical community of such. Patients suffering from stress-related bodily disorders are often left to self-diagnose and self-treat without the knowledge of, consent, or approval from their medical health care provider. Much of this stems from the fact that the signs and symptoms of HPA axis dysfunction can be subtle and often fall outside the category of true "disease" (both physically and diagnostically). In addition to this, researchers have not agreed upon specific diagnostic and therapeutic endpoints by which to evaluate the wide-range of HPA axis disorders.

With these precautions in mind, the growing literature suggests that, in the hands of an educated clinician, the evaluation of the HPA axis may significantly alter the course of therapy in numerous complex chronic disease patients, resulting in positive outcomes. The ease and cost-effective evaluation of adrenal hormones via saliva samples, as well as the number of non-pharmacological lifestyle, diet and nutritional options for supporting HPA function, allow for a flexible matrix of patient-centered therapies and outcomes that are likely to benefit the patient beyond the immediate effects on the HPA axis.

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