

Beyond Adrenal Fatigue: From Anecdotal to Evidence Based Medicine

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Today's clinician is becoming increasingly aware of the detrimental effects of stress on the morbidity and mortality of their patients. However, lack of proper recognition and understanding of stress-related disorders has rendered optimal assessment and treatment elusive. Ample evidence has demonstrated an association between chronic stress exposure and the development of chronic diseases. Ironically, only a small percentage of clinicians understand how dysfunction within the stress management system (HPA axis) alters pathophysiology. To further muddy the waters, the use of simplified terms such as "Adrenal Fatigue" have widened the gap of knowledge by leading many to discredit the very real pathophysiological consequences of HPA axis dysfunction. This paper will provide an evidence based overview of the metabolic and clinical sequelae of stress-induced HPA axis dysfunction manifesting as hypocortisolism, the state of abnormally low daytime cortisol.

The Semantics of Stress

Humans have a complex network of metabolic machinery which maintains normal homeostasis or internal balance. The term "stress" has been coined to describe a state of threatened homeostasis or disharmony. When the body is exposed to stress, a complex counter regulatory "adaptive stress response" occurs, and a cascade of physiologic and behavioral responses ensues to re-establish homeostasis. The stress response system is comprised of 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. Excessive, prolonged or inadequate regulation of the stress response systems will invariably cause individuals to suffer adverse health consequences.

Identification of HPA axis dysfunction can be quite challenging for the clinician since it requires simultaneous assessment of the integrity of the individual's stress response system, the manner in which this dysfunction manifests clinically, and the underlying root cause for the dysfunction. Although incorrect, much of the popular and clinical attention related to stress related disease has unilaterally highlighted the adrenal glands and their production of cortisol. Thus, "Adrenal Fatigue" has now become the 'catch all' term to describe the physiological maladaptation to stress, especially hypocortisolism (states of abnormally low cortisol). While this term has helped to dispel the notion that only extremes of cortisol production, namely Cushing's disease or Addison's disease, are clinically relevant, it does not adequately describe the complexity of the cascade of events involved in the stress response and should be replaced by more appropriate evidence based terminology.

To Stress or Not to Stress

Much of our current understanding of the stress response has evolved from the research and writings of Hans Selye, the ‘father of stress research’. 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 similar physiologic outcomes occurred irrespective of the diverse stressors to which the animals were subjected.

Selye discovered that chronic exposure to a stressor led to a recurring set of physiological outcomes (hypertrophy of the adrenal gland, atrophy of the lymphatic organs, and ulcers in the stomach). Modern epidemiological data suggests that acute, intense episodic or chronic exposure to HPA axis stressors in humans is related to the same phenomena. In fact, over half a century of research has confirmed that the same stress response mechanism is elicited regardless of the type of stressor.

There are many types of stressors capable of altering homeostasis. They may be physical, chemical or emotional; perceived or real. Although sources of acute stress are often apparent, it is of vital importance that clinicians encourage patients to be self aware and accurately identify every potential chronic stressor. Although virtually any event the body considers foreign to its natural function can be perceived as a HPA axis stressor, there are four general categories of chronic HPA-axis stressors: mental/emotional stress, sleep disorders, metabolic/glycemic dysregulation and chronic inflammation.

Mental & Emotional Stress

The biochemical responses of the HPA axis can be easily triggered by non-physical events. Grief, excitement, fear, anxiety, guilt, and embarrassment can all trigger a robust HPA axis response. Events such as public speaking, performance evaluations, skydiving or clinical appointments can cause ACTH and cortisol to rise in most individuals. Interestingly, research has shown that the magnitude of the response and recovery to these stressors is determined by an individual’s perception rather than the stressor itself. The four key factors that determine the magnitude of the HPA axis response to a mental or emotional stressors are: 1) novelty to the individual, 2) unpredictable nature, 3) threat to their person or ego, 4) sense of loss of control. 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 Deprivation

During slow-wave sleep, cortisol release is normally suppressed by a decrease in corticotrophin releasing hormone (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 promote the development of secondary metabolic syndrome, hypertension, and inflammatory diseases..

Metabolic/Glycemic Dysregulation

Cortisol, the body's primary stress hormone, is a key regulator of glucose production. A stress induced rise in cortisol levels ensure that the brain and muscle will maintain adequate glucose reserves required for a robust 'fight or flight' response. While these effects are intended to promote short term survival, they can lead to disastrous consequences if maintained for prolonged periods of time. Individuals who regularly consume high glycemic foods and/or are insulin resistant will often experience a hypoglycemic "crash" after a meal which then triggers a rise in cortisol. Since cortisol can further promote insulin resistance, this vicious cycle can be difficult to control. Patients with central adiposity or insulin resistance should be evaluated for HPA axis dysfunction and be counseled on lifestyle and nutritional modification that improve glycemic control.

Inflammation

Cortisol, 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 fuel HPA axis dysfunction if not corrected. Furthermore, some pharmacologic agents commonly used to treat the symptoms of chronic inflammatory diseases, such as NSAIDS and opiates, can further exacerbate HPA axis dysfunction.

Hypocortisolism: All that is Flat is not Fatigued

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 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.

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 primarily implicated disruptions in these aspects. 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 development 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. 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.

“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. 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. 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.

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). 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.

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. 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.

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 symptomology between hypocortisolism and Addison's disease that the terms "sub-clinical Addison's disease" and "adrenal fatigue" have evolved. Prominent researchers in this field have defined the hypocortisolism 'symptom triad' to consist of the three most common presenting symptoms: high-stress sensitivity, chronic fatigue and chronic pain. Reportedly 20 to 25 percent of patients with stress-related bodily disorders present with these and other symptoms; including functional bowel disturbances, PTSD, chronic pelvic pain, fibromyalgia, chronic fatigue syndrome, low back pain, "burn out" and atypical depression. Blunted morning cortisol levels and flattened daytime cortisol curves have also been implicated in suboptimal development and a diminution in sense of well-being.

Rethinking 'Adrenal Fatigue'

Although the term 'adrenal fatigue' has been beneficial insofar as it has promoted an increased awareness of the relationship between stress and disease, the simplistic nature of this label truly underestimates the complexity of the stress-response system and completely disregards the vital roles that other bodily organs and systems, hormones, and enzymes play in the overall stress response. There is always an underlying etiology behind states of low cortisol, and clinicians who understand the complexity of the HPA axis and discover the underlying root cause of a patient's hypocortisolism will succeed where others may fail.

For a full, referenced review of this topic with treatment suggestions see: Chronic Stress and the HPA Axis, *The Standard Volume 9 No. 2* on the web at www.pointinstitute.org