The Role of Stress and the HPA Axis in Chronic Disease Management
Principles and Protocols for Healthcare Professionals
SECOND EDITION

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 Endocannabinoid System and Stress
Sample Patterns of Diurnal Cortisol and DHEA(S) • Addressing the Key Reversible Stressors
Stress, Mood, and Memory • Nutrient Support Protocols • Adaptogens and other Botanicals

Thomas G. Guillian Ph.D.
The Role of Stress and the HPA Axis in Chronic Disease Management

Principles and Protocols for Healthcare Professionals

SECOND EDITION

by

Thomas G. Guilliams Ph.D.

The Point Institute was founded by Thomas Guilliams, Ph.D. as an independent research organization focused on examining and disseminating information about the use of natural therapeutic options for treating and preventing chronic disease. Along with therapies generally defined as lifestyle interventions, the Point Institute specializes in the evidence and application of nutraceuticals (dietary supplements, herbs, vitamins, minerals, etc.) as therapeutic and preventative agents in clinical practice.
Disclaimer: This publication is intended to help inform and educate healthcare professionals; and combines both established and emerging scientific and nutritional information. The scope of this publication is limited and is not intended to replace the role of comprehensive textbooks on medicine, endocrinology, psychology or nutrition. Nothing herein is intended to replace guideline recommendations or promote specific therapies for individual patients. Healthcare providers are responsible to make their own determination of the usefulness and applicability of the information within this publication. Neither the publisher, author, nor reviewers assume liability for any injury to persons arising from the use of the information found in this publication.
# Table of Contents

## Lifestyle-Based Therapy: Our Core Philosophy
- The Seven Spheres of Lifestyle Signals ................................................................. 12
- Physiological Resilience and Metabolic Reserve .................................................. 13
- A Hierarchy of Lifestyle Therapies ........................................................................ 15
- Prevention-to-Intervention Hierarchy .................................................................. 16

## The Role of Stress on the Human Condition
- The Goal of the Stress Response ........................................................................ 18
- Chronic Stress Depletes Metabolic Reserve ......................................................... 19
- Allostatic Load and the Stress Response ............................................................ 19
- Conditions Related to HPA Axis Dysfunction ....................................................... 20
- The Epigenetics of Stress and the Rise of Chronic Disease ................................ 21
- Hans Selye and His General Adaptation Syndrome ........................................... 22
- Reassessing the Nomenclature of HPA Axis Dysfunction (“Adrenal Fatigue?”) .. 24

## The Stress Response System
- The Sympatho-Adrenomedullary System and the LC/NE ................................... 26
- Hormones of the Adrenal Medulla ..................................................................... 27
- Locus Coeruleus/Norepinephrine System ............................................................ 28
- The HPA Axis: An Overview .............................................................................. 29
- Hypothalamus- Surveying Threats and the Need for Response ...................... 30
- CRH- Beyond the Hypothalamus ....................................................................... 31
- The Pituitary: Relaying the Signals of the HPA axis to Target Tissues .............. 32
- The Pituitary and its Hormones ........................................................................ 32
- Corticotroph Cell .............................................................................................. 33
- Pro-opiomelanocortin (POMC) and its Derivatives ........................................... 33
- The Adrenal Gland ............................................................................................ 34
- The Adrenal Cortex ........................................................................................... 34
- The Adrenal Gland and its Layers ..................................................................... 34
- Adrenal Cortex Steroidogenesis ....................................................................... 35

## Cortisol Signaling: Modulating the Target Tissue Response
- Cortisol Signaling Modulation ........................................................................... 38
- Feedback Inhibition and Target Tissue Function ............................................. 39
- Cortisol Clearance and Metabolism Rate .......................................................... 40
- Primary Cortisol Metabolites ............................................................................ 40
- Corticosteroid Binding Globulin (CBG) and Cortisol Bioavailability .................. 41
- 11-β-Hydroxysteroid Dehydrogenases- Controlling Active Cortisol Concentrations .................................................. 42
  - 11β-HSD2: Protecting Cells from Excessive Cortisol .................................... 42
  - 11β-Hydroxysteroid Dehydrogenase 1 and 2 .................................................. 42
  - 11β-HSD1: Amplifying the Actions of Cortisol ............................................. 43
- Genomic Signaling: The Classic Cortisol-Signaling Effect ............................... 44
- Glucocorticoid Receptor Isoforms and Sensitivity .......................................... 44
- Chaperoning the Cortisol Effect: Heat Shock Proteins and More.................... 46
  - Co-Chaperoning the Stress Response: FKBP51 and FKBP52 ....................... 46
  - GR and Heat Shock Proteins ........................................................................ 47
- The Non-Genomic Signaling of Cortisol ............................................................ 48
- Cortisol and Mitochondrial Signaling ............................................................... 48
- DHEA: Modulating the Effects of Cortisol and More ....................................... 49
  - DHEA-S Levels by Age ............................................................................... 49
  - DHEA Metabolites ....................................................................................... 50
Laboratory Assessment of the HPA Axis

Measuring Cortisol (Serum, Urine, Hair) .................................................................................. 54
Salivary Cortisol: Key Biomarkers for HPA Axis Function Research and Clinical Evaluation ................................................. 54
Diurnal Cortisol Testing/Precautions Using Standard Lab Testing .................................................................................. 57
Cortisol Awakening Response (CAR) .................................................................................................................. 58
Cortisol Measurements for Cushing’s Disease, Pseudo-Cushing’s Syndrome, and Addison’s Disease ............................................. 60
Glucocorticoid Therapy Increases Risk for Adrenal Insufficiency .................................................................................. 62
Testing Salivary DHEA and DHEA-S .................................................................................................................. 63
Cortisol:DHEA(S) Ratio .................................................................................................................................................. 64
Ways to Improve Interpretation of DHEA ............................................................................................................. 64
Salivary Secretory Immunoglobulin-A (sIgA) ............................................................................................................. 65
Salivary Alpha-Amylase (sAA) ........................................................................................................................................... 66
Heart Rate Variability ..................................................................................................................................................... 66
Re-Assessing the Notion of “Pregnenolone Steal” ........................................................................................................ 67
The Progression of Stress Adaptation and HPA Axis Dysfunction .................................................................................. 68
Sample Patterns of Diurnal Salivary Cortisol and DHEA(S) Results .................................................................................. 70
Ideal Subject .................................................................................................................................................. 70
Elevated–Cortisol, Elevated CAR (Only) .................................................................................................................. 71
Elevated–Cortisol (with Diurnal Drop) ................................................................................................................................ 72
Elevated–Cortisol Spikes Due to Exercise .................................................................................................................. 73
Late Evening Elevated Cortisol (Inflammation-Insomnia) ............................................................................................... 74
“Normal” Cortisol with Low DHEA(S), in Subjects with Signs of Perceived Stress ................................................. 75
Blunted Morning Cortisol (Only) .................................................................................................................................. 76
Hypocortisolism (General Pattern) ................................................................................................................................... 77

Modifiable Categories of HPA Axis Stress ................................................................................................................. 82

Glycemic Dysregulation and HPA Axis Activation ........................................................................................................... 84
HPA Axis, Satiety, and Comfort Foods ..................................................................................................................... 84
Breaking the Cycle of Stress, Cortisol, Insulin, Adiposity, and Inflammation ........................................................................ 85
Reducing Glycemic Impact of Diet .................................................................................................................................. 85
Considerations for Supplementing Diet with Insulin-Sensitizing Nutrients ........................................................................ 86
Inflammatory Signaling and the HPA Axis ..................................................................................................................... 87
Circadian Disruption and HPA Axis Dysfunction ......................................................................................................... 88
HPA and Molecular Control of Circadian Rythm ........................................................................................................... 89
Avoiding Circadian Disruptors ...................................................................................................................................... 90
Understanding and Assessing Perceived Stress ........................................................................................................... 93
Perceived Stress Increases HPA Axis Activation ............................................................................................................. 94
Provoking Psychosocial Stress: The Trier Social Stress Test (TSST) ................................................................................ 96
“Burnout” Associated with Decreased HPA Axis Activation .......................................................................................... 98
Helping Patients Take “Control” .................................................................................................................................. 98
Translating Events into Signals of Stress: Neurotransmitters and Beyond ........................................................................... 99
Glutamate Signaling ...................................................................................................................................................... 99
GABA Signaling ............................................................................................................................................................... 100
Depression and HPA Activation .................................................................................................................................. 100
Neurosteroids ................................................................................................................................................................. 101
Monoamines and the HPA Axis ...................................................................................................................................... 101
Supplementing 5-HTP ...................................................................................................................................................... 102
Interplay Between the Endocannabinoid System and HPA Axis ......................................................... 107
Components of the Endocannabinoid System .................................................................................. 107
Endogenous Endocannabinoid Ligands .............................................................................................. 107
Chemical Structures of Phytocannabinoids and Endocannabinoids .................................................. 108
Endocannabinoids Synthesis and Degradation .................................................................................. 108
Cannabinoid Receptors ....................................................................................................................... 108
Retrograde Signaling: Linking Suppression of Neurotransmitter Release to Postsynaptic Activity .... 109
Dynamics of the Endocannabinoid System in Relation to the HPA Axis ............................................... 109
AEA: Gatekeeper of the Stress Response ............................................................................................ 110
2-AG: Terminator of the Stress Response ............................................................................................ 110
2-AG: Glucocorticoid-induced Rapid Feedback Inhibition ................................................................. 110
2-AG: Glucocorticoid-induced Delayed Feedback Inhibition ............................................................ 110
The Endocannabinoid System Response: When Stress Becomes Chronic .......................................... 111
Endocannabinoids as an Intermediator in Other CNS Effects: Memory ........................................... 112

Natural Therapeutic Strategies to Support HPA Axis Function ............................................................ 114
Vitamins and Minerals .......................................................................................................................... 115
Vitamin C (Ascorbic Acid) .................................................................................................................... 115
B-Vitamins ........................................................................................................................................... 116
Minerals ................................................................................................................................................ 116
Omega-3 Fatty Acids and Phospholipids ............................................................................................... 117
Probiotics ............................................................................................................................................. 118
Glandular-Derived Supplements ......................................................................................................... 119
DHEA and Pregnenolone ..................................................................................................................... 119
DHEA Supplementation ....................................................................................................................... 120
Sourcing Bio-Identical Hormones ....................................................................................................... 120
Sublingual vs. Oral Supplementation ................................................................................................. 120
DHEA vs. 7-keto DHEA .......................................................................................................................... 121
Supplementing Pregnenolone .............................................................................................................. 122
Adaptogens and Other Botanicals ........................................................................................................ 123
Eleuthero ............................................................................................................................................. 124
Schisandra ......................................................................................................................................... 125
Rhodiola (Rosenroot) .......................................................................................................................... 125
RSE: Combination Studies of Rhodiola, Schisandra, and Eleuthero .................................................. 126
Ashwagandha ..................................................................................................................................... 126
Panax (American and Korean Ginseng) ............................................................................................... 128
Adaptogens: Proposed Mechanisms ................................................................................................... 128
Other Botanicals/Herbals .................................................................................................................... 129
L-Theanine ......................................................................................................................................... 129
Licorice Root Extract ........................................................................................................................... 130
Mucuna/Cowhage .............................................................................................................................. 131
Physical Activity, Stress, and the HPA Axis .......................................................................................... 132
HPA Axis Activation After Exercise .................................................................................................... 133
Mind/Body Interventions .................................................................................................................... 134
Yoga ..................................................................................................................................................... 134
Mindfulness-Based Stress Reduction .................................................................................................. 135
Biofeedback Techniques ...................................................................................................................... 135
Tai Chi ................................................................................................................................................ 135
Qigong ................................................................................................................................................ 135
Forest Bathing/Green Exercise ........................................................................................................... 135
Religion and Spirituality ....................................................................................................................... 136

The Role of Stress and the HPA Axis in Chronic Disease Management Point Institute
Hans Selye and His General Adaptation Syndrome

Most readers of this text are likely to have at least a rudimentary understanding of how the HPA axis regulates the stress response, the biological function of glucocorticoids, and the general effects of stress on chronic disease. This was certainly not true 75 years ago. In fact, both the biological functions of the HPA axis and the very use of the word “stress” as a biological process were yet to be defined. Most modern researchers look back to a brief “letter” published in Nature in 1936 by Hans Selye entitled “A syndrome produced by diverse nocuous agents” as the starting point of modern stress research. i

This paper was followed by decades of research and publications that have shaped most of today’s foundation for understanding the HPA axis, the role of stress on chronic disease and the role of corticosteroid signaling. Hans Selye (1907-1982) is often referred to as the “Father of Stress Research,” the scientist who, more than any other, brought the concept of stress to the forefront of both scientists and the public. ii,iii His book, The Stress of Life (1956), iv written for the lay audience, popularized the notion of stress as the general response to a wide variety of insults.

In the preface of the original publication he writes:

“Stress is essentially reflected by the rate of all the wear and tear caused by life. It will take a whole book to explain the complex mechanisms through which the body can reduce this type of wear and tear and to define the concept more precisely. But let me say here, by way of an introduction, that although we cannot avoid stress as long as we live, we can learn a great deal about how to keep its damaging side-effects, “distress,” to a minimum. For instance, we are just beginning to see that many common diseases are largely due to errors in our adaptive response to stress, rather than to direct damage by germs, poisons, or life experiences. In this sense many nervous and emotional disturbances, high blood pressure, gastric and duodenal ulcers, and certain types of sexual, allergic, cardiovascular, and renal derangement appear to be essentially diseases of adaptation.” [emphasis in the original]

Selye did most of his research in the laboratory using rats. There, he found that placing animals under a wide range of different physiological stressors resulted in only a few common physiological responses. Through these experiments, he postulated that there was a common, non-specific pathway by which organisms processed “nocuous agents,” or what he called “stressors.” He later revised his definition of “stress,” which he initially considered to be only harmful, to include both harmful stimuli (distress) and helpful or joyful stimuli (eustress). Both, he found, trigger similar biological processes. The three common physiological responses that Selye first described in stressed animals were: 1) the enlargement (hypertrophy) of the adrenal cortex; 2) a shrinking (atrophy) of the thymus and lymph nodes; and 3) erosions and ulcers in the duodenum. By observing animals exposed to both acute and chronic stressors, he also recognized that their ability to resist (or adapt) to these stressors, as measured by relative changes in these three physiological phenomena, involved progressive adaptation. After years of research, Selye proposed his General Adaptation Syndrome, in a monograph published in 1950.iv

The General Adaptation Syndrome is a description of both the stress-induced changes experienced by animals as a consequence of the HPA axis, and also the ability of the animal to resist or adapt.
So far, we have described the rudimentary aspects of 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, influenced 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, able to trigger catabolic activities across many tissues, there are several ways the body buffers and modulates the effects of cortisol on target tissue. Understanding these mechanisms can be just as important as understanding the straightforward signaling within the HPA axis.¹ Here we will discuss the variety of mechanisms used to modulate the cellular actions of cortisol and discuss how they mediate many of the chronic disease manifestations linked to HPA axis dysfunction. Understanding these mechanisms can allow the clinician to leverage specific therapeutic interventions that may mitigate the damage from, or improve the adaptation to, cortisol production and chronic stress. Figure 13 shows a schematic diagram of the specific mechanisms that affect the cortisol signaling process. We will first describe them briefly here, then unpack each of these mechanisms further in the following pages.

Figure 13: 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.
Free vs. Bound Cortisol
Like other circulating steroid hormones, most (~95%) of the cortisol in the serum is bound, either to corticosteroid binding globulin (CBG, ~80%) or albumin. Only free cortisol appears to have cell-signaling effects. Changes in the amount or affinity of CBG can dramatically alter free (active) cortisol levels.

11β-HSD (1 and 2)
11-β hydroxysteroid dehydrogenase enzymes 1 and 2 facilitate the inter-conversion of cortisol (active) and cortisone (inactive). The polymorphisms, expression, activation, and inhibition of these two enzymes affect the intracellular concentration of active cortisol available for signaling and may account for up to 40% of the cortisol available to some tissues.

Classic Genomic Glucocorticoid Signaling
The genomic effects of cortisol are mediated through glucocorticoid (cortisol) receptors, which function as nuclear transcription factors. The different receptor isoforms and splicing variants, along with multiple patterns of dimerization, help determine the genomic activation or repression of glucocorticoid responsive genes. Most of the known effects of cortisol are mediated through genomic signaling.

Heat Shock Proteins and Co-Chaperones
Like most nuclear regulators, cortisol receptors are sequestered within the cytoplasm in the absence of cortisol by heat shock proteins (universal chaperone proteins) and co-chaperones. These proteins not only sequester the cortisol receptors in the cytoplasm, they can also profoundly influence the binding affinity and signaling effects of cortisol. Their expression can be modulated by stress as well as other lifestyle and environmental influences.

Direct Non-Genomic Signaling
Though best known for its genomic effects, several signaling pathways have been described for cortisol that appear to be mediated by membrane-bound receptors or directly through other cytoplasmic signal transduction pathways (independent of the nuclear/genomic signaling pathways and receptors). The importance of these signaling pathways is a new area of research.

Cortisol Metabolism Rate
Like all steroid hormones, cortisol is metabolized and removed from the body. The clearance rate and detoxification of cortisol (and various intermediate metabolites) are potential factors that alter target tissue effects.

DHEA Production
DHEA appears to function as an anabolic counter-regulatory hormone to the catabolic effects of cortisol. Low levels of DHEA allow for more ‘unopposed’ cortisol signaling within tissues. Though the production and release of DHEA and DHEA-S in the adrenal gland are, in part, managed by the HPA axis and “stress” signaling, there are other factors (e.g., aging) that also have a strong influence on production. The function and control of DHEA(S) is discussed on page 49.

Feedback Inhibition and Target Tissue Function
While considering these different ways that cortisol signaling is modulated at the level of various target tissues, it is important to remember that some of these effects are systemic, while many are tissue-specific. Additionally, recall that changes to target-tissue responses to cortisol signaling also impact tissues involved in cortisol feedback inhibition (e.g., amygdala, hippocampus, hypothalamus, and pituitary), so that changes that increase cortisol signaling in these tissues will result in a more profound feedback inhibition (e.g., the use of dexamethasone to suppress the HPA axis and cortisol secretion). Clinicians should keep in mind the tissue-specific cortisol sensitivity and feedback inhibitory dynamics when seeking to diagnose patients based on measured cortisol levels, or in attempting to use supplemental glucocorticoids or agents designed to alter glucocorticoid signaling (see glucocorticoid-induced adrenal insufficiency on page 62). Elevated serum or salivary cortisol levels may be compensated by glucocorticoid resistance in specific tissues and, conversely, low cortisol levels may be compensated by hypersensitivity in specific tissues. Both may explain anomalies between measurements of cortisol circulation and apparent cortisol tissue effects.
Laboratory Assessment of the HPA Axis

While the physiological dysregulations connecting the stress response system and chronic disease have been extensively researched, it is much more challenging for clinicians to identify the specific clinical characteristics of acute and chronic stress. The cumulative effects of allostatic load, resulting in depleted metabolic reserve in a wide range of tissues, is considered one of the leading determinates of chronic disease progression, aging, and mortality. However, measuring the subtle progression of physiological changes caused by allostatic load is not straightforward. Therefore, researchers have explored different sets of biomarkers (or algorithms based on biomarker measurements), attempting to gauge allostatic load as a predictor of aging, mental illness, and chronic disease risk (especially cognition). Beyond the obvious endocrine markers (cortisol, DHEA(S), epinephrine, norepinephrine), the most common biomarkers are those related to inflammation/immunity (CRP, IL-6, IGF-1, TNF-α, fibrinogen), metabolic dysfunction (HDL, TG, HbA1c, glucose), as well as systolic and diastolic blood pressure, BMI, and waist-to-hip ratio. These, along with clinical measures and symptoms of perceived stress (questionnaires, inventories, sleep disturbances, etc.), can be used to assess allostatic load as well as direct therapeutic priorities. Currently there is no consensus on which biomarkers or algorithms are best when assessing or defining allostatic load.

In the clinical setting, especially amongst functional and integrative clinicians, direct measures of the stress response are commonly employed. This is usually accomplished by measuring adrenal hormone output in a basal or provoked state, or another intermediate signaling compound involved with the stress response. Numerous laboratories provide a range of tests that allow clinicians to measure these and other hormones and metabolites within the serum, saliva, urine, and hair. This section will focus on the different biomarkers used for assessing HPA axis (and overall “stress”) that are currently available to the clinician, discussing the available evidence for interpreting these laboratory results (primarily related to cortisol, DHEA, and DHEA-S).

Measuring Cortisol to Assess HPA Axis Status

The most common biomarker used to measure the function of the HPA axis is cortisol, though serum ACTH is also measured in the research setting or when adrenal insufficiency is suspected (see sidebar on page 60). As the most prominent and direct outcome of the HPA axis, cortisol has been used in thousands of clinical trials to measure the function, status, and reactivity of the HPA axis generally, or as a measure of adrenal sufficiency and function when properly provoked. In addition, since the synthesis of cortisol follows a predictable diurnal pattern, is partially responsible for its own synthesis (via feedback inhibition), and can be intentionally suppressed or stimulated with laboratory interventions, cortisol measurements are a critical foundation to HPA axis research and clinical evaluation. We will first describe the clinical measurement of cortisol and then discuss how this measurement (along with DHEA(S) or other measurements) can help assess HPA axis status.

Cortisol can easily be measured from several biological fluids, such as serum, urine, and saliva, as well as from hair and fingernails. Understanding the potential uses of each of these sources of measured cortisol can be beneficial for accessing the published literature and clinical laboratory test results. While each of these measurements will be outlined below, the use salivary free cortisol measurements are likely the best and most easily sampled surrogate marker for the glucocorticoid action (serum free cortisol) available to most target tissues. However, tissue-specific cortisol concentrations (e.g., adipose tissue) may be inferred by other measurements (e.g., the cortisone/cortisol ratio), but they cannot be measured directly without biopsy.
Subject Type: Elevated measures of cortisol throughout the day (at several time-points), but with diurnal rhythm generally intact. Unlike Cushing’s patients (red line in figure) that have very high cortisol levels that show no diurnal drop, most subjects with stress-related elevated cortisol levels will still have a diurnal rhythm similar to the shaded box in the figure. This suggests HPA axis circadian control is intact, though feedback inhibition may be slightly down-regulated (maladapted). This pattern is common in older subjects with failing health, subjects with ongoing job or life stress (high allostatic load), or subjects with melancholic depression.

Cortisol: While the diurnal pattern may represent elevations at each time-point, specific time-point higher than the curve (especially mid-morning and mid-afternoon) may indicate hypoglycemic-induced cortisol or exercise.

CAR (if measured): While CAR is often elevated in these subjects, some individuals present with elevated morning cortisol with flattened CAR (i.e., both waking and 30 minutes post awakening are elevated, resulting in a flattened CAR).

DHEA(S): DHEA and DHEA-S may be slightly elevated just after a strong HPA axis stressor, though most of these subjects (i.e., Stage 1 or 2) are likely to have below normal DHEA(S) levels compared to age-matched individuals with healthy HPA axis function. DHEA(S) levels that are higher in the morning than at bedtime (if reported) is a good sign that there is limited stress-induced depletion of zona reticularis function.

Diagnostic and Therapeutic Strategies:
• Help identify avoidable perceived job/life stressors.
• Ask about normal sleep time, duration, and quality, advise where appropriate.
• Consider general HPA axis nutrient support for elevated-cortisol.
  ° Glycemic-supporting nutrients
  ° Vitamin/mineral support
  ° Adaptogens (consider avoiding licorice root - see page 130)
  ° Additional phosphotidylserine (PS) may improve feedback inhibition
  ° Consider supplementing DHEA only if DHEA(S) measures are low (see page 120)
Assessing the status or function of an individual’s HPA axis (e.g., by measuring their cortisol and DHEA(S) levels) is not the same thing as identifying those unique stressors that have contributed to that status or function. Thankfully, while there are hundreds of internal and external signals that affect the HPA axis, most modifiable stressors can be collected into just a few simple categories. Direct homeostatic signals, such as circadian disruption, glycemic dysregulation and inflammatory signals, and those that are anticipatory and filtered through the higher orders of the brain, what we will call perceived stress. 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 the greatest improvement in the stress response system and, ultimately, help to rebuild metabolic reserves and slow chronic disease progression.

**Figure 25: Modifiable Categories of HPA Axis Stressors.** This diagram shows four of the most important modifiable HPA axis stressors, depicting both the initiating signal (outermost list of signals) as well as intermediate signals that trigger the stress response in the hypothalamus. Note that in the perceived stress quadrant, the initiating signals are mostly filtered through neuronal pathways that are impacted by neurotransmitter, neurosteroid, endocannabinoid, and glucocorticoid signaling. Unlike the filtered responses that drive the anticipatory nature of the perceived stress response, the other three categories of signals have a more direct effect on the stress response, to quickly respond to homeostatic challenges (see inset above).
Glycemic Dysregulation

The stress response system is designed to release energy stores, making them available for important life-saving functions. Clinicians 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, choose diets designed to limit their glycemic impact, and maintain 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 85).

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 the purpose of increasing 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 87).

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 disturbances that are regulated by cortisol signaling or HPA axis function (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 a depleted 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 powerful “therapies” available for reducing HPA axis dysfunction (see page 88). Choosing to eat in a way that reinforces this circadian rhythm, will further benefit the patient.

Perceived Stress

The HPA axis is easily triggered by non-physical signals from outside the body, events which the brain perceives as threatening to our current status in some way. We call these psychosocial events “perceived” stressors because their ability to affect HPA axis function is 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. As we will explore further in this section, the cascade of signals that consolidate the threats from our surroundings is a complex neurocircuitry that includes various interpreting centers of the brain (primarily signaling through classic GABA and glutamate receptors). These signals are then influenced further by signals derived from neurotransmitters, neurosteroids, catecholamines, endocannabinoids, and glucocorticoids. The signals that drive perceived stress are intended to allow the brain to anticipate a stressful situation, allowing for the upregulation of metabolic processes that may be needed to resolve or survive the event (even if it does not actually require a metabolic response to resolve).
The Role of Stress and the HPA Axis in Chronic Disease Management

Point Institute

**Interplay Between the Endocannabinoid System and HPA Axis**

The endocannabinoid system (ECS) is a neuromodulating system ubiquitously present in the human body which helps regulate a variety of physiological systems such as stress, inflammation, pain, and memory. Generally, the ECS consists of four coordinated components: endogenous ligands (i.e., endocannabinoids), the enzymes that synthesize and degrade cannabinoids, cannabinoid receptors, and a cellular transport network. In addition to these four putative components, there are several other receptors and endogenous compounds, along with the well-known exogenous phyto cannabinoids, that influence physiological function through the ECS. Ironically, the phytochemical delta-9-tetrahydrocannabinol (THC) was isolated and identified as the main psychoactive component of *Cannabis sativa* L. (marijuana) in 1964, nearly three decades before scientists discovered the endocannabinoid system, cannabinoid receptors, or their endogenous ligands.

In many ways, there are two overlapping endocannabinoid systems, roughly based on the differential expression of the two main cannabinoid receptors. The cannabinoid receptor type 1 (CB1R) is primarily expressed in the nervous system, where they mediate retrograde inhibition of neurotransmitter release; whereas the cannabinoid receptor type 2 (CB2R) is mainly expressed in immune cells, where they modulate cytokine release and cell migration. Here, we will primarily focus on CB1R-mediated central nervous system effects and the broad interconnected relationship between the endocannabinoid system and the stress response system. Reviews detailing many of the other peripheral actions of endocannabinoids (e.g., cardiovascular system, GI, liver, immune, muscular, bone, reproductive systems, skin, etc.) are readily available, and new reviews are published frequently.

**Components of the Endocannabinoid System**

**Endogenous Endocannabinoid Ligands**

The two putative endogenous lipid-derived ligands are anandamide (N-arachidonylethanolamine or AEA), a name derived from the Sanskrit word *ananda* meaning “bliss”, and 2-arachidonoylglycerol (2-AG). Unlike pre-formed neurotransmitters, both AEA and 2-AG are synthesized on demand from membrane phospholipids upon cellular activation; and, similar to other lipid modulators, they can also be synthesized and catabolized by multiple pathways.

Both AEA and 2-AG are members of two large lipid families, N-acyl-ethanolamines (NAEs) and 2-acylglycerols (2-AcGs), respectively. As such, other related lipids (i.e., AEA/2-AG congeners) may be considered as part of an expanded representation of the endocannabinoid system—the endocannabinoidome. These congeners signal through non-canonical receptors (e.g., PPARα, GPR55/110/119, TRPV1) to exert biological effects that may overlap or function distinctively from the endogenous ligands, AEA, and 2-AG. Some examples of these congeners include NAE members N-palmitoylethanolamine (PEA), N-oleoyl-ethanolamine (OEA), N-linoleoyl-ethanolamine (LEA), N-stearoylethanolamine (SEA), N-docosahexaenoyl ethanolamine (“DHEA”) and 2-AcG members 2-oleoylglycerol (2-OG), 2-linoleoyl glycerol (2-LG), and 2-palmitoyl glycerol (2-PG).

Both AEA and 2-AG act as endogenous agonists at CB1R; however, 2-AG has a lower affinity but higher efficacy relative to AEA, reflecting that 2-AG functions as a full agonist, whereas AEA functions as a partial agonist at CB1R. Comparatively, 2-AG functions as a full agonist at CB2R, whereas AEA, due to its low efficacy, operates as a weak partial agonist at CB2R.

† In this instance, affinity reflects the ability of the endocannabinoid to form a bound complex with the receptor, whereas efficacy reflects the ability of the endocannabinoid to induce signaling via the receptor.
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 summarizes some basic protocols that can be used in most patients with HPA axis dysfunctions giving nuanced applications based on measured cortisol levels. This is 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 nonpharmacological options available to the clinician.
The Relationship Between Stress and Memory

There is a complex bidirectional relationship between the HPA axis and memory. On the one hand, since the HPA axis is tasked with assessing threatening events and environments, the ability to recall past events is a critical tool for evaluating the potential threat of an ongoing (or upcoming) event. Conversely, the ability to acquire, consolidate and recall memories is dependent on neural plasticity and signaling; functions that are affected by acute and chronic stress. It is no surprise, then, that acute stressors and the HPA adaptations to chronic stress can negatively affect short-term, working or long-term memory. In this chapter we summarize the research that explores the relationship between stress and memory, including the special research models used to investigate this relationship, the mechanisms thought to drive these outcomes, the typical presentation of those affected by stress-induced memory dysfunctions, and potential therapeutic options to mitigate these effects. First, however, we need to review the various categories and stages of memory before describing how the stress response influences memory function.

**Figure 33: The Categories of Human Memory.** Human memory is generally subdivided into different categories which include sensory memory, short-term memory, working memory and long-term memory. Long-term memory can be further divided into declarative and non-declarative memories, each of which is further subdivided into different memory types. See text for more details.
Non-declarative, or implicit memories, on the other hand, are unconscious memories for skills, habits, or behaviors. These types of memories are further classified as procedural, priming, conditioning, and non-associative learning. Unlike declarative memories, which can be remembered and retold, implicit memories are expressed through performance or behavior. For example, procedural memory involves learning a skill that is difficult to explain using words, such as learning to ride a bicycle. Priming is defined as an improvement or modification of an individual’s ability to identify, produce, or classify a given stimulus due to a previous encounter with that stimulus. Individuals are exposed to the effects of priming almost every day from advertisements. For instance, if a child sees a commercial for a new ice cream treat just before eating lunch, he or she may be more likely to request ice cream for dessert even after forgetting about the commercial. Non-declarative memories categorized as non-associative describe habituation and sensitization. Habituation occurs when one’s response declines after a stimulus has been presented multiple times. Meanwhile, sensitization occurs when a response is magnified after the repetition of a stimulus.

**Phases of Human Memory**

Now that we have defined the categories of memory, we must briefly describe the processes by which humans store vast amounts of information with the expectation of retrieving that information in the future. In other words, how are short-term memories converted into long-term memories (coincidentally or intentionally) and what affects our ability to recall them on demand? Researchers in memory science defines three basic phases of this process: encoding, storage, and retrieval (see Figure 34). The encoding process is critically important, as it involves both the acquisition and consolidation of the memory, including how that memory will be stored (e.g., will the name of this new acquaintance be stored based on how the person looks, how their name sounds, alphabetically, or some other association?). Following memory acquisition, STMs can undergo memory consolidation where temporary synaptic changes become permanent in the form of LTM.

**Encoding New Memories**

Encoding new memories requires physical changes within the brain in which neurons begin to rewire themselves. Experiences become memories as they become embedded within the brain as synaptic changes to the neural network. These changes are dependent on a process known as synaptic plasticity, a process that can be exploited through learning techniques and training. For example, if a student is preparing for an upcoming exam where it is expected that definitions of remembered words will be required, he or she may attempt to “memorize”...
As most clinicians know, there is complex interrelationship between the stress response controlled by the HPA axis and thyroid-related functions. Since thyroid hormone is needed for normal development and for regulating metabolism in the adult, some suggest that the HPT axis is necessarily down-regulated during stress to conserve energy resources for immediate survival. In this section we provide an overview of how the HPA axis influences thyroid function, as well as the downstream actions of thyroid hormone metabolism. We also discuss how specific stressors with known influences on the HPA axis can affect the HPT axis and thyroid hormone signaling.

Basics of the HPT Axis

The signaling cascade within the hypothalamic-pituitary-thyroid (HPT) axis is quite similar to that of the HPA axis (see Figure 36). Metabolic signals consolidated in the paraventricular nucleus (PVN) of the hypothalamus result in the release of thyrotropin-releasing hormone (TRH), which then stimulates thyrotropin cells within the anterior pituitary gland to produce and release thyroid-stimulating hormone (TSH) into the bloodstream. TSH, in turn, binds to G-protein coupled receptors (i.e., TSH-R) on thyroid follicular cells, which triggers a cascade of metabolic signals that results in the production and secretion of thyroid hormone(s) (TH).

There are several different thyroid hormones, differentiated by the number and location of their attached iodine molecules. Thyroxine (tetraiodothyronine, T4) and 3,5,3’-triiodothyronine (T3) are the primary hormones in circulation. T4 (a relatively inactive hormone) makes up greater than 80% of the hormone secretion of the thyroid gland, while the more active T3 makes up less than 20%; both are bound to transporter proteins, such as thyroxine-binding globulin (TBG), allowing less than 1% of each to be “free.” Conversion of T4 to T3 is accomplished by deiodinase enzymes expressed in the thyroid and, more importantly, in most tissues in the body. The expression of T4 to T3 is accomplished by deiodinase enzymes expressed in the thyroid and, more importantly, in most tissues in the body.

Figure 36: Regulation of the Hypothalamus-Pituitary-Thyroid Axis. Similar to the HPA axis, the HPT axis is regulated by a negative feedback loop beginning in the hypothalamus. Thyrotropin-releasing hormone (TRH) is produced in the paraventricular nucleus (PVN) of the hypothalamus in response to signals (e.g., food intake, cold stress, leptin); TRH is also regulated by circadian rhythmicity. TRH is secreted into the median eminence and transported to the pituitary where it stimulates thyrotrophs to synthesize TSH in the anterior pituitary gland. TSH is also under circadian regulation. TSH binds to the TSH receptor on the thyroid, stimulating the production of thyroid hormones. The thyroid gland predominantly produces T4 and to a lesser extent produces the active T3 hormone. Most T3 is produced in peripheral tissues from the deiodination of T4. A deiodination reaction may also occur which produces the inactive rT3 metabolite from T4. Thyroid hormones (T4 and T3) regulate the synthesis and release of TRH and TSH at the level of the hypothalamus and the pituitary gland via thyroid hormone receptors. (TRH-thyrotropin releasing hormone, TSH-thyroid stimulating hormone, D1, D2, D3-deiodinase enzymes 1, 2, 3).
A Balanced and Evidence-Based Approach

Research over the past few decades has greatly increased our understanding of the role that the HPA axis plays in regulating stress, metabolic, and circadian functions; and how acute and chronic stressors result in predictable patterns of dysfunction. Unfortunately, much of that knowledge is either unknown or unleveraged within most healthcare settings today. While clinicians trained in integrative and functional medicine paradigms are often more aware of these relationships, they are often still using out-of-date nomenclature or oversimplified explanations for stress-related dysfunctions.

The Role of Stress and the HPA Axis in Chronic Disease Management—Second Edition is designed to bridge the gap between the growing clinical research in the area of stress-induced HPA axis dysfunction and the growing clinical burden of diagnosing and treating subjects with stress-related chronic disease patterns. Thoughtfully written and richly illustrated, this Road map is intended as a teaching tool and reference guide for all health professionals interested in alleviating the heavy burden of those experiencing stress or its consequences. This second edition expands upon the ground-breaking work of our first edition, and is updated to include the latest references and relevant information for clinical decision-making.

This Road map 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 Journalists and Writers
- Students of Health Professions
- Manufacturers/Distributors of Food and Dietary Supplements

About the Author:

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 use of nutritional supplements. As the Vice President of Scientific Affairs at Ortho Molecular Products for 24 years, he has worked with thousands of integrative and functional medicine clinicians, and 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 an Adjunct Asst. Professor, and at the University of Minnesota School of Pharmacy. 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