Role of Stress and HPA Axis in Chronic Disease Management

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What we will discuss today

• How to identify the key drivers of the Stress Response System
• How changes to adrenal hormones come from functional changes outside the adrenal gland
• The relationship between the gut and the brain
• The effects of stress and HPA Dysfunction on Immune System surveillance and the connection with cancer
• The effects of stress and HPA Dysfunction on neurotransmitters and mental health
• The effects of stress and HPA Dysfunction on other endocrine glands
• The correct use and interpretation of lab testing
• Effective treatment strategies for common conditions like Depression, Post Traumatic Stress Disorder, Chronic Fatigue, Fibromyalgia, Auto-Immune conditions, IBS
Stress

• **Short-term** it can lead to a wide variety of symptoms such as muscle tension, fatigue, gastrointestinal symptoms, headaches and insomnia.

• **Long-term** chronic stress can have major health consequences, and adversely affect our cardiovascular, immune, neuroendocrine and central nervous systems.

• **Untreated** chronic stress can result in serious health conditions including high blood pressure, heart disease, anxiety, insomnia, depression, weak immune system.
Recent Reported Studies

• ‘Quake brains’ of Cantabarians shows up to 15% decrease in cognitive functioning in a maze test.

• Recently published research in the journal *Health Psychology* states individuals with small social networks may be socially isolated but not necessarily lonely. Likewise, lonely people can have large social networks as loneliness relies on the perception of the quality of one’s social relationships.

• Research has found that those who said they were lonely, suffered with the most severe symptoms of cold, including chills, runny nose, sore throat and headaches.

• Previous research has shown that different psychosocial factors like feeling rejected or left out, and not having strong social bonds make people feel worse physically, mentally and emotionally, and they are more likely to die early or develop heart disease.
Selye’s Contribution

General Adaptation Syndrome (G.A.S)

- Resistance Stage: Body or individual adapts to the stress or stressors. Increased resistance occurs. Alarm reactions disappear.
- Exhaustion Stage: Long-term stress wears down body’s resistance. Adaptation energy is exhausted. Alarm reaction signs reappear. Individual can eventually die.

Diagram showing phases of the General Adaptation Syndrome.
Selye and the Pathophysiology of Stress

Control | “Stress”
---|---

Hypertrophy of Adrenal Gland (HPA)

Atrophy of the thymus and other lymphatic glands (Immune system)

Erosions and ulcers in the duodenum (GI-system)
“Stress is essentially reflected by the rate of all the wear and tear caused by life. ... 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.”
Popular Language for Stress
When did “Stress” become “Adrenals”
Is it Adrenal Fatigue?

According to the Hormone Foundation/Endocrine Society:

“Adrenal fatigue” is not a real medical condition. There are no scientific facts to support the theory that long-term mental, emotional or physical stress drains the adrenal glands and causes many common symptoms. There is no test that can detect adrenal fatigue. Supplements and vitamins made to “treat” adrenal fatigue may not be safe. Taking these supplements when you don’t need them can cause your adrenal glands to stop working and may put your life in danger.”

“Doctors urge you not to waste precious time accepting an unproven diagnosis such as “adrenal fatigue” if you feel tired, weak, or depressed.”
• Primary Adrenal insufficiency is real (though uncommon) and is not a stress-related chronic disease phenomenon.

• Stress-Related changes in adrenal hormone output are regulated by HPA axis- adaptations primarily in the brain, and are not caused by “fatigue” or the inability to produce hormones by the adrenal gland.

Nomenclature matters!
The Adrenals Respond to the Brain

(Feedback inhibition alters cortisol output)

A variety of “Stress” signals from outside the hypothalamus, along with feedback signals of cortisol at the HP, determine the ACTH signal and subsequent adrenal cortisol output.
Is the Endocrine Society right?

Well sort of.....

• The term “Adrenal Fatigue” does not properly describe the stress response that leads to changes in adrenal hormone output or a sense of “fatigue”

So we should stop using this terminology

• But, they are incorrect in their assertions that long term stress has no affect on adrenal hormone output, or that no test is capable of assessing the effects of stress on human physiology.

So we need to re-think how we discuss ‘adrenals’ and… start using different terminology
The HPA axis
Physiological Resilience

• It is the immediate capacity of the cell/tissue and organ to respond to changes in physiological need.

Metabolic Reserve

• Long-term capacity of tissues and organ systems to withstand ongoing and repeated challenges to physiological needs.
Physiological Resilience and Metabolic Reserve

• Capacity of each cell/organ to withstand necessary changes that create the rhythm of a healthy organism.

• When inappropriate or overwhelming signals begin to overpower physiological resistance, the stretching of that system does not resolve immediately and leads to long term chronic dysfunction and disease.
Chronic Stress Depletes Metabolic Reserve

• The stress response system allocates resources and changing metabolic function to allow the best chance of survival for the immediate future.

• This is often at the cost of reducing the organism’s buffer against long term metabolic dysfunction.

• This leads to depletion of essential nutrients.

• This reserve capacity is vulnerable to depletion but managed by being resupplied and strengthened.
Stress Response and Daily Functions

Just like emergency vehicles need to use the same roads used for non-emergency functions, the stress response system uses the same organs, cells, metabolites and signaling mechanisms that the body uses to maintain non-stress metabolic functions.
What is the Correct Terminology?

• Most appropriate overall term:
  
  • HPA Axis Dysfunction
  • Maladaptation to Stress or Stress-response dysfunction, Adaptation to Stress……with consequences.

• Specific Terms (where appropriate)
  
  • Hypocortisolism/Hypercortisolism
  • Low DHEA or DHEA-S
  • High Allostatic Load, or Burnout (properly defined)
Newer Stress Nomenclature: Allostatic Load

The metabolic cost of re-establishing physiological integrity after a stressor

Stress

- **Allostasis** - the ability to achieve stability through change — is critical to survival.

- Stress system - protect the body by responding to internal and external stress.
  - Autonomic nervous system
  - Hypothalamic–pituitary–adrenal (HPA) axis
  - Cardiovascular and metabolic systems
  - Immune systems

- **Allostatic load** - the price of accommodation to stress, (wear and tear) that results from chronic overactivity or underactivity of allostatic systems.

The ‘goal‘ of the stress response

- Maintain effective blood supply (O$_2$/nutrition) to brain, heart, skeletal muscle for immediate survival.
- Increase energy production by recruiting substrates (glucose, FA, AA) from body stores and enhance gluconeogenesis.
- Optimize ATP production for vital short-term needs at the expense of long-term metabolic functions.
- Achieving Physiological Reliance at the Expense of Metabolic Reserve. (akin to Ames’ Triage theory).
Some disorders associated with the stress-response system

**Increased activity of the HPA axis**

- Cushing 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 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 syndrome cure
- Following chronic stress
- Postpartum period
- Adult post-traumatic stress disorder
- Hypothyroidism
- Rheumatoid arthritis
- Asthma, eczema

_Nat Rev Endocrinol_ doi:10.1038/nrendo.2009.106
Stress Response System

**Sympatho-Adrenomedulinary System**
- Hypothalamus
  - Nerve impulses
  - Spinal cord
  - Adrenal medulla
  - Catecholamines (epinephrine and norepinephrine)

**The HPA Axis**
- CRH (corticotropin releasing hormone)
- Corticotroph cells of Anterior pituitary
  - ACTH
  - Adrenal cortex
  - Mineralocorticoids
  - Glucocorticoids
  - DHEA(S)

**Short-term Stress Response**
- Increased heart rate
- Increased blood pressure
- Liver converts glycogen to glucose and releases glucose to blood
- Dilation of bronchioles
- Changes in blood flow patterns leading to increased alertness, decreased digestive system activity, and reduced urine output
- Increased metabolic rate

**Long-term Stress Response**
- Retention of sodium and water by kidneys
- Increased blood volume and blood pressure
- Gluconeogenesis
- Insulin Sensitivity
- GH ↓ T3
- Immune/Inflammatory Response
- Fat & Protein Mobilization
Sympathoadrenal System
HPA axis
The Pituitary Controlling HPA Signals

- Relay station that converts neuroendocrine outputs from the hypothalamus into hormone signals from other endocrine organs.

- As person ages the signaling and endocrine functions within the pituitary are altered.

- Stress affects all endocrine functions with HPA dysfunction, leading to thyroid dysfunction, reproductive cycle dysfunction and pigmentation issues of skin.
Adrenal Gland

Note: There is no ‘pregnenolone steal’
Expression of angiotensin-2 receptors allows synthesis of aldosterone, ↓ RAAS

Expresses ACTH receptor
Hormones and Adrenal Medula

• Extension of CNS secretes two important catecholamines, epinephrine and norepinephrine.

• Acetyicholine from sympathetic neurons trigger a release of epinephrine and norepinephrine almost instantaneously upon encountering a stressor (10 minutes prior to HPA axis cortisol response).

• Biosynthesis of NE from tyrosine occurs like other adrenergic neurons like LC/NE (via tyrosine hydroxylase and dopamine decarboxylase).

• Adrenal medula expresses uniquely PNMT enzyme to allow production of epinephrine (80% E and 20% NE).

• Half life is only a few minutes till degraded by methylation via COMT or deamination by MAO.
Cortisol Signalling
Free cortisol

5α-reductase

5α-tetrahydrocortisol (5α-THF)

5β-reductase

5β-tetrahydrocortisol (5β-THF)

11β-HSD 1

Free cortisone

11β-HSD 2

5β-tetrahydrocortisol (5β-THF)

Tetrahydrocortisone (THE)
The HPA Axis and Stress Response System

Hypothalamus

CRH/AVP

Negative Feedback Loop

ACTH

Target Cell

Cortisol Receptor

11β-HSD2

GRE

Cortisone

Sympathetic Adrenomedullary System

LC/NE

Cortex

Medulla

DHEA

Cortisol-Induced Response

↑ Gluconeogenesis
↓ Insulin Sensitivity
↓ GH, T3
↓ Immune/Inflammatory Response
↑ Fat & Protein Mobilization

HPA Axis

↑ Norepinephrine
↑ Epinephrine

Fight or Flight Response
What makes the brain stressed?

Adapted from: Guilliams TG, The Role of Stress and the HPA Axis in Chronic Disease Management- 2015
HPA axis + Circadian Control

• HPA axis is intermittently tied with controlling circadian rhythm that are entrained by light and dark cycles of day and night.

• Lifestyle choices or needs result in HPA axis dysfunction, leading to metabolic dysfunctions like IR, obesity and neurotransmitter dysregulation.

• Good sleep of 7.5 hours is the greatest ‘reset button’ of the HPA axis.
Dysglycemia + HPA axis

- One of the main functions of HPA axis is glucose regulation, insulin sensitivity and overall energy balance.

- Hypoglycaemia is a potent HPA axis activation.

- Most chronic stressors operate at low levels and go unrecognised by the patient.
Obesity

• Aggressive weight loss is an HPA axis stressor. *(Int J. Obesity* 2012)

*Increased visceral adipose tissue is caused by increased cortisol and insulin*

*Stress inducing inflammatory mediators*
Hippocampus + Metabolic Function + HPA axis

• Hypothalamus is very sensitive to falling ghrelin levels as main source of energy.

• Chronic hyperinsulinemia as in obesity/MS leads to impairment in glucose sensing by the hypothalamus, leading to further underrated metabolic dysfunction.
Inflammation

There is a strong relationship between HPA axis and inflammatory signalling.

**HPA axis**
- Increase cortisol
- Decrease immune function

**Inflammation**
- Increased inflammatory cytokines when chronic, like IL6, IL1 beta, TNF-alpha

**Negative**

**Positive**
Inflammation + HPA axis

- Inflammation anywhere is a HPA stressor.

- Can be from GI tract (food allergies or IBD (leaky gut)/dysbiosis).

- Inflammatory condition Rh diseases.

- Chronic low level inflammation (obesity, cardiometabolic).

- Chronic infection (sinusitis, fungal etc).

- Toxin load creating autoimmune reactions.
HPA axis + Gastrointestinal System

• ‘A troubled intestine can send signals to the brain, just as a troubled brain can send signals to the gut. Hence a person’s gut distress can be the cause or the product of anxiety, stress or depression. They are intermittently connected and for all practical purposes they should be viewed as one system.’
Stress + Gastrointestinal System

• Alterations in gastrointestinal irritability.

• Increase in visceral perception.

• Changes in gastrointestinal secretion.

• Negative effect on GI mucosa blood flow and repair, and increase in IB.

• Negative effect on intestinal flora, neurotransmitter (95% serotonin produced in gut) and cytokine levels.
Cortisol and the Hippocampus

- Repeated stress affects brain function, especially hippocampus.
- High concentrations of cortisol and NMDA receptors.
- Participates in verbal memory and memory context.
- Impairment decreases the reliability and accuracy of contextual memories.
- Damage may exacerbate stress by preventing access to the information needed to decide that a situation is not a threat.
- Regulates the stress response and acts to inhibit the response of the HPA axis to stress.

Cortisol and the Hippocampus

• Hippocampus alterations in both structure and function have been identified in long term stress.

• Volume loss demonstrated in PTSD, Depression, Cushing’s syndrome.

• Functional changes include reduction in hippocampal excitability, long-term potentiation and memory.
Neurotransmitters, Mood and Stress

• The perception of an event must first be translated into neurochemical signals before they trigger HPA axis.

• This is dependent on signaling from neurotransmitters.

• Neurotransmitters that manage mood and effect, overlap with measures of HPA axis activation.

• The symptoms of HPA dysfunction caused by stress include feeling of loss of control, burn out, withdrawal, excessive worry, along with anxiety and depression.
• Elevated activity of HPA activity during depression is a reliable finding of biological psychiatry.

• High cortisol levels are seen in patients with severe depression symptoms.

• The HPA hyper activity in depressed patients is caused by impairment of the negative feedback inhibition, which is less sensitive in elevated cortisol secretion.

Depression and HPA Activation

• Research currently is focused on the function and polymorphisms of the glucocorticoid receptor (GR) within the hippocampus, medulla and hypothalamus.

• Changes to GR function results in a form of glucocorticoid resistance within the neurons, leading to hyper active HPA axis and a blunted feedback inhibition.

• This is also evident with less inhibition noted in dexamethasone suppression test.

• Increased inflammatory signaling can also drive the depression/HPA axis activation with GR resistance in certain immune cells.

Sher L, Combined dexamethasone suppression-corticotropin-releasing hormone stimulation test in studies of depression, alcoholism and suicidal behavior, Oct 2006, Scientific World Journal
Stress, Depression, Immune System & Cancer

- Both stresses and depression are associated with decreased cytotoxic T cell and natural killer cell activities that affect processes such as immune surveillance of tumours and with the events that modulate development and accumulation of somatic mutations and genetic instability.

*Lancet Oncology* 2004
A new view on hypocortisolism

Eva Fries, Judith Hesse, Juliane Hellhammer, Dirk H. Hellhammer*

Department for Psychobiology, University of Trier, Johanniterufer 15, 54290 Trier, Germany

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KEYWORDS
Hypocortisolism; Cortisol; Allostatic load index;

Summary Low cortisol levels have been observed in patients with different stress-related disorders such as chronic fatigue syndrome, fibromyalgia, and post-traumatic stress disorder. Data suggest that these disorders are characterized by a symptom triad of enhanced stress sensitivity, pain, and fatigue. This overview will may be beneficial for health and survival. Most strikingly, the demonstration of a low allostatic load index in hypocortisolemic subjects suggests that a down-regulation of the HPA axis in chronically stressed subjects protects those subjects against the harmful effects of a high allostatic load index.
Hypocortisolism may be an adaptive mechanism to liberate the immune system or protect the nervous system.
**Advanced Adrenal Assessment**

**Ordering physician:**  
Research Only  

**DOB:** 1976-01-01  
**Gender:** Female

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<th>Category</th>
<th>Test</th>
<th>Result</th>
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<th>Normal Range</th>
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<td>18.0</td>
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Other allied investigations

• These are to determine the causes of allostatic load, and can include: complete blood count, CRP, ANA, celiac screen, blood sugar and lipids, screen for possible chronic infections.

• Relevant hormone testing, functional tests like food allergies, stool analysis.

• Assessment of heavy metals and other toxins, oxidative markers, and others as needed.
I think it's stress!!
Management

• The ultimate goal is to discover the route cause of the imbalance related to the stress response and to regain physiological balance, while slowly reversing the chronic manifestations caused by stress.
Case Study Discussion
Strategies for Supporting HPA Axis Function

**CNS Support**

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

- **Balance Neurotransmitters/Neurosteroids**
  - Consider Supplementation Precursors and Cofactors for Neurotransmitter Synthesis
  - Consider Supplemental DHEA & Progesterone

- **Balance Cortisol Feedback Mechanisms**
  - Consider Phosphatidyl Serine
  - Consider Adaptogens

**Adrenal Support**

- **Protect Zone Reticularis**
  - Antioxidants
  - Adaptogens (?)

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

**Target-tissue Cortisol Modulation**

1. **11β-HSD1 Activity**
   - Reduce Inflammation
   - Reduce Insulin Resistance/Insulin
   - Reduce Central Adiposity
   - Consider Physical Activity (not intense)

2. **HSP Modulation of GR**
   - Consider Adaptogens
   - Consider Physical Activity (not intense)

3. **DHEA’s Anti-Glucocorticoid Activity**
   - Consider Suplemental DHEA
Maintain appropriate hypothalamus response to stressors

• **Improve Glycemic Control**
  - MediRestore - Research Nutrition
  - Berberine-500 - Thorne Research
  - GlucoFunction - Pure Encapsulations
  - UltraChrome-500 - Thorne Research

• **Decrease Inflammatory Signalling**
  - Boswelya Plus - Ayush
  - Curcutex - Research Nutrition
  - CytoQuel - Researched Nutritionals
  - ProOmega 2000 - Nordic Naturals

• **Increase Circadian Signalling**
  - 5HTP-CR - Xymogen
  - AyuPhos – Ayush Herbs
  - L-Tyrosine – Thorne Research
  - Magnesium Glycinate - Pure Encapsulations
  - Sleep & Relax - GAIA Herbs
Balance Neurotransmitters/Neurosteroids
- Consider supplementing precursors and cofactors for neurotransmitter synthesis
  - 5HTP-CR - Xymogen
  - Double Strength Zinc Picolinate - Thorne Research
  - L-5MTHF – Research Nutrition
  - L-Tyrosine – Thorne Research
  - Magnesium Glycinate - Pure Encapsulations
  - Methyl Fortify - Research Nutrition

Balance Cortisol Feedback Mechanisms
- Consider phosphatidyl serine and adaptogen’s
  - Ashwagandha – Ayush Herbs
  - Ayu-Phos – Ayush Herbs
  - Cortisol Calm - Pure Encapsulations
  - L-theanine - Xymogen
Protect Zone Reticularis

- Antioxidants and adaptogen’s
  - α-Drenal - RLC Labs
  - CytoQuel - Researched Nutritionals

Nutrient support for adrenal steroidogenesis

- α-Drenal - RLC Labs
- C-RLA – Liposomal Vitamin C - Researched Nutritionals
- Double Strength Zinc Picolinate - Thorne Research
- Magnesium Glycinate - Pure Encapsulations
- Niacinamide B3 - Research Nutrition
- Stress B-Complex – Thorne Research
• Reduce inflammation
• Reduce insulin resistance
• Consider adaptogens

Products as listed earlier
The art of medicine consists of amusing the patient while nature cures the disease

~ Voltaire, 18th Century
Thank you! Any questions?