KRESSER INSTITUTE
FOR FUNCTIONAL AND EVOLUTIONARY MEDICINE

What is HPA Axis Dysregulation?

HPA axis dysregulation (HPA-D) is the scientific term for the popular syndrome known as "adrenal fatigue." It refers to a constellation of signs and symptoms including fatigue, sleep disruption, poor exercise tolerance and recovery, low libido, brain fog, weakened immune function, and reduced stress tolerance. HPA axis dysregulation is caused by many different aspects of the modern lifestyle, including poor diet, sleep deprivation, chronic stress, lack of (or too much) exercise, and inflammation. HPA axis dysregulation affects nearly every cell and tissue in the body. For this reason, it must be addressed in virtually all cases of chronic illness in order for healing to occur.

There are four primary triggers of HPA axis dysregulation, listed below.

Four Triggers of HPA Axis Dysregulation

1. **Perceived Stress.** There are four key determinants that determine the magnitude of HPA response. NUTS is an often-used mnemonic for this.
    a. **Novelty** of the event
    b. **Unpredictable** nature of the event.
    c. Perceived **threat** to body or ego
    d. **Sense** of loss of control
        i. Things like finances, relationships, work, public speaking, and internal stress perception caused by neuronal imbalances.
        ii. Generally, psychological stress is more harmful because there is less sense of control and it lasts much longer.
2. **Circadian Disruption**. The HPA axis and circadian rhythm are intertwined and have the ability to profoundly impact one another.
    a. Sleep deprivation, artificial light exposure, nighttime light exposure, getting too little exposure to natural light during the day, jet lag, shift work, and caffeine.
3. **Glycemic Dysregulation**. There's a bidirectional relationship between the HPA axis and metabolic functions, so a disruption of one will harm the other.
    a. Poor diet, lack of sleep, and lack of exercise.
    b. Visceral fat is caused by elevated cortisol,which in turn triggers inflammatory mediators.
    c. Hypoglycemia leads to HPA axis activation, so impaired glucose sensing can also cause increased cortisol.
4. **Inflammation**. Cortisol is a powerful anti-inflammatory agent, so acute or chronic inflammation triggers the HPA axis and increases cortisol.

Specific examples

Trigger	Effect
Exercise	Overtraining initially increases cortisol but may then cause chronically low cortisol. Being sedentary can lead to sleep disorders and contribute to metabolic dysfunction.
Social Isolation	Social support mitigates the impact of stress. Lack of social support is a major stressor and has been shown to reduce lifespan.
Gut Issues	Multiple Gut-HPA interactions: Intestinal permeability, often caused by stress, can lead to HPA activation. Beneficial bacteria play a role in regulating the HPA axis.
Food Intolerances	Induce intestinal permeability and may cause inflammation.
Chronic Infection	Increases inflammation.
Environmental Toxins	Wide range of effects, including endocrine disruption and oxidative stress.
Thyroid Function	Hypothyroidism increases cortisol levels.
Drugs (caffeine, antidepressants, steroids, etc.)	Dysregulate the axis in multiple ways.

Why Not “Adrenal Fatigue”?

The term “adrenal fatigue” is widely used by both clinicians and patients to refer to the syndrome that is scientifically known as HPA axis dysregulation. However, while “adrenal fatigue” is certainly less of a mouthful than HPA axis dysregulation, it is virtually absent from the scientific literature and poorly describes the range of dysfunction that occurs in this syndrome.

In cases of so-called “adrenal fatigue,” when total cortisol is measured, it is more likely to be high than low. Even when it is low, it’s rarely due to the adrenals being “fatigued” and unable to produce it. We now know that there are multiple brain and tissue-specific mechanisms for regulating cortisol production that have little to do with the adrenal glands themselves. Put more simply, HPA axis dysfunction is better understood as a problem in the brain and central nervous system than in the adrenal glands themselves.

This understanding leads us to a deeper appreciation of the complexity of HPA-D and the involvement of other mechanisms not typically considered under the “adrenal fatigue” umbrella, such as the role of inflammation and blood sugar dysregulation.