KRESSER INSTITUTE
FOR FUNCTIONAL AND EVOLUTIONARY MEDICINE

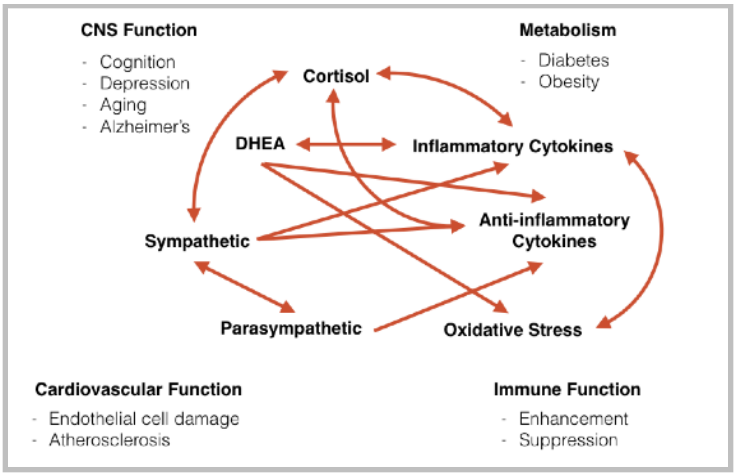
HPA-D Basic Physiology Review

To understand HPA axis dysfunction, you need to understand the stress response and its components. It is impossible to successfully treat a patient with a chronic disease without addressing stress-related dysfunction.

Allostasis is a term that refers to the process of adaptation to acute stress.

The factors that mediate allostasis are interconnected, as you can see below, which means that too much or too little of any mediator can disturb the entire network, leading to dysfunction and disease.

ALLOSTASIS: MAINTAINING STABILITY THROUGH CHANGE



For example, the sympathetic nervous system, which is involved in the fight-or-flight reaction, increases pro-inflammatory cytokines, whereas the parasympathetic nervous system response, rest and digest, decreases inflammatory cytokines. We need both of these systems in relative balance. When cytokine production exceeds the anti-inflammatory capacity of cortisol, we end up with chronic inflammation.

On the other hand, when cortisol suppresses inflammatory cytokines too much, then we have a weakened immune response, and we can see this in increased capacity to get colds and flus and possibly even things like cancer.

ALLOSTATIC LOAD:

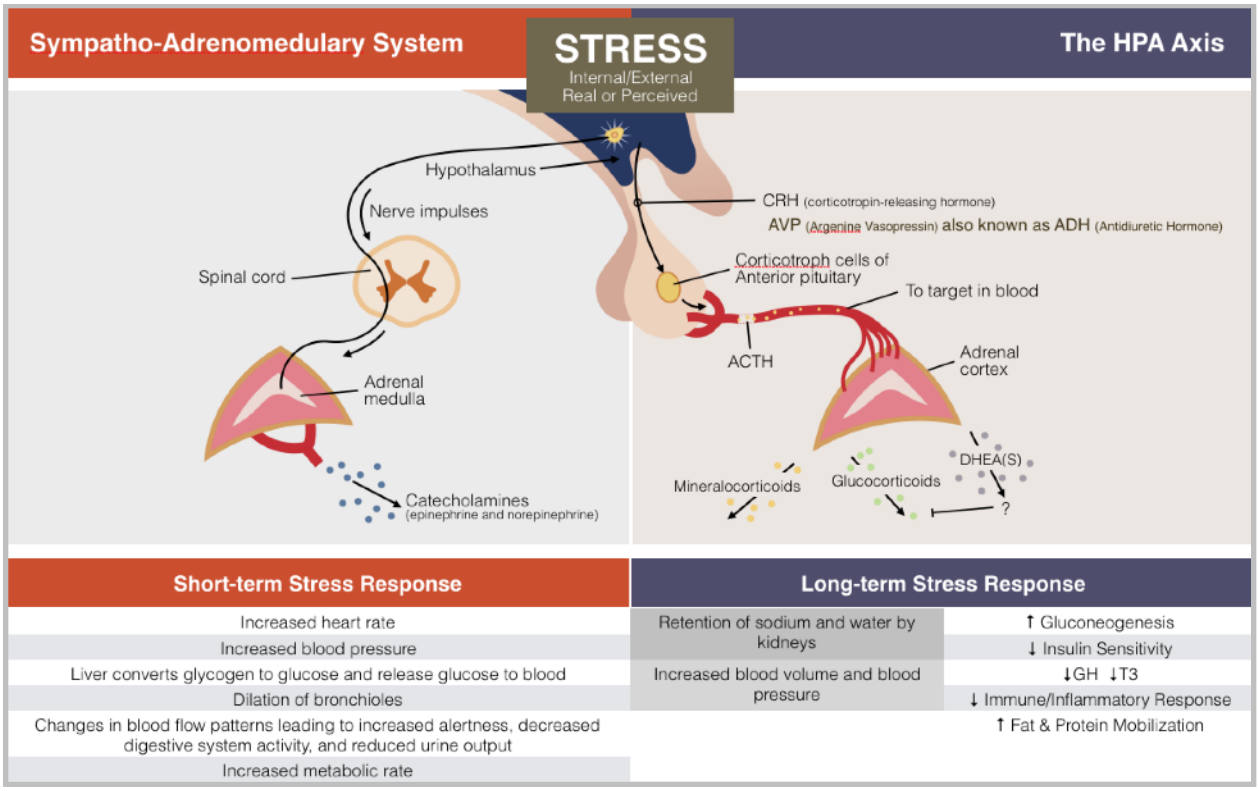
- Is the wear and tear produced by imbalances in the mediators of allostasis.
- In simpler terms, it represents either the presence of too much stress or the inefficient operation of the stress hormone response system
- Examples include hypertension, atherosclerosis, and diabetes, as well as stress-induced remodeling in the parts of the brain that support memory, executive function, and mood.

SOME OF THE PRESENTATIONS THAT CAN MANIFEST WITH ALLOSTATIC LOAD:

1. Normal stress response, where there is a stressor and the activity of the system goes up, and then a recovery period when the activity drops.
2. Prolonged response to stress, where the patient is under continual stress, and the system gets activated and stays activated over time.
3. In some people, this prolonged activity can progress into an inadequate response where they are unable to mount a sufficient response to future stressors.

REVIEW THE DIFFERENCE BETWEEN ALLOSTASIS AND ALLOSTATIC LOAD:

WHAT HAPPENS WHEN WE EXPERIENCE STRESS?



When the hypothalamus is triggered by a stressor, corticotropin-releasing hormone (CRH), which is also known as corticotropin-releasing factor (CRF), and another hormone called arginine vasopressin (AVP), which is also known as antidiuretic hormone (ADH), are released, and these travel down the pituitary and provoke the production of ACTH. They also activate noradrenergic neurons from the locus coeruleus norepinephrine (LC NE) system, not shown in the above diagram, in the brain. Noradrenergic neurons and the LC NE system are responsible for the immediate fight-or-flight response, and they create an almost instantaneous hypervigilant arousal state to allow the brain to respond really quickly to a threat.

The hypothalamus is the major control tower of all hormone production in the body and the governor of the stress response. Two hypothalamic nuclei with the biggest influence on the stress response system are the paraventricular nucleus (PVN) and the suprachiasmatic nucleus (SCN).

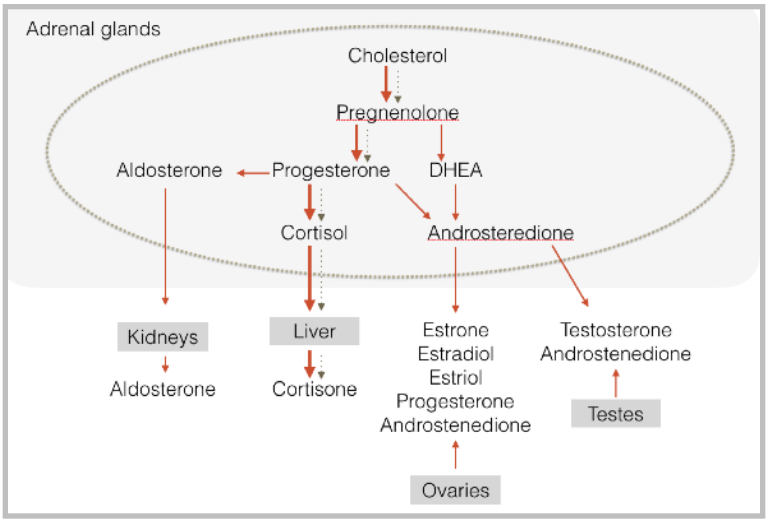
PVN:

- Releases corticotropin-releasing hormone and arginine vasopressin.

SCN:

- Main controller of the circadian clock.
- The circadian clock regulates a wide range of genes that implement things like insulin sensitivity, immune function, antioxidant activity, and pain sensitivity.

It was recently discovered that CRH is also produced outside of the hypothalamus in other areas of the brain but also in other tissues like the gut and the skin.



The adrenal glands produce steroid hormones as part of the stress response. Cortisol, DHEA, testosterone, progesterone, and estrogen are all steroid hormones with molecular structures similar to each other. The adrenals also produce DHEA and pregnenolone, which are known as pro-hormones. They function as hormones themselves, but they also act as precursors to downstream hormones such as cortisol and testosterone, seen in the diagram above.

The adrenal glands have two compartments, the adrenal medulla, which secretes epinephrine and is responsible for the fight-or-flight response, and then the adrenal cortex, which comprises 80 percent and produces glucocorticoids such as cortisol, mineralocorticoids such as aldosterone, and androgens such as DHEA. The adrenal cortex also produces some sex hormones in limited amounts.

PREGNENOLONE

- Pro-hormone made from cholesterol.
- Produced in the adrenals and the central nervous system (CNS).
- Precursor of progesterone, mineralocorticoids, glucocorticoids, androgens, and estrogens, as well as the neuroactive steroids.

- Pregnenolone naturally declines with age and has been proposed as a marker for age-related cognitive decline.

Pregenolone Actions
Protects the brain
Supports cognition, memory, and mood
Improves stress tolerance and well being
Boosts energy

DEHYDROEPIANDROSTERONE (DHEA)

- Considered the daughter of pregnenolone.
- Precursor to testosterone, estrogen, and other corticosteroids.
- A neurosteroid and has many of the same effects as pregnenolone, but it's more potent.
- Plays a fundamental role in the maintenance of hormonal balance and vitality, which is why some have referred to it as an anti-aging hormone, and why it's been proposed along with pregnenolone as a marker for aging.

DHEA is converted into DHEA sulfate in the blood and then back to DHEA when it's taken up by the tissues. The levels of DHEA sulfate are typically much higher than DHEA, so that is often the form that is tested.

DHEA Actions
Promotes blood flow (via NO production)
Protects the brain
Supports cognitive function and mood
Opposes effects of cortisol
Promotes bone health
Regulates blood sugar and insulin sensitivity

All of these functions explain why reduced levels of DHEA are linked with the pathophysiology underlying numerous age-associated disease states such as cognitive decline, cardiovascular disease, bone loss, cancer, depression, sexual dysfunction, and various inflammatory disorders.

CORTISOL:

- Glucocorticoid produced in the adrenal cortex
- Primary stress hormone released in response to stressors but also to low blood sugar.
- When blood sugar drops, cortisol works in tandem with insulin to provide adequate glucose to cells for energy.
- Cortisol is involved with resolution of the inflammatory response.
    - Patients with low cortisol will not be able to turn off that inflammatory cascade, and that can lead to chronic inflammation.
- High cortisol weakens immune function.
- Cortisol contracts the midsized arteries.
- Cortisol reduces bone formation and calcium absorption in the intestine, which explains the connection between high cortisol/stress and osteoporosis.
- It downregulates the synthesis of collagen, an important component of muscles, tendons and joints, which explains why high-cortisol states are associated with muscle wasting.
- Increases sodium retention and potassium excretion.
- Cortisol damages the hippocampus, which impairs learning and inhibits retrieval of stored memories, which explains the connection between stress and cognitive disorders.

CORTISOL RHYTHM:

- Highest levels of cortisol would be produced around 8 a.m.
- Gradual decline throughout the day
- Lowest between midnight and 4 a.m.
- The production of cortisol is regulated by information about the light–dark cycle that's transmitted from the retina to the paired suprachiasmatic nuclei in the hypothalamus.

CORTISOL PRODUCTION IS REGULATED BY A NEGATIVE FEEDBACK CYCLE

Under stress:

Hypothalamus produces CRH –> pituitary produces ACTH –> adrenals produce cholesterol.

Cholesterol is manufactured into pregnenolone, which is eventually converted into cortisol and released in the bloodstream. Then the hypothalamus detects higher levels of cortisol and downregulates CRH and ACTH production.

EPINEPHRINE IS REGULATED BY A POSITIVE FEEDBACK LOOP

Epinephrine in the blood acts on CRH to secrete more epinephrine. This ensures that the body's primed and ready to deal with acute stress. This loop is interrupted by cortisol.

More cortisol	More cortisone
Genetic polymorphisms	Genetic polymorphisms
Hypothyroidism	Hyperthyroidism
Inflammation	Human growth hormone
Visceral obesity	Estradiol
Insulin resistance	Testosterone
Excess sodium	Quality sleep
Licorice	Magnolia, Scutellaria, Zizyphus, Citrus peel
Obesity and insulin resistance	Ketoconazole

SEVEN PRIMARY MECHANISMS THAT DETERMINE THE TISSUE-SPECIFIC REGULATION OF CORTISOL:

1. Metabolic clearance of cortisol
    a. Clearance of cortisol is reduced in critical illness, poor liver function, and hypothyroidism.
    b. Increased in obesity, insulin resistance, and hyperthyroidism.
2. Binding proteins that carry cortisol through the body
    a. 95 to 97 percent of cortisol is bound.
    b. Only free cortisol has cell-signaling effect.
3. Activation / inactivation of cortisol to cortisone and back
4. Genomic signaling
    a. Genomic effects of cortisol are mediated primarily through glucocorticoid receptors.
5. Heat shock proteins and co-chaperones
    a. Cortisol receptors are sequestered within the cell cytoplasm.
    b. A group of chaperone proteins called heat shock proteins influence binding affinity and signaling effects of cortisol, and their expression is modulated by stress, exercise, and other factors.
    c. Adaptogenic herbs are thought to work by regulating heat shock protein expression.

6. Nongenomic signaling
    a. Bioavailability of cortisol is also mediated by membrane-bound receptors or directly through cytoplasmic signal transduction pathways.
7. Adrenal brain DHEA production
    a. DHEA functions as an anabolic counter-regulatory hormone to the catabolic effects of cortisol.
    b. Low DHEA can lead to unopposed actions of cortisol, which creates an ongoing catabolic state.

IMPORTANT TAKEAWAYS:

1. Physiology governing cortisol bioavailability is extremely complicated, far more complicated than the adrenal fatigue model has led on.
2. Sometimes we may need to treat empirically for HPA axis dysfunction rather than relying solely on test results because there are effects that govern cortisol's function and bioavailability in the body that won't necessarily show up on the test results
    a. Consider therapeutic trials

ALDOSTERONE:

- Mineralocorticoid that is produced in the adrenal cortex under the direction of ACTH.
- Secreted in a diurnal rhythm similar to cortisol, so it peaks at 8 a.m. and has a low point of midnight to 4 a.m.
- Plays a central role in regulating blood pressure by increasing reabsorption of ions in water in the kidney and causing the conversion of sodium and secretion of potassium, increasing water retention and blood volume.

TWO KEYS TO REMEMBER ABOUT ALDOSTERONE

As aldosterone goes up due to stress, for example, the concentration of sodium and water rises, potassium drops, fluid is retained, and blood pressure rises, so this is why stress can have such a

significant effect on hypertension. Low aldosterone can lead to low blood pressure, high pulse rate, postural hypotension, getting dizzy when standing up quickly, salt cravings, palpitations, and in severe cases may lead to hyperkalemia and hyponatremia.

CATECHOLAMINES: EPINEPHRINE AND NOREPINEPHRINE:

Together, they comprise the sympathoadrenal medullary system (SAS). The SAS has two components: the adrenomedullary hormone system, which is mediated by epinephrine and adrenaline, and the sympathetic nervous system, mediated by norepinephrine.

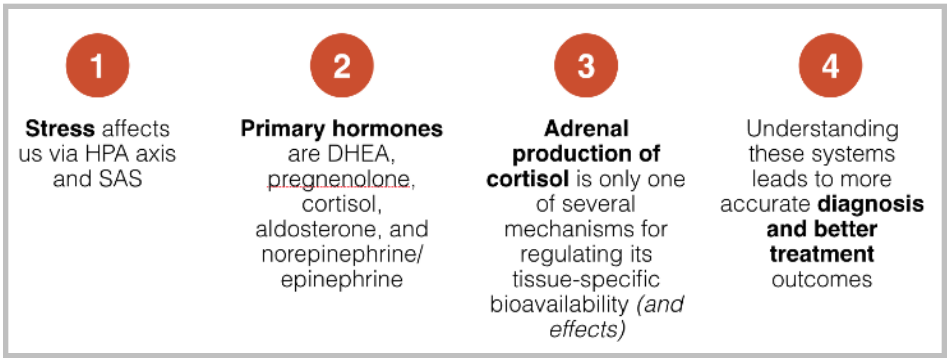
NOREPINEPHRINE

- Synthesized and released in the central nervous system, as well as the sympathetic nervous system, and a smaller amount of norepinephrine, about 7 percent, is made in the adrenal glands.
- Stress enters the body via our senses. It activates the locus coeruleus (LC), which is an area of the brainstem, and then norepinephrine is released.
- Norepinephrine activates the HPA axis and triggers the cascade that ultimately results in the production of cortisol and DHEA immediately.
- Norepinephrine stimulates arousal, so low levels of this neurotransmitter and hormone are associated with brain fog, poor memory, and depression.
- Elevations of norepinephrine can lead to panic, including anxiety, restless sleep, increased startle reflex, palpitations, muscle tension, and teeth grinding.

EPINEPHRINE (ALSO KNOWN AS ADRENALINE):

- A hormone and the primary mediator of the adrenomedullary hormone system.
- 90 percent of it is produced by the adrenal glands in the adrenal medulla, and the remaining 10 percent is produced in certain neurons in the body.
- Plays an important role in the fight-or-flight response.
- Increases heart rate and the strength of heart contractions.
- It constricts blood vessels in veins.
- Is a bronchodilator.
- Inhibits histamine release.
- It stimulates the breakdown of glycogen into glucose in the liver, which results in an increase in blood sugar.

KEY TAKEAWAYS



For example, if a patient wakes up at two in the morning with their heart pounding, wide awake, you should definitely be thinking about stress-related pathology.

Steroid hormone production begins with the conversion of cholesterol into pregnenolone. This primarily happens in the organs themselves, such as the adrenal glands and the gonads. This is really important to understand because when you know that the conversion of cholesterol into pregnenolone primarily happens in the organs and glands, not in the bloodstream, that explains why taking supplemental DHEA and pregnenolone does not significantly increase estrogen and testosterone levels.

CORTISOL:

Adrenal gland: Cholesterol –> pregnenolone –> 17-OH-pregnenolone –> 17-OH-progesterone –> cortisol

Conversion of pregnenolone to 17-OH-pregnenolone is reduced by drugs such as spironolactone or ketoconazole and by hereditary conditions such as congenital adrenal hyperplasia. The conversion of pregnenolone to 17-OH-pregnenolone is increased by high insulin levels, PCOS, hyperglycemia, stress, and alcohol.

Active cortisol can be converted into cortisone, which is relatively inactive. The factors that favor more cortisone include hyperthyroidism, human growth hormone, estradiol, good sleep, drugs such as ketoconazole, and then adaptogenic herbs such as magnolia, scutellaria, and ziziphus, and then finally testosterone. The factors that favor more cortisol, include hypothyroidism, inflammation, visceral obesity, high insulin, excess sodium, and licorice, which increases the half-life of circulating cortisol.

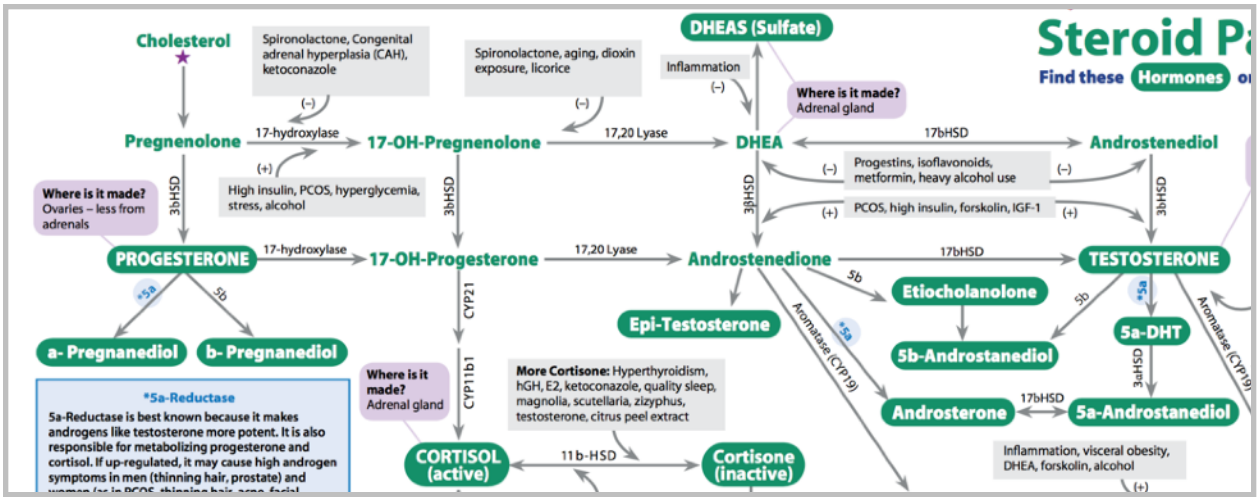
ADRENAL GLAND: DHEA

Cholesterol –> pregnenolone –> 17-OH-pregnenolone –> DHEA.

The conversion of 17-OH-pregnenolone to DHEA is inhibited by spironolactone in addition to exposure to dioxins, which are persistent in environmental pollutants that come from smelting,

chlorine bleaching of paper pulp, herbicides and pesticides, and by licorice root, which is a relatively unknown effect of licorice, and aging.

DHEA has several metabolites. One is DHEA sulfate, also produced in the adrenal gland. DHEA itself is not present in the urine, but DHEA sulfate is. The conversion of DHEA to DHEA sulfate is inhibited by inflammation, so it's possible to have normal DHEA but low DHEA sulfate when inflammation is present.



5-ALPHA REDUCTASE

- Metabolizes progesterone, cortisol, and some of the androgens.
- Responsible for turning testosterone into DHT, which is 10 times more potent than testosterone.
- Upregulated 5-alpha reductase metabolism is associated with prostatitis and prostate cancer in men, hirsutism and PCOS in women, and other conditions caused by elevated androgens.
- The factors that increase 5-alpha reductase metabolism include high insulin, PCOS, and obesity.
- Agents that are known to decrease 5-alpha reductase activity include saw palmetto, nettle, IGM, EGCG, progesterone, zinc, and finasteride.

5-BETA REDUCTASE:

- Less is known about this pathway, but it's seen as a more favorable conversion pathway for androgen metabolism than the 5-alpha pathway.
- When 5-beta reductase is favored, you see higher tetrahydrocortisol relative to alpha-tetrahydrocortisol and tetrahydrocortisone, which is the less active form of cortisol, as well as higher levels of etiocholanolone and 5-beta androstenediol.