WHITE PAPER

Stress: Biomarkers and Physiological Consequences

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Abstract

Stress is ubiquitous. How we respond to it and cope with it depends on our resiliency as well as our perception of that stress. The stress response allows us to adapt to our environment, in some cases challenging or "fighting" a potential adversary, and in some cases wisely fleeing that adversary or negative stressor ("flight").

However, frequent or chronic stress can lead to impaired adaptation and increased risk of systemic inflammation; immune dysfunction; premature aging; cognitive decline; metabolic disorders including cardiovascular disease, diabetes, and inflammatory bowel disease; and even psychological disorders such as anxiety, depression, and PTSD.[1]

Prolonged stress can significantly disrupt psycho-neuro-immune balance, resulting in commonly recognized psychological and physiological symptoms. Biomarkers associated with stress reflect the major systems involved, e.g., the autonomic nervous system (alpha-amylase, epinephrine, norepinephrine), HPA axis activity (cortisol, CRH, ACTH), and immune system activity (inflammatory cytokines, CRP).[2]

Identifying potential stressors, monitoring physiological and psychological changes, and intervening with stress management techniques are crucial steps to addressing stress in a healthy and effective manner.

Introduction

Stress is a broad term referring to a stimulus or event that disturbs homeostasis and generates a response in the stressed individual. Stress may be considered "eustress," meaning it can have a positive, motivating effect. However, we often we think of stress as distress, which can have negative emotional and physical effects, especially if prolonged.

The negative consequences of stress are related to a "crisis mode" emotional and physiological response. This response allows an organism to mobilize resources and either fight the stressor (or aggressor) or take flight in the classic "fight or flight" response.[3] Basically, the stress response puts us into survival mode.

There are biochemical and physiological changes that can be identified and addressed in order to modify the effects of prolonged stress on the body. Fortunately, there are also a number of interventions that can reduce the negative effects of stress. These include active stress management, healthy diet and lifestyle habits, and targeted nutrition support.

This review will cover

- ✓ How We Get Stressed Out
- ✓ Common Sources of Stress
- ✓ The Physiology of Stress
- ✓ Hormonal Control of Stress
- ✓ Immune System Effects of Stress
- ✓ Identifying Stress
- ✓ General Adaptation Syndrome
- ✓ Disorders Associated with Stress
- ✓ Biomarkers of Stress
- ✓ Addressing Stress
- ✓ Nutrition and Stress
- ✓ Optimal Takeaways

How Do We Get Stressed Out?

Our perception of stress and its triggers determines how profound our response to that stress will be. Identifying specific stressors and their source is one of the most important things we can do to anticipate and combat stress.

Stressors may be psychological, physical, or situational. Psychological stressors are often based on fear and anxiety in anticipation of an adverse

event or even an uncontrollable environment. Physical stressors include pain, shock, hemorrhage, extreme exercise, and heat exposure.[4] Situational stressors, for the most part, are out of our immediate control which in turn amplifies the stress.

Inability to respond to stress appropriately may jeopardize both physical and psychological health. Poor adaptation to stress may occur due to lack of coping skills, lack of stress management techniques or intervention, chronic or overwhelming stress, unhealthy lifestyle, and suboptimal nutrition status. Maladaptation to stress can increase vulnerability to substance abuse disorders (SUD).[5]

For some, adopting negative behaviors for coping with stress can actually increase stress in the body and mind. These include abuse of drugs, alcohol, or cigarettes; overeating, especially palatable but nutritionally-deficient foods; extreme behavior; overspending; emotional outbursts; overconsuming media; and feeling helpless or overwhelmed.[6]

Common sources of stress:[7] [8] [9]

Physical Sources of Stress

- Alcohol or caffeine in excess
- Allergies
- Chronic illness
- Drug use, withdrawal
- Extreme temperature changes
- Food deprivation
- Food insecurity
- Hormone imbalances
- Hunger
- Infection
- Injury
- Medication
- Nutrient deficiencies
- Physical abuse
- Physical assault
- Physical neglect
- Sleep deprivation
- Thirst
- Toxin exposure

Situational/Psychological Sources of Stress

- Being overwhelmed
- Chronic stress
- Emotional abuse
- Financial problems
- Homelessness
- Inability to manage problems
- Illness of a loved one
- Interpersonal conflicts
- Isolation, loneliness
- Job-related stress
- Legal troubles
- Living arrangement difficulties
- Poor academic performance
- Relationship difficulties
- Unfaithful significant other
- Unfulfilled plans, desires
- Witnessed violence

Life Event Sources of Stress

- Accidents
- Catastrophic events
- Divorce, separation
- Isolation, abandonment
- Loss of a loved one
- Loss of home
- Victim of violence

The Physiology of Stress

The stress response is physiologically complex and recruits the endocrine, nervous, and immune systems in order to mount an effective adaptive response. While an acute response may keep an organism out of harm's way, chronic exposure to stress will eventually promote a maladaptive response that disrupts physiology and contributes to cardiovascular disease, gastrointestinal ulcers, immune suppression, sleep dysregulation, and mood and behavioral disorders.[10]

The brain itself is directly affected by stress and the hippocampus, amygdala, and temporal lobe can all be negatively impacted. Chronic exposure to stress hormones can lead to brain atrophy with associated impairment of memory and cognition and even mood disorders. Exposure to synthetic anti-

inflammatories may also contribute to hippocampal atrophy and memory dysfunction.[11]

Once a threat has been perceived, the body goes into overdrive to cope with it and then, ideally, puts on the brakes in an effort to return to normal. Although individuals may respond to stress in different ways, a number of physiological responses are common. The main physiological response to stress increases availability of energy, oxygen, and strength; decreases feeding, appetite, and reproductive physiology; and modulates immune response and function.[12]

Early on, a cascade of compounds is released via the hypothalamic-pituitary-adrenal (HPA) axis in order to provide resources for the physical stress response. The sympathetic branch of the autonomic nervous system (ANS) then increases heart rate and blood pressure to facilitate fighting or fleeing.[13] Blood glucose increases as an immediate energy source, and cardiac output and oxygen uptake increase as well in order to facilitate a physical altercation or escape.[14]

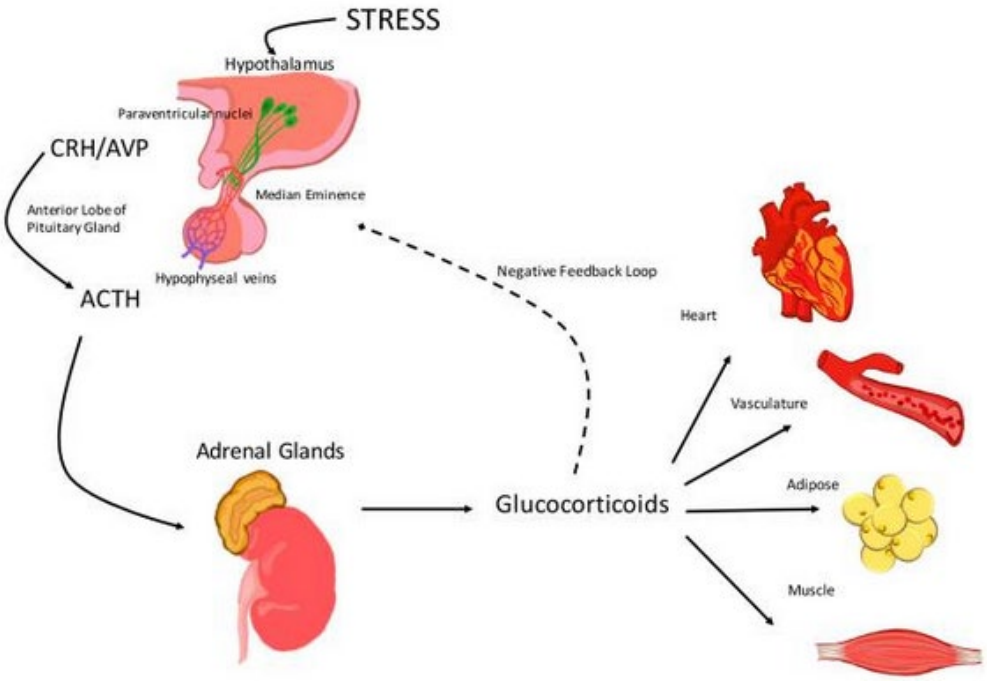
Once the threat has passed, the parasympathetic branch of the ANS does its part and opposes sympathetic branch actions, bringing the body back into a balanced state of homeostasis.

This “relaxation response” or “rest and digest” phase will reduce heart rate and blood pressure, slow breathing, and direct blood flow back to internal organs (including digestive organs). Then digestion resumes, sweating diminishes, and blood glucose should come back down to normal levels.[15]

However, if stress is sustained, then the relaxation response is delayed. The physiological changes associated with adaptation to stress are referred to as allostatic load and include blood pressure, serum glucose, insulin, and lipids, inflammatory markers, and waist circumference. A high allostatic load, representing prolonged stress over time, is reflected in low morning cortisol and reduced cortisol response to stress.

This hypocortisolemic state can be seen in “burnout”, the term often used for excessive stress that leads to exhaustion. Other physiological changes seen with burnout include systemic inflammation, compromised immunity, increased risk of infection, dyslipidemia, and altered glucose regulation. Unhealthy lifestyle habits are also associated with burnout and include reliance on fast food, lack of exercise, and increased consumption of alcohol and pain killers.[16]

The activation of the hypothalamic-pituitary-adrenal (HPA) axis.



Response to a stress stimulus is routed to the hypophysiotropic neurons in the paraventricular nucleus (PVN) of the hypothalamus. These neurosecretory cells release corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP), which travel through the median eminence and hypophyseal portal vessels. Once CRH reaches the anterior pituitary, it binds CRF type 1 receptors of pituitary corticotroph cells. Adrenocorticotropic hormone (ACTH) is released into circulation, binds its receptors in the zona fasiculata of the adrenal cortex, and causes release of glucocorticoids. Glucocorticoids in circulation act on target cardiovascular tissues (including, the heart, the vasculature, adipose tissue and muscle) then feedback to the level of the central nervous system (CNS) to inhibit activation of the HPA axis.

Source: Burford, Natalie G et al. “Hypothalamic-Pituitary-Adrenal Axis Modulation of Glucocorticoids in the Cardiovascular System.” International journal of molecular sciences vol. 18,10 2150. 16 Oct. 2017, doi:10.3390/ijms18102150 [R]

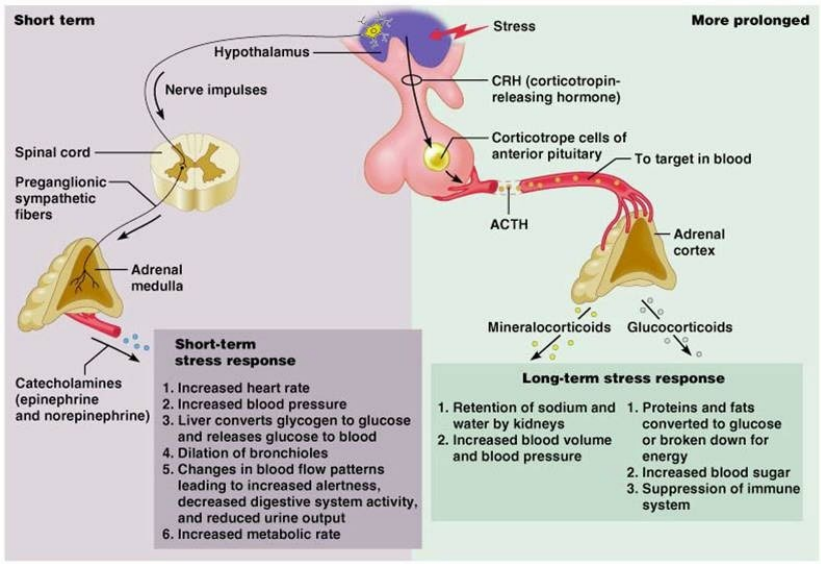
Hormonal Control of the Stress Response

Major hormonal changes that occur in response to stress include:[17]

- ✓ Catecholamines increase
- ✓ Corticosteroids increase
- ✓ Vasopressin increases
- ✓ Growth hormone increases (mainly in physical stress)
- ✓ Prolactin may increase or decrease
- ✓ Gonadotropins decrease
- ✓ Insulin decreases
- ✓ TSH, T3, and T4 decrease

Hormonal facilitation of the stress response involves the anterior hypothalamus, corticotropin releasing hormone, anterior pituitary, adrenocorticotropic hormone (ACTH), and finally the adrenal cortex which releases glucocorticoids and mineralocorticoids (corticosteroids):[18]

Cortisol (glucocorticoid)	Aldosterone (mineralocorticoid)
• Mobilizes free fatty acids • Mobilizes protein and amino acids • Initiates gluconeogenesis • Increases serum glucose levels • Promotes muscle wasting • Damages antibodies • Impairs immune system • Depletes micronutrients • Causes beta cell depletion • Decreases insulin production • Increases arterial blood pressure	• Promotes sodium retention • Enhances potassium elimination • Increases osmotic retention of water • Increases blood pressure by increasing blood volume



Source: Lee, Do Yup et al. "Technical and clinical aspects of cortisol as a biochemical marker of chronic stress." BMB reports vol. 48,4 (2015): 209-16. doi:10.5483/bmbrep.2015.48.4.275 [R] This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License ([R])

Catecholamines

cause general physiological changes that prepare the body for physical activity (fight-or-flight response) in the short term response. Some typical effects include increases in heart rate, blood pressure, and blood glucose levels, and other general reactions of the sympathetic nervous system. Corticoids are involved in a wide range of physiological processes including chronic stress response, immune response, and regulations of inflammation, carbohydrate metabolism, protein catabolism, blood electrolyte levels, and behavior.

Summary of the physiological changes of the stress response: [19]

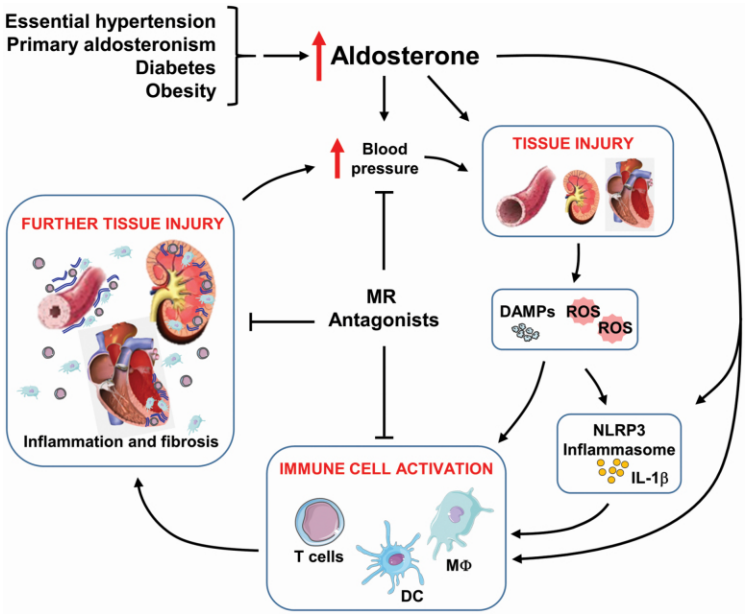
- ✓ Mobilization of energy to maintain brain and muscle function
- ✓ Sharpened and focused attention on the perceived threat
- ✓ Increased cerebral perfusion rates and local cerebral glucose utilization
- ✓ Enhanced cardiovascular output and respiration
- ✓ Redistribution of blood flow
- ✓ Modulation of immune function
- ✓ Inhibition of reproductive physiology and sexual behavior
- ✓ Decreased feeding and appetite
- ✓ Adapting to a stressor occurs as a phase-based phenomenon called the General Adaptation Syndrome:
    - Alarm
    - Resistance
    - Exhaustion

Immune System Effects of Stress

The link between stress and suppressed immunity is widely recognized.[20] Exposure to stress can reduce circulating lymphocytes and interfere with their function, possibly impairing overall immunity. Stress-related cortisol has an immune-suppressing effect which can increase susceptibility to infection. In some cases, stress may enhance the immune inflammatory response and increase circulating pro-inflammatory cytokines.[21]

The increase in aldosterone associated with stress can amplify its effects on immunity including activation of the innate and adaptive immune systems resulting in increased inflammation, oxidative stress, endothelial dysfunction, and hypertension.[22]

Immune Effects of Aldosterone



Source: Ferreira, Nathanne S et al. "Aldosterone, Inflammation, Immune System, and Hypertension." American journal of hypertension vol. 34,1 (2021): 15-27. doi:10.1093/ajh/hpaa137 [R] This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License ([R])

Identifying Stress

The response to stress may vary from person to person and will likely be based on the perceived severity of the threat or stressor, or even the emotional state of the stressee.[23]

However, there are some basic internal and external signs of stress that are common. Early investigation and observation of the effects of stress were described as the General Adaptation Syndrome (GAS). The GAS takes into consideration physical and emotional causes and effects of stress.

General Adaptation Syndrome

The theory of a general adaptation syndrome (GAS) was developed in the 1930s by researcher Hans Selye who observed physiological changes that occurred in response to different types of stressors. Animals in the experiments ultimately experienced adrenal gland hypertrophy, lymphatic organ atrophy (i.e., thymus, spleen, and lymph nodes), and bleeding gastric ulcers as a result of prolonged stress.[24]

From Hans Selye's "The Physiology and Pathology of Exposure to Stress" (1950):[25]

> "A variety of "stressors" (such as emotional upsets, exposure to extremes of temperature, and anoxia) set into motion defense reactions mediated through the nervous and the hormonal systems.
>
> These affect blood pressure, body temperature, blood sugar level, blood clotting, osmotic pressure and tissue hydration. During prolonged, severe systemic stress there are 3 phases: "shock," adaptation, and exhaustion. Strong emotions are particularly effective in eliciting the somatic manifestations of the general adaptation-syndrome.
>
> Psychosomatic derangements as well as a variety of neuropsychiatric disturbances are likely to fall into the steadily broadening category of "diseases of (mal)adaptation" to biological stresses."[26]

The three stages of the stress response are still taken into account today, as researchers observe characteristic signs and symptoms of stress: [27]

Alarm stage "fight or flight"

- ✓ Increased epinephrine, norepinephrine
- ✓ Increased heart rate
- ✓ Increased arterial pressure
- ✓ Increased blood flow to muscles
- ✓ Decreased blood flow to organs not needed for locomotion
- ✓ Increased coagulation
- ✓ Increased cellular metabolism
- ✓ Increased muscle strength
- ✓ Increased mental activity
- ✓ Increased blood glucose
- ✓ Increased glycolysis

Resistance phase

- ✓ Poor concentration
- ✓ Irritability
- ✓ Frustration

Exhaustion phase

- ✓ Anxiety
- ✓ Burnout
- ✓ Depression
- ✓ Fatigue
- ✓ Reduced stress tolerance
- ✓ Decreased immunity

Early in the stress response, both cortisol and DHEA increase but can return to baseline fairly quickly. Symptoms may not be present at this stage. However, if stress continues, the adaption phase will be characterized by persistently high cortisol, declining DHEA, and mood changes including anxiety. In the exhaustion phase, dysfunction progresses toward adrenal hypofunction with low cortisol and low DHEA. Additional consequences can occur at this stage including severe fatigue, hormone imbalance, hair loss, muscle and bone loss, immune dysfunction, arthritis, weight gain, insomnia, anxiety, and depression.[28]

Disorders Associated with Stress[29]

- ✓ Angina
- ✓ Asthma
- ✓ Autoimmune disease
- ✓ Cancer
- ✓ Cardiovascular disease
- ✓ Common cold
- ✓ Depression
- ✓ Diabetes mellitus (type 2)
- ✓ Headaches
- ✓ Hypertension
- ✓ Immune suppression
- ✓ Irritable bowel syndrome
- ✓ Menstrual irregularities
- ✓ Rheumatoid arthritis
- ✓ Ulcerative colitis
- ✓ Ulcers

Cardiovascular Disease and Stress

Exposure to chronic stress is considered a CVD risk factor, likely through chronic activation of the HPA axis, inflammation, oxidative stress, and acceleration of the atherosclerotic process. Chronically elevated cortisol and aldosterone can contribute to hypertension and may promote myocardial necrosis and fibrosis as well. The CVD effects of stress may be especially significant for those experiencing stress-related anger, anxiety, and depression.[30]

It is important to recognize that dysregulation of the endocrine, immune, and nervous systems due to prolonged stress can contribute to hypertension, vascular damage, and even cardiac arrest.[31] Sources and effects of stress should be identified and addressed early on to reduce the risk of cardiovascular dysfunction and disease.

Stress Testing

Reaction and tolerance to stress reflects the health of the cardiovascular system. The conventional cardiac stress test uses physical activity (e.g., treadmill activity) as a stressor by increasing the heart rate to a target of 80-90% maximal (maximal heart rate is 220 minus a patient's age). If advanced atherosclerosis or arterial occlusion are present, the arteries won't be able to meet the increased demand for blood that the heart requires and symptoms

such as fatigue, chest pain, tachycardia, arrhythmias, dyspnea, decreased blood pressure, and electroencephalogram abnormalities can occur.[32]

Heart rate variability (HRV) appears to be a useful marker of stress as it reflects the heart's ability to response to stimuli. The heart rate will normally vary with activities such as exercise, breathing, sleeping, stress, and metabolic and hemodynamic changes. Low HRV may indicate impaired autonomic nervous system function and a diminished ability to cope with stress. The heart rate is regulated by both the sympathetic and parasympathetic branches of the ANS, and dysregulation contributes to ventricular arrhythmias and coronary artery disease.[33]

Obesity and Stress

Chronic stress and prolonged activation of the HPA axis may promote weight gain, especially visceral adiposity. Chronically elevated cortisol promotes deposition of abdominal fat; decreases leptin signals and satiety; and increases ghrelin signals, appetite, and food intake. [34] Increased aldosterone associated with stress can decrease insulin sensitivity by decreasing adiponectin, further promoting risk of inflammation and obesity.[35]

Also, stress may amplify or trigger comorbidities in those who are already obese. The combination of psychological stress, impaired sleep, increased appetite and cravings, and decreased enthusiasm for physical activity can place someone who is stressed on the road to obesity, metabolic syndrome, and increased risk of chronic disease.[36]

Therefore, it is imperative to address stressors and stress management when addressing the epidemic of obesity occurring in the developed world. It is important to note that individuals should be assessed for abdominal obesity and lean body mass and not just changes in BMI. Someone can be at an ideal BMI but have increased abdominal obesity and decreased muscle mass. On the other hand, an elevated BMI may reflect increased muscle mass and not adiposity.

Post-Traumatic Stress Disorder (PTSD)

Although our bodies are designed to respond acutely to stress and then reverse that response and return to homeostasis, the effects of stress may be extreme and may linger in some individuals. Severe effects and triggering events may cause an individual to relive a traumatic experience psychologically and physically. Disruption of the normal feedback loop involving cortisol and the HPA axis can further distort the reaction to ongoing stressors.

The occurrence of PTSD is associated with chronic disease including metabolic syndrome, CVD, autoimmune disorders, pulmonary disease, and additional psychiatric disorders. Research indicates that persistent low-grade inflammation may underlie PTSD and the chronic disorders associated with it. A review of the literature revealed significantly increased biomarkers of inflammation including acute-phase proteins, pro-inflammatory cytokines, and C-reactive protein in those with PTSD.[37]

In one study of premenopausal women with PTSD, an increased release of DHEA in response to adrenal activation was associated with alleviation of adverse mood symptoms and severity of PTSD. Research suggests that DHEA may counteract the negative effects of cortisol on the brain including changes in brain structure and neurotransmitter balance.[38] The increased levels of DHEA and DHEA-S seen in PTSD are likely associated with the body's attempt to manage stress and may facilitate coping in those affected.[39]

Biomarkers of Stress

A biomarker reflects underlying physiology and reflects either homeostasis or dysfunction. Blood chemistry biomarkers that reflect HPA axis activity and the physiological stress response include cortisol and DHEA/DHEA-S, corticotropin releasing hormone (CRH), adrenocorticotropic hormone (ACTH), anti-diuretic hormone (also known as vasopressin or arginine vasopressin), epinephrine, norepinephrine, and aldosterone. Prolonged stress

can also prolong disruption to the HPA axis and promote metabolic and cardiovascular consequences.[40]

Examples of the association between biomarker changes and stress include: [41]

- Four weeks of intense combat training, a source of stress, were found to increase serum IL-6, TNF-a, and cortisol. These changes were associated with gastrointestinal distress.
- Elevated cortisol in healthy adults predicted the development of hypertension up to three years later.
- In a group of breast cancer patients, stress management, yoga, and meditation were found to reduce proinflammatory cytokines.

Ultimately, stress manifests as an increase in blood glucose, blood pressure, heart rate, cardiac contractility, and pupil dilation, and a decrease in gastrointestinal function. Prolongation of this sympathetic nervous system activation can become detrimental and damage tissues and organs.[42]

Biomarker Changes and Stress

The stress response is characterized by measurable biochemical changes including:[43] [44] [45] [46] [47] [48] [49] [50]

Increased

- ✓ ACTH
- ✓ Advanced glycosylation products
- ✓ Aldosterone
- ✓ Antidiuretic hormone (vasopressin)
- ✓ Catalase
- ✓ Copeptin
- ✓ Clotting factors
- ✓ Corticotropin-releasing hormone
- ✓ Cortisol
- ✓ DHEA (increases acutely)
- ✓ Epinephrine and norepinephrine
- ✓ Glucagon
- ✓ Glucose
- ✓ Glutathione peroxidase
- ✓ Growth hormone (physical stress)
- ✓ Hemoglobin A1C
- ✓ Histamine
- ✓ Inflammatory cytokines
- ✓ Isoprostanes

- ✓ Malondialdehyde
- ✓ Myeloperoxidase
- ✓ Oxidized glutathione
- ✓ Oxidized LDL
- ✓ Oxytocin
- ✓ Prooxidant enzymes
- ✓ Protein carbonyl groups (from cell membrane lipid oxidation)
- ✓ NADPH oxidase
- ✓ Renin
- ✓ Superoxide dismutase
- ✓ T3, T4 (Graves')
- ✓ Thiobarbituric acid-reactive substances (TBARS)
- ✓ Uric acid
- ✓ White blood cells
- ✓ Xanthine oxidase

Decreased

- ✓ Acetylcholine
- ✓ Albumin (acute stress)
- ✓ Basophils
- ✓ Bilirubin
- ✓ Gonadotropins
- ✓ Growth hormone (prolonged psychological stress)
- ✓ Insulin
- ✓ Lysozyme
- ✓ Prolactin (may increase or decrease)
- ✓ Reduced glutathione
- ✓ Secretory IgA
- ✓ TSH and T3, T4 in non-Graves'
- ✓ Thyroid-binding globulin (major stress)

Cortisol

The glucocorticoid cortisol at first glance is a beneficial compound that decreases inflammation and mobilizes stored energy reserves for immediate use. Cortisol suppresses insulin, delays wound healing, and suppresses the immune inflammatory response in order to focus resources on the task at hand. However, prolonged cortisol stimulation will have detrimental catabolic and immune-suppressive effects.[51]

Cortisol production is regulated by the HPA axis. Corticotropin-releasing hormone (CRH) from the hypothalamus stimulates the anterior pituitary to produce adrenocorticotropic hormone (ACTH). It is ACTH that then stimulates the adrenal gland to produce and release cortisol. The subsequent

increase in serum cortisol feeds back and reduces production of CRH and ACTH. Without this feedback, excess ACTH will signal the adrenal gland to continue to make cortisol. However, elevated ACTH will not result in increased cortisol production in adrenal insufficiency or hypofunction, and cortisol levels will remain insufficient. Failure of the adrenal gland to produce cortisol may be caused by damage, autoimmune disorder, congenital disease, or prolonged use of steroids which suppress adrenal function. Pathological insufficiency of cortisol is known as Addison's disease while excess production of cortisol manifests as Cushing's syndrome.[52]

Cortisol normally increases in the early morning and then declines during the day and into nighttime. However, persistent elevations in cortisol, as seen with acute stress, can have detrimental effects throughout the body.[53]

Elevated cortisol can promote beta cell dysfunction and impair glucose regulation. One cross-sectional population-based study of 1,071 Japanese participants found that a fasting morning cortisol above 11 ug/dL was significantly associated with reduced insulin secretion and beta cell function.[54] Further evaluation should be completed to fully assess glucose regulation parameters if morning cortisol continues to increase.[55]

Stress is initially characterized by elevated cortisol and decreased DHEA (after a short-term initial increase), demonstrating a shift into stress hormone production. If prolonged, chronic stress can lead to adrenal exhaustion with low cortisol and low DHEA. Chronically elevated cortisol can also have adverse effects on the brain and contribute to anxiety and depression as cortisol shunts tryptophan away from the production of serotonin and melatonin.[56]

The ratio of cortisol to DHEA or DHEA-S (the more abundant sulfated form of DHEA) may help predict tolerance to stress. A higher ratio of cortisol to DHEA was associated with increased arousal, anxiety, fear, and startle response in a clinical study of 30 volunteers. A lower ratio is believed to buffer the negative effects of acute stress.[57] Interestingly, estradiol may temper the cortisol response to stress by increasing corticosteroid-binding globulin, therefore decreasing free cortisol.[58]

DHEA, DHEA-S

Dehydroepiandrosterone (DHEA) is an anabolic steroid produced by the adrenal glands. The most abundant form in circulation is DHEA-S, the stable sulfated form. DHEA is a precursor to testosterone but also has restorative effects that support immunity, wellbeing, mood, and behavior. A meta-analysis of 14 studies indicates that DHEA increases with acute stress in response to adrenocorticotropic hormone. This protective response helps buffer the negative effects of cortisol and may support mood following acute mental stress. DHEA levels rise within the first hour, peak, and then decline. Elevations were more pronounced in younger individuals, obese individuals, and females.[59]

In stress, DHEA is considered a biomarker of HPA axis activity along with CRH, ACTH, and cortisol. DHEA is able to buffer the effects of cortisol, especially persistently higher levels of cortisol that are associated with impaired cognitive function, anxiety, depression, and coronary heart disease. Not surprisingly, insufficient DHEA may exacerbate the negative effects of excess cortisol.[60]

Chronic or prolonged stress will lead to the downregulation of DHEA production, followed by downregulation of cortisol production, a pattern characteristic of adrenal hypofunction or exhaustion. The resulting increased cortisol to DHEA ratio has been reported in those exposed to long-term stress or experiencing clinical burnout. Increased cortisol:DHEA ratio has also been reported in association with workdays, increased stressful events in the year prior, overtraining, and caring for Alzheimer's patients (Kamin 2017).[61]

Aldosterone

Although not commonly thought of as a stress hormone, the adrenal mineralocorticoid aldosterone increases in response to stress and HPA activation and is further influenced by the sympathetic-adrenomedullary system. Research suggests that elevated aldosterone may be associated with increased risk of metabolic dysfunction and cardiovascular risk via a number of different actions as it: [62]

- ✓ Increases water and sodium retention
- ✓ Facilitates potassium excretion
- ✓ Increases risk of hypertension
- ✓ Increases pro-inflammatory mediators
- ✓ Decreases adiponectin and insulin sensitivity
- ✓ Activates the mineralocorticoid receptor (MR)
- ✓ Levels increase with sodium intake
- ✓ Levels increase with stress
- ✓ Increased aldosterone may contribute to mood disorders including anxiety and depression

The link between aldosterone and essential hypertension was investigated in a study of 113 hypertensive subjects who did not have primary aldosteronism. In those with an exaggerated response to stress/ACTH stimulation, blood pressure was normalized with the use of mineralocorticoid receptor antagonists.[63]

Aldosterone's effect on the immune system may be a link to its cardiovascular effects as well. Excess aldosterone can activate immune cells and promote a Th17-based immune response that contributes to hypertension, vascular injury, and cardiovascular fibrosis.[64]

Sodium and Potassium

Stress-induced increases in aldosterone will affect sodium-potassium balance by causing sodium and water retention and potassium excretion. An increase in plasma sodium:potassium ratio is associated with significantly increased risk of hypertension as demonstrated in a community study of 549 volunteers. Assessing the ratio of sodium to potassium was more useful than assessing either electrolyte alone. The study also noted that hypertensive subjects had significantly increased levels of hs-CRP, ferritin, and malondialdehyde, and significantly decreased glutathione, SOD, NO, and catalase.[65]

An increased serum sodium:potassium ratio, especially above 34, suggests a potassium depletion. A ratio below 28 suggests sodium depletion as well as insufficiency of magnesium and vitamin E. [66] An elevated sodium:potassium

ratio may be indicative of acute stress while a decrease in sodium:potassium ratio may occur with chronic stress and adrenal insufficiency.

Interestingly, a low-salt diet can activate the sympathetic nervous system and stimulate production of aldosterone. A study of 152 healthy subjects found that a low-salt diet was associated with significantly increased serum aldosterone with a mean of 21 ng/dL on the low-salt diet versus 3.4 ng/dL on the high-salt diet. Researchers associated a low-salt diet with insulin resistance in this cohort.[67]

Glucose

Stress triggers a short-term elevation in blood glucose that can be used for energy.

- ✓ The glucocorticoid cortisol promotes the conversion of protein/amino acids to glucose through the process of gluconeogenesis.
- ✓ Pancreatic glucagon also increases serum glucose by stimulating gluconeogenesis and glycogen breakdown in the liver.[68]
- ✓ Both epinephrine and norepinephrine will promote an increase in blood glucose.[69]
- ✓ Even moderate elevation in fasting blood glucose at 95-99 mg/dL (5.27-5.49 mmol/L) can increase cardiovascular risk significantly compared to lower levels below 80 mg/dL (4.44 mmol/L).[70]

Blood glucose can increase in situations that may not traditionally be thought of as stress. These include myocardial infarction, stroke, anesthesia, burns, and strenuous exercise.[71] Even exposure to stress during pregnancy can increase the chance of blood glucose dysregulation in the child.[72]

Lipids

Stress is also associated with alterations in serum lipids. Review of the data from 9,752 individuals taking part in the Isfahan Healthy Heart Program found that elevated psychological stress was associated with significant elevations in total and LDL cholesterol and decreases in HDL-C. Researchers note that

previous studies had also demonstrated an increase in triglyceride levels associated with stress.[73]

In one historical cohort study of ~5,000 subjects, researchers note that both physical and psychological stress can alter serum lipids, especially with advancing age and obesity. Triglycerides and LDL were highest, and HDL lowest, in subjects with heavy physical activity/stress. This group had the greatest number of subjects with triglycerides greater than 200 mg/dL (2.26 mmol/L), LDL greater than 130 mg/dL (3.37 mmol/L), and HDL below 45 mg/dL (1.17 mmol/L). Total cholesterol above 200 mg/dl (5.18 mmol/L) was most prevalent in subjects with both psychological stress and physical work/stress.[74]

Another study of 208 undergraduate students found that the examination period, a source of psychological stress, was associated with significantly increased cortisol, epinephrine, total cholesterol, HDL-C, and LDL-C.[75]

Oxidative Stress

The stress response involves interactions between immune cytokines and the HPA axis which result in biochemical and physiological changes. Ultimately the cardiovascular, nervous, renal, hepato-biliary, and digestive systems become involved.

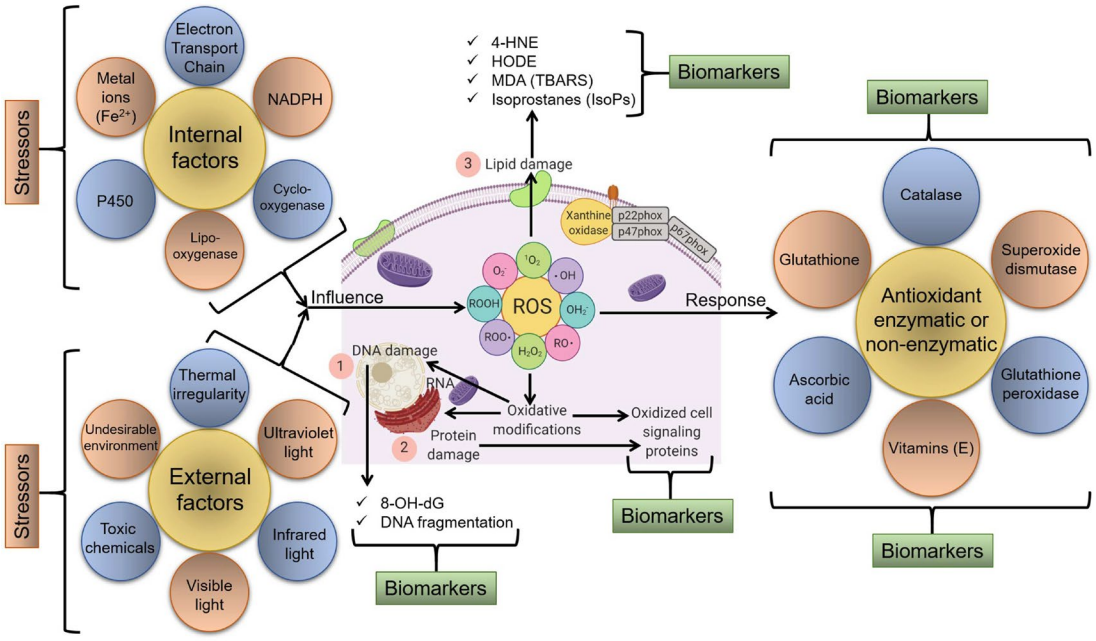
Generation of oxidative stress and corresponding antioxidant and inflammatory activity is also a hallmark of stress. An overwhelming imbalance that favors oxidative stress will be detrimental to DNA and RNA and eventually cause cell and organ dysfunction. Red blood cells are particularly vulnerable to oxidative stress and can be assessed with a complete blood count (CBC).

Oxidative stress can be countered by antioxidants and endogenous antioxidant enzymes including catalase, glutathione peroxidase, glutathione reductase, and superoxide dismutase. Of course, prevention is preferable, and

therefore causes of oxidative stress should be minimized. These causes include:[76]

- ✓ Nutrient depletions, poor diet
- ✓ Pathological microbes
- ✓ Pollutants
- ✓ Radiation, ionizing and nonionizing
- ✓ Toxic gasses, ozone, oxidizing disinfectants
- ✓ Toxins, biological and chemical

Schematic representation of various endogenous and exogenous factors that act as stressors and lead to the generation of ROS and oxidative stress/modification.



In response, various molecular and cellular redox-sensitive processes start that can be tracked as biomarkers of oxidative stress. For instance, major biomarkers include (1) markers of DNA/RNA damage/oxidation, (2) markers of protein damage/oxidation, and (3) markers of lipid damage via the oxidation of membrane components and available lipids, etc.

Source: Dhama, Kuldeep et al. "Biomarkers in Stress Related Diseases/Disorders: Diagnostic, Prognostic, and Therapeutic Values." Frontiers in molecular biosciences vol. 6 91. 18 Oct. 2019, doi:10.3389/fmolb.2019.00091 [R] This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY).

Biomarker Patterns of Adrenal Stress and Exhaustion

Recognition of the patterns associated with acute or chronic stress may help address which phase of the stress response an individual is experiencing. Note the biomarker shifts as one transitions from acute to chronic stress:

Acute stress, adrenal hyperfunction:

- ✓ Elevated catecholamines, ACTH, cortisol, DHEA (initially), aldosterone, sodium, chloride, sodium:potassium ratio
- ✓ Decreased potassium
- ✓ Decreased triglycerides and cholesterol (though they may increase acutely as well)

Chronic stress, adrenal hypofunction:

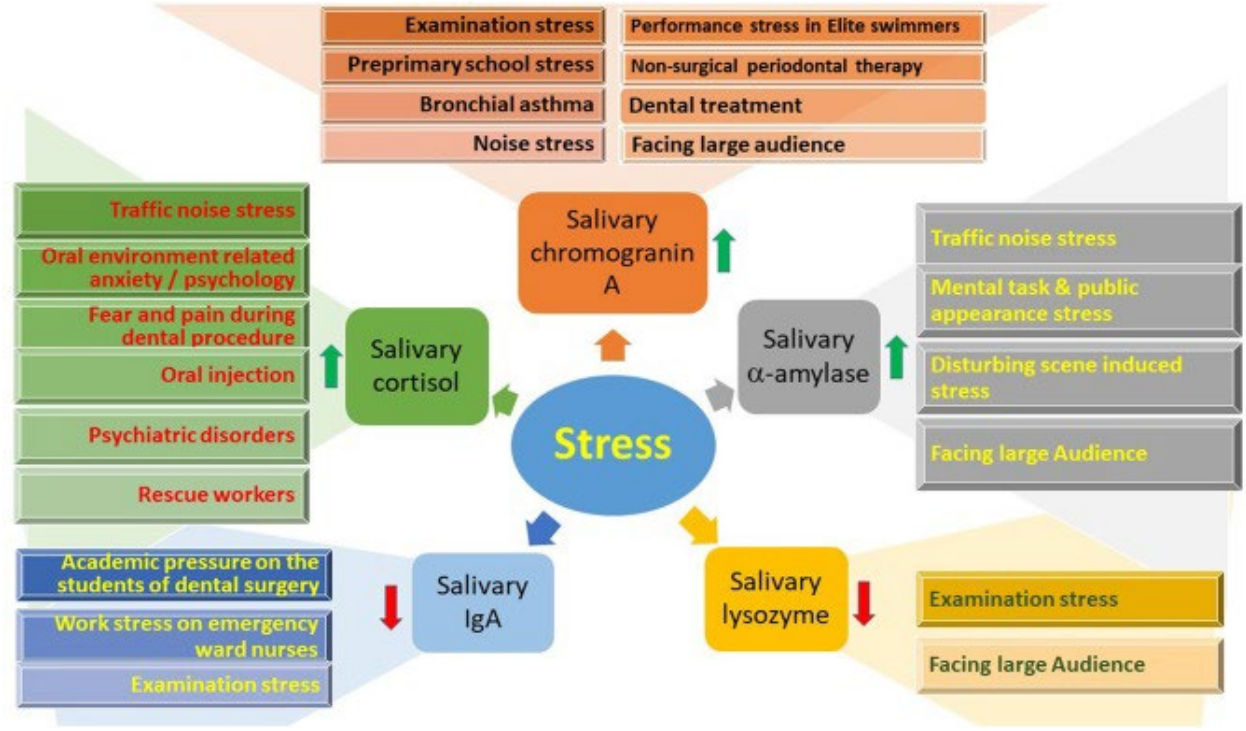
- ✓ Elevated ACTH, potassium, triglycerides, cholesterol
- ✓ Decreased cortisol, DHEA, aldosterone, sodium, chloride

Salivary measurement of stress biomarkers

Stress markers may also be measured and monitored in saliva as concentrations often mirror circulating levels.[77] Cortisol and DHEA can be easily measured in blood or saliva. Another marker, salivary alpha-amylase (SAA), appears to parallel stress-induced increases in norepinephrine and catecholamine activity. Researchers suggest that SAA may be a surrogate marker for activation of the sympathetic-adreno-medullary axis.[78]

Salivary measurement of cortisol, DHEA-S, and SAA in a study of young healthy males demonstrates a normal pattern of activity including: [79]

- ✓ Cortisol increases significantly upon awakening and then decreases 45 minutes later, reaching nadir in the evening.
- ✓ DHEA-S starts relatively high in the morning, decreases for the first 60 minutes after awakening, and then steadily decreases until nadir in the evening.
- ✓ Alpha-amylase decreases immediately upon awakening, returns to baseline 30-60 minutes after awakening, and then increases during the day, reaching peak in the evening.



Various stresses affecting the salivary stress biomarkers: cortisol, chromogragranin A and a-amylase are increased whilst salivary IgA and lysozyme are decreased with an increase in level of stress.

Source: Dhama, Kuldeep et al. "Biomarkers in Stress Related Diseases/Disorders: Diagnostic, Prognostic, and Therapeutic Values." Frontiers in molecular biosciences vol. 6 91. 18 Oct. 2019, doi:10.3389/fmolb.2019.00091 [R] This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY).

However, measurement of inflammatory cytokines in saliva may not accurately mirror circulating levels, especially if oral infection or inflammation is present. Cytokines are larger molecules and are less stable than cortisol. Salivary CRP may have some correlation with blood levels as it is not produced locally in the mouth. However, research into the reliability of salivary CRP as a marker of stress is currently limited.[80]

Addressing Stress: Can We Treat It or Beat It?

How can we get stress out after being stressed out? The first step is to identify primary stressors as well as underlying causes and contributors to stress. No matter the source of stress, an individual's response to or management of that stress will determine its pathogenicity. Coping with stress requires conscious decisions and actions, including optimal lifestyle and nutrition choices.

Stress Management Techniques[81] [82]

- ✓ Deep breathing
- ✓ Exercise
- ✓ Healthy diet
- ✓ Healthy sleep routine
- ✓ Meditation
- ✓ Mindfulness
- ✓ Music therapy
- ✓ Progressive relaxation
- ✓ Yoga
- ✓ Social support
- ✓ Stay grounded
- ✓ Time management

Quick Tips for Breathing Deeply

Diaphragmatic breathing can activate the parasympathetic system and help reverse the stress response.

With one hand on the abdomen and one hand on the chest, breathe in deeply and slowly through the nostrils for at least 4 counts, pause for 4 counts, then exhale completely through the mouth for 4 counts or more. If able, hold the breath out for a count of 4 as well, and then start again.

Lying on the ground or floor with knees bent may be helpful, especially for maintaining focus on the breath.

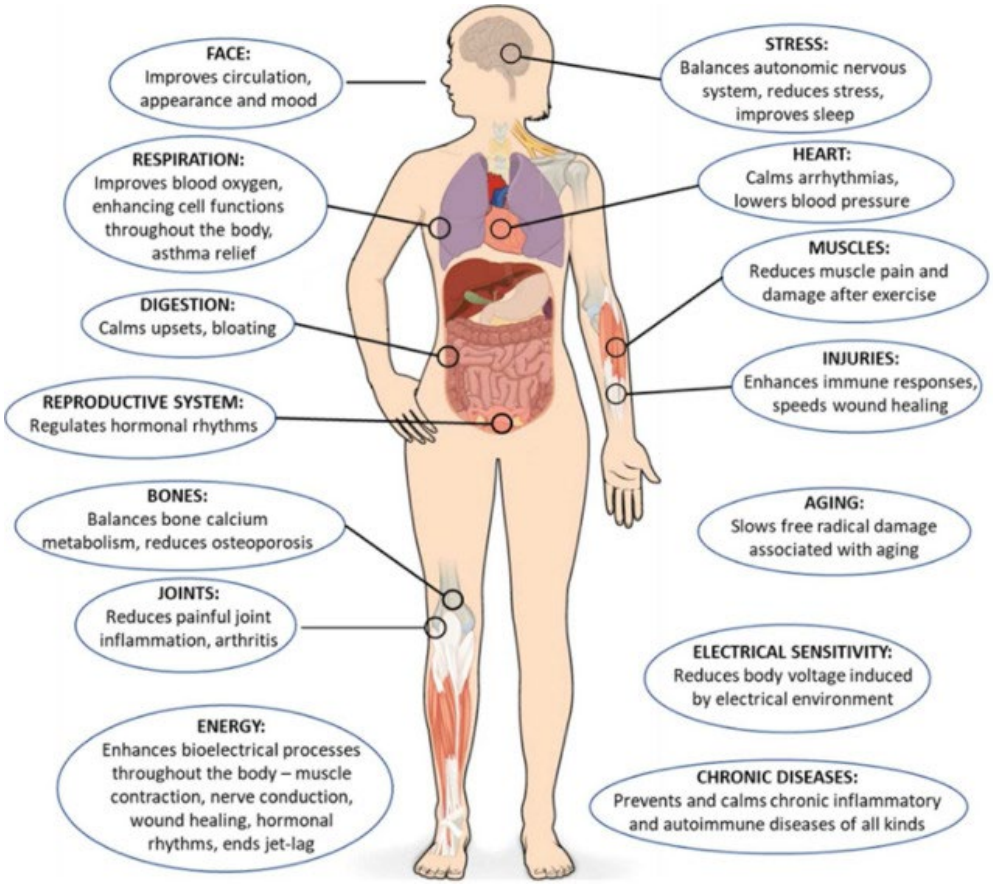
Do this a few times per day to invoke the "rest and digest" relaxation response.

Stay Grounded

It's not just a saying— staying grounded can help reduce inflammation, improve health, and optimize stress management. The practical technique of grounding, or "Earthing," involves direct contact with the ground and can be as simple as standing or walking barefoot outside.[83] Grounding not only connects us with our natural surroundings but reduces the swelling, pain, and loss of function caused by inflammation; facilitates wound healing; and even

reduces elevated white blood cells. Researchers suggest it is the free flow of electrons into the body that provides an antioxidant effect, protecting cells and organs from oxidative stress. The practice also appears to improve sleep and increase tolerance to stress by shifting the nervous system to parasympathetic control. Subjects report a reduction in irritability, anxiety, and depression when sleeping grounded for eight weeks.[84]

Potential Systemic Benefits of Earthing



Source: Menigoz, Wendy et al. "Integrative and lifestyle medicine strategies should include Earthing (grounding): Review of research evidence and clinical observations." Explore (New York, N.Y.) vol. 16,3 (2020): 152-160. doi:10.1016/j.explore.2019.10.005 [R] This is an open access article under the CC BY-NC-ND license. ([R])

Nutrition and Stress

The stress response ultimately requires macronutrients and micronutrients to sustain it. This is an especially important time to consume nutrient-dense foods and minimize highly processed foods, especially those high in excess sugar and trans fats. Unfortunately, many comfort foods fall into the latter category but can be modified to improve their nutrition profile or can be limited to minimize their negative impact.

A healthy diet should be based on fresh unprocessed plant-based foods including fruits, vegetables, whole grains, legumes, nuts, seeds, herbs, and spices. The addition of high-quality sources of protein may include cold-water fish, seafood, organic meats, eggs, and dairy. High quality sources of fat include extra virgin olive oil, olives, avocado, coconut, flax seeds, chia seeds, hemp seeds, and nuts. Foods should be minimally processed in order to maximize nutrition density; while processed and deep-fried foods should be eliminated or minimized.

Food and nutrients that help balance the stress response: [85] [86] [87] [88]

Nutrients:

- ✓ Alpha-lipoic acid
- ✓ Amino acids theanine, tryptophan, tyrosine, phenylalanine
- ✓ B vitamins
- ✓ Calcium
- ✓ Carotenoids
- ✓ Folate
- ✓ Magnesium
- ✓ Omega-3 fatty acids
- ✓ Selenium
- ✓ Vitamin C
- ✓ Vitamin D
- ✓ Vitamin E
- ✓ Zinc

Foods

- ✓ Banana
- ✓ Blueberries
- ✓ Brazil nuts
- ✓ Broccoli
- ✓ Coffee
- ✓ Complex carbohydrates
- ✓ Dark chocolate
- ✓ Eggs
- ✓ Fish
- ✓ Flax seeds
- ✓ Kiwi fruit

- ✓ Oranges
- ✓ Probiotics
- ✓ Spinach
- ✓ Tea
- ✓ Turkey
- ✓ Walnuts
- ✓ Whole grains

Botanicals[89] [90]

- ✓ Ashwagandha
- ✓ Ginseng, Chinese, Siberian
- ✓ Kava kava
- ✓ Passionflower
- ✓ Rhodiola
- ✓ Ziziphus spinosa

Essential Oils

Essential oils are plant-based compounds that have been used therapeutically for millennia. They can be concentrated and applied topically or taken in though inhalation, which is one of the most common modes. Essential oils that have a positive modulating effect on stress include cedarwood, clary sage, chamomile, ginseng, lavender, jasmine, neroli, rose, sandalwood, Siberian ginseng, vetiver, ylang ylang.[91] [92] [93] [94] [95]

Vitamin C and Stress

Ascorbic acid, more commonly known as vitamin C, plays a role in regulation of the stress response. Vitamin C is stored to some extent in the adrenal gland and is released when cortisol levels increase. The increase in circulating vitamin C is able to "put the brakes" on hyperactivation of the HPA axis.

Vitamin C also acts as a neuromodulator and may have an antidepressant effect. Supplementation was found to improve depressive symptoms and reduce psychological stress in hospitalized patients. Even increasing consumption of vitamin C containing foods such as kiwifruit dramatically improved mood disturbances and fatigue in a group of non-smoking male students.[96] Vitamin C is essential to a healthy stress response as it: [97]

- ✓ Modulates the HPA axis
- ✓ Counteracts stress
- ✓ Has an antianxiety and antidepressant effects
- ✓ Promotes neuroplasticity

Most mammals produce their own vitamin C from glucose-6-phosphate in the liver. However, humans have lost the ability to do so and are completely dependent on dietary intake. When under stress, other mammals increase production and release of ascorbic acid which supports hemodynamic reserve, immune function, and protection from oxidative stress. For example, a goat produces an estimated 2-4 grams of vitamin C under normal conditions. However, production increases significantly under stress. Without this flexible ability to synthesize vitamin C, humans have an impaired response to stress. Insufficiency of vitamin C will also impede the myriad functions that vitamin C participates in including antioxidant, anti-inflammatory, immune, anti-thrombotic, and adrenergic functions. Vitamin C is also essential to catecholamine synthesis, wound healing, and microcirculation.[98]

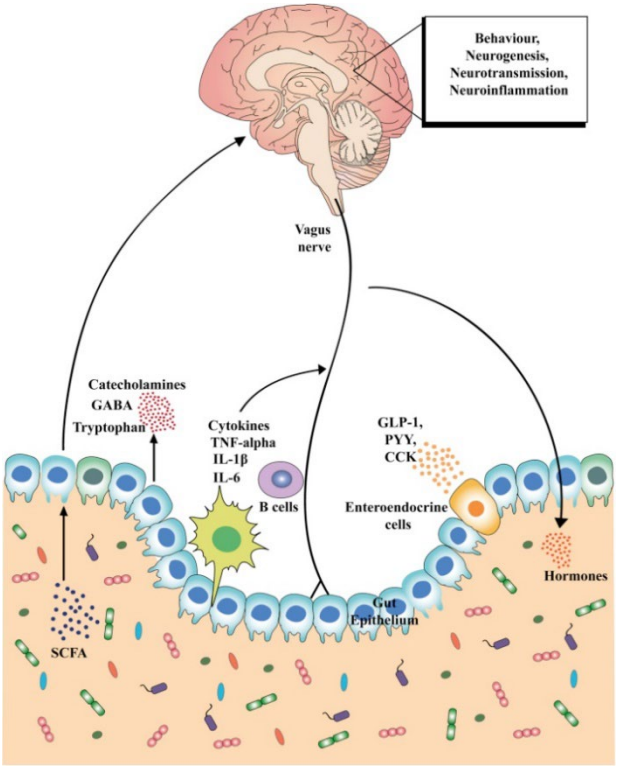
In one randomized double-blind, placebo-controlled study, supplementation with 3,000 mg/day of sustained-release vitamin C effectively reduced blood pressure and subjective response to acute psychological stress. Supplementation also facilitated a faster normalization of blood pressure and salivary cortisol. The improvement in systolic blood pressure was superior to that achieved with beta-blocker antihypertensives. Plasma vitamin C increased significantly from a baseline mean of 1.55 mg/dL (88 umol/L) to 2.65 mg/dL (150.5 umol/L) in subjects taking vitamin C.[99]

Stress and the gut microbiome

The gut-brain axis plays a role in regulating the stress response, and resident microbiota participate as well in what is known as the microbiota-gut-brain axis. Ongoing research suggests that the gut microbiota and their optimization through pre- and pro-biotic supplementation may favorably modify the HPA axis, cortisol levels, and an individual's response to acute and chronic stress.[100]

Irritable bowel syndrome (IBS) is a stress-related (or "stress-adjacent") condition characterized by abdominal pain, visceral sensitivity, and significantly altered gastrointestinal motility. Stress can exacerbate gastrointestinal symptoms and even induce visceral pain in IBS. The gut microbiota may be a factor in the symptomatology and pathophysiology of

IBS and its related anxiety and depression. Research suggests that dysbiosis caused by antibiotics can predispose an individual to a heightened sensitivity to visceral pain and may contribute to IBS directly. Supporting and restoring the gut microbiome, i.e., microorganisms, their collective genes, and factors they produce,[101] may be therapeutic in IBS though further human studies are needed. Stress may also contribute to increased intestinal permeability or "leaky gut syndrome," which in turn may contribute to bacterial translocation, inflammation, immune activation, and GI distress.[102]



Microbiota-Gut Interactions

Key communication pathways of the microbiota–gut–brain axis. There are numerous mechanisms through which the gut microbiota can signal to the brain. These include activation of the vagus nerve, production of microbial antigens that recruit immune B cell responses, production of microbial metabolites (i.e. short-chain fatty acids [SCFAs]), and enteroendocrine signaling from gut epithelial cells (e.g., I-cells that release CCK, and L-cells that release GLP-1, PYY and other peptides). Through these routes of communication, the microbiota–gut–brain axis controls central physiological processes, such as neurotransmission, neurogenesis, neuroinflammation and neuroendocrine signaling that are all implicated in stress-related responses. Dysregulation of the gut microbiota subsequently leads to alterations in all of these central processes and potentially contributes to stress-related disorders.

Source: Foster, Jane A et al. "Stress & the gut-brain axis: Regulation by the microbiome." Neurobiology of stress vol. 7 124-136. 19 Mar. 2017, doi:10.1016/j.ynstr.2017.03.001 [R]

Early stress creates later stress

Early stress, even in utero, can significantly impact the HPA axis and an individual's ability to mount a healthy response to, and recovery from, stress. Such early stress and associated cortisol elevations can alter the gastrointestinal microbiome, promote dysbiosis, and further exacerbate the impaired response to stress. Research suggests that stress can increase the permeability not only of the GI tract, but of the blood brain barrier (BBB) as well. An increase in BBB permeability can increase neuroinflammation, further amplifying the negative effects of chronic stress.[103]

The stress-induced dysfunctional relationship created between the gut, the brain, and the microbiota may contribute to mood disorders, behavioral abnormalities, autism, Alzheimer's, Parkinson's, brain injury, and stroke.[104]

Optimal Takeaways

Tackling stress means not only addressing and regulating external stressors but modulating the internal response to stress.

Identify and address major stressors including

- ✓ Physical stressors such as nutrient insufficiencies, hormone imbalances, sleep deprivation, toxin exposure, abuse, or assault
- ✓ Situational/psychological stressors such as interpersonal conflicts, relationship difficulties, isolation, financial strain, legal troubles, becoming overwhelmed
- ✓ Life events such as catastrophic events, accidents, divorce, loss of a loved one, violence

The physiological changes associated with stress ultimately[105]

- ✓ Mobilize energy to maintain brain and muscle function
- ✓ Focus attention on the threat
- ✓ Prepare the body for fight or flight

- ✓ Modulate the immune system
- ✓ Decrease feeding, appetite, and reproductive physiology
- ✓ Reflect the General Adaptation Syndrome which is characterized by phases:
  - ✓ Alarm
  - ✓ Resistance
  - ✓ Exhaustion

Chronic exposure to stress can eventually contribute to the following:

- ✓ Blood glucose dysregulation
- ✓ Hypertension
- ✓ Cardiovascular disease
- ✓ Obesity
- ✓ Inflammatory disorders
- ✓ Psychological disorders
- ✓ PTSD
- ✓ Cognitive decline

Main Biomarkers of Stress

Increased

- ✓ ACTH
- ✓ Aldosterone
- ✓ Antidiuretic hormone
- ✓ Cortisol
- ✓ Cortisol to DHEA ratio
- ✓ CRH
- ✓ Epinephrine and norepinephrine
- ✓ Glucagon
- ✓ Glucose
- ✓ Histamine
- ✓ Inflammatory cytokines
- ✓ Oxidative stress markers
  Uric acid
- ✓ White blood cells

Decreased

- ✓ Acetylcholine
- ✓ Albumin
- ✓ Bilirubin
- ✓ Growth hormone
- ✓ Insulin
- ✓ Reduced glutathione
- ✓ Secretory IgA
- ✓ TSH, T3, T4

Nutrition is key to increasing your resilience to stress

- ✓ Consume a healthy plant-based diet full of fresh fruits and vegetables, whole grains, legumes, nuts, seeds, herbs, and spices, along with high-quality protein and fats.
- ✓ Minimize highly processed foods, junk food, fast foods, trans fats, sweetened beverages, and concentrated sweets (unless homemade and healthy!).
- ✓ Pay close attention to micronutrient intake and supplement when needed, B vitamins and vitamin C are especially important.
- ✓ Consider botanicals or essential oils to help cope with stress and its negative effects.
- ✓ Maintain a healthy gut microbiome
- ✓ Hydrate with plenty of purified mineral-rich water

Stress management techniques are key to minimizing the negative effects of stress

- ✓ Deep breathing, meditation, yoga, progressive relaxation
- ✓ Social support, time management, mindfulness, music
- ✓ Healthy diet, balanced sleep routine, regular exercise, walking
- ✓ Take the time to connect with nature, walk in the woods, lie down in green pastures, Earthing/grounding
- ✓ Take a few deep breaths before each meal to help facilitate the “rest and digest” response
- ✓ Practice gratitude daily

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