Nutritional and Botanical Interventions to Assist with the Adaptation to Stress

by Gregory S. Kelly, ND

Abstract

Prolonged stress, whether a result of mental/emotional upset or due to physical factors such as malnutrition, surgery, chemical exposure, excessive exercise, sleep deprivation, or a host of other environmental causes, results in predictable systemic effects. The systemic effects of stress include increased levels of stress hormones such as cortisol, a decline in certain aspects of immune system function such as natural killer cell cytotoxicity or secretory-IgA levels, and a disruption of gastrointestinal microflora balance. These systemic changes might be a substantial contributor to many of the stress-associated declines in health. Based on human and animal research, it appears a variety of nutritional and botanical substances — such as adaptogenic herbs, specific vitamins including ascorbic acid, vitamins B1 and B6, the coenzyme forms of vitamin B5 (pantethine) and B12 (methylcobalamin), the amino acid tyrosine, and other nutrients such as lipoic acid, phosphatidylserine, and plant sterol/sterolin combinations — may allow individuals to sustain an adaptive response and minimize some of the systemic effects of stress.

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Introduction

Stress is a broad, ambiguous, and often poorly understood concept. In its most simplified sense, stress is what one feels when life's demands exceed one's ability to meet those demands. In a much more elaborate sense, stress goes far beyond what one actually feels, causing predictable changes in immune function, hormone levels, enzymes, and gastrointestinal function. In fact, prolonged stress, whether a result of mental/emotional upset or due to physical factors such as malnutrition, surgery, chemical exposure, excessive exercise, sleep deprivation, or a host of other environmental causes, results in predictable systemic effects.

All individuals have different capacities to perform and accommodate when faced with stress. But ultimately we all have a breaking point; add enough total stress and performance suffers. The work of Hans Selye provides the classic model for adaptation to stress (Table 1). He observed that given any source of external biological stress, an organism would respond with a predictable biological pattern in an attempt to restore its internal homeostasis. He termed this the General Adaptation Syndrome or Biological Stress Syndrome, and divided the response into four categories: 1) the "alarm reaction" characterized by an immediate activation of the nervous system and adrenal glands; 2) a "resistance phase" characterized by hypothalamic-pituitary-adrenal (HPA) axis activation; 3) a stage of adrenal hypertrophy, gastrointestinal

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Table 1. Biological Stress Syndrome of Hans Selye.[1]

Phase	Neuroendocrine effect
Alarm reaction	Activation of nervous system & adrenal glands
Resistance phase	HPA axis activation
Tissue changes	Adrenal hypertrophy, gastrointestinal ulceration, thymic and lymphoid atrophy
Exhaustion phase	May culminate in death

ulceration, along with thymic and lymphoid atrophy; and 4) an exhaustion phase which may culminate with death.[1]

Selye observed that prolonged stress ultimately forces organisms to accommodate to maintain a relative balance in the face of the continued challenges. But, at some point, all organisms reach a point beyond which compromises are no longer possible and function suffers. If stress persists long enough or with enough intensity, one begins to experience a decline in performance (maladaptive response). Based on human and animal research, a variety of substances, such as adaptogenic herbs, specific vitamins including ascorbic acid, vitamins B1, B5, and B6, the amino acid tyrosine, nutrients such as lipoic acid and phosphatidylserine, and plant sterol/sterolin combinations may allow individuals to sustain an adaptive response to stress.

Physiology of Stress

Within seconds after an acutely stressful event or danger, norepinephrine is released from nerve endings in preparation for a rapid response. Almost instantly, the adrenal glands release epinephrine and norepinephrine into the bloodstream. The combination of the release of norepinephrine and epinephrine results in the familiar "fight or flight" response. Within minutes of a stressful event (and possibly lasting for several hours), a much more elaborate interaction between the nervous and endocrine systems and other forms of internal communication occurs, resulting in a very complex adaptive response to deal with the stress. At this point adrenal glands release extra amounts of cortisol into the circulation.

Several other endocrine glands are also critical to the stress response. The hypothalamus, located in the brain, is often thought of as the "master" gland; it responds to stress by releasing a hormone called corticotropin-releasing factor (CRF). This hormone signals the pituitary gland to release adrenocorticotropic hormone (ACTH), which stimulates the adrenal glands to release cortisol. With the rise in stress hormones, a complex mechanism of feedback controls is set in motion, eventually signaling the hypothalamus to stop producing its messenger hormone (Figure 1).

A wide range of events, based on their ability to prompt the adrenal glands to release stress hormones, are considered physiologically stressful. These occurrences include calorie restriction,[2-6] surgery,[7] sleep deprivation,[8,9] and excessive exercise.[2,10-12] Even one's mental state can induce an increase of cortisol and catecholamine stress hormones.[13,14]

Stress exerts a disruptive influence on normal circadian release of the adrenal hormone cortisol. A study was conducted on military cadets subjected to a five-day training course of heavy physical exercise and food and sleep deprivation. Not surprisingly, due to the stressful nature of this training, cortisol levels went up and performance deteriorated. The

researchers also found, "the circadian rhythm was extinguished." Even after 4-5 days of rest, circadian rhythms had not completely normalized.[2]

As this and other research demonstrates, the physiological and psychological consequences of acute and chronic stress can and do persist well beyond actual cessation of a stressful event.[2,15]

Health Consequences of Chronic Stress

General Effects

From headaches to heart disease and immune deficiencies to digestive problems, stress is a factor in many illnesses. A substantial contributor to stress-induced decline in health appears to be an increased production of stress hormones and subsequent decreased immune function.[16]

Researchers have found that people dramatically increase their use of the medical system during times of job insecurity. Visits to doctors increased 150 percent, episodes of illness increased 70 percent, and visits to hospital outpatient departments increased 160 percent.[17]

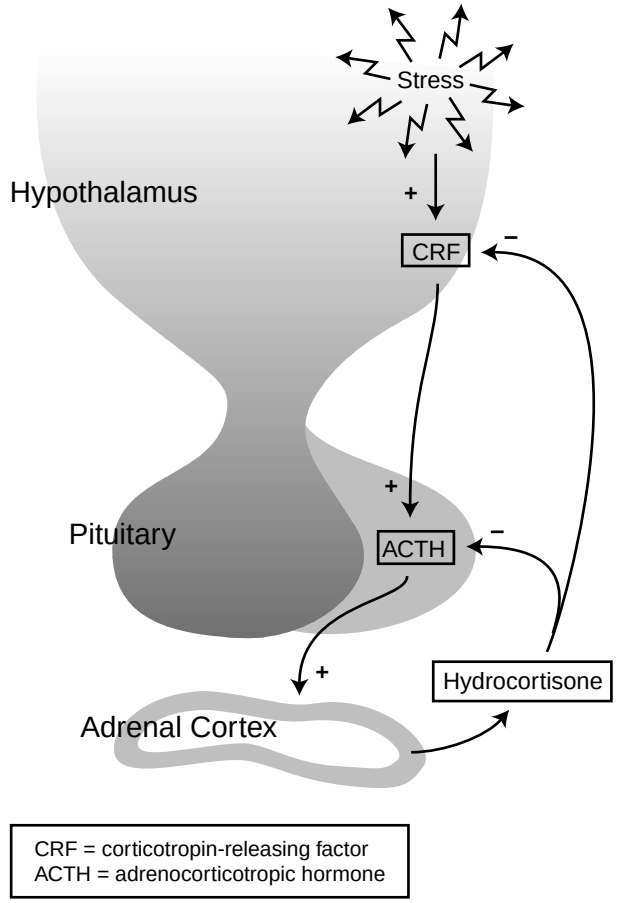
Other evidence clearly demonstrates workers reporting the highest level of perceived stress due to job dissatisfaction (with working conditions or supervisory style being the most common stress reported), family problems, and personal conflict are the most likely to experience somatic symptoms.[18]

Cardiovascular Health

Stress and emotions associated with stress are important risk factors for cardiovascular problems. The Mayo Clinic reported psychological stress is the strongest risk factor predictive of future cardiac events, including myocardial infarction and cardiac death, among individuals with existing coronary artery disease. In this study, the economic cost of high and low stress was compared in terms of the mean rehospitalization costs: $9,504 versus $2,146.[19]

When researchers interviewed survivors of heart attacks, they found the intensity and timing of a stressful emotion like anger dramatically increased their risk.[20] The Normative Aging Study also provided compelling evidence that emotions associated with a higher stress level are significant risk factors

Figure 1. The HPA Hormone Cascade and Feedback Loop.



for coronary heart disease (CHD) and myocardial infarction (MI):

● **Anger:** Compared with men reporting the lowest levels of anger, relative risk among men reporting the highest levels of anger is 3.15 ((95% confidence interval) [CI]: 0.94-10.5) for total CHD (nonfatal MI plus fatal CHD). A dose-response relation was found between level of anger and overall CHD risk.[21]

● **Anxiety:** Compared with men reporting no symptoms of anxiety, men reporting two or more anxiety symptoms had elevated risks of fatal CHD (age-adjusted odds ratio [OR] = 3.20, 95% CI: 1.27-8.09), and sudden death (age-adjusted OR = 5.73, 95% CI: 1.26-26.1).[22]

● **Worry:** Compared with men reporting the lowest levels of worry, men reporting the highest levels had multivariate adjusted relative risks of 2.41 (95% CI: 1.40-4.13) for nonfatal MI and 1.48 (95% CI: 0.99-2.20) for total CHD (nonfatal MI and fatal CHD). A dose-response relation was found between level of worry and both nonfatal MI and total CHD.[23]

Table 2. Some Health Consequences of Chronic Stress.

↓ NK cell activity
↓ S-IgA activity
↓ Bifidobacterium and Lactobacilli
↑ E. Coli and Enterobacteria

Immune Performance

Research clearly indicates a bout of acute stress in virtually any form will cause, at the very least, a temporary decrease in functioning of the immune system, while chronic stress will result in continued decline in immune system function (Table 2).

Natural Killer Cell Cytotoxicity: Overwhelming evidence has demonstrated virtually any type of stress has a detrimental effect on the ability to maintain optimal levels of natural killer (NK) cell cytotoxic activity.[24-27] In fact, a severe life stress may be associated with up to a 50-percent reduction of NK cell activity.[28] Since NK cell activity plays a vital role in immune system surveillance against viral-infected and cancer cells, one can ill afford any sustained decrease in this aspect of immune performance.

A study of breast cancer patients found test scores assessing an individual's overall stress level due to the diagnosis of breast cancer were strongly correlated to NK cell activity. In these women, a high degree of stress predicted a lowered ability of NK cells to destroy cancer cells. A high degree of stress also significantly predicted a poorer response to interventions aimed at improving NK cell activity.[29]

Chronic stress preceding an acutely stressful event significantly impacts NK cell activity. A study examined two groups, one consisting of individuals experiencing chronic stress, and a second group who were relatively stress-free. A single acutely stressful event experienced by both groups resulted — in the people who suffered chronic stress — in a much greater sense of subjective distress, higher peak levels of epinephrine, a more pronounced immediate reduction in NK cell activity, and a protracted decline of NK cell activity. Individuals without chronic stress readily rebounded from the acute stress with no long-term impact on NK cell activity. This study clearly demonstrates chronic stress

measurably reduces the ability of the immune system to respond to an acute psychological challenge.[30]

Secretory IgA: The ability to produce secretory IgA (sIgA) also appears to be influenced by stress.[31-33]

SIgA, as the first line of defense, is probably the single most important aspect of humoral immunity in the mucus secretions of the digestive system, mouth, lungs, urinary tract, and other body cavities. Any decline in levels of sIgA decreases one's resistance to microbial pathogens.[34]

Higher levels of the catecholamine stress hormone epinephrine are significantly associated with lower sIgA concentrations.[35] Daily problems, lack of a sense of humor,[36] and negative emotions can decrease sIgA levels.[14] To demonstrate the profound effect of emotions associated with stress on sIgA levels, a single five-minute experience of anger can produce a significant decrease in sIgA levels that can still be measured up to five hours after the emotional experience.[14]

Intestinal Microflora

Stress has a significant influence on the balance of intestinal microflora.[37] In fact, Moore et al found, "the composition of the flora was not significantly affected by drastic changes in diet, but statistically significant shifts in the proportions of some species were noted in individuals under conditions of anger or fear stress."[38]

To examine the impact of high stress on intestinal microflora, Lizko et al investigated the preparation for and participation in space flight. During the preparation phase they found a distinct decrease in the numbers of Bifidobacterium and Lactobacilli, and a corresponding increase in the numbers of E. coli and of Enterobacteria. These imbalances worsened until launch, illuminating the effect of nervous-emotional stress on altering the balance of beneficial and pathogenic organisms. After the flight the number of potentially pathogenic Enterobacteria and Clostridia were also substantially increased, while the number of Lactobacilli were decreased, suggesting the physiological strain of space flight also disrupted microflora balance.[39]

Nutrients and Botanicals to Counteract Stress Maladaptation: Adaptogenic Herbs, Vitamins, and Other Nutritional Supplements

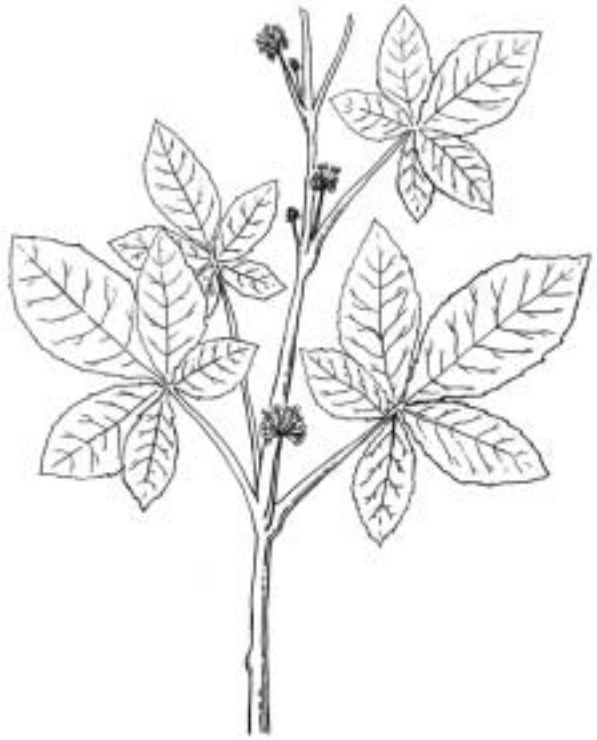
Adaptogenic Botanicals

The term "adaptogen" is used to categorize plants which improve the nonspecific response to and promote recovery from stress. In the 1950s, Soviet researchers determined that many plants, especially those belonging to the Araliaceae family, have adaptogenic properties. Perhaps the two best known adaptogens are *Panax ginseng* (Korean or Chinese ginseng) and *Eleutherococcus senticosus* (Siberian ginseng). Other adaptogenic plants include *Withania somnifera* (Ashwagandha), *Azardirachta indica* (Neem), *Boerhaavia diffusa, Glycyrrhiza glabra* (licorice), and *Rhodiola rosea*.

***Panax ginseng* (Korean ginseng)**: An abundance of research has demonstrated an enhanced response to physical or chemical stress in animals administered *Panax ginseng* or its active components.[40-44] The combination of *Panax ginseng* and a multivitamin-mineral preparation appears to have an additive adaptogenic effect.[45]

While *Panax ginseng's* anti-stress mechanisms of action are not completely understood, experiments have demonstrated a variety of actions on both the adrenal glands and the HPA axis. In animals, administration of ginseng extract resulted in a significant increase in the mean size and distribution of cells in the adrenal zona fasciculata, with the trend favoring intermediate and large cells.

Figure 2. Eleutherococcus senticosus (Siberian Ginseng).



Since mean cell area is recognized as associated with cell activity, it is assumed ginseng stimulated the adrenal cells to improve the response to an increased demand for activity.[46] However, ginsenosides Rb1, Rb2, Rc, and Rg1 appeared to inhibit steroidogenesis induced by a maximally active dose of corticotropin in isolated rat adrenal cells,[47] suggesting these isolated ginseng compounds might also buffer against an over-exaggerated adrenal response to stress or against cortisol hypersecretion. Adding further complexity, ginseng saponins have been shown to inhibit the increase of serum corticosterone in rats but increase the level of serum corticosterone in mice when both types of animals are subjected to the same type of stress in the form of a cold-water swim.[48]

At the level of the brain or HPA axis, ginseng saponins also appeared to stimulate ACTH and subsequently, cortisol production, suggesting ginseng might help potentiate an acute stress response.[49] The binding of corticosteroids to certain regions of the brain was increased in adrenalectomized rats given ginseng saponins,[50] possibly indicating ginseng acts to improve the negative feedback loop and sensitivity of the HPA axis to cortisol.

Although the available evidence shows a variety of activities, some of which appears contradictory, ginseng clearly has the ability to directly impact both the adrenal glands and the HPA axis. One possible explanation for some of the apparently contrasting actions might lie in the definition of adaptogen, which implies the capability for a bi-directional or normalizing effect on physiological function. However, since the activity of ginseng on aspects of the stress response in animals appears to vary from one species to another under the same stress conditions, it is unclear to what extent the findings on its mechanisms of action are relevant to humans undergoing stress.

Unfortunately, while animal studies on *Panax ginseng* and stress are relatively abundant, human studies are extremely limited. However, in a double-blind study, ginseng root extract added to the base of a multivitamin improved subjective parameters in a population exposed to the stress of high physical and mental activity, suggesting an adaptogenic or anti-stress ability of this combination in humans.[51]

Eleutherococcus senticosus (Siberian Ginseng): Experimental evidence supports the use of *Eleutherococcus senticosus* (Figure 2) as an adaptogen. Extracts of Eleutherococcus prolonged the exercise time to exhaustion in swimming rats,[52] and modulated changes of the HPA axis in rats under extreme conditions.[53,54]

The preponderance of clinical trials of Eleutherococcus with regard to its anti-stress effects in humans was conducted by Soviet

researchers and most have not been published in English language journals. However, Farnsworth et al reviewed the results of many of these clinical trials on more than 2,100 healthy human subjects, ranging in age from 19 to 72 years. The data indicated ingestion of extracts from the plant increased the ability to accommodate to adverse physical conditions, improved mental performance, and enhanced the quality of work under stressful conditions.[55]

***Withania somnifera* (Ashwagandha):** *Withania somnifera* has been called Indian ginseng and is considered the pre-eminent adaptogen from the Ayurvedic medical system. In situations of experimental physical stress in animals, it has shown similar anti-stress and anabolic activity to *Panax ginseng*.[43] When Withania was administered to animals, it counteracted many of the biological changes accompanying extreme stress, including changes in blood sugar, adrenal weight, and cortisol levels.[56,57] The withanolides found in *Withania somnifera* are biological substances with a sterol structure and are thought to be the component responsible for adaptogenic and glucocorticoid-like effects.[58]

Withania somnifera has also been investigated as a possible means to counteract radiation and chemotherapeutic stress on the hematopoietic system. Results in animal models have been promising, with Withania appearing to be capable of stimulating stem cell proliferation and improving red blood cell, white blood cell, and platelet parameters.[59,60] Unfortunately, human studies on the anti-stress or adaptogenic capabilities of *Withania somnifera* are lacking.

***Rhodiola rosea and Rhodiola sp.*:** *Rhodiola rosea* is another adaptogenic plant which appears to have anti-stress activity. Although administration of extracts have been shown to increase the swimming time of animals by 135-159 percent,[61] the majority of animal evidence has been focused on the effect on cardiac function secondary to stress.

Rhodiola rosea has been shown to prevent stress-induced catecholamine activity in cardiac tissue[62] and to reduce adrenaline-induced arrhythmias in animals.[63] Treatment with *Rhodiola rosea* extract prevented the decrease in cardiac contractile force secondary to environmental stress (in the form of acute cooling) and contributed to stable contractility.[64] Injection of an extract of Rhodiola was also found to prevent stress-induced increases in cAMP and decreases in cGMP in heart tissue of experimental animals.[65] Animal studies have also found *Rhodiola rosea* extract can prevent stress-induced increases in beta-endorphin.[66] While available animal evidence suggests significant stress-induced cardio-protective activity (particularly regarding catecholamine-induced alterations in function), these experiments have utilized intravenous or intraperitoneal administration routes; thus it is unclear if similar activity would be found subsequent to an oral dose.

As with the other adaptogens mentioned, human trials are nonexistent. However, investigators found that *Rhodiola kirilowii* protected from the typical abnormalities in cardiopulmonary function generally experienced when subjects ascended from an altitude of 2,500 meters to an altitude of 4,475 meters.[67] This adaptogenic plant appears to mitigate stress-induced decrements in cardiopulmonary performance in humans.

***Azardirachta indica* (Neem):** *Azardirachta indica* is an adaptogen indigenous to India. In animal experiments administration buffered the stress-induced suppression of gamma glutamyl transpeptidase activity in lymphoid tissues such as the spleen, thymus, and macrophages.[68] *Azardirachta indica* also dose-dependently reduced gastric ulcer severity in rats subjected to stress. The anti-ulcer activity appeared to be secondary to prevention of mast

cell degranulation and to increased gastric mucus.[69] Human trials on stress-induced alterations of physiology have not been published.

Boerhaavia diffusa: In animal studies, the alkaloid fraction of the root of *Boerhaavia diffusa* had a dramatic effect in buffering the elevation of plasma cortisol levels which typically occur under stressful conditions, and prevented the subsequent drop in immune system performance. Exhibiting true adaptogenic activity, these same plant alkaloids also reversed the depletion of adrenal cortisol associated with adrenal exhaustion.[70]

***Glycyrrhiza sp.* (licorice):** Glycyrrhiza appears to have modest glucocorticoid activity and might act synergistically with cortisol. Although components of licorice (primarily glycyrrhizin which is structurally similar to corticoids) can bind to glucocorticoid and mineralocorticoid receptors, weakly mimicking the role of endogenous steroid hormones,[71] and can spare cortisol, essentially extending its half-life by suppressing 5-beta reductase activity,[72] components of licorice can also counteract some of the adverse immunosuppressive effects of excess levels of glucocorticoid.[73]

Glycyrrhiza at high doses can result in side effects such as hypertension, edema, headache, and shortness of breath in about 20 percent of the population. The dose generally needed to cause these side effects is 10-14 grams of crude plant, but can vary dramatically from as little as 1-2 grams in some individuals to as high as 30 grams in others. The side effects often subside with a reduction of dose; however, some people will need to discontinue Glycyrrhiza and supplement additional potassium to reverse these side effects.[74]

Based on available evidence, Glycyrrhiza would seem to be most appropriate for individuals producing inadequate levels of cortisol, perhaps correlating best with Selye's fourth stage of "Exhaustion." In support of this, *Glycyrrhiza uralensis* has been used in China in combination with corticosteroids in the early stages of Addison's disease.[75]

The potential synergistic effect of Glycyrrhiza on cortisol has prompted some concerns about the prudence of administration to individuals with already normal or high levels of cortisol; however, in human subjects given a hot-water extract of 100 grams of Glycyrrhiza daily (equivalent to 0.7 g/d of glycyrrhizic acid), plasma cortisol remained stable while urinary cortisol increased.[76]

Vitamins and Stress

Available evidence suggests ascorbic acid in levels significantly greater than the RDA can support adrenal function and decrease high cortisol levels. Administration of ascorbic acid improved the capacity of the adrenals to adapt to surgical stress by normalizing cortisol and ACTH in patients with lung cancer.[77] Ascorbic acid given orally (1 gram t.i.d.) also buffered exogenous ACTH-induced increases in cortisol; however, it had no significant effect on fasting cortisol levels.[78]

Experimental and clinical results have shown thiamin to be an effective nutrient to protect the adrenal gland from functional exhaustion secondary to surgery. Intramuscular injections of thiamin in a dose of 0.12 g per day, starting several days prior to surgery and 1.5-2.0 hours immediately prior to surgery, reduced the cortisol reaction, both prior to the operation and at the height of the surgery. Continued administration of thiamin post-surgery prevented the usual post-surgery reduction in blood cortisol levels.[79]

A combination of ascorbic acid (300 mg t.i.d.) and vitamins B1 and B6 administered intravenously improved glucocorticoid function of the adrenal glands and simultaneously normalized the rhythmic activity of the gland.[80]

Evidence indicates adrenal cortex function is compromised in the event of a deficiency of vitamin B5 derivatives and metabolites. On the other hand, the administration of pantethine in several experimental animal models appeared to enhance adrenal cortex function.[81-83] Administration of pantethine to humans with a variety of clinical conditions buffered the rise in urinary cortisol metabolites expected to occur secondary to a loading dose of ACTH,[84] suggesting pantethine can down-regulate hypersecretion of cortisol secondary to high stress conditions.

Additional Nutritional Supplements: Lipoic Acid, Tyrosine, Phosphatidylserine, and Plant Sterol/Sterolins.

Lipoic acid: Lipoic acid, primarily known as a superior antioxidant, has been shown to prevent the accumulation of catecholamines in cardiac tissue secondary to stress. Lipoic acid also enhances the elimination of catecholamine degradation products.[85] Lipoic acid might be of indirect benefit when cortisol levels are high, since it can partially restore the hydrocortisone-induced suppression of helper T-cell activity.[86]

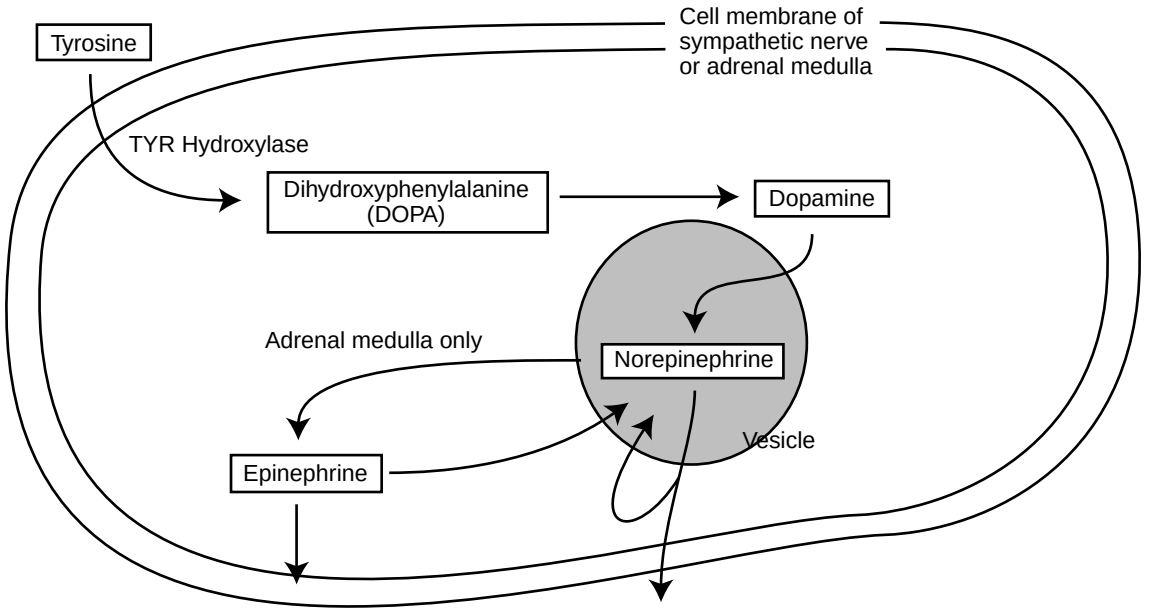
Tyrosine: Findings from several studies suggest supplementation with tyrosine might, under circumstances characterized by psychosocial and physical stress, reduce the acute effects of stress and fatigue on task performance. Stress depletes the brain reserves of the catecholamine neurotransmitters norepinephrine and dopamine in animals; and it appears that depletion, especially of norepinephrine, is closely related to stress-induced performance decline in animals. Administration of tyrosine, an amino acid precursor of catecholamines (Figure 3), alleviates both the depletion of brain catecholamines and the stress-induced decline in performance in these animals.[87] In humans, tyrosine supplementation appears to work in precisely the same manner, alleviating the stress-induced decline in nervous system noradrenaline and, subsequently, enhancing performance under a variety of circumstances including sleep deprivation, combat training, cold exposure, and unpleasant background noise.[88]

In humans, sustained and continuous work periods, exceeding 12 hours and often involving sleep loss and fatigue, can result in increased stress and anxiety, mood deterioration, and performance decrement.[87] To test the effect of tyrosine under these circumstances, Neri et al implemented a battery of performance tasks and mood scales during a night of sleep deprivation beginning at 7:30 pm and ending at 8:20 am the following day. All subjects had been awake throughout the day on which the experiment began. Tyrosine (150 mg/kg) or placebo was given six hours after the experiment began. Tyrosine was able to offset declines in performance and vigilance with improvements lasting about three hours.[89]

Deijen et al investigated the effects of tyrosine on 21 cadets during a demanding military combat training course. Ten subjects received five daily doses of a protein-rich drink containing 2 g tyrosine, and 11 subjects received a carbohydrate rich drink with the same amount of calories. The group supplied with the tyrosine-rich drink performed better on tasks involving memory and tracking. Tyrosine supplementation also decreased systolic blood pressure.[90]

Acute exposure to cold acts as a physiological stressor and can negatively influence aspects of performance such as memory. Consistent with previous research, Shurtleff et al demonstrated a decline in matching accuracy performance (a test of short term memory) when temperature was reduced to four degrees C during the sessions. However, supplementation with tyrosine (150 mg/kg) two hours prior to the cold exposure returned performance to the level found when ambient temperature was 22 degrees C.[91]

Figure 3. Synthesis of Catecholamines from Tyrosine.



Adapted from Ross G. *Essentials of Human Physiology*

Bandaret et al also showed tyrosine (100 mg/kg) supplementation improved mood and memory in humans subjected to a 4.5 hour exposure to an environmental stress consisting of cold and hypoxia.[92]

Deijen et al investigated the effect of tyrosine (100 mg/kg) administration on subjects performing a number of stress-sensitive tasks while concurrently exposed to stress-inducing 90 dB background noise. Tyrosine was found to improve performance on two cognitive tasks and transiently decreased diastolic blood pressure.[93]

Tyrosine (100 mg/kg) also enhanced measured aspects of cardiovascular and cognitive performance in humans exposed to low negative pressure sessions (-50 mm Hg) for a maximum of 30 minutes.[94]

Phosphatidylserine: Some researchers have suggested that chronic oral administration of phos-phatidylserine (PS) might counteract stress-induced activation of the HPA axis. PS appears to have an ability to beneficially modulate aspects of this endocrine system response to exercise by exerting a buffering effect on the over-production of cortisol and ACTH in response to physical stress.

A double-blind, cross-over study measured the hormonal and perceptual effects of 800 mg daily soybean-derived phosphatidylserine or placebo on 11 male subjects undergoing two weeks of intensive weight training. PS resulted in decreased post-exercise cortisol levels and attenuated the perception of muscle soreness and psychological depression which often accompanies overtraining.[95]

Pretreatment of eight healthy men with both 50 and 75 mg of intravenous brain cortex-derived phosphatidylserine within ten minutes of the start of exercise blunted the ACTH and cortisol response to physical stress.[96] Oral administration of brain cortex-derived phosphatidylserine (800 mg/d for 10 days) has also been shown to significantly blunt the

ACTH and cortisol responses to physical exercise (P = 0.003 and 0.03, respectively). The effect of phosphatidylserine on the HPA axis appears to be dose-dependent since, although participants receiving a dose of 400 mg/d of phosphatidylserine also experienced reductions in plasma cortisol, the effectiveness of the lower dose was substantially less than the 800 mg dose.[97]

Plant Sterols and Sterolins

Plant sterols and sterolins are phytochemicals generally described as plant "fats" which are chemically very similar to cholesterol but appear to have "adaptogenic" biological activity. Running a marathon consistently stresses the immune system and adrenals.[11,12] Bouic et al investigated the effects of a 100:1 mixture of plant sterols/sterolins in a double-blind trial on marathon runners. This mixture given prior to participation in the marathon offset the post-marathon declines in red and white blood cell counts seen in the placebo group. CD3 and CD4 lymphocyte subsets increased in the sterol/sterolin group and declined in the placebo group. Neutrophils rose in the placebo group (possibly indicating an infection) but remained stable in the treatment group. Interleukin-6 (a cytokine which indicates an inflammatory response) increased in the subjects given placebo, but decreased in the sterol/sterolin treatment group. Consistent with all previous research, cortisol levels increased in the marathon runners receiving the placebo; however, cortisol levels remained constant in the sterol/sterolin treatment group, indicating a reduction in the adrenal stress response to the event. Also indicative of a buffering effect on the stress response, the treatment group experienced an increase in DHEA levels and a decrease in the cortisol:DHEA ratio.[98]

Nutrients and Stress: Resetting the 24-Hour Clock

Stress results in disruption of the circadian rhythmic secretion of cortisol. There are currently several tools which can reset the 24-hour clock. Exposure to sunshine or a bright light between 6:00 and 8:00 am, regulating the light in the sleeping environment, and schedule restructuring are all possible strategies. Two supplements have also been used to reset this rhythm — the well-known pineal gland hormone, melatonin, and methylcobalamin, a coenzyme form of vitamin B12. While these techniques do not work for everyone, one or a combination of several of the above appear to be successful in at least two-thirds of people with primary circadian rhythm problems.[99,100]

An effective method to phase-shift the human circadian rhythm is the use of a combination of bright-light exposure and methylcobalamin. Methylcobalamin is thought to assist bright light in resetting the circadian rhythm by enhancing the light sensitivity of the circadian clock.[101,102] Methylcobalamin also appears to generate the right quality of sleep activity by both reducing sleep time and improving sleep quality, resulting in feeling refreshed upon waking.[103-105]

Perhaps the greatest advantage of methylcobalamin as a supplement for people with disrupted circadian rhythms secondary to stress may be its impact on cortisol. Although methylcobalamin does not impact total levels of cortisol, evidence suggests it might help shift the cortisol secretion peak, helping place the cortisol clock back on schedule.[106]

Conclusion

Acute and chronic exposure to stress results in measurable changes to a variety of critical aspects of immune, enzyme, and hormone function. While the scientific investigation of the use of nutritional supplements and herbal adaptogens to counteract some of these detrimental effects remains in its infancy,

based on available research, some recommendations might be suggested.

Positive results of experimental and clinical studies support supplementation of ascorbic acid and vitamins B1 and B6 in doses significantly higher than the RDA to support adrenal gland function. An oral dose of ascorbic acid in the amount of 1 gram three times daily appeared to be effective in one trial; however, oral dosages of vitamins B1 and B6 cannot be readily extrapolated from available data since administration routes were either intramuscular or intravenous.

Based on available evidence from animal and human trials, vitamin B5 should be supplemented to assure adequate levels in individuals under stress. Although information in available studies was limited to pantethine, it is possible that its less active form, pantothenic acid, might also prove beneficial.

Tyrosine appears to be an extremely useful supplement to consider for offsetting the effects of acute stress on performance. The studied dose was 100-150 mg/kg of body weight. The usefulness of tyrosine supplementation for performance enhancement secondary to chronic stress has not been evaluated, so it is probably prudent to restrict the high dose administration of tyrosine to conditions of acute stress. Because of lipoic acid's ability to prevent the accumulation of catecholamines in cardiac tissue, it might be a useful addition during a period of acute stress. Based on the observed mechanisms of action of Rhodeola sp., this plant might also prove to be extremely valuable under conditions of acute physiological stress.

The anti-stress effects of the other adaptogens appear to center primarily around the HPA axis and adrenal cortisol secretion. *Panax ginseng, Eleutherococcus senticosus,* and *Withania somnifera* all have long histories of use as adaptogens, are routinely used by many practitioners, and have excellent safety records; however, information on optimal doses to counteract stress-induced declines in systemic function is lacking. While no trials on the adaptogenic activity of either *Boerhaavia diffusa* or its alkaloid fraction have been conducted in humans, the preliminary animal results indicating a potential to buffer stress-induced cortisol hypersecretion, while conversely being capable of raising cortisol levels under circumstances of decreased production, are intriguing and suggest a potential future role for this plant as a biomodulator against stress-induced declines in physiological performance. Based on the mechanisms of action of Glycyrrhiza, it seems to be best utilized under circumstances of prolonged stress, where the ability of the adrenal gland to respond by releasing cortisol has become compromised.

Phosphatidylserine appears to have substantial anti-stress activity related to its buffering effect on the HPA axis and adrenal cortisol production. The optimal dose appears to be approximately 800 mg/day.

While the results of a plant sterols/sterolin mixture are preliminary, if they can ameliorate the immunosuppressive response to a physiological stress the magnitude of a marathon, these phytochemicals might be a valuable nutrient intervention to counteract the systemic effects of stress under other circumstances as well.

A combination of exposure to early morning sunlight (6-8 am) and an oral dose of 3 mg methylcobalamin daily appears to be a reasonable regime to consider for disrupted circadian rhythms secondary to stress. Although this combination has no effect on cortisol levels, evidence suggests it helps normalize the peak of cortisol secretion.

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