Review Article

Nutrients and Botanicals for Treatment of Stress: Adrenal Fatigue, Neurotransmitter Imbalance, Anxiety, and Restless Sleep

Kathleen A. Head, ND, and Gregory S. Kelly, ND

Abstract

Research shows a dramatic increase in use of the medical system during times of stress, such as job insecurity. Stress is a factor in many illnesses – from headaches to heart disease, and immune deficiencies to digestive problems. A substantial contributor to stress-induced decline in health appears to be an increased production of stress hormones and subsequent decreased immune function. Non-pharmaceutical approaches have much to offer such patients. This article focuses on the use of nutrients and botanicals to support the adrenals, balance neurotransmitters, treat acute anxiety, and support restful sleep. *(Altern Med Rev* 2009;14(2):114-140)

Introduction

It is estimated that 75-90 percent of visits to primary care physicians are related to stress – either acutely or because of chronic problems associated with stress.[1] An October 2008 American Psychological Association (APA) press release on stress in America claims eight of 10 Americans cite the economy as a significant source of stress, up from 66 percent six months earlier. In June 2008, more people were reporting symptoms associated with stress compared to the previous year, with nearly half polled indicating stress had increased in the past year. The APA conducted an online Harris poll. Table 1 outlines some of the results.[2]

Stress responses have evolved from the original "fight or flight" mechanism, designed to protect from imminent physical danger. Chronic exposure to psychological stress results in chronic engagement of the fight or flight mechanism. Physiological changes associated with the fight or flight mechanism include increased blood pressure, heart rate, and blood sugar. In addition, blood tends to be shunted away from the digestive system. These effects are associated with overreaction of the sympathetic nervous system that ramps up secretion of stress hormones such as cortisol and epinephrine.[1]

Physiology of Stress

Within seconds of an acutely stressful event, norepinephrine is released from nerve endings in preparation for a rapid response, and the adrenal glands release epinephrine and norepinephrine into the bloodstream, resulting in the familiar fight or flight response. Within minutes of a stressful event (and possibly lasting for several hours), a much more complex interaction between the nervous and endocrine systems and other forms of internal communication occurs, resulting in an intricate stress adaptation response. During this time the adrenal glands release extra cortisol into the circulation.

Kathleen A. Head, ND – 1985 graduate of National College of Naturopathic Medicine; Technical Advisor, Thorne Research, Inc; Editor-in-chief, *Alternative Medicine Review.*
Correspondence address: Thorne Research, Inc, PO Box 25, Dover, ID 83825
Email: kathih@thorne.com

Gregory Kelly, ND – Founding partner of Direct Access eHealth; contributing editor, *Alternative Medicine Review*; past instructor at the University of Bridgeport in the College of Naturopathic Medicine; published articles on various aspects of natural medicine and contributed three chapters to the *Textbook of Natural Medicine*, 2nd edition; teaches courses on weight management, the role of stress in health and disease, chronobiology of performance and health, and mind-body medicine.

Table 1. Stress-Associated Behaviors

Stress-Associated Behavior	Percent Reporting this Behavior
Overeating/eating unhealthful foods	48%
Skipped meals	39%
Fatigue	52%
Drink alcohol to manage stress	18%
Smoke to handle stress	16%
Lying awake at night	52%
Feeling of anger/irritability	60%

Several other endocrine glands are critical to the stress response. The hypothalamus, the "master gland" in the brain, responds to stress by releasing 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 CRF (Figure 1).

A wide range of events or conditions is considered physiologically stressful because the adrenals are stimulated to release stress hormones. These occurrences include calorie restriction,[3-7] surgery,[8] sleep deprivation,[9,10] excessive exercise,[3,11-13] and various mental states – all of which can result in elevated cortisol and catecholamine stress hormones.[14,15]

Stress exerts a disruptive influence on normal circadian release of cortisol. A study conducted on military cadets subjected to a five-day training course of heavy physical exercise and food and sleep deprivation found cortisol levels went up and performance deteriorated due to the stressful nature of the training. The researchers also found, "the circadian rhythm was extinguished." Even after 4-5 days of rest, circadian rhythms had not completely normalized.[3] This and other research demonstrates the physiological and psychological consequences of acute and chronic stress can persist well past cessation of a stressful event.[3,16]

Health Consequences of Chronic Stress

Stress is a factor in many illnesses – from headaches to heart disease, and immune deficiencies to digestive problems (Table 2). A substantial contributor to stress-induced decline in health appears to be an increased production of stress hormones and subsequently decreased immune function.[17]

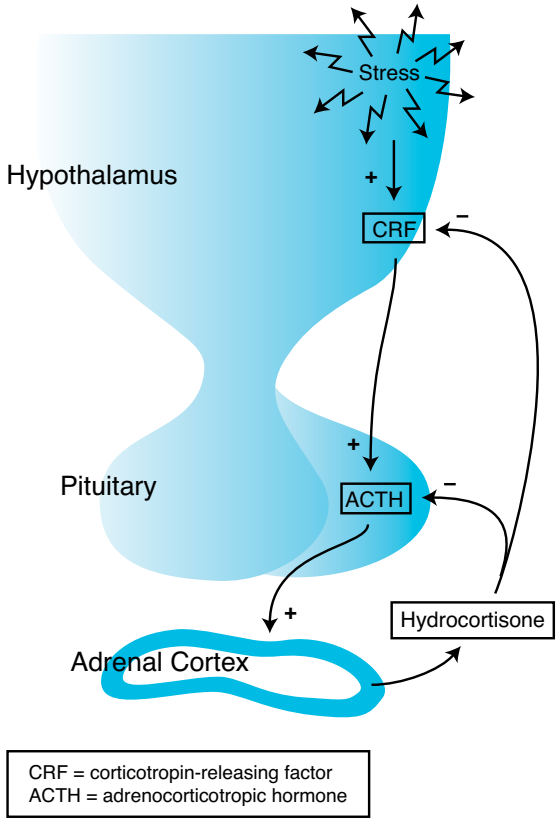
Cardiovascular Health

Stress and emotions associated with stress are important risk factors for cardiovascular disease. The Mayo Clinic reported that among individuals with existing coronary artery disease psychological stress is the strongest risk factor predictive of future cardiac events, including myocardial infarction (MI) and cardiac death. In this study, the economic cost because of rehospitalization comparing individuals experiencing high and low stress was $9,504 and $2,146, respectively.[18]

When researchers interviewed heart attack survivors they found the intensity and timing of a stressful emotion, like anger, dramatically increased their risk.[19] The Normative Aging Study also provided compelling evidence that emotions associated with a higher stress level are significant risk factors for coronary heart disease (CHD) and 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.[20]
- 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).[21]
- 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.[22]

Figure 1. The Hypothalamic-Pituitary-Adrenal Hormone Cascade and Feedback Loop



Immune Performance

Research indicates a bout of acute stress of any kind will cause a temporary decrease in immune system functioning, while chronic stress will result in continued decline in immunity.

Natural Killer Cell Cytotoxicity

Overwhelming evidence demonstrates virtually any type of stress has a detrimental effect on the ability to maintain optimal levels of natural killer (NK) cell cytotoxic activity.[14,23-25] A severe life stress may be associated with up to a 50-percent reduction of NK-cell activity.[26] Since NK-cell activity plays a vital role in immune system surveillance against viruses and cancer cells, a sustained decrease in this aspect of immune performance can have serious consequences.

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. A high degree of stress predicted a lowered ability of NK cells to destroy cancer cells and significantly predicted a poorer response to interventions aimed at improving NK-cell activity.[27]

Chronic stress preceding an acutely stressful event can significantly impact NK-cell activity. A study examined two groups, one experiencing chronic stress and a second relatively stress-free. A single acutely stressful event experienced by both groups resulted in a 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 in the individuals suffering from chronic stress. Individuals without chronic stress readily rebounded from the acute stress with no long-term impact on NK-cell activity. This study demonstrates chronic stress can measurably reduce the ability of the immune system to respond to an acute psychological challenge.[28]

Secretory IgA

The ability to produce secretory IgA (sIgA) also appears to be influenced by stress.[29-31] sIgA may be the single-most important aspect of humoral immunity in the mucus secretions of the digestive system, mouth, lungs, urinary tract, and other body cavities, and any decline in its levels can decrease resistance to microbial pathogens.[32]

Higher levels of the catecholamine stress hormone epinephrine are significantly associated with lower sIgA concentrations.[33] Daily problems, lack of a sense of humor,[34] and negative emotions can decrease sIgA levels.[15] To demonstrate the profound effect of emotions, a single five-minute experience of anger can produce a significant decrease in sIgA levels that can be measured up to five hours after the experience.[15]

Intestinal Microflora

Stress has a significant influence on the balance of intestinal microflora.[35] 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."[36]

Table 2. Health Consequences of Chronic Stress

Health Consequence	Specific Effect
Natural killer cell activity	⇓
Secretory IgA	⇓
Bifidobacteria and Lactobacilli	⇓
Enterobacteria and *E. coli*	⇑
Risk for myocardial infarction	⇑

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 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 numbers of potentially pathogenic Enterobacteria and Clostridia were also substantially increased, while the number of Lactobacilli was decreased, suggesting the physiological strain of space flight disrupted the microflora balance.[37]

Botanicals: Adrenal/Central Nervous System Adaptogens

The term "adaptogen" categorizes plants that improve the non-specific response to and promote recovery from stress. Coined by researcher I.I. Brekhman, an adaptogen has four general properties: (1) it is harmless to the host; (2) it has a general, rather nonspecific effect; (3) it increases the resistance of the recipient to a variety of physical, chemical, or biological stressors; and (4) it acts as a general stabilizer/normalizer.[38]

In the 1950s, Soviet researchers determined that many plants, especially those in the Araliaceae family, have adaptogenic properties. The two best-known adaptogens are *Panax ginseng* and *Eleutherococcus senticosus*. Other adaptogenic plants include *Withania somnifera*, Glycyrrhiza species, and *Rhodiola rosea*. Panax, Eleutherococcus, and Withania appear to exert adaptogenic effects primarily on the adrenal glands; whereas, Rhodiola appears to be primarily a central nervous system (CNS) adaptogen.

Panax ginseng (Korean ginseng)

An abundance of research demonstrates an enhanced response to physical or chemical stress in animals administered *Panax ginseng* or its active components.[39-43] The combination of *Panax ginseng* and a multivitamin-mineral preparation appears to have an additive adaptogenic effect.[44]

While the anti-stress mechanisms of *Panax ginseng* are not completely understood, experiments demonstrate a variety of actions on both the adrenal glands and the hypothalamic-pituitary-adrenal (HPA) axis. Animal studies show contradictory effects of ginseng, some indicating increased activity,[45,46] while others demonstrate an inhibition of steroidogenesis.[46,47] At the level of the brain or HPA axis, ginseng saponins appear to stimulate ACTH and subsequent cortisol production, suggesting ginseng might help potentiate an acute stress response.[48] The binding of corticosteroids to certain regions of the brain was increased in adrenalectomized rats given ginseng saponins,[49] possibly indicating ginseng acts to improve the negative feedback loop and sensitivity of the HPA axis to cortisol.

Although available evidence demonstrates multiple activities, some of which appear contradictory, ginseng clearly has the ability to directly impact both the adrenal glands and the HPA axis. An 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. Unfortunately, while animal studies on *Panax ginseng* and stress are relatively abundant, human studies are limited. 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 effect of such a combination in humans.[50]

In a study of endurance athletes experiencing training stress, 2 g/day dried Panax root for six weeks had no effect on measured immune parameters or cortisol, testosterone, or testosterone:cortisol ratios.[51]

Eleutherococcus senticosus

Experimental evidence supports the use of *Eleutherococcus senticosus* (also known as *Acanthopanax senticosus* or Ciwujia, and previously known as Siberian ginseng) 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]

Most clinical trials examining the anti-stress effects of Eleutherococcus in humans have been conducted by Soviet researchers and generally 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 19-72 years. The data indicates Eleutherococcus increases the ability to accommodate to adverse physical conditions, improves mental performance, and enhances the quality of work under stressful conditions.[55]

In a double-blind study, 45 healthy volunteers (20 men, 25 women; ages 18-30) were randomized to receive *Eleutherococcus senticosus* or placebo for 30 days. Patients were subject to the Stroop Colour-Word (Stroop CW) test to assess stress response, along with heart rate and systolic and diastolic blood pressure, before and after treatment. Unlike placebo, those taking the herb had a 40-percent reduction in heart rate response to the Stroop CW stressor. Moreover, in females but not males, Eleutherococcus accounted for a 60-percent reduction in systolic blood pressure response to the cognitive challenge test. These facts suggest Eleutherococcus may be helpful for stress adaptation.[56]

The study cited on endurance athletes in the discussion of *Panax ginseng* was a double-blind, placebo-controlled trial that also included a group who took Eleutherococcus (8 mL daily of a 33-percent ethanolic extract equivalent to 4 g/day) for six weeks. The group taking Eleutherococcus (ES) experienced a significant decrease in the testosterone:cortisol ratio, with elevated cortisol being the primary contributor to the ratio change. The authors said this result, "may be consistent with animal research suggesting a threshold of stress below which ES increases the stress response and above which ES decreases the stress response." This is the definition of an adaptogen.[51]

Glycyrrhiza glabra (licorice)/ Glycyrrhiza uralensis

Glycyrrhiza appears to have modest glucocorticoid activity and might act synergistically with cortisol. 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,[57] and can spare cortisol, essentially extending its half-life by suppressing 5-beta reductase activity.[58] Components of licorice can also counteract some of the adverse immunosuppressive effects of excess levels of glucocorticoid.[59] Glycyrrhiza attenuated the effects of vibrational stress on red blood cell indices in an animal model.[60]

Based on available evidence, Glycyrrhiza would seem to be appropriate for individuals producing inadequate levels of cortisol. In support of this, *Glycyrrhiza uralensis* has been used in China in combination with corticosteroids in the early stages of Addison's disease.[61]

The potential synergistic effect of Glycyrrhiza on cortisol has prompted concern about the prudence of administering it to individuals with already normal or high levels of cortisol. However, in human subjects given a hot-water extract of 100 g Glycyrrhiza daily (equivalent to 0.7 g/day glycyrrhizic acid), plasma cortisol remained stable while urinary cortisol increased.[62]

Withania somnifera (Ashwagandha)

Withania somnifera (ashwagandha), also called Indian ginseng, is considered to be the pre-eminent adaptogen from the Ayurvedic medical system. In situations of experimental physical stress in animals, it has shown anti-stress and anabolic activity similar to *Panax ginseng*.[42] 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.[63,64] The withanolides in *Withania somnifera* are biological substances with a sterol structure and are thought to be the component responsible for its adaptogenic and glucocorticoid-like effects.[65]

An animal study found Withania improved depression- and anxiety-associated behavior caused by social isolation.[66] In an animal model of chronic stress, *Withania somnifera* and *Panax ginseng* extracts

were compared for the ability to attenuate the effects of chronic stress. Both botanicals decreased the number and severity of stress-induced ulcers, reversed stress-induced inhibition of male sexual behavior, and inhibited the adverse effects of stress on retention of learned tasks. While both botanicals reversed stress-induced immunosuppression, only Withania increased peritoneal macrophage activity. Although the activity of Withania was approximately equal to that of *Panax ginseng*, Withania has an advantage over *Panax ginseng* in that it does not appear to result in ginseng-abuse syndrome, a condition characterized by high blood pressure, water retention, muscle tension, and insomnia when excess amounts are consumed.[67]

Withania somnifera has been investigated as a means to counteract radiation and chemotherapeutic stress on the hematopoietic system. Results in animal models are promising, with Withania appearing to stimulate stem cell proliferation and improve red blood cell, white blood cell, and platelet parameters.[68,69]

Rhodiola rosea

The adaptogenic properties, cardiopulmonary protective effects, and CNS activities of *Rhodiola rosea* have been attributed primarily to its ability to influence levels and activity of the biogenic monoamines serotonin, dopamine, and norepinephrine in the cerebral cortex, brain stem, and hypothalamus. It is believed the changes in monoamine levels are due to inhibition of the activity of enzymes responsible for monoamine degradation and facilitation of neurotransmitter transport within the brain.[70]

In addition to these central effects, Rhodiola has been reported to prevent both catecholamine release and subsequent cyclic AMP elevation in the myocardium and the depletion of adrenal catecholamines induced by acute stress.[71] Rhodiola's adaptogenic activity might also be secondary to induction of opioid peptide biosynthesis and activation of both central and peripheral opioid receptors.[72-75]

Rhodiola has been shown to prevent stress-induced catecholamine activity in cardiac tissue[71] and to reduce adrenaline-induced arrhythmias in animals.[76] *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.[77] Injection of a Rhodiola extract was found to prevent stress-induced increases in cAMP and decreases in cGMP in heart tissue of experimental animals.[78] Animal studies have also found *Rhodiola rosea* extract can prevent stress-induced increases in beta-endorphin,[72] as well as behavioral changes brought on by chronic stress.[79]

It is suggested Rhodiola has utility as a therapy in asthenic conditions (decline in work performance, sleep disturbances, poor appetite, irritability, hypertension, headaches, and fatigue) developing subsequent to intense physical or intellectual strain or illness.[80]

A small pilot study was conducted to determine the effects of Rhodiola on patients with generalized anxiety disorder (GAD). Participants with DMS-IV diagnosed GAD received 170 mg *Rhodiola rosea* (Rhodax®) twice daily for 10 weeks. Subjects experienced significant ($p=0.001$) differences between baseline (23.4 ± 6.0) and post-Rhodiola (14.10 ± 8.0) scores on the Hamilton Anxiety Rating Scale (HAM-A).[81]

In a double-blind, randomized, controlled trial (RCT) 60 subjects with stress-related fatigue were given a standardized proprietary *Rhodiola rosea* product (SHR-5; 576 mg) or placebo in two daily doses (morning and lunchtime) for 28 days. The Rhodiola group experienced improved concentration associated with decreased stress-related fatigue and significant decreases in salivary cortisol compared to the placebo group.[82]

Rhodiola supplementation (SHR-5) favorably influenced fatigue and mental performance in physicians during the first two weeks on night duty.[83] Students receiving 50 mg twice daily of a standardized extract of *Rhodiola rosea* (SHR-5) demonstrated significant improvements in physical fitness, psychomotor function, mental performance, and general well-being. Subjects receiving the Rhodiola extract reported statistically significant reductions in mental fatigue, improved sleep patterns, a reduced need for sleep, greater mood stability, and a greater motivation to study. The average exam scores between students receiving the Rhodiola extract and placebo were 3.47 and 3.20, respectively.[84]

Studies of Combination Adaptogens

A commercial combination of Rhodiola, Eleutherococcus, and *Schisandra chinensis* (ADAPT-232) was given to mice for seven days prior to swimming until exhaustion, resulting in a seven-fold increase in swimming time. Repeated dosing of the herbal combination also resulted in a dose-dependent increase in Hep72, a protein induced by stressful conditions, including hyperthermia, oxidative stress, and pH changes.[85]

In a clinical study, the effect of adaptogens on ultra-weak photon emission (UPE) was examined. UPEs are a result of weak light emitted from living organisms. UPE emission can increase in disease states and under stressful conditions. In a double-blind RCT, 30 subjects were assigned to *Rhodiola rosea* (SHR-5 containing 144 mg Rhodiola, 2.7% rosavins), ADAPT-232 (140 mg of proprietary blend including Schizandra, Rhodiola, and Eleutherococcus; 0.5% schizandrin, 0.47% salidroside, 0.59% rosavins, 11% eleuth B, and 19% eleuth E), or placebo (10 in each group) for one week. UPE was measured on the dorsal side of the hand before and after one week of supplementation. In addition, subjects were evaluated for perceived levels of stress and fatigue. After one week, subjects in the Rhodiola group experienced a significant decrease in UPE and level of fatigue compared to placebo ($p=0.027$ and $p=0.049$, respectively).[86]

Cortisol Modulators

Phosphatidylserine

Some researchers suggest chronic oral administration of phosphatidylserine (PS) might counteract stress-induced activation of the HPA axis. PS appears to beneficially modulate aspects of this endocrine response by exerting a buffering effect on the over-production of cortisol and ACTH in response to physical stress.

A double-blind, crossover study measured the hormonal and perceptual effects of 800 mg PS daily 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 the psychological depression that often accompanies overtraining.[87]

Pretreatment of eight healthy men with 50 and 75 mg of intravenous PS within 10 minutes of commencing exercise blunted the ACTH and cortisol response to physical stress.[88] Oral administration of 800 mg PS daily for 10 days significantly blunted the ACTH and cortisol responses to physical exercise ($p=0.003$ and $p=0.03$, respectively). The effect of PS on the HPA axis appears to be dose-dependent; participants receiving 400 mg PS daily experienced plasma cortisol reductions, although the effectiveness of the lower dose was substantially less than the 800-mg dose.[89]

In a crossover RCT, 10 healthy males given 600 mg PS for 10 days exhibited significant decreases in peak cortisol and area under the curve (AUC) for cortisol compared to placebo.[90]

Although most studies have examined the effect of PS on exercise-induced stress, a small study examined its effect on mental/emotional stress. Four groups of 20 subjects each were given a phosphatidic acid complex and phosphatidylserine (PAS) at a dose of 400 mg, 600 mg, 800 mg, or placebo for three weeks. At the end of three weeks the subjects were exposed to stress by the Trier Social Stress Test (TSST). The 400-mg PAS group experienced blunting of serum ACTH and serum and salivary cortisol and decreased emotional responses to TSST-induced stress; no statistically significant effects were noted with placebo or the higher-dose PAS groups. The authors did not speculate on the lack of effect with higher doses.[91]

Fish Oil

In a small study, plasma levels of cortisol and epinephrine (also typically elevated by stress) were measured in seven healthy men exposed to 30 minutes of mental stress (math test) before and after three weeks of fish oil supplementation (7.2 g daily). At baseline, average epinephrine levels were 60.9 and 89.3 pg/mL and cortisol levels were 291 and 372 µmol/L before and after test stress, respectively. After three weeks of fish oil supplementation, the cortisol spike following test stress was abolished and the epinephrine spike significantly blunted.[92]

EPA and DHA or DHA alone lowers norepinephrine levels in healthy non-stressed subjects as well as students experiencing stress from taking exams.[93,94]

Plant Sterols and Sterolins

Plant sterols and sterolins are phytochemicals generally described as plant "fats" that, while chemically very similar to cholesterol, appear to have biological "adaptogenic" activity. Running a marathon consistently stresses the immune system and adrenals.[12,13] In a double-blind trial of marathon runners, Bouic et al investigated the effects of a 100:1 mixture of plant sterols/sterolins on stress-induced immune system depression. Given prior to participation in a marathon this mixture offset 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 (an inflammatory cytokine) decreased in the sterol/sterolin treatment group but increased in the placebo group. Consistent with previous research, cortisol levels increased in 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 dehydroepiandrosterone (DHEA) levels and a decrease in the cortisol:DHEA ratio.[95]

alpha-Lipoic Acid

alpha-Lipoic acid might be of indirect benefit when cortisol levels are high since it can partially restore hydrocortisone-induced suppression of helper T-cell activity.[96] Lipoic acid, primarily known as an antioxidant, has also been shown to prevent accumulation of catecholamines in cardiac tissue secondary to stress and enhance the elimination of catecholamine degradation products.[97]

Anxiolytic/Sedative Botanicals and Plant Extracts

A number of botanicals have been used historically as sedative/calmatives – including L-theanine, *Passiflora incarnata*, *Valeriana officinalis*, *Humulus lupulus*, *Matricaria chamomilla*, *Galphimia glauca*, *Bacopa monniera*, *Centella asiatica*, *Melissa officinalis*, *Piper methysticum*, *Scutellaria lateriflora*, and *Ziziphus jujuba*. These can be beneficial for anxiety during the day as well as for sleep disturbances.

L-Theanine

L-theanine is an amino acid extracted from green or black tea. A cup of black tea contains approximately 20 mg theanine. In the brain L-theanine increases dopamine,[98,99] serotonin,[98] and the inhibitory neurotransmitter glycine.[99]

Green tea is often used as a relaxing beverage. Although it can contain more caffeine than coffee, theanine appears to counteract its stimulant effect to some degree. In rats, theanine administered intravenously after caffeine dosing, and at approximately the same dose, blunted the stimulant effect of caffeine seen on electroencephalographic recordings. When given by itself in a smaller dose (20-40% of the original dose), theanine administration resulted in excitatory effects, suggesting a dual activity of theanine depending on the dose.[100]

Studies show L-theanine induces alpha-brain wave activity, which correlates with a perceived state of relaxation. A small Japanese study of university students showed oral L-theanine administration of 200 mg led to increased alpha-brain waves and a subjective sense of relaxation. Theanine administration caused a dose-dependent relaxed, yet alert, state of mind without sedation, beginning approximately 40 minutes after oral dosing.[101] A study determined more recently that even lower doses of L-theanine can induce alpha-wave production. Electroencephalogram (EEG) tracings were obtained from 54 healthy participants at baseline and 45, 60, 75, 90, and 105 minutes after 50 mg L-theanine (n=16) or placebo (n=19). The theanine group demonstrated a statistically significantly greater increase in alpha-wave production ($p<0.05$) than the placebo group; both groups sat quietly with eyes closed during the EEG evaluations.[102]

The acute stress response elicited by a math test was attenuated by 200 mg theanine – assessed by heart rate and salivary sIgA.[103]

Bacopa monniera

Both animal and clinical research supports the traditional Ayurvedic use of *Bacopa monniera* (Brahmi) for anxiety. Research using a rat model of clinical anxiety demonstrated a Bacopa extract of 25-percent bacoside A exerted anxiolytic activity comparable to lorazepam, a common benzodiazepine anxiolytic drug. Importantly,

the Bacopa extract did not induce amnesia, a side effect associated with lorazepam, but instead had a memory-enhancing effect.[104]

A one-month, limited clinical trial of 35 patients with diagnosed anxiety neurosis demonstrated that administration of Brahmi syrup (30 mL daily in two divided doses, equivalent to 12 g dry crude extract of Bacopa) resulted in a significant decrease in anxiety symptoms, level of anxiety, level of disability, and mental fatigue, and an increase in immediate memory span. Other changes noted were increased body weight and decreased respiration rate and systolic blood pressure.[105]

An RCT examining Bacopa's effect on cognitive function found significant improvement in anxiety ($p<0.001$). Subjects were randomized to receive 300 mg Bacopa or placebo for 12 weeks; improvements were most pronounced after 12 weeks compared to assessment at five weeks.[106]

In an RCT conducted on the mental and emotional effects of Bacopa in the elderly, with a six-week placebo run-in period, 54 subjects (age 65 or older; mean age 73.5) were randomized to receive 300 mg/day Bacopa or placebo for 12 weeks. Subjects taking Bacopa experienced significant improvement in anxiety (measured by combined state plus trait anxiety scores) compared to placebo, in addition to improvements in cognitive performance and depression scores.[107]

Valeriana officinalis

Valeriana officinalis (valerian) is well known for its anxiolytic and sedative effects. The essential oils in valerian appear to provide its sedative activity, while its valepotriates exert a regulatory effect on the autonomic nervous system.[108] Although more than 150 constituents have been identified, none appear to be solely responsible for valerian's effects, suggesting its compounds act synergistically.[109,110]

Valerian interacts with neurotransmitters such as gamma-aminobutyric acid (GABA),[111,112] producing a dose-dependent release of GABA.[113] Valerian also inhibits the enzyme-induced breakdown of GABA in the brain, with concomitant sedation.[114] Valerian's inherent GABA content could directly cause sedation, although reservations exist regarding bioavailability.[112,115,116] The valerian lignan hydroxypinoresinol has been found to bind to benzodiazepine receptors.[117] Valerian's sedative effect acts more as a nervous system depressant than as a muscle relaxant.[118]

In a double-blind trial of 48 adults placed in an experimental situation of social stress, valerian reduced subjective sensations of anxiety and did not cause measurable sedation.[119]

In comparison to diazepam (2.5 mg three times daily), a valerian preparation (50 mg three times daily, standardized to 80% dihydrovaltrate) showed a similar significant reduction in symptoms of anxiety measured on HAM-A after four weeks.[120]

Valerian and *Piper methysticum* were compared to each other and placebo in a standardized mental stress test in 54 healthy individuals. Unlike placebo, both preparations decreased systolic blood pressure responsiveness and self-reported feelings of stress, and inhibited a stress-induced rise in heart rate.[121]

Valerian is also beneficial for sleep disorders, often associated with stress and anxiety. Four placebo-controlled studies present the best evidence of the effectiveness of valerian in the treatment of insomnia. In a crossover RCT valerian improved sleep latency (time to fall asleep) and quality compared to placebo. The effects of 400 mg aqueous valerian were noteworthy, with only mild improvement at a higher dose of 900 mg.[122] In a study of 128 participants given 400 mg aqueous valerian extract or placebo, improvement was noted in sleep latency and sleep quality in four groups – young, elderly, women, and men.[123] In another study 121 patients were given 600 mg/day valerian extract or placebo for four weeks and assessed for clinical effectiveness using four validated rating scales. After 14 days valerian was rated better than placebo on the Clinical Global Impression Scale (CGIS); at study conclusion (day 28), 66 percent of patients rated valerian effective for sleep compared to 26 percent taking placebo.[124] Using polysomnographic recordings and questionnaires, Donath et al found sleep latency was significantly reduced in 16 insomnia patients treated with valerian compared to placebo ($p<0.05$). The percentage of slow-wave sleep also increased compared to placebo ($p<0.05$).[125]

Other studies support valerian in insomnia. Valerian (600 mg daily) was compared to the benzodiazepine oxazepam (10 mg daily) in 202 patients for six weeks with positive effects on sleep quality, measured by the Sleep Questionnaire, CGIS, and Global Assessment

of Efficacy. Mild-to-moderate adverse effects were reported in 36 percent of patients taking oxazepam compared with 28 percent in the valerian group.[126] A trial of valerian use after benzodiazepine withdrawal produced subjective improvement in sleep quality after two weeks at 100 mg three times daily.[127] In a study of patients complaining of insufficient sleep, significant improvement was noted after two weeks using 470-1,410 mg of valerian at bedtime.[128]

An animal study comparing valerian with a combination of valerian, Rhodiola, and L-theanine found significant and comparable shortening of sleep latency in both groups.[129]

Passiflora incarnata

When administered intraperitoneally to rats, *Passiflora incarnata* (passionflower) extract significantly prolonged sleep time.[130] Other animal models demonstrate Passiflora exerts anxiolytic effects via opioid[132] and GABA/benzodiazepine receptors.[131,132] The anxiolytic effects of Passiflora are thought to be attributed to a specific benzoflavone compound.[133]

In a four-week RCT, 36 patients (18 in each group) with general anxiety disorder were assigned to 45 drops/day Passiflora plus a placebo tablet or 30 mg/day oxazepam plus placebo drops. Both were effective at decreasing anxiety, with no significant differences between the groups; the oxazepam group experienced significant impairment of job performance.[134]

Humulus lupulus

Humulus lupulus (hops) is often used as a mild sedative for anxiety, nervousness, and insomnia. Much of this use stems from the observation of sleepiness in European hops-pickers. *The Complete German Commission E Monographs* lists hops as an approved herb for "mood disturbances such as restlessness and anxiety, sleep disturbances."[135]

Although there have been no meaningful clinical studies to support hops alone as a sedative, several European studies have demonstrated formulas combining hops with other sedative herbs are effective for insomnia. A pilot study using a preparation containing 500 mg valerian extract combined with 120 mg hops extract at bedtime for 30 patients with mild-to-moderate insomnia resulted in a decline in sleep latency and wake time. Insomnia was diagnosed using a polysomnographic standard examination, and a positive treatment effect was based on two weeks of treatment with re-examination.[136] Additionally, a similar hop-valerian preparation demonstrated efficacy and tolerability equivalent to a benzodiazepine for the treatment of non-chronic and non-psychiatric sleep disorders.[137]

Combinations of hops with valerian and Passiflora or *Melissa officinalis* are also approved by the German Commission E as sedative and sleep-promoting formulas. Further studies are needed to determine whether hops acts as a mild sedative independently, as a synergist, or is absent of sedative action.

Matricaria chamomilla

To examine the sedative effects of *Matricaria chamomilla* (German chamomile), a study using intraperitoneal administration of chamomile extract in mice concluded apigenin functions as a ligand for benzodiazepine receptors, resulting in anxiolytic and mild sedative effects, but no muscle relaxant or anticonvulsant effects.[138] In contrast to diazepam, apigenin does not cause memory impairment. A lyophilized infusion of chamomile, also administered intraperitoneally in mice, elicited a depressive effect on the CNS.[139]

In an open case study to examine the effects of two cups of chamomile tea on patients undergoing cardiac catheterization, 10 of 12 patients in the study achieved deep sleep within 10 minutes of drinking the tea.[140] In an animal study chamomile extract, but not Passiflora extract, significantly reduced sleep latency.[141]

Galphimia glauca

Galphimia glauca (thryallis; rain-of-gold) is a botanical used as a nervine and sedative in traditional Latin American medicine. This herb has demonstrated anxiolytic effects in a mouse model.[142] Galphimia has been the subject of significant scrutiny to determine its active, anxiolytic constituents. The constituent originally thought to provide an anxiolytic effect is galphimine B.[143] In a mouse model galphimine A and B and a galphimine-rich fraction exhibited similar anxiolytic effects. The presence of a hydroxyl group at C-4, C-6, and C-7 and a double-bond in the A ring seem to be primary determining factors for the anxiolytic effects of the constituents.[144]

In an RCT the effectiveness of a standardized extract of *Galphimia glauca* was compared to the

benzodiazepine lorazepam in patients with GAD; inclusion criteria included a score of ≥19 on HAM-A. Subjects (n=152; 114 completers) were randomized to receive 310 mg Galphimia (containing 0.348 mg galphimine B) (n=72; 55 completers) or 1 mg lorazepam, each twice daily for four weeks. Galphimia was comparable to lorazepam in regard to lowering HAM-A scores – reduced by 17.65 points in each group (61.2% and 60.3% in the Galphimia and lorazepam groups, respectively). Anxiolytic effects of the herb were noted within the first week. The side effect of excessive sedation was reported in 6.8 percent of subjects in the Galphimia group and 21.3 percent in the lorazepam group.[145]

Centella asiatica

Centella asiatica (gotu kola) has a long history of use in Ayurvedic and Chinese medicine for treatment of anxiety and depression. In an RCT 40 subjects (20 in each group) were assigned to one large dose (12 g) Centella or placebo prior to testing for acoustic startle response (ASR), an accepted measure of anxiety. The herb significantly decreased the ASR amplitude 30 and 60 minutes after treatment compared to placebo.[146] Significantly lower doses (750 mg daily) were used long-term to improve mood and cognition in an elderly population.[147]

Anxiolytic effects of Centella have also been demonstrated in an animal model[148] and *in vitro*. *In vitro* studies have helped elucidate Centella's anxiolytic mechanisms, one of which is stimulation of glutamic acid decarboxylase, the enzyme responsible for conversion of the excitatory amino acid glutamic acid to the inhibitory neurotransmitter GABA.[149]

Melissa officinalis

In an *in vitro* study, *Melissa officinalis* (lemon balm), compared to other herbs tested, demonstrated the greatest inhibition of GABA-transaminase, the enzyme responsible for degradation of GABA.[149] Further research identified rosmarinic acid as the primary constituent responsible for this inhibition (40% inhibition at 100 mcg/mL).[150]

Clinical studies have examined the effects of Melissa in combination with valerian, but not alone. A crossover RCT of 24 healthy volunteers examined the effect of a single dose (600 mg, 1200 mg, or 1800 mg) of a Melissa/valerian combination (80 mg Melissa/120 mg valerian per tablet) or placebo on separate days separated by seven-day washout periods. Effects on mood and anxiety were assessed pre-dosing and one, three, and six hours post-dosing via completion of the Defined Intensity Stressor Stimulation questionnaire. While the 600-mg dose ameliorated stress induced by the questionnaire, the 1800-mg dose appeared to enhance anxiety.[151]

Another study examined the combination of valerian and Melissa for restlessness and sleep problems in children. A specific formulation, Euvegal® forte (80 mg lemon balm and 160 mg valerian per tablet) was evaluated in an open-label, multi-center trial of 918 children (average age 8.3 years). Dosage was up to four tablets daily (74.6% took the maximum dose). At baseline, 61.7 percent of children reported symptoms compared to 12.5 percent after four weeks. While restlessness and sleep problems were moderate-to-severe at baseline in the majority of subjects, after four weeks these symptoms were absent or rated mild in the majority of children.[152]

Piper methysticum

Extracts of *Piper methysticum* (kava kava) have been found to be effective anxiolytic agents. In a double-blind RCT, 29 subjects were treated for four weeks with 100 mg kava extract three times daily, standardized to contain 70-percent kava lactones. Compared to placebo, the kava group experienced significant decreases in anxiety symptoms measured by HAM-A.[153] In another double-blind RCT of two groups of 20 women using the same dosage as the previous trial, kava was found effective for decreasing anxiety associated with menopause.[154]

In a number of studies, kava extracts compare favorably to prescription medications such as benzodiazepines and tricyclic antidepressants (often used to treat anxiety disorders), and without the side effects commonly seen with these drugs.[155,156] Not only does kava not impair reaction time, it appears to improve concentration. In two separate studies, oxazepam slowed reaction time while kava actually enhanced performance.[157,158]

In a five-week RCT, kava (increasing doses of 50-300 mg daily during the first week) or placebo was prescribed to 40 patients tapering off benzodiazepines

Table 3. Anxiolytic Botanicals and Mechanisms of Action

Botanical/Extract	Proposed Mechanisms of Action
Bacopa monniera (Brahmi)	Mediates calcium-ion influx; anxiolytic effects not completely understood
Centella asiatica (gotu kola)	Stimulates conversion of glutamic acid to GABA
Galphimia glauca (thryallis; rain-of-gold)	Modifies synaptic transmission at dopaminergic neurons
Humulus lupulus (hops)	Sedative mechanisms still under investigation
L-Theanine (from *Camellia sinensis*)	Increases alpha-brain wave activity; increases dopamine, serotonin, and glycine (an inhibitory neurotransmitter)
Matricaria chamomilla (German chamomile)	Interacts with benzodiazepine receptors
Melissa officinalis (lemon balm)	Inhibits GABA degradation
Passiflora incarnata (passionflower)	Interacts with opioid and GABA-benzodiazepine receptors
Piper methysticum (kava kava)	Binds to GABA receptors; inhibits norepinephrine uptake
Scutellaria lateriflora (blue skullcap)	Binds to GABA-benzodiazepine receptors; contains GABA
Valeriana officinalis (valerian)	Increases GABA release and inhibits GABA breakdown; binds to benzodiazepine receptors
Ziziphus jujuba (jujabe)	Induces sleep via serotonergic pathways

over the first two weeks of the study. Kava was statistically superior to placebo as determined by the HAM-A.[159] In an eight-week, multi-center RTC, 129 patients with generalized anxiety disorder received 400 mg kava, 10 mg buspirone, or 100 mg opipramol (a tricyclic antidepressant). No significant differences on HAM-A were noted among the three groups, with 75 percent in each group responding (defined as at least 50-percent improvement in symptom scores); 60 percent achieved complete remission.[160]

In a dose-effectiveness RCT with 50 subjects, lower kava doses of 50 mg three times daily for four weeks were shown effective based on HAMA-A, without side effects or other signs of toxicity.[161]

Scutellaria lateriflora

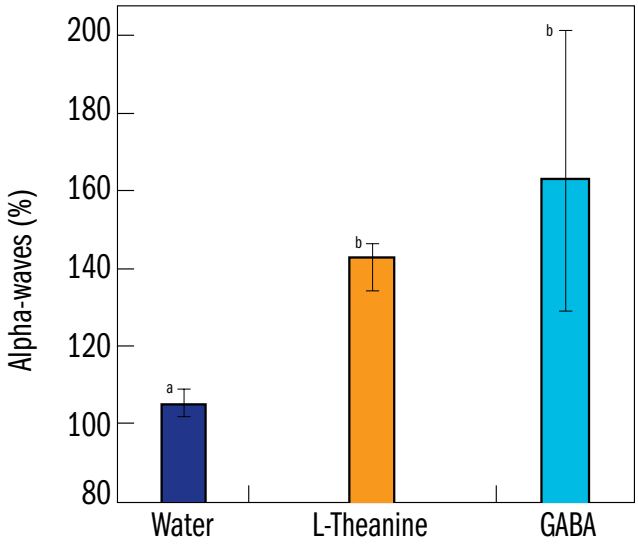
Scutellaria lateriflora (blue skullcap) was used traditionally by the eclectic physicians for anxiety, restlessness, irritability, and insomnia. In a controlled trial, 19 healthy subjects were given four treatment protocols in random order with at least a two-day washout period between protocols: (1) 1 capsule 350 mg organic, freeze-dried skullcap; (2) 1 capsule 100 mg organic, freeze-dried skullcap (different manufacturer; authors associated with this company); (3) 2 capsules of the same 100-mg organic freeze-dried skullcap as in protocol number 2; and (4) two placebo capsules. The effect of each protocol on symptoms of anxiety, cognition, and energy was evaluated using a 10-point scale at baseline and 30, 60, 90, and 120 minutes after administration. While an anxiolytic effect was noted for each skullcap preparation, with the greatest effect reported with the 200-mg dose, statistical significance was apparently not determined.[162]

Ziziphus jujuba var. spinosa

Ziziphus jujuba (jujabe) has a long history of use in traditional Chinese medicine for anxiety and insomnia. Several animal studies support the use of *Ziziphus jujuba* var. spinosa as a sedative botanical. Ziziphus saponins have been shown to possess major sedative and hypnotic properties.[163] The flavonoids from this plant possess sedative properties that are not as potent as the saponins.[164]

In a mouse model the constituent spinosin enhanced pentobarbital-induced sleep time and latency; an effect further augmented by the addition

Figure 2. GABA's Effect on Brain Alpha Waves



Values are means ± SEM of waves ratios of three measurements (at 0, 30, and 60 minutes after each administration). Values with different letters are significantly different at p<0.05.

of 5-hydroxytryptophan (5-HTP).[165] Another mouse study found ethanolic extracts of Ziziphus possessed anxiolytic effects at lower doses and sedative effects at higher doses.[166]

Table 3 summarizes anxiolytic herbs and their mechanisms of action.

Neurotransmitters and Their Precursors

gamma-Aminobutyric Acid

gamma-Aminobutyric acid is a major neurotransmitter widely distributed throughout the CNS. Because too much excitation can lead to irritability, restlessness, insomnia, seizures, and movement disorders, it must be balanced with inhibition. GABA – the most important inhibitory neurotransmitter in the brain provides this inhibition, acting like a "brake" during times of runaway stress. Medications for anxiety, such as benzodiazepines, stimulate GABA receptors and induce relaxation. Either low GABA levels or decreased GABA function in the brain is associated with several psychiatric and neurological disorders, including anxiety, depression, insomnia, and epilepsy. Studies indicate GABA can improve relaxation and enhance sleep.

GABA mediates pre-synaptic inhibition of primary afferent fibers in the motor system. It regulates brain excitability via $GABA_A$ receptors, which are classified into three major groups (alpha, beta, and gamma) with subunits that determine its pharmacological activity. For instance, certain benzodiazepines have a strong binding affinity for the alpha1 subunit, while others bind to other alpha subunits.[167] Low GABA levels are associated with several psychiatric and neurological disorders, including anxiety, depression, and insomnia.[168-172]

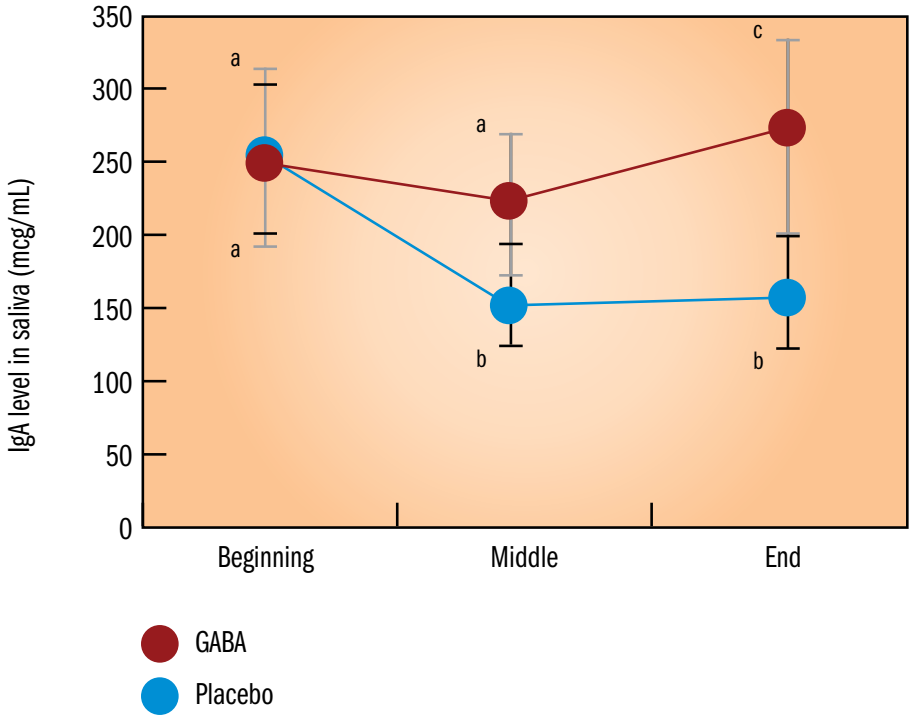
Because of the association between low GABA levels and these conditions, many anti-anxiety and sleep-enhancing drugs have been developed that interact primarily with GABA receptors. These include the benzodiazepine drugs – alprazolam (Xanax®), diazepam (Valium®), flurazepam (Dalmane®), quazepam (Doral®), temazepam (Restoril®), and triazolam (Halcion®) – and zolpidem tartrate (Ambien®) and baclofen (Kemstro® and Lioresal®).

Because inadequate GABA brain activity or low levels of GABA have been associated with anxiety, many anti-anxiety drugs, some in use for more than 40 years, target the $GABA_A$ receptor.[173] A small preliminary study of six subjects found gabapentin (structurally similar to GABA; increases brain GABA levels) to be effective for panic disorder.[174] Natural therapies that produce relaxation also act, at least in part, by enhancing GABA levels. A controlled pilot study found brain GABA levels were significantly increased after a single 60-minute yoga session compared to a 60-minute reading session.[175] Another study found valerenic acid, an active component of valerian, modulates $GABA_A$ receptors.[176]

In a study comparing veterans with (n=9) and without (n=7) post-traumatic stress disorder (PTSD), veterans with PTSD showed reduced $GABA_A$-benzodiazepine receptor binding, demonstrated by positron emission tomography (PET) scan.[177]

In an unpublished, double-blind comparison trial, a natural-source GABA (PharmaGABA®), but not synthetic GABA, was shown to produce relaxation as evidenced by changes in brain wave patterns, diameter of the pupil, and heart rate, as well as reduction of the stress markers salivary cortisol and chromogranin A (markers of adrenal stress).[178]

Figure 3. Salivary Immunoglobulin A Levels of Acrophobic Volunteers Crossing a Suspension Foot Bridge



Values are means ± SEM of IgA levels in eight volunteers at beginning, middle, and end of the bridge. Values with different letters are significantly different at p<0.05.

On EEG, alpha waves are generated in a relaxed state, whereas beta waves are seen in stressful situations that make mental concentration difficult. Therefore, the ratio of alpha-to-beta waves is used as an indication of relaxation and better concentration. In general, the greater the alpha-to-beta ratio, the more relaxed and alert the person is.

A small pilot study conducted at the University of Shizuoka in Japan enrolled 13 healthy volunteers, seven males and six females, ages 21-35. Two hours prior to commencement of the study, subjects were not allowed to eat, drink, or use any form of tobacco. EEG tracings were recorded before and after each of three administrations of 200 mL distilled water: (1) only distilled water; (2) distilled water containing 100 mg natural GABA (PharmaGABA); and (3) distilled water containing 200 mg L-theanine. Tests of the three administrations were separated by seven-day intervals. EEG recordings were obtained with the subject resting quietly with closed eyes before administration, then at 0, 30, and 60 minutes after each administration for five-minute recording sessions. Alpha and beta waves were calculated as a percentage and pre- and post-administration values were compared. Alpha-to-beta ratios were calculated as a ratio between alpha and beta percentage values. GABA produced significant effects on both increasing alpha waves (Figure 2) and decreasing beta waves, resulting in a highly significant increase in the alpha-to-beta wave ratio.[179]

Another study yielded further evidence of natural GABA's anti-stress activity. In blinded fashion, eight subjects (ages 25-30) with acrophobia (fear of heights) were given 200 mg natural-source GABA (PharmaGABA) or placebo before traversing a suspension bridge that spanned a 150-foot canyon.[179] Salivary sIgA was determined from samples taken before crossing, halfway across, and after crossing the bridge. Relaxation results in significant ($p<0.001$) increases in sIgA levels,[180] while stress results in decreased salivary sIgA. In this study, sIgA levels decreased by approximately 35 percent in subjects in the control group; however, individuals in the GABA group maintained salivary sIgA levels at the halfway point on the bridge and actually demonstrated increased levels upon completion of the crossing (Figure 3). In order to offset the potential confounding effect of saliva quantity (stress can cause "dry mouth"), the absolute concentrations of sIgA were determined in mcg/mL.[179]

A second unpublished study, using the same suspension bridge and different subjects (n=13), produced additional support for GABA's ability to reduce markers of stress. Subjects given 200 mg natural-source GABA experienced a 20-percent decrease in salivary levels of the adrenal stress marker chromogranin A at the halfway point across the bridge compared to starting values; the control group demonstrated a 20-percent increase in chromogranin A.[178]

Due to its relaxation effects, GABA may be considered to be a sleep aid. $GABA_A$ receptors are highly expressed in the thalamus, a region of the brain involved with sleep processes.[181] GABA-agonist drugs, such as Ambien and Restoril, are sedatives used to treat insomnia.[182,183] The synthetic GABA-like drug gabapentin that increases brain GABA levels has been found to improve sleep disturbances associated with alcohol consumption.[184] In a small, unpublished study, 100 mg natural-source GABA reduced sleep latency by 20 percent, while increasing the time spent in deep sleep by 20 percent.[178]

L-Tryptophan/5-Hydroxytryptophan

L-tryptophan, a large neutral amino acid essential to human metabolism, is the metabolic precursor of serotonin (a neurotransmitter), melatonin (a neurohormone), and niacin (vitamin B3).

Tryptophan has been researched for sleep disorders for 30 years. Improvement of sleep latency has been noted,[185,186] even at doses as low as 1 g;[187] increased stage IV sleep has been noted at even lower doses – 250 mg tryptophan.[187] Significant improvement in obstructive sleep apnea, but not central sleep apnea, has been noted at doses of 2.5 g at bedtime, with those experiencing the most severe apnea demonstrating the best response.[188] While many sedative medications have opioid-like effects, L-tryptophan administration does not limit cognitive performance or inhibit arousal from sleep.[189]

Tryptophan hydroxylase is the rate-limiting enzyme for serotonin production and involves the conversion of tryptophan to 5-HTP. This enzyme can be inhibited by stress, insulin resistance, magnesium or vitamin B_6 deficiency, or increasing age.[190] The decarboxylation of 5-HTP to serotonin is dependent on the presence of the active form of vitamin B_6, pyridoxal 5'-phosphate (P5P), while the further conversion to melatonin necessitates S-adenosyl-L-methionine (SAMe).

5-Hydroxytryptophan acts primarily by increasing CNS levels of serotonin. Other neurotransmitters and CNS chemicals, such as melatonin, dopamine, norepinephrine, and beta-endorphin, have also been shown to increase following oral administration of 5-HTP.[191-193]

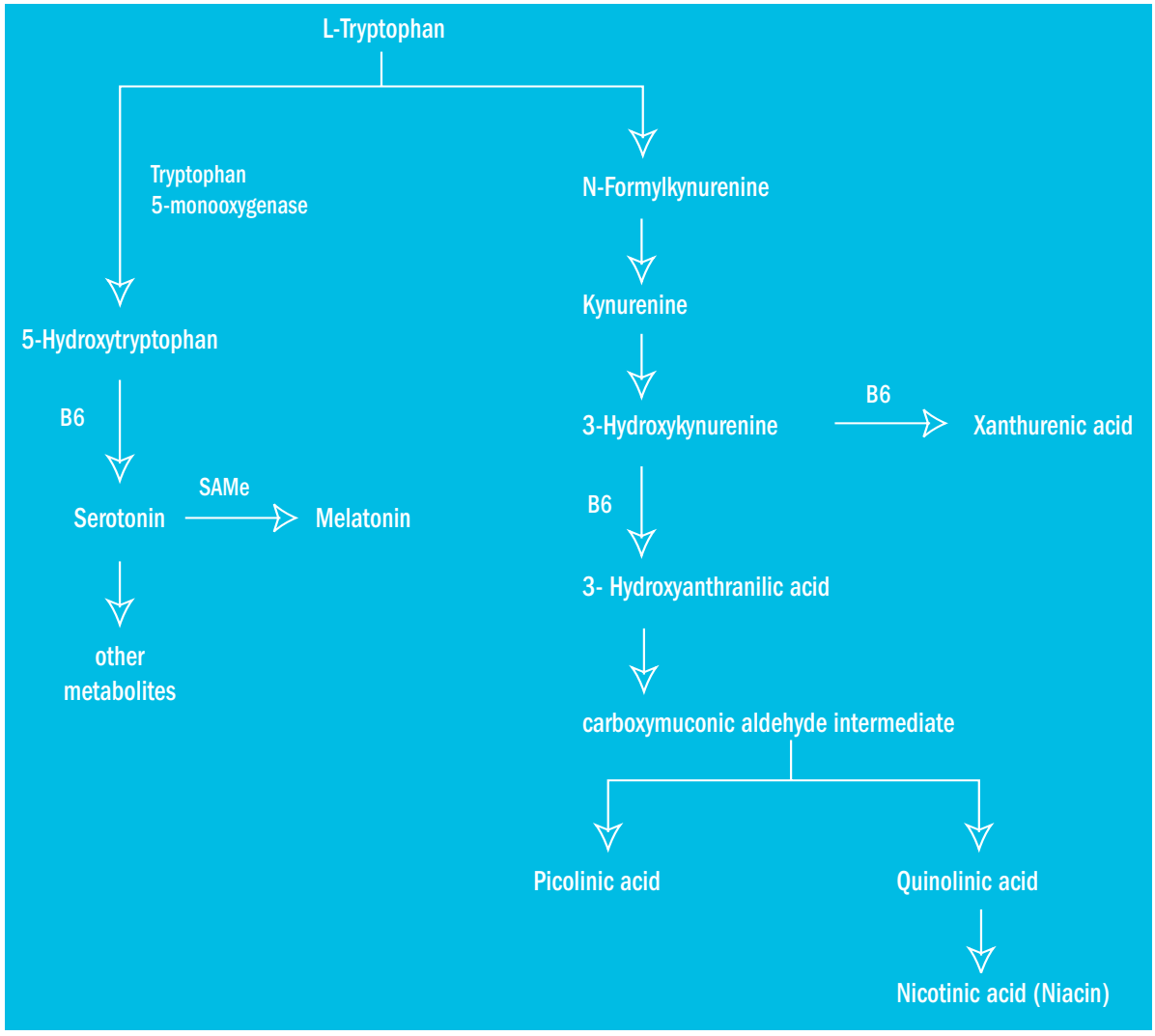
The effect of 5-HTP has been examined for panic disorders. In one RCT, panic was experimentally induced by cholecystokinin-tetrapeptide (CCK-4) in 32 healthy volunteers. Subjects received 200 mg 5-HTP or placebo 90 minutes prior to CCK-4 administration. Panic was experienced by 19 percent of the 5-HTP group and 44 percent of the placebo group (p=0.13). While this seems clinically relevant, it was not statistically significant, most likely due to the small sample size.[194] Another study examined the effect of 200 mg 5-HTP or placebo in 24 individuals with panic disorder and 24 healthy volunteers. In CO_2-induced panic, 5-HTP resulted in significant decrease in subjective assessment of panic, panic symptom scores, and number of panic attacks compared to placebo in the individuals who suffered from panic attacks; no differences were noted between 5-HTP and placebo in healthy individuals.[195]

Because of its enhancement of serotonin and then melatonin, 5-HTP benefits sleep disorders. 5-HTP has been shown to benefit children with sleep terrors (sudden waking from sleep with persistent fear). In a sleep terror study of 45 children (ages 3-10 years), 31 were randomly selected to receive 2 mg/kg 5-HTP at bedtime for 20 days. Assessment after one month demonstrated 29/31 (93.5%) responded positively, compared to 4/10 in the untreated group; at the six-month assessment 26/31 in the 5-HTP group were terror-free compared to 4/14 in the untreated group.[196]

Melatonin

Melatonin, the primary hormone of the pineal gland, acts as a powerful "chronobiotic," maintaining normal circadian rhythms. In patients with sleep disorders and altered circadian rhythms, such as occur in jet lag, night shift work, and various neuropsychiatric disorders, oral administration of melatonin can provide the necessary resynchronization of those cycles. The

Figure 4. Tryptophan Metabolism



following is a sampling of melatonin-sleep studies; an exhaustive exploration of this topic is beyond the scope of this article.

The primary physiological role identified for melatonin is its ability to influence circadian rhythms. When administered in pharmacological doses melatonin maintains synchronicity.[197] Because the hours of highest melatonin secretion correlate to normal hours of sleep, it has been investigated for use in sleep disorders. Attenburrow et al demonstrated that patients with insomnia have decreased nocturnal melatonin secretion.[198]

In a placebo-controlled trial of eight subjects with delayed sleep-phase insomnia, Dahlitz et al found melatonin acts as a "phase-setter" for sleep-wake cycles. Subjects were given placebo or melatonin (5 mg nightly at 10 pm) for four weeks with a one-week washout period before crossing over to the other treatment and were allowed to awaken naturally. In all subjects, the onset of sleep occurred earlier during melatonin treatment (mean change of 82 minutes; $p<0.01$); there was also a slight decrease in the total amount of time asleep.[199] Similar results were obtained by another

group of researchers who administered 5 mg melatonin nightly to six subjects with delayed sleep-phase insomnia. The onset of sleep was an average of 115 minutes earlier when taking melatonin compared to pre-melatonin findings.[200] In the past 10 years, numerous other randomized, controlled trials support melatonin's effectiveness for improving various aspects of normal sleep.

L-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 depletion, especially of norepinephrine, is closely related to stress-induced performance decline in animals. Administration of tyrosine, an amino acid precursor of catecholamines, alleviates depletion of brain catecholamines and stress-induced decline in performance in these animals.[201] In humans, tyrosine supplementation appears to work in the same manner, alleviating stress-induced decline in nervous system norepinephrine and subsequently enhancing performance under a variety of circumstances, including sleep deprivation, combat training, cold exposure, and unpleasant background noise.[202]

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.[201] 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. Given six hours after the experiment began, tyrosine (150 mg/kg) but not placebo was able to offset declines in performance and vigilance for three hours.[203]

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.[204]

Acute exposure to cold is 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 4° C during 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° C.[205] Bandaret et al showed tyrosine (100 mg/kg) supplementation improved mood and memory in individuals subjected to a 4.5-hour exposure to cold and hypoxia.[206] A more recent study found similar results. In a within-subject RCT, individuals taking 300 mg/kg tyrosine or placebo prior to cold emersion better resisted stress after ingestion of tyrosine than placebo.[207]

Deijen et al investigated the effect of tyrosine (100 mg/kg) administration to subjects performing a number of stress-sensitive tasks while concurrently exposed to stress-inducing 90 dB background noise. Tyrosine improved performance on two cognitive tasks and transiently decreased diastolic blood pressure.[208]

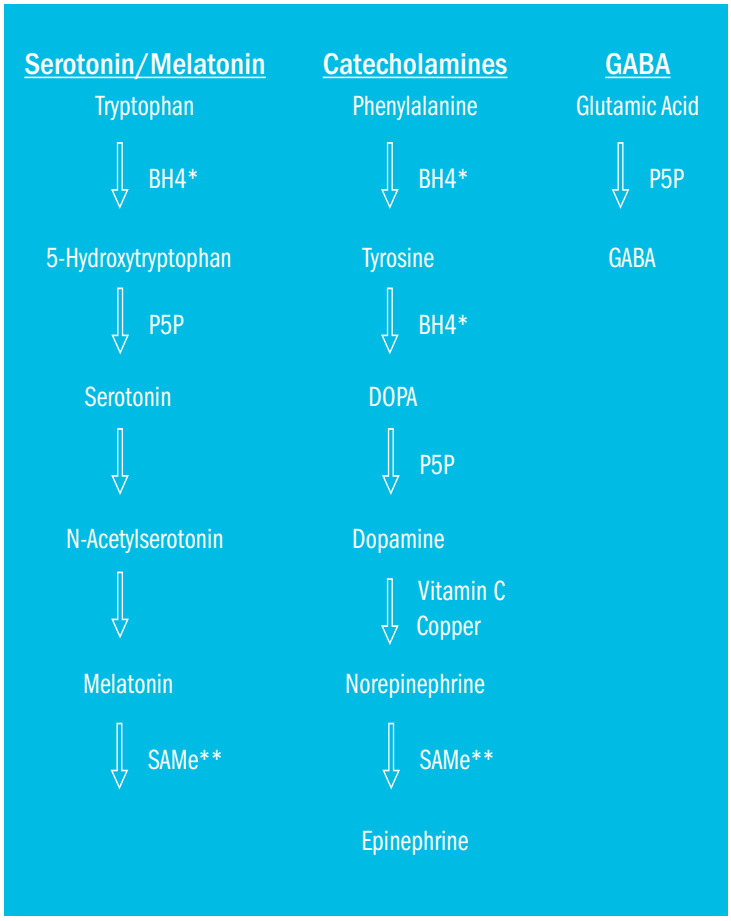
Tyrosine (100 mg/kg) also enhanced measured aspects of cardiovascular and cognitive performance in subjects exposed to stress-inducing low negative-pressure sessions (-50 mm Hg) for a maximum of 30 minutes.[209]

Vitamins: As Neurotransmitter Cofactors and other Supportive Mechanisms

Thiamin (Vitamin B1)

Experimental and clinical results have shown thiamin to be an effective nutrient in protecting the adrenal gland from functional exhaustion secondary to surgery. Intramuscular injections of thiamin in a dose of 120 mg 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 and at the height of the surgery. Continued administration of thiamin post-surgery prevented the usual post-surgery reduction in blood cortisol levels.[8]

Figure 5. Neurotransmitter Pathways



Niacinamide (Vitamin B3)

Niacinamide might be helpful for sleep enhancement. A small, three-week study of six subjects with normal sleep patterns and two with insomnia used electroencephalograms, electromyograms, and electrooculograms to evaluate sleep patterns at baseline and after niacinamide treatment (500 mg twice daily during one week, 1,000 mg twice daily during the second week, and 1,000 mg three times daily during the third week). There was a significant increase in REM sleep in all normal-sleeping subjects (p=0.0002). The two subjects with moderate-to-severe insomnia experienced significant increases in REM sleep by the third week (p=0.001); awake time was also significantly decreased. Sleep efficiency in the two with insomnia was 58.5 percent at baseline, dropped to 55.7 percent after two weeks, but was at 79.5 percent after three weeks. After withdrawing niacinamide, sleep efficiency dropped to 41.5 percent. Because tryptophan can either be converted to protein, niacin, or serotonin, niacinamide may signal via feedback inhibition to decrease the activity of tryptophan pyrrolase (the enzyme that converts tryptophan to niacin). This would allow more tryptophan to be converted to 5-HTP and then to serotonin.[210] Figure 4 illustrates the pathways L-tryptophan can take in the synthesis of niacin or 5-HTP/serotonin/melatonin. Note vitamin B6 is an important cofactor for several enzymes, in both the serotonin and niacin pathways.

Pantethine/Pantothenic Acid (Vitamin B_5)

Evidence indicates adrenal cortex function is compromised in the event of a deficiency of vitamin B_5 derivatives and metabolites. On the other hand, administration of pantethine (active vitamin B_5) in several experimental animal models appeared to enhance adrenal cortex function.[211-213] 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,[214] suggesting pantethine can down-regulate hypersecretion of cortisol secondary to high stress conditions.

Men receiving 10 g pantothenic acid daily for six weeks had a less pronounced drop in white blood cell counts and vitamin C levels subsequent to cold-water immersion stress, compared to pre-supplementation values.[215]

Pyridoxal 5'-Phosphate (Active Vitamin B_6)

Pyridoxal 5'-phosphate (the active form of vitamin B_6) is a necessary cofactor for the formation of several important neurotransmitters associated with stress. Within the brain, glutamic acid is converted to GABA via the enzyme glutamate decarboxylase and its cofactor pyridoxal 5'-phosphate. GABA is metabolized

by gamma-aminobutyrate transaminase, also a P5P-dependent enzyme, forming an intermediate metabolite succinate semialdehyde.

P5P is a cofactor in the conversion of 5-HTP to serotonin. Furthermore, conversion of L-tryptophan to 5-HTP, the rate-limiting step in serotonin synthesis, can be inhibited by stress, insulin resistance, magnesium or vitamin B_6 deficiency, or increasing age.[191] The decarboxylation of 5-HTP to serotonin is dependent on the presence of pyridoxal 5'-phosphate. P5P is also a cofactor in the synthesis of dopa to dopamine in the pathway converting tyrosine to epinephrine and norepinephrine. Figure 5 illustrates the role P5P and other nutrient cofactors play in neurotransmitter synthesis.

Table 4. Summary of B Vitamins and Their Relationship to Stress

B Vitamin	Function Regarding Stress
Thiamin (Vitamin B1)	Protective nutrient for the adrenals; decreases stress-induced cortisol response
Niacinamide (Vitamin B3)	Improves sleep quantity and quality; shunts tryptophan to serotonin
Pantethine/Pantothenic Acid (Vitamin B5)	Protective nutrient for the adrenals; decreases stress-induced cortisol response
Pyridoxal 5'phosphate (P5P; Vitamin B6)	Cofactor for synthesis of GABA, serotonin, and dopamine
Methylcobalamin (Vitamin B12)	Reset circadian rhythms for improved sleep and normalizing cortisol peak
5-Methyltetrahydrofolate (5-MTHF; Folate)	Regenerates BH4* essential for neurotransmitter formation (serotonin, dopamine, norepinephrine, epinephrine)

Methylcobalamin (Vitamin B_{12})

Stress disrupts the circadian rhythmic secretion of cortisol. An effective method to phase-shift circadian rhythm is 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.[216,217] 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.[218-220]

Perhaps the greatest advantage of methylcobalamin's effect on resetting circadian rhythms secondary to stress is its impact on cortisol. Although methylcobalamin does not impact total levels of cortisol, evidence suggests it helps shift the cortisol secretion peak, helping place the cortisol clock back on schedule.[221]

5-Methyltetrahydrofolate (5-MTHF; active folate)

Folate appears to be important in regenerating tetrahydrobiopterin (BH4), which is highly susceptible to oxidation. BH4 is a nutrient cofactor essential to the formation of the monoamine neurotransmitters serotonin, dopamine, norepinephrine, and epinephrine. BH4 acts as a rate-limiting enzyme cofactor to the hydroxylase enzymes that metabolize tryptophan to 5-hydroxytryptophan, phenylalanine to tyrosine, and tyrosine to dopa. Other research suggests folate is necessary as a starting material for pterin synthesis, which may be the focus of the folate/BH4 relationship.[222]

Table 4 summarizes B vitamins and their association with the stress response.

Ascorbic Acid (Vitamin C)

Ascorbic acid is another cofactor in the rate-limiting hydroxylase enzymes involved in monoamine neurotransmitter synthesis. This essential antioxidant is both a cofactor at the enzyme level and a stabilizer of BH4, which prevents oxidation of BH4 and increases BH4 levels. It appears intracellular BH4

levels are critically dependent on cellular levels of ascorbate.[223,224]

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.[225] Ascorbic acid given orally (1 g three times daily) also buffered exogenous ACTH-induced increases in cortisol, although it had no significant effect on fasting cortisol levels.[226]

Vitamins in Combination

A combination of ascorbic acid (300 mg three times daily) and vitamins B_1 and B_6 administered intravenously improved glucocorticoid function of the adrenal glands and simultaneously normalized the rhythmic activity of the gland.[22]

Conclusion

Stress is an unavoidable fact of everyday life and is associated with significant morbidity and even mortality. In addition to generalized anxiety and sleep disorders, it can result in significant physiological problems, including cardiovascular, gastrointestinal, and immunological.

In addition to lifestyle considerations – good diet, exercise, meditation, etc. – a number of nutrients and botanicals can provide support for stress-related conditions. Such support requires a five-pronged approach: (1) support for the adrenals with adaptogenic botanicals, (2) use of nutrients to normalize cortisol levels, (3) prescription of anxiolytic herbs to handle sleep disorders and the symptoms of acute anxiety, (4) balance neurotransmitters with amino acid precursors, and (5) provide necessary nutrient cofactors.

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