

Anxiety and Stress  
Updated: 08/26/2004

## ABSTRACTS

Effect of green tea rich in gamma-aminobutyric acid on blood pressure of Dahl salt-sensitive rats.

Abe Y, Umemura S, Sugimoto K, et al.

*Am J Hypertens.* 1995 Jan; 8(1):74-9.

gamma-Aminobutyric acid (GABA) is known to be involved in the regulation of blood pressure by modulating the neurotransmitter release in the central and peripheral sympathetic nervous systems. This study investigated the antihypertensive effect of green tea rich in GABA (GABA-rich tea) in young and old Dahl salt-sensitive (S) rats. GABA-rich tea was made by fermenting fresh green tea leaves under nitrogen gas. In experiment 1, 21 11-month-old rats, fed a 4% NaCl diet for 3 weeks, were given water (group W), an ordinary tea solution (group T), or a GABA-rich tea solution (group G) for 4 weeks. The average GABA intake was 4.0 mg/rat per day. After 4 weeks of the treatment, blood pressure was significantly decreased in group G (176 +/- 4; P < .01) compared with group W (207 +/- 9) or group T (193 +/- 5 mm Hg). Plasma GABA levels were more elevated in group G (111 +/- 54) than in group W (not detectable) or group T (14 +/- 8 ng/mL; P < .01 v G). In experiment 2, 21 5-week-old rats, fed a 4% NaCl diet, were divided into groups W, T, and G. The average GABA intake was 1.8 mg/rat per day. Body weight or chow and beverage consumption did not differ significantly among the three groups. After 4 weeks of the treatment, although blood pressure was comparable in groups W and T (165 +/- 3 v 164 +/- 5 mm Hg, mean +/- SE), it was significantly lower in group G (142 +/- 3 mm Hg) than in the other groups (P < .01). (ABSTRACT TRUNCATED AT 250 WORDS)

Piper methysticum (kava kava).

Anon.

*Altern Med Rev.* 1998; 3(6):459-60.

Efficacy of kava extract for treating anxiety: systematic review and meta-analysis.

Anon.

*J Clin Psychopharmacol.* 2000;(20):84-9.

Healing Anxiety Naturally.

Bloomfield H.

1998;

Gender differences in phobias: results of the ECA community survey.

Bourdon KHBHRDS.

*J Anxiety Disorders.* 1998;(2):227-41.

Herbal Prescriptions for Better Health.

Brown D.

1996;

Aerobic fitness and leisure physical activity as moderators of the stress-illness relation.

Carmack CL, Boudreaux E, Amaral-Melendez M, et al.

*Ann Behav Med.* 1999; 21(3):251-7.

Exercise as a moderator of the stress-illness relation was examined by exploring leisure physical activity and aerobic fitness as potential "buffers" of the association between minor stress on physical and psychological symptoms in a sample of 135 college students. The goal was to gather information regarding the mechanisms by which exercise exhibits its buffering effects. Researchers have examined both physical activity and physical fitness in an attempt to demonstrate this effect; however, whether both of these components are necessary to achieve the protective effects against stress is unknown. This study examined engaging in leisure physical activity and having high aerobic fitness to determine if both were necessary for the stress-buffering effects or if one factor was more important than the other. Findings suggested a buffering effect for leisure physical activity against physical symptoms and anxiety associated with minor stress. This effect was not found with depression. Additionally, there was no moderating effect for aerobic fitness on physical or psychological symptoms. Collectively, the data suggested that participation in leisure physical activity as opposed to level of aerobic fitness is important to the stress-buffering effect of exercise. Implications for exercise prescription are discussed

Kava: Nature's Answer to Stress, Anxiety, and Insomnia.

Cass H.

1998;

Aromatherapy: a systematic review.

Cook BEE.

*Br J Gen Pract.* 2000; 50((455)):493-6.

Trauma: the impact of post-traumatic stress disorder.

Davidson JR.

*J Psychopharmacol.* 2000; 14(2 Suppl 1):S5-12.

Trauma has an enormous impact on both individuals and society as a whole. Recognition of the extent of this impact by the medical profession has been relatively slow but, with our growing appreciation of the prevalence of trauma exposure in civilian as well as combat populations, the true scale of trauma-related psychiatric consequences is beginning to emerge. It has been reported that more than 60% of men and 51% of women experience at least one traumatic event in their lifetimes. Of these, 8% and 20%, respectively, fall victim to post-traumatic stress disorder (PTSD) indicating that more women are at risk for developing PTSD. Individuals experience severe psychiatric stress that is compounded by significant comorbid illness. This impacts critically upon quality of life resulting in grave functional and emotional impairment. In addition, there is a detrimental cost to society with high financial and social consequences from the significantly elevated rates of hospitalization, suicide attempts and alcohol abuse

Eleutherococcus senticosus (Rupr. & Maxim.) Maxim. (Araliaceae) as an adaptogen: a closer look.

Davydov M, Krikorian AD.

*J Ethnopharmacol.* 2000 Oct; 72(3):345-93.

The adaptogen concept is examined from an historical, biological, chemical, pharmacological and medical perspective using a wide variety of primary and secondary literature. The definition of an adaptogen first proposed by Soviet scientists in the late 1950s, namely that an adaptogen is any substance that exerts effects on both sick and healthy individuals by 'correcting' any dysfunction(s) without producing unwanted side effects, was used as a point of departure. We attempted to identify critically what an adaptogen supposedly does and to determine whether the word embodies in and of itself any concept(s) acceptable to western conventional (allopathic) medicine. Special attention was paid to the reported pharmacological effects of the 'adaptogen-containing plant' *Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim. (Araliaceae), referred to by some as 'Siberian ginseng', and to its secondary chemical composition. We conclude that so far as specific pharmacological activities are concerned there are a number of valid arguments for equating the action of so-called adaptogens with those of medicinal agents that have

activities as anti-oxidants, and/or anti-cancerogenic, immunomodulatory and hypocholesterolemic as well as hypoglycemic and choleric action. However, 'adaptogens' and 'anti-oxidants' etc. also show significant dissimilarities and these are discussed. Significantly, the classical definition of an adaptogen has much in common with views currently being invoked to describe and explain the 'placebo effect'. Nevertheless, the chemistry of the secondary compounds of *Eleutherococcus* isolated thus far and their pharmacological effects support our hypothesis that the reported beneficial effects of adaptogens derive from their capacity to exert protective and/or inhibitory action against free radicals. An inventory of the secondary substances contained in *Eleutherococcus* discloses a potential for a wide range of activities reported from work on cultured cell lines, small laboratory animals and human subjects. Much of the cited work (although not all) has been published in peer-reviewed journals. Six compounds show various levels of activity as anti-oxidants, four show anti-cancer action, three show hypocholesterolemic activity, two show immunostimulatory effects, one has choleric activity and one has the ability to decrease/moderate insulin levels, one has activity as a radioprotectant, one shows anti-inflammatory and anti-pyretic activities and yet another has shown activity as an antibacterial agent. Some of the compounds show more than one pharmacological effect and some show similar effects although they belong to different chemical classes. Clearly, *Eleutherococcus* contains pharmacologically active compounds but one wishes that the term adaptogen could be dropped from the literature because it is vague and conveys no insights into the mechanism(s) of action. If a precise action can be attributed to it, then the exact term for said action should obviously be used; if not, we strongly urge that generalities be avoided. Also, comparison of *Eleutherococcus* with the more familiar *Panax ginseng* C.A. Meyer (Araliaceae), 'true ginseng' has underscored that they differ considerably chemically and pharmacologically and cannot be justifiably considered as mutually interchangeable. Accordingly, we recommend that the designation 'Siberian ginseng' be dropped and be replaced with '*Eleutherococcus*'. In the case of both *Eleutherococcus* and true ginseng, problems inherent in herbal preparation use include inconsistencies not only in terms of indications for use, but in the nomenclature of constituent chemical compounds, standardization, dosage and product labeling. (ABSTRACT TRUNCATED)

Body, Mind and Sport.

Douillard JKBJNM.

2001;

Massage therapy reduces anxiety and enhances EEG pattern of alertness and math computations.

Field T, Ironson G, Scafidi F, et al.

*Int J Neurosci.* 1996 Sep; 86(3-4):197-205.

Twenty-six adults were given a chair massage and 24 control group adults were asked to relax in the massage chair for 15 minutes, two times per week for five weeks. On the first and last days of the study they were monitored for EEG, before, during and after the sessions. In addition, before and after the sessions they performed math computations, they completed POMS Depression and State Anxiety Scales and they provided a saliva sample for cortisol. At the beginning of the sessions they completed Life Events, Job Stress and Chronic POMS Depression Scales. Group by repeated measures and post hoc analyses revealed the following: 1) frontal delta power increased for both groups, suggesting relaxation; 2) the massage group showed decreased frontal alpha and beta power (suggesting enhanced alertness); while the control group showed increased alpha and beta power; 3) the massage group showed increased speed and accuracy on math computations while the control group did not change; 4) anxiety levels were lower following the massage but not the control sessions, although mood state was less depressed following both the massage and control sessions; 5) salivary cortisol levels were lower following the massage but not the control sessions but only on the first day; and 6) at the end of the 5 week period depression scores were lower for both groups but job stress score were lower only for the massage group

Job stress reduction therapies.

Field T, Quintino O, Henteleff T, et al.

*Altern Ther Health Med.* 1997 Jul; 3(4):54-6.

**BACKGROUND:** Job stress among healthcare workers has received more attention in recent years, perhaps because these professionals are prime candidates for high stress levels. **METHOD:** The immediate effects of brief massage therapy, music relaxation with visual imagery, muscle relaxation, and social support group sessions were assessed in 100 hospital employees at a major public hospital. **DESIGN:** The effects of the therapies were assessed using a within-subjects pre-post test design and by comparisons across groups. **RESULTS:** Groups reported decreases in anxiety, depression, fatigue, and confusion, as well as increased vigor following the sessions. **CONCLUSION:** That the groups did not differ on these variables suggests that these particular therapies, when applied for short periods of time, are equally effective for reducing stress among hospital employees

The effects of the transcendental meditation technique and progressive muscle relaxation on EEG coherence, stress reactivity,

and mental health in black adults.

Gaylord C, Orme-Johnson D, Travis F.

*Int J Neurosci.* 1989 May; 46(1-2):77-86.

Eighty-three black college students, staff and adults were pretested on EEG coherence, skin potential (SP) habituation to a series of loud tones, psychometric measures of mental health (Tennessee Self-Concept Empirical Scales and Spielberger State-Trait Anxiety Inventory) and IQ. They were then randomly assigned to one of the three treatment groups: the Transcendental Meditation technique (TM); Progressive Muscle Relaxation (PR); or cognitive-behavioral strategies (C). Approximately one year later, they were posttested. TM and PR increased significantly on an overall mental health factor ( $p$  less than .036) and anxiety ( $p$  less than .0006). TM showed a greater reduction in neuroticism than PR and C ( $p$  less than .032). TM also showed global increases in alpha and theta coherence among frontal and central leads during the TM period compared to eyes closed ( $p$  less than .016), whereas PR and C did not show EEG state changes. The coherence increases during TM were most marked in the right hemisphere (F4C4). TM showed faster SP habituation at posttest compared to pretest ( $p$  less than .047) whereas PR did not (data was missing for C). None of the groups showed longitudinal changes in EEG, perhaps due to lack of regularity of participation in the treatment programs

Premenstrual symptoms are relieved by massage therapy.

Hernandez-Reif M, Martinez A, Field T, et al.

*J Psychosom Obstet Gynaecol.* 2000 Mar; 21(1):9-15.

Twenty-four women meeting Diagnostic and Statistical Manual of Mental Disorders (4th edn; DSM-IV) criteria for premenstrual dysphoric disorder (PDD) were randomly assigned to a massage therapy or a relaxation therapy group. The massage group showed decreases in anxiety, depressed mood and pain immediately after the first and last massage sessions. The longer term (5 week) effects of massage therapy included a reduction in pain and water retention and overall menstrual distress. However, no long-term changes were observed in the massaged group's activity level or mood. Future studies might examine the effects of a longer massage therapy program on these symptoms. Overall, the findings from this study suggest that massage therapy may be an effective adjunct therapy for treating severe premenstrual symptoms

Medicinal Mushrooms.

Hobbs C.

1996;

Efficacy of Tai Chi, brisk walking, meditation, and reading in reducing mental and emotional stress.

Jin P.

*J Psychosom Res.* 1992 May; 36(4):361-70.

Tai Chi, a moving meditation, is examined for its efficacy in post-stressor recovery. Forty-eight male and 48 female Tai Chi practitioners were randomly assigned to four treatment groups: Tai Chi, brisk walking, meditation and neutral reading. Mental arithmetic and other difficult tests were chosen as mental challenges, and a stressful film was used to produce emotional disturbance. Tai Chi and the other treatments were applied after these stressors. After all treatments, the salivary cortisol level dropped significantly, and the mood states were also improved. In general the stress-reduction effect of Tai Chi characterized moderate physical exercise. Heart rate, blood pressure, and urinary catecholamine changes for Tai Chi were found to be similar to those for walking at a speed of 6 km/hr. Although Tai Chi appeared to be superior to neutral reading in the reduction of state anxiety and the enhancement of vigour, this effect could be partially accounted for by the subjects' high expectations about gains from Tai Chi. Approaches controlling for expectancy level are recommended for further assessment

Full Catastrophe Living.

Kabat-Zinn J.

1990;

Effectiveness of a meditation-based stress reduction program in the treatment of anxiety disorders.

Kabat-Zinn J, Massion AO, Kristeller J, et al.

*Am J Psychiatry.* 1992 Jul; 149(7):936-43.

**OBJECTIVE:** This study was designed to determine the effectiveness of a group stress reduction program based on mindfulness meditation for patients with anxiety disorders. **METHOD:** The 22 study participants were screened with a structured clinical interview and found to meet the DSM-III-R criteria for generalized anxiety disorder or panic disorder with or without agoraphobia. Assessments, including self-ratings and therapists' ratings, were obtained weekly before and during the meditation-based stress reduction and relaxation program and monthly during the 3-month follow-up period. **RESULTS:** Repeated measures analyses of variance documented significant reductions in anxiety and depression scores after treatment for 20 of the subjects--changes that were maintained at follow-up. The number of subjects experiencing panic symptoms was also substantially reduced. A comparison of the study subjects with a group of nonstudy participants in the program who met the initial screening criteria for entry into the study showed that both groups achieved similar reductions in anxiety scores on the SCL-90-R and on the Medical Symptom Checklist, suggesting generalizability of the study findings. **CONCLUSIONS:** A group mindfulness meditation training program can effectively reduce symptoms of anxiety and panic and can help maintain these reductions in patients with generalized anxiety disorder, panic disorder, or panic disorder with agoraphobia

Wherever You Go There You Are.

Kabat-Zinn J.

1994;

Inhibiting effects of theanine on caffeine stimulation evaluated by EEG in the rat.

Kakuda T, Nozawa A, Unno T, et al.

*Biosci Biotechnol Biochem.* 2000 Feb; 64(2):287-93.

In this study, the inhibiting action of theanine on the excitation by caffeine at the concentration regularly associated with drinking tea was investigated using electroencephalography (EEG) in rats. First, the stimulatory action by caffeine i.v. administration at a level higher than 5 micromol/kg (0.970 mg/kg) b.w. was shown by means of brain wave analysis, and this level was suggested as the minimum dose of caffeine as a stimulant. Next, the stimulatory effects of caffeine were inhibited by an i.v. administration of theanine at a level higher than 5 micromol/kg (0.781 mg/kg) b.w., and the results suggested that theanine has an antagonistic effect on caffeine's stimulatory action at an almost equivalent molar concentration. On the other hand, the excitatory effects were shown in the rat i.v. administered 1 and 2 micromol/kg (0.174 and 0.348 mg/kg) b.w. of theanine alone. These results suggested two effects of theanine, depending on its concentration

Exercise intensity and self-efficacy effects on anxiety reduction in healthy, older adults.

Katula JA, Blissmer BJ, McAuley E.

*J Behav Med.* 1999 Jun; 22(3):233-47.

The purpose of the present study was to examine the effects of varying exercise intensities and changes in self-efficacy on anxiety reduction in a sample of healthy, older adults. Eighty older adults from a randomized controlled exercise trial participated in this study and completed measures of self-efficacy and the State Anxiety Inventory (SAI) prior to and following light-, moderate-, and high-intensity exercise. Latent growth curve modeling analyses revealed that although anxiety was reduced following the light-intensity condition, no significant changes in anxiety occurred following the moderate-intensity condition, and anxiety increased following the high-intensity condition. In addition, changes in self-efficacy were related to anxiety responses only in the moderate-intensity condition. An analysis of SAI items indicated that although the light-intensity condition resulted in decreased arousal and anxiousness, the high-intensity condition resulted in increased arousal and decreased anxiousness. These results are discussed in terms of social cognitive theory and the appropriateness of the SAI for use in exercise settings

Between Heaven and Earth: A Guide to Chinese Medicine.

Korngold E.

1991;

[D,L-kavain in comparison with oxazepam in anxiety disorders. A double-blind study of clinical effectiveness].

Lindenberg D, Pitule-Schodel H.

*Fortschr Med.* 1990 Jan 20; 108(2):49-4.

In a placebo-controlled double blind clinical trial, 38 out-patients with anxiety associated with neurotic or psychosomatic disturbances were treated with D,L-Kavain (Neuronika) or Oxazepam. The anxiolytic effectiveness of the two preparations was judged by means of the Anxiety Status Inventory (ASI) and the Self-Rating Anxiety Scale (SAS) of Zung. The substances proved to be equivalent in the nature and potency of anxiolytic action. No adverse drug reactions occurred

Development of the cerebral cortex: XII. Stress and brain development: I.

Lombroso PJ, Sapolsky R.

*J Am Acad Child Adolesc Psychiatry.* 1998 Dec; 37(12):1337-9.

Stress due to exams in medical students--role of yoga.

Malathi A, Damodaran A.

*Indian J Physiol Pharmacol.* 1999 Apr; 43(2):218-24.

A student under optimal stress does bring out his or her best, However extremes of stress can result in stress induced disorders and deteriorating performance. Can yoga be of benefit in stress induced effects in medical students? The present study was conducted in first MBBS students (n = 50) to determine the benefit if any of yogic practices on anxiety status during routine activities and prior to examination. Feedback scores were assessed to determine how the students had benefited from the practices. Anxiety status as assessed by Spillberger's anxiety scale showed a statistically significant reduction following practice. In addition the anxiety score which rose prior to exams showed a statistically significant reduction on the day of exam after practice. These results point to the beneficial role of yoga in not only causing reduction in basal anxiety level but also attenuating the increase in anxiety score in stressful state such as exams. The results of the exam indicated a statistically significant reduction in number of failures in yoga group as compared to the control group. The improvement in various parameters such as better sense of well being, feeling of relaxation, improved concentration, self confidence, improved efficiency, good interpersonal relationship, increased attentiveness, lowered irritability levels, and an optimistic outlook in life were some of the beneficial effects enjoyed by the yoga group indicated by feedback score

The impact of a new emotional self-management program on stress, emotions, heart rate variability, DHEA and cortisol.

McCraty R, Barrios-Choplin B, Rozman D, et al.

*Integr Physiol Behav Sci.* 1998 Apr; 33(2):151-70.

This study examined the effects on healthy adults of a new emotional self-management program, consisting of two key techniques, "Cut-Thru" and the "Heart Lock-In." These techniques are designed to eliminate negative thought loops and promote sustained positive emotional states. The hypotheses were that training and practice in these techniques would yield lowered levels of stress and negative emotion and cortisol, while resulting in increased positive emotion and DHEA levels over a one-month period. In addition, we hypothesized that increased coherence in heart rate variability patterns would be observed during the practice of the techniques. Forty-five healthy adults participated in the study, fifteen of whom acted as a comparison group for the psychological measures. Salivary DHEA/DHEAS and cortisol levels were measured, autonomic nervous system function was assessed by heart rate variability analysis, and emotions were measured using a psychological questionnaire. Individuals in the experimental group were assessed before and four weeks after receiving training in the self-management techniques. The experimental group experienced significant increases in the positive affect scales of Caring and Vigor and significant decreases in the negative affect scales of Guilt, Hostility, Burnout, Anxiety and Stress Effects, while no significant changes were seen in the comparison group. There was a mean 23 percent reduction in cortisol and a 100 percent increase in DHEA/DHEAS in the experimental group. DHEA was significantly and positively related to the affective state Warmheartedness, whereas cortisol was significantly and positively related to Stress Effects. Increased coherence in heart rate variability patterns was measured in 80 percent of the experimental group during the use of the techniques. The results suggest that techniques designed to eliminate negative thought loops can have important positive effects on stress, emotions and key physiological systems. The implications are that relatively inexpensive interventions may dramatically and positively impact individuals' health and well-being. Thus,

individuals may have greater control over their minds, bodies and health than previously suspected

[Stress and hippocampus. An update on current knowledge].

McEwen BS.

*Presse Med.* 1991 Nov 14; 20(37):1801-6.

Glucocorticoids are major protectors during and after stress. Centrally, glucocorticoids counterbalance and regulate three neurochemical systems active during stress: the noradrenergic system, the serotonin system and the GABA benzodiazepin system. But glucocorticoids can compromise immune defence systems leading to nerve cell destruction in the hippocampus. Certain types of stress can also lead to loss of neurons in the hippocampus, one of the most stress susceptible regions. Tianeptine decreases morning hypersecretion of glucocorticoids induced by a contention (1 hour) stress. Moreover, tianeptine inhibits the decrease in the number of type I glucocorticoid receptors induced by isolation stress. Tianeptine inhibits the increase in the tyrosine hydroxylase messenger RNA, also induced by isolation stress. Finally, tianeptine tends to increase dendrite ramifications of the hippocampus' pyramidal neurons (CA3) in isolated rats, thus counteracting the effect of isolation stress. Because of the positive results obtained with tianeptine on the hypophyseal-adrenal gland function and on the hippocampus, the authors are pursuing further investigations to determine whether tianeptine can inhibit the loss of hippocampus nerve cells induced by repeated glucocorticoid administration or repeated stress and whether it potentializes the beneficial effects of glucocorticoids on the noradrenergic, serotonin and GABA benzodiazepin systems

Possible mechanisms for atrophy of the human hippocampus.

McEwen BS.

*Mol Psychiatry.* 1997 May; 2(3):255-62.

Recently published work using MRI to image the human brain has revealed that the hippocampal formation undergoes a selective atrophy in diverse conditions such as Cushing's syndrome, post-traumatic stress disorder, recurrent depressive illness, normal aging preceding dementia and in Alzheimer's disease. Hippocampal shrinkage is usually accompanied by deficits in declarative, episodic, spatial and contextual memory performance and the hippocampal changes provide a neural substrate for changes in cognitive function that have been recognized to accompany these various conditions. The hippocampus has long been known as a target of stress hormones, and it is an especially plastic and vulnerable region of the brain. However, the prominence of the hippocampus as a glucocorticoid target has obscured the fact that other factors besides glucocorticoid hormones are involved in the process of hippocampal atrophy. Excitatory amino acids and NMDA receptors are prominent in their involvement in an animal model of hippocampal atrophy as well as in neuronal death. Further-more, the finding of hippocampal atrophy does not necessarily imply a permanent loss of cells, and this aspect deserves careful investigation, both to analyze the underlying anatomical changes and to investigate the possibility of pharmacological treatment to reverse the process. In cases where atrophy is due to cell loss, the time course of the disease process will provide much useful information about mechanism and offer the possibility of early intervention to arrest or slow the pathological process

Stress effects on morphology and function of the hippocampus.

McEwen BS, Magarinos AM.

*Ann N Y Acad Sci.* 1997 Jun 21; 821:271-84.

The hippocampal formation, which contains high levels of adrenal steroid receptors, is vulnerable to insults such as stroke, seizures, and head trauma, and it is also sensitive and vulnerable to the effects of stress. We have discovered that the hippocampus of rodents and tree shrews shows atrophy of pyramidal neurons in the CA3 region. Psychosocial stress and restraint stress produce atrophy over approximately 3-4 weeks. Atrophy is blocked by inhibiting adrenal steroid formation and by blocking the actions of excitatory amino acids using Dilantin or NMDA receptor inhibitors. Glucocorticoid administration also blocks CA3 atrophy, but Dilantin administration blocks this as well, indicating that excitatory amino acid release mediates the atrophy, which likely involves disassembly of the dendritic cytoskeleton. Studies with in vivo microdialysis in several laboratories have shown that glutamate release in the hippocampus increases in stress and that stress-induced glutamate release is reduced by adrenalectomy. Recent electron microscopy of mossy fiber terminals on CA3 neurons has revealed a depletion of synaptic vesicles as a result of repeated stress. The mossy fiber terminals appear to be responsible for driving atrophy of CA3 neurons, which involves principally atrophy of the apical dendrites. These results are discussed in relation to data from MRI showing atrophy of the whole human hippocampus in Cushing's disease, recurrent depressive illness, PTSD, and normal aging as well as dementia

Stress and hippocampal plasticity.

McEwen BS.

*Annu Rev Neurosci.* 1999; 22:105-22.

The hippocampus is a target of stress hormones, and it is an especially plastic and vulnerable region of the brain. It also responds to gonadal, thyroid, and adrenal hormones, which modulate changes in synapse formation and dendritic structure and regulate dentate gyrus volume during development and in adult life. Two forms of structural plasticity are affected by stress: Repeated stress causes atrophy of dendrites in the CA3 region, and both acute and chronic stress suppresses neurogenesis of dentate gyrus granule neurons. Besides glucocorticoids, excitatory amino acids and N-methyl-D-aspartate (NMDA) receptors are involved in these two forms of plasticity as well as in neuronal death that is caused in pyramidal neurons by seizures and by ischemia. The two forms of hippocampal structural plasticity are relevant to the human hippocampus, which undergoes a selective atrophy in a number of disorders, accompanied by deficits in declarative episodic, spatial, and contextual memory performance. It is important, from a therapeutic standpoint, to distinguish between a permanent loss of cells and a reversible atrophy

Effects of adverse experiences for brain structure and function.

McEwen BS.

*Biol Psychiatry.* 2000 Oct 15; 48(8):721-31.

Studies of the hippocampus as a target of stress and stress hormones have revealed a considerable degree of structural plasticity in the adult brain. Repeated stress causes shortening and debranching of dendrites in the CA3 region of the hippocampus and suppresses neurogenesis of dentate gyrus granule neurons. Both forms of structural remodeling of the hippocampus appear to be reversible and are mediated by glucocorticoid hormones working in concert with excitatory amino acids (EAA) and N-methyl-D-aspartate (NMDA) receptors, along with transmitters such as serotonin and the GABA-benzodiazepine system. Glucocorticoids, EAA, and NMDA receptors are also involved in neuronal damage and death that is caused in pyramidal neurons by seizures and by ischemia. A similar mechanism may be involved in hippocampal damage caused by severe and prolonged psychosocial stress. Studies using magnetic resonance imaging have shown that there is a selective atrophy of the human hippocampus in a number of psychiatric disorders, as well as during aging in some individuals, accompanied by deficits in declarative, spatial, and contextual memory performance. It is therefore important to appreciate how hippocampal dysfunction may play a role in the symptoms of the psychiatric illness and, from a therapeutic standpoint, to distinguish between a permanent loss of cells and a reversible remodeling to develop treatment strategies to prevent or reverse deficits. Remodeling of the hippocampus may be only the tip of the iceberg; other brain regions may also be affected

Three-year follow-up and clinical implications of a mindfulness meditation-based stress reduction intervention in the treatment of anxiety disorders.

Miller JJ, Fletcher K, Kabat-Zinn J.

*Gen Hosp Psychiatry.* 1995 May; 17(3):192-200.

A previous study of 22 medical patients with DSM-III-R-defined anxiety disorders showed clinically and statistically significant improvements in subjective and objective symptoms of anxiety and panic following an 8-week outpatient physician-referred group stress reduction intervention based on mindfulness meditation. Twenty subjects demonstrated significant reductions in Hamilton and Beck Anxiety and Depression scores postintervention and at 3-month follow-up. In this study, 3-year follow-up data were obtained and analyzed on 18 of the original 22 subjects to probe long-term effects. Repeated measures analysis showed maintenance of the gains obtained in the original study on the Hamilton [ $F(2,32) = 13.22$ ;  $p < 0.001$ ] and Beck [ $F(2,32) = 9.83$ ;  $p < 0.001$ ] anxiety scales as well as on their respective depression scales, on the Hamilton panic score, the number and severity of panic attacks, and on the Mobility Index-Accompanied and the Fear Survey. A 3-year follow-up comparison of this cohort with a larger group of subjects from the intervention who had met criteria for screening for the original study suggests generalizability of the results obtained with the smaller, more intensively studied cohort. Ongoing compliance with the meditation practice was also demonstrated in the majority of subjects at 3 years. We conclude that an intensive but time-limited group stress reduction intervention based on mindfulness meditation can have long-term beneficial effects in the treatment of people diagnosed with anxiety disorders

Scientific basis for the therapeutic use of *Withania somnifera* (ashwagandha): a review.

Mishra LC, Singh BB, Dagenais S.

**OBJECTIVE:** The objective of this paper is to review the literature regarding *Withania somnifera* (ashwagandha, WS) a commonly used herb in Ayurvedic medicine. Specifically, the literature was reviewed for articles pertaining to chemical properties, therapeutic benefits, and toxicity. **DESIGN:** This review is in a narrative format and consists of all publications relevant to ashwagandha that were identified by the authors through a systematic search of major computerized medical databases; no statistical pooling of results or evaluation of the quality of the studies was performed due to the widely different methods employed by each study. **RESULTS:** Studies indicate ashwagandha possesses anti-inflammatory, antitumor, antistress, antioxidant, immunomodulatory, hemopoietic, and rejuvenating properties. It also appears to exert a positive influence on the endocrine, cardiopulmonary, and central nervous systems. The mechanisms of action for these properties are not fully understood. Toxicity studies reveal that ashwagandha appears to be a safe compound. **CONCLUSION:** Preliminary studies have found various constituents of ashwagandha exhibit a variety of therapeutic effects with little or no associated toxicity. These results are very encouraging and indicate this herb should be studied more extensively to confirm these results and reveal other potential therapeutic effects. Clinical trials using ashwagandha for a variety of conditions should also be conducted

NIMH Epidemiology Note: Prevalence of anxiety disorders.

Narrow WERDSRDA.

7777

Efficacy of kava extract for treating anxiety: systematic review and meta-analysis.

Pittler MH, Ernst E.

*J Clin Psychopharmacol.* 2000 Feb; 20(1):84-9.

Synthetic anxiolytic drugs are effective for treating anxiety, but they are burdened with adverse effects. Constraints on resources and time often render therapies such as psychologic interventions impracticable. Thus, an effective oral medication with few adverse effects would be a welcome addition to the therapeutic repertoire. This systematic review and meta-analysis was aimed at assessing the evidence for or against the efficacy of kava extract as a symptomatic treatment for anxiety. Systematic literature searches were performed in the computerized databases MEDLINE, EMBASE, BIOSIS, AMED, CISCOP, and the Cochrane Library (all from their respective inception to June 1998). The search terms used were kava, kawa, kavain, Piper methysticum, and Rauschpfeffer (German term for Piper methysticum). Experts on the subject were contacted to provide further information. There were no restrictions regarding the language of publication. Double-blind, randomized, placebo-controlled trials of oral kava extract for the treatment of anxiety were included. All publications were blinded before assessment by a person not involved in the study. Data were extracted in a standardized, predefined fashion independently by the two reviewers. The methodologic quality of all trials was assessed. Superiority of kava extract over placebo was suggested by all seven reviewed trials. The meta-analysis of three trials suggests a significant difference in the reduction of the total score on the Hamilton Rating Scale for Anxiety in favor of kava extract (weighted mean difference, 9.69; 95% confidence interval, 3.54-15.83). These data imply that kava extract is superior to placebo as a symptomatic treatment for anxiety. Therefore, kava extract is an herbal treatment option for anxiety that is worthy of consideration

Psychiatric Disorders in America: The Epidemiologic Catchment Area Study 1991.

Robins LN.

1991;

Effects of physical exercise on anxiety, depression, and sensitivity to stress: a unifying theory.

Salmon P.

*Clin Psychol Rev.* 2001 Feb; 21(1):33-61.

Until recently, claims for the psychological benefits of physical exercise have tended to precede supportive evidence. Acutely, emotional effects of exercise remain confusing, both positive and negative effects being reported. Results of cross-sectional and longitudinal studies are more consistent in indicating that aerobic exercise training has antidepressant and anxiolytic effects and protects against harmful consequences of stress. Details of each of these effects remain unclear. Antidepressant and anxiolytic effects have been demonstrated most clearly in subclinical disorder, and clinical applications remain to be exploited. Cross-sectional studies link exercise habits to protection from harmful effects of stress on physical and mental health, but causality is

not clear. Nevertheless, the pattern of evidence suggests the theory that exercise training recruits a process which confers enduring resilience to stress. This view allows the effects of exercise to be understood in terms of existing psychobiological knowledge, and it can thereby provide the theoretical base that is needed to guide future research in this area. Clinically, exercise training continues to offer clinical psychologists a vehicle for nonspecific therapeutic social and psychological processes. It also offers a specific psychological treatment that may be particularly effective for patients for whom more conventional psychological interventions are less acceptable

Why stress is bad for your brain.

Sapolsky RM.

*Science*. 1996 Aug 9; 273(5276):749-50.

Stress, Glucocorticoids, and Damage to the Nervous System: The Current State of Confusion.

Sapolsky RM.

*Stress*. 1996 Jul; 1(1):1-19.

An extensive literature demonstrates that glucocorticoids (GCs), the adrenal steroids secreted during stress, can have a broad range of deleterious effects in the brain. The actions occur predominately, but not exclusively, in the hippocampus, a structure rich in corticosteroid receptors and particularly sensitive to GCs. The first half of this review considers three types of GC effects: a) GC-induced atrophy, in which a few weeks' exposure to high GC concentrations or to stress causes reversible atrophy of dendritic processes in the hippocampus; b) GC neurotoxicity where, over the course of months, GC exposure kills hippocampal neurons; c) GC neuroendangerment, in which elevated GC concentrations at the time of a neurological insult such as a stroke or seizure impairs the ability of neurons to survive the insult. The second half considers the rather confusing literature as to the possible mechanisms underlying these deleterious GC actions. Five broad themes are discerned: a) that GCs induce a metabolic vulnerability in neurons due to inhibition of glucose uptake; b) that GCs exacerbate various steps in a damaging cascade of glutamate excess, calcium mobilization and oxygen radical generation. In a review a number of years ago, I concluded that these two components accounted for the deleterious GC effects. Specifically, the energetic vulnerability induced by GCs left neurons metabolically compromised, and less able to carry out the costly task of containing glutamate, calcium and oxygen radicals. More recent work has shown this conclusion to be simplistic, and GC actions are shown to probably involve at least three additional components: c) that GCs impair a variety of neuronal defenses against neurologic insults; d) that GCs disrupt the mobilization of neurotrophins; e) that GCs have a variety of electrophysiological effects which can damage neurons. The relevance of each of those mechanisms to GC-induced atrophy, neurotoxicity and neuroendangerment is considered, as are the likely interactions among them

Coffee and tea intake and the risk of myocardial infarction.

Sesso HD, Gaziano JM, Buring JE, et al.

*Am J Epidemiol*. 1999 Jan 15; 149(2):162-7.

The authors investigated the association of caffeinated coffee, decaffeinated coffee, and tea with myocardial infarction in a study of 340 cases and age-, sex-, and community-matched controls. The odds ratio for drinking > or = 4 cups/day of caffeinated coffee versus drinking 1 cup/day of decaffeinated coffee versus nondrinkers was 1.25 (95% CI 0.76-2.04). For tea, the odds ratio for drinking > or = 1 cup/day versus nondrinkers was 0.56 (95% CI 0.35-0.90). In these data, only tea was associated with a lower risk of myocardial infarction

Effects of mindfulness-based stress reduction on medical and premedical students.

Shapiro SL, Schwartz GE, Bonner G.

*J Behav Med*. 1998 Dec; 21(6):581-99.

The inability to cope successfully with the enormous stress of medical education may lead to a cascade of consequences at both a personal and professional level. The present study examined the short-term effects of an 8-week meditation-based stress reduction intervention on premedical and medical students using a well-controlled statistical design. Findings indicate that participation in the intervention can effectively (1) reduce self-reported state and trait anxiety, (2) reduce reports of overall psychological distress including depression, (3) increase scores on overall empathy levels, and (4) increase scores on a measure of spiritual experiences assessed at termination of intervention. These results (5) replicated in the wait-list control

group, (6) held across different experiments, and (7) were observed during the exam period. Future research should address potential long-term effects of mindfulness training for medical and premedical students

Reorganization of the morphology of hippocampal neurites and synapses after stress-induced damage correlates with behavioral improvement.

Sousa N, Lukoyanov NV, Madeira MD, et al.

*Neuroscience*. 2000; 97(2):253-66.

We recently demonstrated that stress-induced cognitive deficits in rats do not correlate with hippocampal neuronal loss. Working on the premise that subtle structural changes may however be involved, we here evaluated the effects of chronic stress on hippocampal dendrite morphology, the volume of the mossy fiber system, and number and morphology of synapses between mossy fibers and CA3 dendritic excrescences. To better understand the mechanisms by which stress exerts its structural effects, we also studied these parameters in rats given exogenous corticosterone. Further, to search for signs of structural reorganization following the termination of the stress and corticosterone treatments, we analysed groups of rats returned to treatment-free conditions. All animals were assessed for spatial learning and memory performance in the Morris water maze. Consistent with previous findings, dendritic atrophy was observed in the CA3 hippocampal region of chronically stressed and corticosterone-treated rats; in addition, we observed atrophy in granule and CA1 pyramidal cells following these treatments. Additionally, profound changes in the morphology of the mossy fiber terminals and significant loss of synapses were detected in both conditions. These alterations were partially reversible following rehabilitation from stress or corticosterone treatments. The fine structural changes, which resulted from prolonged hypercortisolism, were accompanied by impairments in spatial learning and memory; the latter were undetectable following rehabilitation. We conclude that there is an intimate relationship between corticosteroid levels, hippocampal neuritic structure and hippocampal-dependent learning and memory

Effect of Korean red ginseng on psychological functions in patients with severe climacteric syndromes.

Tode T, Kikuchi Y, Hirata J, et al.

*Int J Gynaecol Obstet*. 1999 Dec; 67(3):169-74.

**OBJECTIVE:** To evaluate the degree of psychological dysfunction and levels of stress hormones in postmenopausal women with climacteric syndromes and effect of Korean red ginseng (RG) on them. **METHODS:** ACTH, cortisol and DHEA-S in peripheral blood from 12 postmenopausal women with climacteric syndromes or 8 postmenopausal women without any climacteric syndrome were measured before and 30 days after treatment with daily oral administration of 6 g RG. Blood samples were collected in the early morning on the bed-rest. In postmenopausal women with climacteric syndromes such as fatigue, insomnia and depression, psychological tests using the Cornell Medical Index (CMI) and the State-Trait Anxiety Inventory (STAI) were performed before and 30 days after treatment with RG. **RESULTS:** CMI score as well as anxiety (A)-state in STAI score in postmenopausal women with climacteric syndromes was significantly higher than that without climacteric syndrome, while DHEA-S levels in postmenopausal women with climacteric syndromes were about a half of those without climacteric syndrome. Consequently, cortisol/DHEA-S (C/D) ratio was significantly higher in postmenopausal women with climacteric syndromes than in those without climacteric syndrome. When postmenopausal women with climacteric syndromes were treated with daily oral administration of 6 g RG for 30 days, CMI and STAI A-state scores decreased within normal range. Although the decreased DHEA-S levels were not restored to the levels in postmenopausal women without climacteric syndrome, the C/D ratio decreased significantly after treatment with RG. **CONCLUSIONS:** Improvement of CMI and STAI scores in postmenopausal women suffering climacteric syndromes, particularly fatigue, insomnia and depression, by RG seemed to be brought about in part by effects of RG on stress-related hormones as shown by a decrease in C/D ratio

Neurotoxicity of glucocorticoids in the primate brain.

Uno H, Eisele S, Sakai A, et al.

*Horm Behav*. 1994 Dec; 28(4):336-48.

Severe and prolonged physical and psychological stress is known to cause brain damage; long-term torture victims in prison have later developed psychiatric disorders and cerebral cortical atrophy observed in CT scans (Jensen, Genefke, Hyldebrandt, Pedersen, Petersen, and Weile, 1982). In nonhuman primates, we observed degeneration and depletion of the hippocampal neurons in African green monkeys that had been severely abused by cagemates and died with complications of multiple gastric ulcers and adrenal cortical hyperplasia (Uno, Tarara, Else, Suleman and Sapolsky, 1989). In our previous studies the administration of dexamethasone (DEX) (5 mg/kg) to pregnant rhesus monkeys at 132 to 133 days of gestation induced degeneration and depletion of the hippocampal pyramidal and dentate granular neurons in the brains of 135-gestation-day fetuses, and these changes were retained in the brains of fetuses at near term, 165 days of gestation (Uno, Lohmiller, Thieme,

Kemnitz, Engle, Roecker, and Farrell, 1990). We also found that implantation of a cortisol pellet in the vicinity of the hippocampus in adult vervet monkeys induced degeneration of the CA3 pyramidal neurons and their dendritic branches (Sapolsky, Uno, Rebert, and Finch, 1990). Thus, hippocampal pyramidal neurons containing a high concentration of glucocorticoid receptors appear to be highly vulnerable to either hypercortisolemia caused by severe stress or to exposure to exogenous glucocorticoids. To study the long-term postnatal sequelae of prenatal brain damage, eight rhesus monkeys were treated with either DEX (5 mg/kg), 5 animals, or vehicle, 3 animals, at 132 to 133 days of gestation. After natural birth, all animals lived with their mothers for 1 year. At 9 months of age, we found that DEX-treated animals had significantly high plasma cortisol at both base and post-stress (isolation) levels compared to age-matched vehicle-treated animals. Magnetic resonance images (MRI) of the brain at 20 months of age showed an approximately 30% reduction in size and segmental volumes of the hippocampus in DEX-treated compared to vehicle-treated animals. Measurements of whole brain volume by MRI showed no significant differences between DEX and vehicle groups. Prenatal administration of a potent glucocorticoid (DEX) induced an irreversible deficiency of the hippocampal neurons and high plasma cortisol at the circadian baseline and post-stress levels in juvenile rhesus monkeys. These results suggest that the hippocampus mediates negative feedback of cortisol release; a lack or deficiency of the hippocampal neurons attenuates this feedback resulting in hypercortisolemia.(ABSTRACT TRUNCATED AT 400 WORDS)

[Psychosomatic dysfunctions in the female climacteric. Clinical effectiveness and tolerance of Kava Extract WS 1490].

Warnecke G.

*Fortschr Med.* 1991 Feb 10; 109(4):119-22.

Within the framework of a randomized, placebo-controlled double-blind study, two groups each containing 20 patients with climacteric-related symptomatology were treated for a period of 8 weeks with kava WS 1490 extract 3 X 100 mg/day or a placebo preparation. The target variable - the HAMA overall score of anxiety symptomatology - revealed a significant difference in the drug-receiving group vis-a-vis the placebo group already after only 1 week of treatment. The course of such further parameters as depressive mood (DSI), subjective well-being (patient diary), severity of the disease (CGI), and the climacteric symptomatology (Kuppermann Index and Schneider scale) over the overall period of treatment demonstrate a high level of efficacy of kava extract WS 1490 in neurovegetative and psychosomatic dysfunctions in the climacteric, associated with very good tolerance of the preparation

A comparison of kava special extract WS 1490 and benzodiazepines in patients with anxiety.

Woelk H.

*Z Allg Med.* 1993;(69):271-7.

Reduction effect of theanine on blood pressure and brain 5-hydroxyindoles in spontaneously hypertensive rats.

Yokogoshi H, Kato Y, Sagesaka YM, et al.

*Biosci Biotechnol Biochem.* 1995 Apr; 59(4):615-8.

The effect of theanine, one of the components of green tea, on the blood pressure and brain 5-hydroxyindoles in spontaneously hypertensive rats (SHR) and Wistar Kyoto rats (WKY) was investigated by intraperitoneally administering theanine. The effect of glutamine, which is structurally similar to theanine, was also examined. When SHR were injected with various amounts of theanine (0, 500, 1000, 1500, and 2000 mg/kg), the change was dose-dependent, and a significant decrease in blood pressure was observed with the high doses (1500 and 2000 mg/kg). A dose of 2000 mg/kg of theanine did not alter the blood pressure of WKY, while the same dose to SHR decreased it significantly. On the other hand, glutamine administration to SHR did not change either the blood pressure or the heart rate. The brain 5-hydroxyindole level was significantly decreased by theanine administration to both WKY and SHR, the decrease being dose-dependent

Hypotensive effect of gamma-glutamylmethylamide in spontaneously hypertensive rats.

Yokogoshi H, Kobayashi M.

*Life Sci.* 1998; 62(12):1065-8.

The effect of gamma-glutamylmethylamide(GMA), one of the components of green tea extract, on the blood pressure in spontaneously hypertensive rats (SHR) was investigated. The effect of glutamic acid and r-glutamylethylamide (theanine), which is structurally similar to GMA, was also examined. When SHR were injected with glutamic acid (2000mg/kg), the blood pressure

was not altered. The same dose of theanine decreased it significantly. GMA administration to SHR reduced the blood pressure significantly, and its degree of hypotensive action was more effective than that by theanine administration

Effect of theanine, r-glutamylethylamide, on brain monoamines and striatal dopamine release in conscious rats.

Yokogoshi H, Kobayashi M, Mochizuki M, et al.

*Neurochem Res.* 1998 May; 23(5):667-73.

Theanine, r-glutamylethylamide, is one of the major components of amino acids in Japanese green tea. Effect of theanine on brain amino acids and monoamines, and the striatal release of dopamine (DA) was investigated. Determination of amino acids in the brain after the intragastric administration of theanine showed that theanine was incorporated into brain through blood-brain barrier via leucine-preferring transport system. The concentrations of norepinephrine, 3,4-dihydroxyphenylacetic acid (DOPAC) and 5-hydroxyindole acetic acid (5HIAA) in the brain regions were unaffected by the theanine administration except in striatum. Theanine administration caused significant increases in serotonin and/or DA concentrations in the brain, especially in striatum, hypothalamus and hippocampus. Direct administration of theanine into brain striatum by microinjection caused a significant increase of DA release in a dose-dependent manner. Microdialysis of brain with calcium-free Ringer buffer attenuated the theanine-induced DA release. Pretreatment with the Ringer buffer containing an antagonist of non-NMDA (N-methyl-D-aspartate) glutamate receptor, MK-801, for 1 hr did not change the significant increase of DA release induced by theanine. However, in the case of pretreatment with AP-5, (+/-)-2-amino-5-phosphonopentanoic acid; antagonist of NMDA glutamate receptor, the theanine-induced DA release from striatum was significantly inhibited. These results suggest that theanine might affect the metabolism and/or the release of some neurotransmitters in the brain, such as DA

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