Health Effects of Coffee and Caffeine on Stress

Reviewed by Meri Rafetto, RD, Stephen Cherniske, MS and Gerri French, Rd, MS, CDE.

None of us can escape the influence of stress in our lives, nor would we choose to eliminate stress entirely. The feelings of arousal experienced while under stress can be energizing and motivating in the short-term. Stress can provide the motivating push to focus the mind and meet a deadline, complete a project, serve the winning volley in a tennis match, or help us escape from a life-threatening or dangerous situation. In short bursts, the cascade of hormones and neurotransmitters involved in the experience of stress can be lifesaving and performance-enhancing; but on a long-term basis, the effects of these hormones constantly coursing through the body can be disabling, contributing to a number of disease processes. Coffee drinking and caffeine intake stimulate the cascade of hormones and increase levels of cortisol, one of the body's stress hormones, intensifying and increasing the chronicity of the physical stress response.

Combining our pressured lifestyle that involves demands from every direction with our frequent physical inactivity, stress and its associated hormones can build up in the body with detrimental effects. Coffee and caffeine consumption negatively impact our physical and psychological experience of stress by affecting the interrelated group of hormones and neurotransmitters involved in the body's stress response; particularly the hypothalamus-pituitary-adrenal axis. Not only are we living a lifestyle that increases the damaging levels of stress hormones, but the foods and drinks we ingest exacerbate the effects of this pervasive stress in our bodies.

The Physiology of Stress and Stress hormones

The brain is constantly analyzing our internal and external environments. In response to stimuli thought to be threatening or extreme, a cascade of neurotransmitters and hormones are released. The hormones and neurotransmitters identified as being part of the stress response include: the catecholamines epinephrine, norepinephrine and dopamine, cortisol releasing hormone and cortisol, and the glucocorticoids. The nervous system component of the stress response is the sympathetic nervous system and adrenal medulla. Many of the hormones in the stress response are produced in the adrenal glands.

When these hormones and neurotransmitters are released and activated, concentration becomes more pointed and focused, strength and agility increase, and reaction times speed up. In order to create these effects, heart rate increases, blood sugar rises, circulation is diverted from the digestive system to the brain and extremities, allowing for a heightened response of the muscles and concentration, but slowing the processes of digestion and elimination.[1] Designed to be expended during intense physical activity, the body's emergency stress response should return to normal homeostasis in a relatively short period of time.

The Health Consequences of Chronically Elevated Stress Hormones

When stress hormones are chronically elevated, which occur as a result of our sedentary lifestyle combined with the daily ingesting of coffee and caffeine, mental concentration is not sustained as anxiety and feelings of tension increase while fine motor coordination is impaired.[2] The consumption of caffeine or coffee significantly adds to the endogenous hormone cascade by further increasing cortisol and norepinephrine, potentiating the body's stress response. If coffee is used habitually, the body does not become immune to its effect; the synergistic exacerbation of the stress hormone cascade is not

dampened, and tolerance does not develop.[3] The following consequences of chronically elevated stress hormones have a deleterious effect on health:

- **Stress hormones affect the hypothalamic-pituitary-adrenal axis**

The hypothalamic-pituitary-adrenal (HPA) axis is the central nervous system/endocrine control of the interrelated endocrine, immune, and nervous systems. Chronic and/or excessive cortisol release through constant psychosocial or physical stress, coffee, or caffeine intake can negatively affect the usually tightly controlled hormonal balance providing homeostasis. The chronic release of cortisol and activation of norepinephrine and the sympathetic autonomic nervous system causes a cascade of effects, including: inhibiting secretion of growth hormone, inhibiting thyroid function, inhibiting reproductive system function, promoting fat deposits in the abdominal area, increasing insulin resistance, hypertension, and interfering with proper bone deposition.[4]

Oversecretion of cortisol can lead to adrenal exhaustion or adrenopause, characterized by a relative excess of cortisol and a corresponding insufficiency of or decline in the adrenal hormone DHEA, which is integral to the body's repair mechanisms. This is related to a number of clinical illnesses, including: osteopenia, impairment of cognitive functioning or mood, progression of coronary artery disease and atherosclerosis, and immune system depletion.[5] Situations where there is chronic release of cortisol and other corticosteroids by the adrenal glands have been implicated in neural degeneration and interference with the hippocampus and memory formation.[6] Abnormalities in this system and overproduction of cortisol are observed in a number of psychiatric disorders including depression, anxiety, eating disorders, and addiction.[7]

- **Stress hormones increase weight gain**

The HPA axis is involved in weight maintenance through interrelated control of the pituitary, thyroid and adrenal glands. Chronically elevated levels of stress hormones, through lifestyle and dietary factors, cause insulin resistance resulting in increased deposition of adipose tissue in the abdominal area. This leads to the dangerous apple-shaped pattern of weight gain, which increases risk of heart disease and diabetes. Elevated stress hormones stimulate the increased consumption of fat and sugars, creating overall increased caloric intake.[8] Night eating is also increased during the physical or psychological experience of stress, and interferes with weight loss.[9]

- **Stress hormones compromise the immune system**

Recent research reveals that long-term exposure to stress hormones can be damaging to the body, particularly by compromising integrity of telomeres, end sequences located on cellular DNA. This damage may be a significant mechanism by which chronic stress accelerates a number of disease processes, including cardiovascular disease and immune system dysfunction.[10,11,12]

Stress hormones cause a biphasic response on the immune system, first stimulating immune response, and then suppressing immune system activity on a long-term basis. When stress hormones are first released in the body, within 30 minutes their presence causes the immune system to be stimulated, as the ancient fight or flight response is preparing the body to be wounded. This immune system activation is helpful to develop antibodies in response to an invading organism, or for white blood cell proliferation to fight a wound infection. Leukocytes are also redistributed, and often redirected to the skin to aid in possible wound healing.[13] But, after this initial, short-term response, immune system response is decreased again, in order to protect the body from the dangers of an autoimmune response developing.

In the presence of chronic elevation of stress hormones including cortisol and the glucocorticoids, the immune system becomes depressed.[14,15]

Immune system depression results from a number of different factors. One is by interfering with the thymus gland. The thymus gland is behind the sternum and is important in T cell proliferation and management. It used to be thought that the thymus gland shrinks with age, but this is not been shown to be the case.[16] But, chronic, elevated levels of stress hormones, particularly of glucocorticoids, causes atrophy of the thymus because of cell death.[17] Chronic elevation of glucocorticoid levels also interferes with the reactions of antigen-specific cell-mediated immune responses to the presence of bacteria, viruses, fungi, some tumors, and other invading organisms.[18] Glucocorticoids can also cause cell death of a variety of lymphocytes, or white blood cells.[19,20,21]

- **Stress hormones increase risk factors for cardiovascular disease**

High blood pressure is linked to increased stress, coffee drinking, and caffeine consumption.[22] Nearly one in three Americans have blood pressure that is higher than normal. A person may not realize they have high blood pressure; by itself it creates few symptoms, making it is a silent disease. But it can create devastating complications, including hardening of the arteries, kidney and heart problems, eye difficulties, aneurysms (or bulges in blood vessels), and heart attacks. It is widely acknowledged to be one of the most significant risk factors for other cardiovascular diseases. [23,24] Not only does stress by itself increase blood pressure, but caffeine and coffee consumption cause levels to rise.[25] The combined effect of stress and caffeine is particularly noticeable.[26]

This effect persists throughout the day with repeated coffee drinking and daily lifestyle stress.[27] Lifestyle changes, including reducing stress and modifications in diet and increased exercise, can make significant changes in blood pressure.[28] When regular coffee drinkers cease drinking coffee, which reduces the amounts of stress hormones coursing through the body, they experience significant reductions in measured blood pressure.[29]

- **Stress hormones interfere with sleep**

Chronic stress also disrupts sleep, which further inhibits the body's ability to repair itself. Elevated levels of cortisol are associated with insomnia and sleep disruption,[30] and activation of the HPA axis leads to sleeplessness and arousal, while sleep inhibits the HPA axis.[31]

Elevated Stress Hormones Compromise Cognition and Memory

Although the coursing of neurotransmitters like epinephrine and hormones including cortisol can sharpen the mind on a short-term basis to encourage a focuses fight-or-flight response, longer term exposure to glucocorticoids and other chemicals in the endogenous stress response can be damaging to the brain and impair optimal mental function.[32] Oversecretion of glucocorticoids, corticosteroids and other stress hormones is associated with cell death through metabolic disruption, excitotoxicity, lack of oxygen, increased concentrations of the reactive neurotransmitter glutamate, excessive intracellular calcium release and increased free radical activity.[33] Increased depression along with mood and nervous system disorders are associated with stress-related neuronal cell death.[34,35]

The processes of executive function, which include decision-making, reasoning, planning and goal-making, located in the prefrontal cortex, are compromised in chronic stress.[36] Chronic stress also interferes with working memory, the ability to keep a fact at the forefront of the mind.[37] Overall, increased experience of stress leads to higher incidence of depression in susceptible persons.[38]

The increased glucocorticoid secretions associated with chronic stress and frequent consumption of caffeine and coffee is damaging to the hippocampus and can cause cellular atrophy.[39] The hippocampus is not only responsible for the formation of memories but also the retrieval of information. It contains a high density of corticosteroids, making it especially vulnerable to chronic stress. Neurotoxicity can occur in the hippocampus, causing memory problems, even after merely weeks or months of chronic stress, causing high levels of glucocorticoid release, which becomes intensified when coffee drinking is combined with external stressors.

In animal studies, DHEA has been shown to have a protective effect against stress-related neuronal damage,[40] but since caffeine and coffee-related stress hormone release is shown to lower DHEA levels, the ability of DHEA to perform this essential repair function is compromised.

Cortisol Production Competes with DHEA Production

Dehydroepiandrosterone (DHEA) is an essential steroid hormone, produced by the adrenal glands, that is a significant contributor to the body's repair processes. DHEA functions to stimulate the immune system,[41] reduces inflammation,[42] and is involved in memory formation.[43] The presence of DHEA has a protective effect on illness related to stress, including: heart disease, cognitive impairment, immunodeficiency, obesity, osteoporosis, heart disease, and diabetes.[44,45] Importantly, DHEA stimulates the immune system, [46] which becomes compromised when the body is experiencing a chronic release of stress hormones. DHEA levels are reduced when cortisol and stress hormones are increased, as is the case with the chronic elevation of these hormones during periods of stress or coffee and caffeine consumption.[47]

Stress Hormones Aggravate Gastrointestinal Conditions

Stress can have devastating effects on the entire gastrointestinal tract. Studies show that elevated stress hormones exacerbate symptoms of acid reflux, GERDS, irritable bowel syndrome and other inflammatory bowel diseases. Stress is implicated in the development of ulcers. Stress hormones interfere with the binding of GABA to GABA receptors in the intestinal tract, preventing it from performing its calming function.

The following characteristics of coffee and caffeine intensify the effects of stress:

1) Coffee and Caffeine Increase the Stress Response

- **Coffee Elevates Stress Hormones and Stimulates the Sympathetic Nervous System**
  - Caffeine in coffee stimulates the production of the stress hormones cortisol and the glucocorticoids, as well as the catecholamines: epinephrine (also known as adrenalin), norepinephrine and dopamine.[48,49,50,51] This increase is over and above increased levels already observed under mental exertion, heightening the body's own stress response. [52,53] This elevation is present even hours after consumption.[54]
  - Decaffeinated coffee also stimulates the autonomic nervous system[55] and associated stress response demonstrating that other components in coffee besides caffeine contribute to coffee's stimulating effect.
  - Chronic metabolic acidity associated with coffee consumption stimulates cortisol secretion, further activating the stress response.[56]

    - Today's sedentary lifestyle coupled with caffeine and coffee consumption creates chronic levels of stress hormones in the body.[57]
- **Caffeine Interferes with GABA Metabolism**
    - GABA (Gamma-aminobutyric acid) is a neurotransmitter naturally produced in the brain, nervous system, and the heart. It plays an important role in mood and stress management and influences heart rate and function.
    - Caffeine has been found to interfere with binding of GABA to GABA receptors, preventing it from performing its calming function.[58] GABA's role in stress management is compromised in the presence of caffeine.
- **Increased Stress, Caffeine and Coffee Drinking Suppresses the Immune System**
    - Chronic stress from psychobiological factors or intake of caffeine and coffee inhibit optimal immune system function.[59] Stress is related to numbers of circulating white blood cells, immunoglobulin levels, and measurements of antibodies. Immune system response varies with the duration of the stress; chronic stress causes more significant decrease of function.[60]
- **Increased Stress, Caffeine and Coffee Drinking Interferes with Sleep**
    - When there are increased levels of stress-related hormones in the body, insomnia and sleep disruption become more frequent.[61]
    - Drinking coffee can cause insomnia and sleep deprivation, which have been found to increase insulin resistance, reduce glucose tolerance, stimulate the sympathetic nervous system, and increase concentrations of blood cortisol. [62,63,64]

2) Stress, Coffee and Caffeine Lead to Weight Gain

- **Coffee Exacerbates Stress-Induced Weight Gain**
    - Coffee drinking and caffeine consumption can further elevate cortisol levels, increasing insulin resistance, which leads to abdominal obesity. Deposition of abdominal fat further increases stress hormone release, creating a dangerous positive feedback loop interfering with weight loss, and increasing the risk of developing cardiovascular disease, insulin resistance and diabetes.[65]
- **Increased Stress Leads to Overeating**
    - A chronic state of increased stress aggravated by caffeine is associated with a markedly increased tendency to overeat. CNS stimulants such as caffeine increase feelings of anxiety. Caffeine consumption increases the tendency of people to overeat or binge-eat and abuse laxatives and diet pills. [66,67]
    - Coffee drinking increases physiological measurements of stress, and although this effect is greater with increased caffeine levels, decaffeinated coffee may also influence stress as factors other than caffeine in coffee are associated with stress.[68]
    - Elevation of stress hormones leads to fat cravings.[69]
    - Elevated levels of cortisol increase appetite.[70]

3) Stress, Coffee and Caffeine Compromise the Cardiovascular System

- **Stress and Coffee Drinking Raise Blood Pressure**
    - Acute caffeine intake has been shown to significantly increase both systolic and diastolic blood pressure while people are drinking coffee at work.[71,72] Drinking coffee within three hours causes a measurable rise in both systolic and diastolic blood pressure, and that effect can persist even into the following day.[73, 74] In people prone to hypertension, drinking coffee may be harmful.[75]

- **Coffee Drinking is Associated with Increased Heart Attack Risk**
    - Stress is one of the risk factors for succumbing to a heart attack, and independent of any other risk factors for heart disease, heavy coffee consumption has been shown to increase heart attack risk.[76] A J-shaped association is suggested for the link between coffee drinking and risk of developing acute coronary disease: the more coffee consumed, the greater the risk.[77]
- **Coffee Drinking Increases Stress-Related Heart Rhythm Irregularities**
    - Coffee drinking and the subsequent stress-related cortisol surge increase the incidence of heart palpitations and cardiac arrhythmias.[78,79,80]

4) Stress, Coffee, and Caffeine Negatively Affect Memory, Cognition and Mood

- **Stress and Coffee Drinking Interfere with Memory and the Hippocampus**
    - Caffeine-induced glucocorticoid secretion interferes with working memory, short term memory and formation and retrieval of long-term memory due to deleterious effects on the normal physiological processes of the hippocampus.[81,82]
- **Stress, Caffeine and Coffee Compromise Higher Cognitive Function**
    - The effects of stress, whether endogenous or initiated by coffee or caffeine consumption have been shown to disrupt the processes in the prefrontal cortex which include executive function, decision-making, and mood. [83,84,85]
- **Stress, Caffeine and Coffee Contribute to Increased Depression**
    - The psychobiological experience of stress and the coffee and caffeine-induced increase in stress hormone secretion leads to a heightened vulnerability to depression.[86,87,88,89]

5) Stress, Coffee, Caffeine Aggravate Gastrointestinal Conditions

- **Stress hormones affect neurological control of the intestines**
    - Neurological control of the entire gastrointestinal tract is affected by emotions, our subjective experience of stress, and the physiological presence of stress hormones such as cortisol and the glucocorticoids.[90,91]
- **Stress and Coffee Drinking Exacerbates Ulcers and Heartburn**
    - Both increased levels of stress as well as coffee consumption increase the risk of developing ulcers and can exacerbate ulcers in susceptible people.[92]
    - Feelings of stress or heightened anxiety, as well as coffee consumption also increase incidence of gastrointestinal reflux disease, or GERD, which is related to heartburn and esophageal ulcer formation.[93,94]
- **Stress and Coffee Drinking Contribute to Irritable Bowel Syndrome**
    - Irritable bowel syndrome and irritable bowel disease are both sensitive to the effects of prolonged stress and chronic exposure to stress hormones. Coffee drinking and caffeine consumption further exacerbate the disease process in these individuals. [95,96,97]

Managing Stress through Reducing Coffee and Caffeine Intake

Although we can endeavor to include stress reduction as a regular regime, coffee drinking and caffeine consumption creates a physical stress response even in the absence of psychobiological stressors and by intensifying the effects of internal and external stress. Reducing caffeine and coffee can help the body better repair from the effects of endogenous stress hormones and reduce the damaging effects of chronic hormone secretion.

However, of all the lifestyle modifications that people find difficult to change, coffee drinking is one of the most challenging because it is so entrenched in cultural habits and caffeine addiction.[98] Withdrawal

symptoms can involve painful headaches, nausea, vomiting, and loose stools, as well as depression, fatigue and anxiety. [99,100] People whose health problems would be ameliorated if they gave up coffee can improve their chance for successfully quitting coffee if they have both a satisfying alternative and a method to slowly decrease their caffeine intake to reduce withdrawal symptoms.

Recommendation:

Individuals who suffer from or are susceptible to high levels of stress would do well to avoid coffee. Dietary changes that include weaning off of coffee and all other sources of caffeine can help lower the stress threshold as caffeine increases the reactivity of the body to the stress of everyday life as well as increases blood pressure and heart rate.[101] Nutrition professionals can support stress management patients by guiding them through the process of substituting a non-caffeinated, alkaline herbal coffee that brews and tastes just like coffee.

Kicking the Caffeine Habit:

The social prevalence of coffee drinking and the addictive side effects of caffeine can cause problems with patient compliance. Caffeine-free herbal coffee marketed under the brand name of Teeccino® helps coffee drinkers replace their regular or decaf coffee with a satisfying alternative. Coffee drinkers need a dark, full-bodied, robust brew to help satisfy their coffee craving. Teeccino satisfies the 4 needs coffee drinkers require in a coffee alternative:

1) Teeccino brews just like coffee, allowing coffee drinkers to keep their same brewing ritual.
2) It has a delicious, deep roasted flavor that is very coffee-like.
3) It wafts an enticing aroma.
4) It gives a natural energy boost from 65 mg of potassium in each cup.

Teeccino offers the following health benefits to protect against the damaging effects of stress:

Beneficial Features of Teeccino	**Teeccino Ingredients**:[103, 104, 105, 106, 107, 108, 109, 110, 111, 112]

▪ Inulin fiber from chicory
  ▪ Unlike coffee, Teeccino has nutritional value, including soluble inulin fiber, a pre-biotic that helps support a healthy population of beneficial microflora.
  ▪ Inulin improves mineral absorption
▪ 65 mg of Potassium
  ▪ Teeccino is a source of potassium. In liquid form, potassium is easily absorbed to support the nervous system recover from stress, relieve muscle fatigue, maintain normal heart rhythm and blood pressure, and help prevent strokes.
▪ Alkaline – helps reduce acidity
  ▪ As opposed to acidic coffee, Teeccino is alkaline, which reduces stress-related metabolic acidity.
▪ Gluten Free
  ▪ Gluten does not extract into boiling water. Tests show Teeccino is gluten free although it contains barley.
▪ Naturally Caffeine-free
  ▪ No chemical processing like decaffeinated coffee.
	▪ Carob
	  ▪ Consumption of water-soluble fiber from carob lowers elevated blood cholesterol in healthy people, reducing risk of stress-related cardiovascular disease.
	▪ Barley
	  ▪ Contains niacin, a B vitamin important as an antioxidant and for heart function.
	  ▪ Shown to have a beneficial effect on lipid metabolism.
	▪ Almond
	  ▪ Has a beneficial effect on serum lipid levels, reducing stress-related cardiovascular risk
	▪ Figs
	  ▪ Contain polyphenols, plant compounds that act as antioxidants, important for recovering from the effects of stress and aging.
	  ▪ A good source of potassium.
	▪ Dates
	  ▪ Contains potassium and magnesium, important for nervous system function and maintaining heart rhythm.
	▪ Chicory root
	  ▪ Improves mineral absorption.

Kicking the Coffee Habit: The Pain-free Way to Wean off of Coffee

Start by mixing normal coffee 3/4 to 1/4 Teeccino Herbal Coffee. Gradually reduce the percentage of coffee over a two to three week period until only 100% Teeccino Herbal Coffee is brewed. Gradual reduction of caffeine is recommended.[102] Side effects such as headaches, fatigue, and brain fogginess can be avoided as the body gradually adjusts to less reliance on stimulants.

Example: Use the following proportions if you make a 10-cup pot of coffee daily:

DAY	**Regular Coffee**	**Teeccino**
Day 1-3:	4 tablespoons	1 tablespoon
Day 4-6:	3 tablespoons	2 tablespoons
Day 7-9:	2 tablespoons	3 tablespoons
Day 10:	1 1/2 tablespoons	3 1/2 tablespoons
Day 11:	1 tablespoon	4 tablespoons
Day 12-13:	1/2 tablespoon	4 1/2 tablespoons
Day 14:	0	5 tablespoons

References

[1] Habib, K.E., Gold, P.W., and Chrousos, G.P. 2001. Neuroendocrinology of stress. Endocrinology and Metabolism Clinics of North America. 30(3):695-728.

[2] Jacobson, B.H. and Thurman-Lacey, S.R. 1992. Effect of caffeine on motor performance by caffeine-naive and -familiar subjects. Perceptual and Motor Skills. 74(1):151-7.

[3] Lane, J.D., Adcock, R.A., Williams, R.B. and Kuhn, C.M. 1990. Caffeine effects on cardiovascular and neuroendocrine responses to acute psychosocial stress and their relationship to level of habitual caffeine consumption. Psychosomatic Medicine. 52(3):320-36.

[4] Tsigos, C. and Chrousos, G.P. 2002. Hypothalamic-pituitary-adrenal axis, neuroendocrine factors and stress. Journal of Psychosomatic Research. 53(4):865-71.

[5] Valenti, G. 2002. Adrenopause: an imbalance between dehydroepiandrosterone (DHEA) and cortisol secretion. Endocrinol Invest. TK 25(10 Suppl):29-35.

[6] Davies, E. and MacKenzie, S.M. 2003. Extra-adrenal production of corticosteroids. Clinical Experiments in Pharmacological Physiology, 30(7):437-45.

[7] Contoreggi, C., Rice, K.C. and Chrousos, G. 2004. Nonpeptide Corticotropin-Releasing Hormone Receptor Type 1 Antagonists and Their Applications in Psychosomatic Disorders. Neuroendocrinology. 80(2):111-123

[8] Bjorntorp, P. 2001. Do stress reactions cause abdominal obesity and comorbidities? Obesity Reviews. 2(2):73-86.

[9] Takeda, E., Terao, J., Nakaya, Y., Miyamoto, K., Baba, Y., Chuman, H., Kaji, R., Ohmori, T. and Rokutan, K. 2004. Stress control and human nutrition. Journal of Medical Investigation. 51(3-4):139-45.

[10] Epel, E.S., Blackburn, E.H., Lin, J., Dhabhar, F.S., Adler, N.E., Morrow, J.D., and Cawthon, R.M. 2004. Accelerated telomere shortening in response to life stress. Proceeding of the National Academy of Sciences U.S.A. 101(49):17312-5.

[11] Kurz, D.J., Decary, S., Hong, Y., Trivier, E., Akhmedov, A., and Erusalimsky, J.D. 2004. Chronic oxidative stress compromises telomere integrity and accelerates the onset of senescence in human endothelial cells. Journal of Cell Science. 117(Pt 11):2417-26.

[12] Minamino, T., and Komuro, I. 2002. Role of telomere in endothelial dysfunction in atherosclerosis. Current Opinion in Lipidology. 13(5):537-43.

[13] Herbert, T.B., and Cohen, S. 1993. Stress and immunity in humans: a meta-analytic review. Psychosomatic Medicine. 55(4):364-79.

[14] McEwen, B.S. 2000. The neurobiology of stress: from serendipity to clinical relevance. Brain Research. 886:172-189.

[15] Sapolsky, R.M. 2004. Why Zebras Don't Get Ulcers. Henry Holt and Company, New York.

[16] Shanker, A. 2004. Is thymus redundant after adulthood? Immunology Letters. 91(2-3):79-86.

[17] Kinoshita, Y., and Hato, F. 2001. Cellular and molecular interactions of thymus with endocrine organs and nervous system. Cellular and Molecular Biology. 47(1):103-17.

[18] Dhabhar, F.S., and McEwen, B.S. 1997. Acute stress enhances while chronic stress suppresses cell-mediated immunity in vivo: a potential role for leukocyte trafficking. Brain, Behavior, and Immunity. 11(4):286-306.

[19] Wyllie, A.H. 1980. Glucocorticoid-induced thymocyte apoptosis is associated with endogenous endonuclease activation. Nature. 284(5756):555-6.

[20] Blewitt, R.W., Abbott, A.C., and Bird, C.C. 1983. Mode of cell death induced in human lymphoid cells by high and low doses of glucocorticoid. British Journal of Cancer. 47(4):477-86

[21] Cidlowski, J.A., King, K.L., Evans-Storms, R.B., Montague, J.W., Bortner, C.D., and Hughes, F.M. Jr. 1996. The biochemistry and molecular biology of glucocorticoid-induced apoptosis in the immune system. Recent Progress in Hormone Research. 51:457-90, 490-1.

[22] Nurminen, M.L., Niittynen, L., Korpela, R. and Vapaatalo, H. 1999. Coffee, caffeine and blood pressure: a critical review. European Journal of Clinical Nutrition. 53(11):831-9.

[23] National Heart, Lung and Blood Institute, High Blood Pressure. Copyright 2004.

[24] Miura, K. 2004. Strategies for prevention and management of hypertension throughout life. Journal of Epidemiology. 14(4):112-7.

[25] Lane, J.D., Phillips-Bute, B.G. and Pieper, C.F. 1998. Caffeine raises blood pressure at work. Psychosomatic Medicine. 60(3):327-30.

[26] al'Absi M, Lovallo WR, McKey B, Sung BH, Whitsett TL, Wilson MF. 1998. Hypothalamic-pituitary-adrenocortical responses to psychological stress and caffeine in men at high and low risk for hypertension. Psychosomatic Medicine. 60(4):521-7.

[27] Lane, J.D. and Manus, D.C. 1989. Persistent cardiovascular effects with repeated caffeine administration. Psychosomatic Medicine. 51(4): 373-80.

[28] Miller, E.R. 3rd, Erlinger, T.P., Young, D.R., Jehn, M., Charlestonm J., Rhodes, D., Wasan, S.K. and Appel, L.J. 2002. Results of the Diet, Exercise, and Weight Loss Intervention Trial (DEW-IT).Hypertension. 2002;40:612.

[29] Superko, H.R., Myll, J., DiRicco, C., Williams, P.T., Bortz, W.M. and Wood, P.D. 1994. Effects of cessation of caffeinated-coffee consumption on ambulatory and resting blood pressure in men. American Journal of Cardiology. 73(11):780-4.

[30] Vgontzas, A.N., Bixler, E.O., Lin, H.M., Prolo, P., Mastorakos, G., Vela-Bueno, A., Kales, A., and Chrousos, G.P. 2001. Chronic insomnia is associated with nyctohemeral activation of the hypothalamic-pituitary-adrenal axis: clinical implications. The Journal of Clinical Endocrinology and Metabolism. 86(9):3787-94.

[31] Vgontzas, A.N., and Chrousos, G.P. 2002. Sleep, the hypothalamic-pituitary-adrenal axis, and cytokines: multiple interactions and disturbances in sleep disorders. Endocrinology and Metabolism Clinics of North America. 31(1):15-36.

[32] Arnsten, A.F. 1998. The biology of being frazzled. Science. 280(5370):1711-2.

[33] Roy, M. and Sapolsky, R.M. 2003. The exacerbation of hippocampal excitotoxicity by glucocorticoids is not mediated by apoptosis. Neuroendocrinology. 77(1):24-31.

[34] Lee, A.L., Ogle, W.O. and Sapolsky, R.M. 2002. Stress and depression: possible links to neuron death in the hippocampus. Bipolar Disorder. 4(2): 117-28.

[35] Arango, C., Kirkpatrick, B. and Koenig, J. 2001. At issue: stress, hippocampal neuronal turnover, and neuropsychiatric disorders. Schizophrenia Bulletin. 27(3): 477-80.

[36] Arnsten, A.F. 2000. Stress impairs prefrontal cortical function in rats and monkeys: role of dopamine D1 and norepinephrine alpha-1 receptor mechanisms. Progress in Brain Research. 126:183-92.

[37] Mizoguchi, K., Yuzurihara, M., Ishige, A., Sasaki, H., Chui, D.H., and Tabira, T. 2000. Chronic stress induces impairment of spatial working memory because of prefrontal dopaminergic dysfunction. Journal of Neuroscience. 20(4):1568-74.

[38] Leonard, B.E. 2001. Stress, norepinephrine and depression. Journal of Psychiatry and Neuroscience. 26 Suppl:S11-6.

[39] Sapolsky, R.M. 1996. Stress, Glucocorticoids, and Damage to the Nervous System: The Current State of Confusion. Stress. 1(1): 1-19.

[40] Kurata, K., Takebayashi, M., Morinobu, S., Yamawaki, S. 2004. beta-estradiol, dehydroepiandrosterone, and dehydroepiandrosterone sulfate protect against N-methyl-D-aspartate-induced neurotoxicity in rat hippocampal neurons by different mechanisms. The Journal of Pharmacology and Experimental Therapeutics. 311(1):237-45.

[41] Nawata, H., Yanase, T., Goto, K., Okabe, T., Nomura, M., Ashida, K. and Watanabe, T. 2004. Adrenopause. Hormone Research. 62(Suppl 3):110-4.

[42] Schwartz, A.G. and Pashko, L.L. 2004. Dehydroepiandrosterone, glucose-6-phosphate dehydrogenase, and longevity. Ageing Research Reviews. 3(2), 171-87.

[43] Reddy, D.S. 2003. Pharmacology of endogenous neuroactive steroids. Critical Reviews in Neurobiology. 15(3-4):197-234.

[44] Barrou, Z., Charru, P. and Lidy, C. 1997. Dehydroepiandrosterone (DHEA) and aging. Archives of Gerontology and Geriatrics. 24(3): 233-41.

[45] Nawata, H., Yanase, T., Goto, K., Okabe, T., Nomura, M., Ashida, K. and Watanabe, T. 2004. Adrenopause. Hormone Research. 62(Suppl 3):110-4.

[46] Nawata, H., Yanase, T., Goto, K., Okabe, T., Nomura, M., Ashida, K. and Watanabe, T. 2004. Adrenopause. Hormone Research. 62(Suppl 3):110-4.

[47] Wolkowitz, O.M., Epel, E.S. and Reus, V.I. 2001. Stress hormone-related psychopathology: pathophysiological and treatment implications. World Journal of Biological Psychiatry. 2(3): 115-43.

[48] Robertson, D., Frolich, J.C., Carr, R.K., Watson, J.T., Hollifield, J.W., Shand, D.G. and J.A. Oates. 1978. Effects of caffeine on plasma renin activity, catecholamines and blood pressure. New England Journal of Medicine. 298(4):181-6.

[49] Lane, J.D., Adcock, R.A., Williams, R.B. and C.M. Kuhn. 1990. Caffeine effects on cardiovascular and neuroendocrine responses to acute psychosocial stress and their relationship to level of habitual caffeine consumption. Psychosomatic Medicine. 52(3):320-36.

[50] Lane, J.D. 1994. Neuroendrocine Responses to Caffeine in the Work Environment. Psychosomatic Medicine. 546:267-70.

[51] Kerr, D., Sherwin, R.S., Pavalkis, F., Fayad, P.B., Sikorski, L., Rife, F., Tamborlane, W.V. and During, M.J. 1993. Effect of caffeine on the recognition of and responses to hypoglycemia in humans. Annals of Internal Medicine. 119(8):799-804.

[52] Papadelis, C., Kourtidou-Papadeli, C., Vlachogiannis, E., Skepastianos, P., Bamidis, P., Maglaveras, N. and Pappas, K. 2003. Effects of mental workload and caffeine on catecholamines and blood pressure compared to performance variations. Brain Cognition. 51(1):143-54.

[53] al'Absi, M., Lovallo, W.R., McKey, B., Sung, B.H., Whitsett, T.L. and Wilson, M.F. 1998. Hypothalamic-pituitary-adrenocortical responses to psychological stress and caffeine in men at high and low risk for hypertension. Psychosomatic Medicine. 60(4):521-7.

[54] Lovallo, W.R., Al'Absi, M., Blick, K., Whitsett, T.L. and Wilson, M.F. 1996. Stress-like adrenocorticotropin responses to caffeine in young healthy men. Pharmacology, Biochemistry and Behavior. 55(3):365-9.

[55] Quinlan, P.T., Lane, J., Moore, K.L., Aspen, J., Rycroft, J.A.and O'Brien, D.C. 2000. The acute physiological and mood effects of tea and coffee: the role of caffeine level. Pharmacology of Biochemistry and Behavior. 66(1):19-28.

[56] Maurer, M., Riesen, W., Muser, J., Hulter, H.N. and Krapf, R. 2003. Neutralization of Western diet inhibits bone resorption independently of K intake and reduces cortisol secretion in humans. American Journal of Physiology. Renal Physiology. 284(1):F32-40.

[57] Lane, J.D., Pieper, C.F., Phillips-Bute, B.G., Bryant, J.E. and Kuhn, C.M. 2002. Caffeine affects cardiovascular and neuroendocrine activation at work and home. Psychosomatic Medicine. 64(4):595-603.

[58] Roca, D.J., G.D. Schiller, and D.H. Farb. 1988. Chronic Caffeine or Theophylline Exposure Reduces Gamma-aminobutyric Acid/Benzodiazepine Receptor Site Interactions. Molecular Pharmacology, May;33(5):481-85.

[59] Cohen, S., and Herbert, T.B. 1996. Health psychology: psychological factors and physical disease from the perspective of human psychoneuroimmunology. Annual Review of Psychology. 47:113-42.

[60] Herbert, T.B., and Cohen, S. 1993. Stress and immunity in humans: a meta-analytic review. Psychosomatic Medicine. 55(4):354-79.

[61] Vgontzas, A.N., Bixler, E.O., Lin, H.M., Prolo, P., Mastorakos, G., Vela-Bueno, A., Kales, A., and Chrousos, G.P. 2001. Chronic insomnia is associated with nyctohemeral activation of the hypothalamic-pituitary-adrenal axis: clinical implications. The Journal of Clinical Endocrinology and Metabolism. 86(9):3787-94.

[62] Boutrel, B. and Koob, G.F. 2004. What keeps us awake: the neuropharmacology of stimulants and wakefulness-promoting medications. Sleep. 27(6): 1181-94.

[63] Spiegel, K., Leproult, R. and Van Cauter, E. 1999. Impact of sleep debt on metabolic and endocrine function. Lancet. 354(9188): 1435-9.

[64] VanHelder, T., Symons, J.D. and Radomski, M.W. 1993. Effects of sleep deprivation and exercise on glucose tolerance. Aviation, Space, and Environmental Medicine. 64(6):487-92.

[65] Dallman, M.F., la Fleur, S.E., Pecoraro, N.C., Gomez, F., Houshyar, H., Akana, S.F. 2004. Minireview: glucocorticoids--food intake, abdominal obesity, and wealthy nations in 2004. Endocrinology. 145(6): 2633-8.

[66] Krahn, D.D., Hasse, S., Ray, A., Gosnell, B. and Drewnowski, A. 1991. Caffeine consumption in patients with eating disorders. Hospital and Community Psychiatry. 42(3)313-5.

[67] Livermore, B. 1991. Caffeine Boosts Eating Disorders. Health. June: 16.

[68] Quinlan, P.T., Lane, J., Moore, K.L., Aspen, J., Rycroft, J.A. and O'Brien, D.C. 2000. The acute physiological and mood effects of tea and coffee: the role of caffeine level. Pharmacology, Biochemistry, and Behavior. 66(1):19-28.

[69] Castonguay, T.W. 1991. Glucocorticoids as modulators in the control of feeding. Brain Research Bulletin. 27(3-4):423-8.

[70] Takeda, E., Terao, J., Nakaya, Y., Miyamoto, K., Baba, Y., Chuman, H., Kaji, R., Ohmori, T. and Rokutan, K. 2004. Stress control and human nutrition. Journal of Medical Investigation. 51(3-4): 139-45.

[71] Waring, W.S., Goudsmit, J., Marwick, J., Webb, D.J. and Maxwell, S.R.J. 2003. Acute caffeine intake influences central more than peripheral blood pressure in young adults. American Journal of Hypertension. 16(11): 919-24.

[72] Jeong, D.U. and Dimsdale, J.E. 1990. The effects of caffeine on blood pressure in the work environment. American Journal of Hypertension. 3(10): 749-53.

[73] Shirlow, M.J., Berry, G. and Stokes, G. 1988. Caffeine consumption and blood pressure: an epidemiological study. International Journal of Epidemiology. 17(1):90-7.

[74] James, J.E. 1994. Chronic effects of habitual caffeine consumption on laboratory and ambulatory blood pressure levels. Journal of Cardiovascular Risk. 1(2): 159-64.

[75] Nurminen, M.L., Niittynen, L., Korpela, R. and Vapaatalo, H. 1999. Coffee, caffeine and blood pressure: a critical review. European Journal of Clinical Nutrition. 53(11):831-9.

[76] Happonen P, Voutilainen S, Salonen JT. 2004. Coffee drinking is dose-dependently related to the risk of acute coronary events in middle-aged men. Journal of Nutrition. 134(9):2381-6.

[77] Panagiotakos, D.B., Pitsavos, C., Chrysohoou, C., Kokkinos, P., Toutouzas, P. and Stefanadis, C. 2003. The J-shaped effect of coffee consumption on the risk of developing acute coronary syndromes: the CARDIO2000 case-control study. Journal of Nutrition. 133(10):3228-32.

[78] Lochen ML, Rasmussen K. 1996. Palpitations and lifestyle: impact of depression and self-rated health. The Nordland Health Study. Scandinavian journal of social medicine. 24(2):140-4.

[79] Shirlow, M.J. and Mathers, C.D. 1985. A study of caffeine consumption and symptoms; indigestion, palpitations, tremor, headache and insomnia. International Journal of Epidemiology. 14(2):239-48.

[80] Rosmarin PC. 1989. Coffee and coronary heart disease: a review. Progress in Cardiovascular Diseases. 32(3):239-45.

[81] Sapolsky, R.M. 1996. Stress, Glucocorticoids, and Damage to the Nervous System: The Current State of Confusion. Stress. 1(1):1-19.

[82] Yusim, A., Ajilore, O., Bliss, T., and Sapolsky, R. 2000. Glucocorticoids exacerbate insult-induced declines in metabolism in selectively vulnerable hippocampal cell fields. Brain Research. 870(1-2):109-17.

[83] Arnsten, A.F. 1998. The biology of being frazzled. Science. 280(5370):1711-2.

[84] Tassin, J.P. 1998. Norepinephrine-dopamine interactions in the prefrontal cortex and the ventral tegmental area: relevance to mental diseases. Advances in Pharmacology. 42:712-6.

[85] Arnsten, A.F., and Goldman-Rakic, P.S. 1998. Noise stress impairs prefrontal cortical cognitive function in monkeys: evidence for a hyperdopaminergic mechanism. Archives of General Psychiatry. 55(4):362-8.

[86] Sapolsky, R.M. 2000. The possibility of neurotoxicity in the hippocampus in major depression: a primer on neuron death. Biological Psychiatry. 48(8):755-65.

[87] Lee, A.L., Ogle, W.O., and Sapolsky, R.M. 2002. Stress and depression: possible links to neuron death in the hippocampus. Bipolar Disorder. 4(2):117-28.

[88] van Praag, H.M.2004. Can stress cause depression? Progress in Neuro-Psychopharmacology & Biological Psychiatry. 28(5):891-907.

[89] Ressler, K.J., and Nemeroff CB. 2000. Role of serotonergic and noradrenergic systems in the pathophysiology of depression and anxiety disorders. Depression and Anxiety. 12(Suppl 1):2-19.

[90] Mulak, A. and B. Bonaz. 2004. Irritable bowel syndrome: a model of the brain-gut interactions. Medical Science Monitor : International Medical Journal of Experimental and Clinical Research 10(4):RA55-62.

[91] Lea, R. and Whorwell, P.J. 2004. Psychological influences on the irritable bowel syndrome. Minerva Medica. 95(5):443-50

[92] Abu Farsakh, N.A. 2002. Risk factors for duodenal ulcer disease. Saudi Medical Journal. 23(2):168-72.

[93] Feldman, M. and Barnett, C. 1995. Relationships between the acidity and osmolality of Popular Beverages and reported Postprandial Heartburn. Gastroenterology. 108(1): 125-31.

[94] Naliboff BD, Mayer M, Fass R, Fitzgerald LZ, Chang L, Bolus R, Mayer EA. 2004. The effect of life stress on symptoms of heartburn. Psychosomatic Medicine. 66(3):426-34.

[95] Lea, R. and Whorwell, P.J. 2004. Psychological influences on the irritable bowel syndrome. Minerva Medica. 95(5):443-50.

[96] Lea R, Whorwell PJ. 2003. New insights into the psychosocial aspects of irritable bowel syndrome. Current Gastroenterology Reports. 5(4):343-50.

[97] Dapoigny, M., R.W. Stockbrugger, F. Azpiroz, S. Collins, G. Coremans, S. Muller-Lissner, A. Oberndorff, F. Pace, A. Smout, M. Vatn, and P. Whorwell. 2003. Role of Alimentation on Irritable Bowel Syndrome. Digestion, 67(4):225-33.

[98] Braun, S. Buzz: The Science and Lore of Alcohol and Caffeine. Copyright 1996.

[99] Strain, E.C., G.K. Mumford, K. Silverman, and R.R. Griffiths. 1994. Caffeine dependence syndrome. Journal of the American Medical Association, 272:1043-1048.

[100] Silverman, K., Evans, S.M., Strain, E.C. and Griffiths, R.R. 1992 Withdrawl Syndrome after the Double-Blind Cessation of Caffeine Consumption. The New England Journal of Medicine. 16(327): 1109-14.

[101] Lane, J.D., Pieper, C.F., Phillips-Bute, B.G., Bryant, J.E. and Kuhn, C.M. 2002. Caffeine affects cardiovascular and neuroendocrine activation at work and home. Psychosomatic Medicine. 64(4):595-603.

[102] Silverman, K., Evans, S.M., Strain, E.C. and Griffiths, R.R. 1992 Withdrawl Syndrome after the Double-Blind Cessation of Caffeine Consumption. The New England Journal of Medicine. 16(327): 1109-14.

[103] Physicians Desk Reference for Herbal Medicines. Second Edition. Copyright 2000.

[104] Roehl, E. Whole Foods Facts: The Complete Reference Guide. Copyright 1996.

[105] Roberfroid MB. 1997. Health benefits of non-digestible oligosaccharides. Advances in Experimental Medicine and Biology. 427: 211-9.

[106] Biddle, W. 2003. Gastroesophageal reflux disease: current treatment approaches. Gastroenterology Nursing : The Official Journal of the Society of Gastroenterology Nurses and Associates. 26(6):228-36.

[107] Kim M, Shin HK. 1996. The water-soluble extract of chicory reduces glucose uptake from the perfused jejunum in rats. Journal of Nutrition. 126(9):2236-42.

[108] Al-Shahib W, Marshall RJ. (2003) The fruit of the date palm: its possible use as the best food for the future? International Journal of Food Sciences and Nutrition. 54(4):247-59.

[109] Gums JG. 2004. Magnesium in cardiovascular and other disorders. American Journal of Health-System Pharmacy : AJHP : Official Journal of the American Society of Health-System Pharmacists. 61(15):1569-76.

[110] Li, J., Kaneko, T., Qin, L.Q., Wang, J. and Wang, Y. 2003. Effects of barley intake on glucose tolerance, lipid metabolism, and bowel function in women. Nutrition. 19(11-12). 926-9.

[111] Lovejoy, J.C., Most, M.M., Lefevre, M., Greenway, F.L. and Rood, J.C. 2002. Effect of diets enriched in almonds on insulin action and serum lipids in adults with normal glucose tolerance or type 2 diabetes. American Journal of Clinical Nutrition. 76(5):1000-6.

[112] Haskell, W.L., Spiller, G.A., Jensen, C.D., Ellis, B.K. and Gates, J.E. 1992. Role of water-soluble dietary fiber in the management of elevated plasma cholesterol in healthy subjects. American Journal of Cardiology. 69(5):433-9.