

## REPORT

### Cortisol

#### Keeping a Dangerous Hormone in Check

By Dave Tuttle



*Cortisol is an essential hormone that plays many vital roles, including helping the human body adapt to stress. Yet this naturally occurring hormone is one of the few whose levels in the body increase with age, with potentially damaging consequences that have been linked to depression, Alzheimer's disease, and other maladies.*

*The good news is, new research on nutrients such as phosphatidylserine, DHEA, and ginkgo biloba offers valuable insights on how to control cortisol levels to promote optimal health.*

Declining hormone levels are a hallmark of the aging process. The body's production of DHEA, pregnenolone, and testosterone drops significantly as we age, and these changes in hormone levels can have dramatic effects on our health.

But not all hormones follow this pattern. One major exception is cortisol, a hormone released in response to stress. While cortisol plays vital roles in the body, excessive secretions of this hormone can have serious health implications, including loss of mental function, depression, and a reduction in lean tissue. Extreme overproduction of cortisol, as occurs in Cushing's syndrome, results in increased body fat, decreased bone density, and severe muscle weakness. Thus it is critical to maintain cortisol levels within a healthy range. Fortunately, scientists have discovered that phosphatidylserine, DHEA, and ginkgo biloba can reduce cortisol levels, helping to keep this catabolic hormone from damaging your body.

### Cortisol's Many Roles

Cortisol is one of several hormones in the hypothalamic-pituitary-adrenal axis. This auto-regulating system maintains a tight integration of the endocrine, nervous, and immune systems, constantly reacting to a variety of internal and external stimuli.<sup>1</sup> This allows the body to adapt to a broad range of changing circumstances, promoting survival and longevity. When this axis is partially inactivated or functions improperly, the body may be exposed to excessive amounts of neural, endocrine, and immune stress, resulting in pathological consequences.



When the body experiences stress, the hypothalamus sends corticotropin-releasing hormone to the pituitary gland through a specialized circulation system called the hypophyseal portal duct. This stimulates the anterior lobe of the pituitary gland to secrete larger amounts of a hormone known as adrenocorticotropin, or ACTH. This hormone regulates the activities of the outer portion of the adrenal gland known as the adrenal cortex, where cortisol is produced.

An enhanced secretion of ACTH triggers increased production of cortisol and other related glucocorticoids in the adrenal cortex. Cortisol, also called hydrocortisone, is responsible for about 95% of the body's glucocorticoid activity. It has several important metabolic and non-metabolic effects in the body.<sup>2</sup> Cortisol increases the mobilization of free fatty acids, making them more available as an energy source. It decreases glucose use, sparing it for essential brain functions. Cortisol also stimulates protein catabolism (breakdown) so that amino acids can be released for use in repair, enzyme synthesis, and energy production, while stimulating gluconeogenesis, the process by which protein or fat is converted into glucose. Cortisol even serves as an insulin antagonist by inhibiting glucose uptake and oxidation. The principal non-metabolic activities of cortisol include restraining the immune system's production of inflammatory cytokines, increasing catecholamine release to improve blood flow and distribution, and enhancing mental acuity.

Cortisol has short-term anti-inflammatory properties, which is why it was used to treat arthritis when first made available as a drug in the 1950s. Unfortunately, cortisol also depresses immune reactions, and as a result produces serious negative effects when administered for prolonged periods. Once considered wonder drugs, cortisol-based drugs are now used only as a last resort, and even then only for short periods. High levels of cortisol in the body also have been shown to produce hypertension, poor wound healing, bone loss, muscle wasting, thin skin, increased abdominal fat, insulin resistance, and sleep fragmentation, all of which are common in older individuals.



Clearly, cortisol is a double-edged sword. We cannot live without it, nor would we want to, as it helps the body adapt to stressful situations, such as illness or a deadline at work. Yet for reasons that remain unknown, the body's cortisol-regulation system can spin out of control as we age, especially in the frail, sending cortisol production soaring to damaging levels. A recent German study found that daily cortisol production increased by 54% from a group of 21- to 30-year-old men to a group of men over 70, all of whom were otherwise healthy.<sup>3</sup> This excess cortisol has been implicated in numerous diseases of aging, making proper regulation of cortisol levels a vital necessity.

### **Implicated in Depression and Alzheimer's**

Cortisol levels increase as much as fivefold even in healthy individuals when they are confronted with stressful events. Everyday hassles and the distress and agitation that accompany them are associated with greater cortisol

production in all of us. But when someone has a depressive disorder, cortisol levels increase even more; in fact, considerable evidence suggests that hypercortisolemia secondary to increased corticotropin release is involved in the pathogenesis of depressive disorders.<sup>4</sup> Minor stressful events can lead to increased adrenocortical activity and depression in vulnerable individuals, and the elevated cortisol levels associated with these stressful events can in turn worsen the condition of the depressed patients. The number of secretory pulses increases in these individuals, as reflected in their high daily rates of cortisol production.

Researchers have found that cortisol can affect mood and behavior, and disrupt memory and recall.<sup>5</sup> Administering cortisol to healthy volunteers has been shown to alter processes associated with prefrontal cortex functions, such as inhibitory control, attention regulation, and planning. Cortisol has significant interactions with the neurotransmitters, neuropeptides, and brain circuits that are associated with depressive symptoms. Because elevated cortisol levels also can affect the endocrine, metabolic, pro-inflammatory, and hemostatic factors that increase vulnerability to cardiovascular disease and other medical conditions, it is not surprising that depression is an independent risk factor for coronary artery disease. Even worse, recurring depressive symptoms result in cumulative injury to the hippocampus, which can further impair the feedback pathways for the hypothalamic-pituitary-adrenal axis and send already depressed individuals into even deeper depression.

Cortisol also plays a role in the progression of Alzheimer's disease. The hippocampus is closely associated with the acquisition, retrieval, and consolidation of new memories. Excessive cortisol levels have neurotoxic effects on the hippocampus, resulting in atrophy and memory impairment.<sup>6</sup> A study conducted at the University of Genova, Italy, found that cortisol levels are directly related to the degree of cognitive impairment in people with Alzheimer's disease.<sup>7</sup> These patients also had much lower levels of DHEA sulfate (DHEA-S), and therefore a dramatically higher cortisol:DHEA-S ratio than individuals without Alzheimer's. This suggests that a reduction in cortisol levels could help treat people with Alzheimer's, particularly when linked to DHEA supplementation.

The negative effects of cortisol on memory and cognitive decline are not limited to people with Alzheimer's. A four-year longitudinal study found a significant relationship between increasing cortisol levels and the impairment of explicit memory and selective attention performance in otherwise healthy individuals.<sup>8</sup> This long-term rise in cortisol production is even more problematic in light of declining levels of DHEA and other neuroprotective hormones. In fact, some scientists now believe that brain aging depends on cumulative exposure to increasing cortisol levels throughout life, particularly when this occurs along with reduced secretions of the protective androgen hormones. Cortisol also enhances the expression of the 5-lipoxygenase (5-LOX) enzyme, which is the central enzyme responsible for synthesis of the inflammatory leukotrienes involved in neurodegeneration. These interrelationships underscore the importance of controlling cortisol production.

### **Phosphatidylserine Reduces Cortisol**

Phosphatidylserine is an essential nutrient for cells, and one of a number of phospholipids that help hold together the large molecules that make up the cell membrane. Phosphatidylserine is particularly plentiful in nerve cells. Studies have shown that phosphatidylserine helps these cells communicate with other cells by promoting the accumulation, storage, and release of neurotransmitters such as dopamine.<sup>9</sup> Phosphatidylserine also is important in supporting homeostasis in each cell.

Phosphatidylserine assists the proteins that manage membrane functions, apparently anchoring many of these proteins in the

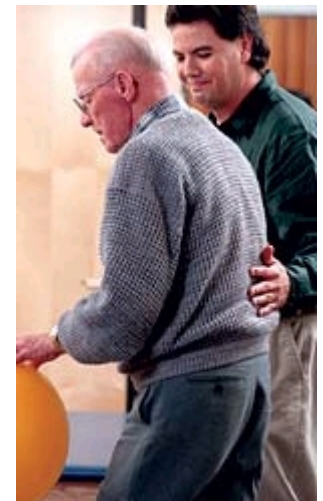
### **CORTISOL IS RELEASED IN RESPONSE TO STRESS**

#### **Major Life Stressors (chronic)**

- Divorce
- Death of a family member
- Prolonged illness
- Poverty
- Unhappiness in the workplace

#### **Daily Life Stressors (acute)**

- Traffic jams
- Bill-paying
- Family tension
- Noise
- Crowds
- Sleep disturbance
- Isolation
- Hunger
- Danger



matrix of the membrane, permitting them to operate at peak efficiency. Functions facilitated by phosphatidylserine include entry of nutrients into the cell and exit of waste products from the cell, movement of charged atoms (ions) into and out of the cell, transmission of molecular messages, changes in cell movement and shape, and cell-to-cell communication.

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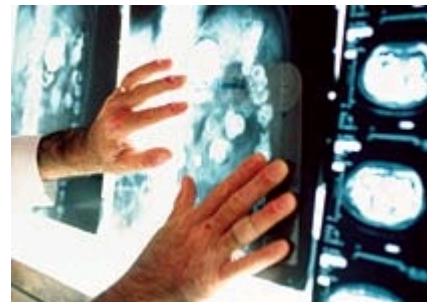
Three studies have examined phosphatidylserine's ability to reduce cortisol levels. In the first, a double-blind, randomized study conducted at the University of Naples, Italy, eight healthy males exercised on a bicycle ergometer (designed to increase their cortisol levels) on three separate days one week apart.<sup>10</sup> Before each exercise session, the test subjects were given either a placebo or a 50- or 75-mg intravenous dose of phosphatidylserine. As expected, ACTH and cortisol levels rose after this intensive exercise protocol, but the increases in the subjects who received the 50- or 75-mg dose of phosphatidylserine were approximately 33% and 45% less, respectively, than in those who received the placebo.

In a second study, the Italian scientists tried the same experiment using 400 mg and 800 mg of phosphatidylserine taken orally.<sup>11</sup> They found that the plasma cortisol responses were 16% and 25% lower, respectively. These reduced percentages suggest that part of the orally administered phosphatidylserine was degraded before it reached the bloodstream.

In the third study, a double-blind, crossover study conducted at California State University at Chino, 10 men were given 800 mg of phosphatidylserine a day and then put through a vigorous whole-body workout (designed to elicit a cortisol response) four times a week.<sup>12</sup> Each participant received phosphatidylserine for two weeks and then repeated the workout program for another two weeks with a placebo after a washout period of three and one-half weeks. Blood samples were taken 15 minutes after each workout. This study found that phosphatidylserine reduced cortisol levels after exercise by 20%.

The researchers also found that testosterone levels, which normally decline after intensive exercise, were not reduced. In exit interviews, the subjects said they "felt better" while taking phosphatidylserine, and their perceived exertion also dropped.

These experiments show that phosphatidylserine is able to reduce cortisol levels when the body experiences stress. While the studies used exercise to produce the stress, the same principle holds for other types of stress, such as that elicited by mental exertion or physically demanding tasks. This makes phosphatidylserine a valuable tool for controlling cortisol levels. Bear in mind, however, that not all exercise results in increased cortisol production. Scientists have discovered that short-term, moderate exercise does not increase cortisol concentration in plasma at all, and only minor changes in cortisol concentration occur during more intensive exercise lasting less than an hour.<sup>13</sup> Thus there is no need to avoid exercise for fear of boosting one's cortisol level. A game of tennis, bike ride, or walk around the block will not increase cortisol production. In fact, the stress-reducing benefits of moderate exercise help to keep cortisol in check. Physical activity also promotes cardiovascular health and mental acuity, helping to maintain a higher quality of life as we age.



Unfortunately, phosphatidylserine is found in only trace amounts in common foods. Although the body is able to produce phosphatidylserine on its own, it must go through a series of reactions that require a substantial investment of energy. This makes supplementation an attractive option. When phosphatidylserine is taken orally, the non-degraded portion is rapidly assimilated and easily crosses the blood-brain barrier. Because phosphatidylserine can produce nausea if taken on an empty stomach, it should be taken with meals. Phosphatidylserine should not be taken just before going to bed, as the neurotransmitters it helps to release could make it harder to fall asleep. Phosphatidylserine does not appear to have any other side effects when taken at the recommended dosages.



### Yet Another Benefit of DHEA

Life Extension members are well aware of the multiple benefits of DHEA, which range from increased energy and reduced heart disease risk to greater fat loss and better immune function. Now scientists have discovered yet another benefit: cortisol reduction. In a single-blind, placebo-controlled study at the University of Pittsburgh, seven men and seven women with an average age of 70 took 200 mg of DHEA for 15 days.<sup>14</sup> Each dose was taken in the morning 30 minutes after a light breakfast. The researchers found a significant reduction in cortisol concentrations in both sexes, ranging from a 26% drop in the women to a still-impressive 18% decline in the men. The normal diurnal pattern in plasma cortisol levels, which includes an early-morning peak and an evening nadir, was preserved, though the extent of cortisol release

during these periods was reduced after DHEA administration.

The scientists did not address possible reasons for these dramatic reductions, but they suggested that either DHEA or its sulfated form, DHEA-S, may have an inhibitory effect on the activity of the hypothalamic-pituitary-adrenal axis. While the researchers do not believe that DHEA or DHEA-S directly inhibits ACTH or cortisol release, they suggest that some alteration in the availability of corticotropin-releasing factor may be responsible for the observed changes.

It should be noted that Life Extension does not recommend a 200-mg dose of DHEA unless prior blood testing reveals a low level of this hormone. Just as low levels of this or any hormone can be damaging to long-term health, so can hormone levels that exceed the normal physiological range. Life Extension strongly recommends a DHEA blood test before one considers such a high level of supplementation. Fortunately, a study at the University of Pisa, Italy, has shown a progressive drop in cortisol levels even when a more moderate 50-mg dose of DHEA was administered daily for a six-month period.<sup>15</sup> These results were obtained in both early postmenopausal women (50-55 years old) and late postmenopausal women (60-65 years old). While men were not tested in this study, there is no reason to believe they would not achieve equivalent benefits.

### Ginkgo Biloba Also Lowers Cortisol

The leaf extract from the ginkgo biloba tree has a multitude of beneficial effects on the human body, from improved cognitive function to regained sexual potency. Ginkgo biloba promotes blood flow to the brain, enhancing mood while also helping to reduce memory loss, confusion, and fatigue. Ginkgo biloba also has antioxidant properties, making it a very desirable supplement for older individuals.

As if this were not enough, a recent study conducted in Slovakia found that a standardized extract of ginkgo biloba is able to reduce cortisol levels.<sup>16</sup> Seventy volunteers from the University of Bratislava participated in this double-blind, placebo-controlled study, which measured the effect of a 120-mg dose of ginkgo on the cortisol produced by a stress model that included a mental challenge and a static exercise test. Measurements were performed in the morning and evening to capture the normal high points in daily cortisol production. The researchers found that ginkgo inhibited the rise in salivary cortisol levels after the stress test, with the greatest benefit in the afternoon.

### How to Lighten Your Load

Given the damaging effects of cortisol, taking steps to reduce the body's concentration of this circulating hormone is highly recommended. A first step should be supplementation with nutrients that have been proven to overcome any increase in cortisol levels that occurs with age. Phosphatidylserine, DHEA, and ginkgo biloba all have been shown to reduce the amount of cortisol produced during stressful events, and these stress fighters can help retard the negative consequences of this hormone.

Another factor should be taken into consideration as well—one's lifestyle and approach to handling everyday stress. Simple, age-old methods such as breathing exercises, biofeedback, massage, and meditation can help put life's travails in proper perspective, helping to remove the underlying stress that causes excessive cortisol production in the first place. While some life situations are largely unchangeable, others can be modified with a bit of effort and the will to improve one's quality of life. Nutrients such as phosphatidylserine, DHEA, and ginkgo biloba are natural complements to an overall stress-reduction regimen, and can help you achieve a lifelong reduction in cortisol secretion and all of the benefits that come with it.



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## References

1. Ferrari E, Cravello L, Muzzoni B, et al. Age-Related changes of the hypothalamic-pituitary-adrenal axis: pathophysiological correlates. *Euro J Endocrin.* 2001 Apr;144(4):319- 29.
2. Wilmore J, Costill D. *Physiology of Sport and Exercise.* Champaign, IL: Human Kinetics; 1999.
3. Elmlinger MW, Dengler T, Weinstock C, Keuhnel W. Endocrine alterations in the aging male. *Clin Chem Lab Med.* 2003 Jul;41

4. Sher L. Daily hassles, cortisol, and the pathogenesis of depression. *Med Hypotheses*. 2004;62(2):198-02.
5. Gold PW, Drevets WC, Charney DS. New insights into the role of cortisol and the glucocorticoid receptor in severe depression. *Biol Psychiatry*. 2002 Sep 1;52(5):381-5.
6. Pomara N, Greenberg WM, Branford MD, Doraiswamy PM. Therapeutic implications of HPA axis abnormalities in Alzheimer's disease: review and update. *Psychopharmacol Bull*. 2003;37(2):120-34.
7. Murialdo G, Barreca A, Nobili F, et al. Relationships between cortisol, dehydroepiandrosterone sulfate and insulin-like growth factor-I system in dementia. *J Endocrinol Invest*. 2001 Mar;24(3):139-46.
8. Lupien S, Lecours AR, Lussoer I, Schwartz G, Nair NP, Meaney M. Basal cortisol levels and cognitive deficits in human aging. *J Neurosci*. 1994 May;14(5 Pt 1):2893-903.
9. Kidd, P. *Phosphatidylserine: A Remarkable Brain Cell Nutrient*. Decatur, IL: Lucas Meyer, Inc. 1997.
10. Monteleone P, Beinat L, Tanzillo C, Maj M, Kemali D. Effects of phosphatidylserine on the neuroendocrine response to physical stress in humans. *Neuroendocrin*. 1990 Sep;52(3):243-8.
11. Monteleone P, Maj M, Beinat L, Natale M, Kemali D. Blunting by chronic phosphatidylserine administration of the stress-induced activation of the hypothalamo-pituitary-adrenal axis in healthy men. *Eur J Clin Pharmacol*. 1992;42(4):385-8.
12. Fahey TD, Pearl MS. The hormonal and perceptive effects of phosphatidylserine administration during two weeks of resistive exercise-induced overtraining. *Biol Sport*. 1998;15:135-144.
13. Pedersen BK, Hoffman-Goetz L. Exercise and the immune system: regulation, integration, and adaptation. *Physiol Rev*. 2000 Jul;80(3):1055-81.
14. Kroboth PD, Amico JA, Stone RA, et al. Influence of DHEA administration on 24-hour cortisol concentrations. *J Clin Psychopharmacol*. 2003 Feb;23(1):96-9.
15. Stomati M, Monteleone P, Casarosa E, et al. Six-month oral dehydroepiandrosterone supplementation in early and late post menopause. *Gynecol Endocrinol*. 2000 Oct;14(5):342-63.
16. Jezova D, Duncko R, Lassanova M, Kriska M, Moncek F. Reduction of rise in blood pressure and cortisol release during stress by ginkgo biloba extract (EGB 761) in healthy volunteers. *J Physiol Pharmacol*. 2002 Sep;53(3):337-48.

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