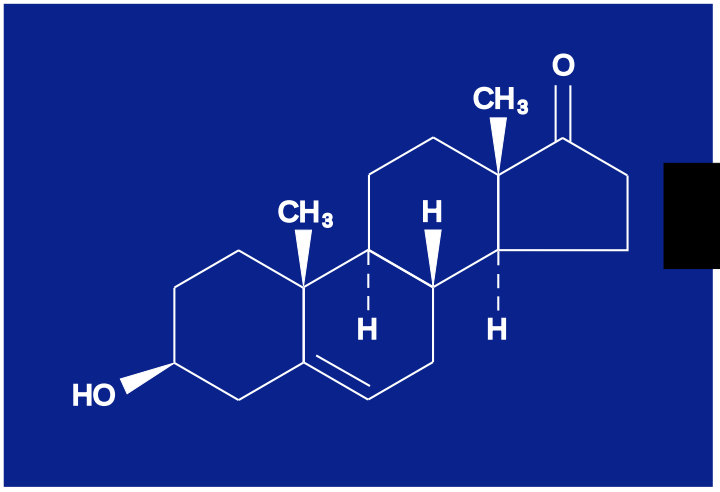

Monograph

DHEA

Introduction

Dehydroepiandrosterone (DHEA) is a steroid hormone secreted primarily by the adrenal glands and to a lesser extent by the brain, skin, testes, and ovaries. It is the most abundant circulating steroid in humans and can be converted into other hormones, including estrogen and testosterone. It has been characterized as a pleiotropic "buffer hormone," with receptor sites in the liver, kidney, and testes, and has a key role in a wide range of physiological responses. Circulating levels of DHEA decline with age and a relationship has been suggested between lower DHEA levels and heart disease, cancer, diabetes, obesity, chronic fatigue syndrome, AIDS, and Alzheimer's disease. Other research suggests that autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis, and multiple sclerosis might be associated with declining DHEA levels.[1]

Biochemistry

DHEA is a 19-carbon steroid hormone, classified as an adrenal androgen. Plasma levels decline progressively with age beginning around age 40; therefore, the level of DHEA at age 70 is only about 20 percent as high as that in young adults.[2] DHEA is synthesized from pregnenalone (derived from cholesterol) and is rapidly sulfated to yield its ester, DHEA-S, the predominant form found circulating in the plasma.[1] DHEA is metabolized via two pathways— through hepatic circulation or via a cutaneous pathway where it is metabolized by the skin and other tissues sensitive to sex steroids.[3,4] DHEA appears to act directly on targeted cells through specific receptor sites,[5] as well as indirectly to buffer corticosteroids, inhibiting stress-mediated tissue injury.[3]

Clinical Indications

Anti-aging Hormone

Clinical evidence supporting DHEA's use as an anti-aging hormone is inconclusive. However, in one double-blind, cross-over study of 30 subjects, age 40 to 70 years, supplementing 50 mg/day DHEA or placebo for three months, 67 percent of men and 84 percent of women in the DHEA group reported a remarkable increase in physical and psychological wellbeing; no side effects were reported.[6] Supporting these results, mice treated with DHEA had glossier coats and less gray hair than control animals.[7] Anecdotal reports indicate treating elderly patients with 5-20 mg/day DHEA often results in improved mood, energy levels, memory, appetite, and skin condition.[8]

Cancer Prevention

Animal studies have shown DHEA administration to inhibit breast,[9] colon,[10] and liver cancers,[11] as well as skin papillomas.[12] In women with breast cancer, plasma DHEA levels vary significantly depending on whether the women are pre- or postmenopausal. Premenopausal women with breast cancer had lower levels than normal for age, while postmenopausal women with breast cancer had higher levels than age-matched controls.[13] These studies suggest DHEA may have anti-carcinogenic properties; but further research is needed before DHEA can be used safely in cancer therapy, particularly in patients with, or at risk for developing, hormone-dependent cancers.

Immune Modulation

DHEA has several different effects on the immune system, some of which are likely to be a result of its anti-glucocorticoid action. Animal studies have shown DHEA to preserve immune competence and prevent immune suppression caused by viral infections.[14,15] Human studies of postmenopausal women given 50 mg/day DHEA demonstrated increased natural killer cell activity and a six-percent decrease in the proportion of T-helper cells.[16] DHEA levels have also been found to be low in people infected with HIV. A study of 108 HIV-infected men found those with low DHEA levels were 2.3 times more likely to progress to AIDS.[17]

Autoimmune Diseases

Studies have shown DHEA to be of therapeutic value in SLE,[18] rheumatoid arthritis,[19] autoimmune hemolytic anemia,[20] and multiple sclerosis.[21] DHEA levels are often low in patients with these diseases, at least in part due to adrenal suppressive drugs such as prednisone. A return to normal physiologic levels appears to reduce immune complex formation, inhibit lymphocyte proliferation, and increase stamina and sense of wellbeing.[1]

In a small clinical trial in which 10 women with mild to moderate SLE were given 200 mg/day DHEA for three to six months, eight of the 10 women reported improvement in fatigue, energy levels, and overall wellbeing.[22] Another double-blind, placebo-controlled, randomized, clinical trial of 21 patients with severe, active SLE demonstrated that 200 mg/day DHEA for six months, in addition to conventional SLE therapy, resulted in a protective effect with respect to corticosteroid-induced osteopenia.[23] An additional study was conducted in which 50 women with mild to moderate SLE were given 50-200 mg/day DHEA for six to 12 months. Thirty-four patients completed six months of treatment and 21 patients were treated for 12 months. Results demonstrated decreasing disease activity over the entire treatment period, as measured by the SLE Disease Activity Index. Benefits were sustained one year post-treatment, regardless of menopausal status.[24]

Allergic Disorders

Several clinical studies have demonstrated DHEA, given in doses of 10-74 mg/day, to be of benefit in treating food allergy, multiple chemical sensitivity, asthma, and hereditary angioedema. These studies reported a decrease in severity of symptoms regardless of whether patients were receiving corticosteroid therapy or not.[25,26]

Obesity

Animal studies demonstrated DHEA administration to genetically obese mice resulted in a significant weight decrease, without any change in diet or exercise.[1] DHEA's weight-loss properties are thought to be a result of its inhibition of glucose-6-phosphate dehydrogenase, an enzyme responsible

for fat accumulation.[27] Human obesity studies with DHEA are few. One study of 659 fasting postmenopausal women, not on estrogen replacement therapy or antidiabetic drugs, demonstrated a positive association between elevated DHEA-S and central obesity, which contradicts the theory that DHEA-S protects against obesity in postmenopausal females.[28]

Cardiovascular Disease

Low plasma DHEA-S levels and decreased insulin sensitivity have been associated with an increased risk of heart disease in men. In women, the reverse has been found. Women with DHEA-S levels in the upper tertile had the highest cardiovascular death rate.[30] A recent clinical study of 1,167 men was conducted to determine whether serum DHEA and DHEA-S levels could predict ischemic heart disease over a nine-year interval. Men with serum DHEA and DHEA-S levels in the lowest quartile at baseline were significantly more likely to develop ischemic heart disease.[31]

Osteoporosis

Serum DHEA levels decline by more than 60 percent with onset of menopause, partially because ovarian production of it ceases. The subsequent loss of bone mineral density (BMD) has been shown to be significant, due at least in part to the rapid decline of DHEA. In a study of 457 women and 534 men the association between endogenous sex steroids and BMD was measured. Higher levels of circulating DHEA were positively associated with BMD of the radius, spine, and hip in women, but not in men.[32] DHEA's role in osteoporosis prevention may be attributed to three mechanisms: (1) inhibition of bone resorption; (2) DHEA and testosterone stimulation of bone formation and calcium absorption; and (3) conversion to estrogen or testosterone, providing extra protection against bone loss.[33]

Alzheimer's Disease/Dementia

DHEA status in Alzheimer's disease and dementia is unclear with most studies having been conducted in animal models. An animal study using mice demonstrated DHEA's memory-enhancing effects, which may be due in part to its action on GABA neurotransmitters. One small, uncontrolled study of male Alzheimer's patients found DHEA administration resulted in modest improvements in cognition and behavior.[34]

Diabetes

Animal studies have demonstrated a correlation between diabetes and obesity that can be reversed by DHEA administration.[1,27] DHEA's anti-glucocorticoid property may result in protection from diabetes, and insulin resistance appears to decrease when DHEA levels are returned to normal.[28,35]

Safety and Toxicity

Despite being a steroid hormone, DHEA appears to be relatively safe if given at normal physiological doses. Among the few side effects noted with administration of physiological doses are breast tenderness, reversible hirsutism in women, and mild to moderate acne due to sebaceous secretion. Doses above 1500 mg/day have been known to result in insulin resistance in humans[35] and pre-neoplastic pancreatic lesions in rats.[36] Potential interactions between DHEA and pharmaceuticals include enhanced sedation seen in patients on benzodiazepines and related CNS active drugs,[21] as well as possible thyrotoxicosis in patients taking thyroid hormones.[37] As the long-term effects of DHEA administration are not known, it should therefore be used with caution, particularly in patients at risk for developing hormone-dependent cancers.

Dosage

DHEA is usually administered as an encapsulated powder in two or three divided doses. Appropriate physiologic doses are not well defined and differ in men and women. Many of the clinical studies have been conducted using 50 mg/day for women and 100 mg/day for men, but it is possible these doses are supraphysiologic. Positive effects have been seen with doses as low as 5-10 mg/day for women and 10-20 mg/day for men. The one exception to this is in the treatment of SLE, which requires doses of 50-200 mg/day to show benefit. Studies of long-term DHEA administration are lacking.

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