Dehydroepiandrosterone: Biological Effects and Clinical Significance

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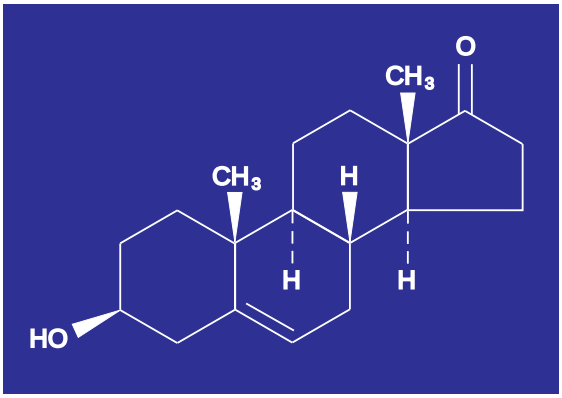
Abstract

Dehydroepiandrosterone (DHEA) is a steroid hormone secreted in greater quantity by the adrenal glands than any other adrenal steroid. For many years, scientists assumed that DHEA merely functioned as a reservoir upon which the body could draw to produce other hormones, such as estrogen and testosterone. However, the recent identification of DHEA receptors in the liver, kidney and testes of rats strongly suggests that DHEA may have specific physiologic actions of its own. Circulating levels of DHEA decline progressively with age; this age-related decline does not occur with any of the other adrenal steroids. Epidemiologic evidence indicates that higher DHEA levels are associated with increased longevity and prevention of heart disease and cancer, suggesting that some of the manifestations of aging may be caused by DHEA deficiency. Animal and laboratory data indicate that administration of DHEA may prevent obesity, diabetes, cancer (breast, colon and liver), and heart disease; enhance the functioning of the immune system; and prolong life. In humans, evidence exists that DHEA might be associated with autoimmune diseases such as lupus, rheumatoid arthritis and multiple sclerosis; chronic fatigue syndrome; acquired immunodeficiency syndrome (AIDS); allergic disorders; osteoporosis; and Alzheimer's disease. Although administration of DHEA appears to be safe, its long-term effects are unknown, and it is possible that adverse consequences will become evident with chronic use. It is therefore important that this hormone be used with care and that practitioners err on the side of caution when contemplating DHEA supplementation.
(Alt Med Rev 1996;1(2):60-69.)

Introduction

Dehydroepiandrosterone (DHEA) (see Figure 1) is a steroid hormone secreted by the adrenal glands and to a lesser extent by the testes and ovaries. First identified in 1934, DHEA was subsequently shown to be produced in greater quantity than any other adrenal steroid. However, although circulating levels of DHEA and its ester DHEA-sulfate (DHEA-S) are 20 times higher than those of any other adrenal steroid, the function of DHEA in the body was, until recently, unknown. Since DHEA can be converted into other hormones, including estrogen and testosterone, scientists assumed that DHEA is merely a "buffer hormone;" i.e., a reservoir upon which the body can draw to produce the other hormones (see Figure 2). However, the recent identification of DHEA receptors in the liver, kidney and testes of rats strongly suggests that DHEA has specific physiologic actions of its own.[1]

FIGURE 1. Structure of DHEA.



During the past several years, there has been a great deal of interest in DHEA as a possible anti-aging hormone and as a potential treatment for a wide array of medical conditions. This interest has been sparked by two different lines of evidence. First, circulating levels of DHEA decline progressively with age; the levels in 70-year-old individuals are only about 20% as high as those in young adults. This age-related decline does not occur with any of the other adrenal steroids. Furthermore, epidemiologic evidence suggests that higher DHEA levels are associated with increased longevity and prevention of heart disease and cancer. It has therefore been suggested that some of the manifestations of aging may be caused by DHEA deficiency.

Second, numerous animal studies have shown that administration of DHEA prevents obesity, diabetes, cancer, and heart disease; enhances the functioning of the immune system; and prolongs life.[2] Since most of these studies were done in rodents, which have little circulating DHEA, it is not clear whether the results have relevance to human health. However, a growing body of human research, combined with the intriguing observations of innovative clinicians, suggests that DHEA may indeed have value in the treatment of various medical conditions. If this hormone can be convincingly shown to retard the aging process and to fight certain diseases, then DHEA therapy will be recognized as a major breakthrough in clinical medicine.

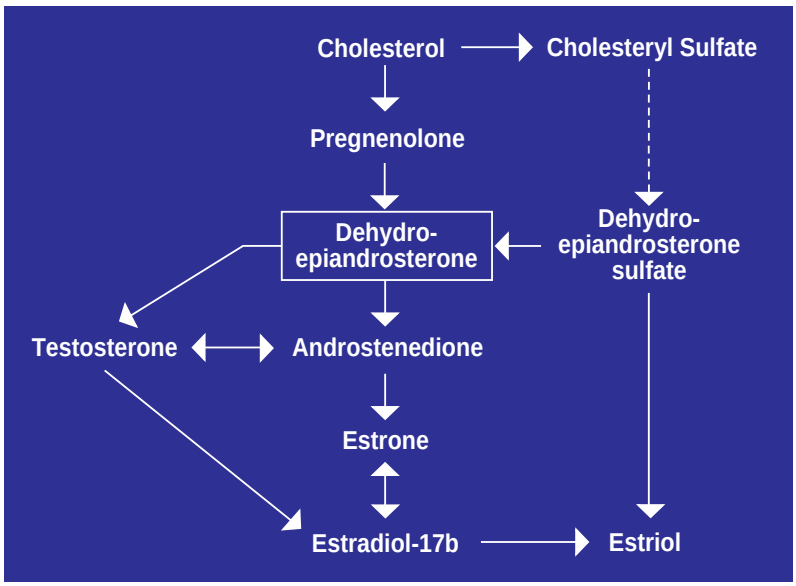


FIGURE 2. Biosynthetic Pathways of DHEA and its Metabolites.

DHEA as an "Anti-aging" Hormone

Preliminary results in mice suggest that DHEA might retard the aging process. Animals treated with this hormone looked younger, had glossier coats, and less gray hair than control animals.[3]

In a recent study, 30 individuals between the ages of 40 and 70 years received 50 mg/day of DHEA or a placebo, each for 3 months, in double-blind crossover fashion. During DHEA treatment, a remarkable increase in physical and psychological well-being was reported by 67% of the men and 84% of the

women. There was no change in libido and no side effects were seen.[4]

In my experience, elderly patients who suffer from weakness, muscle wasting, tremulousness, fatigue, depression, declining memory, and other signs of aging frequently have serum DHEA-S levels near or below the lower limit of normal. Treatment with DHEA (usually 5-10 mg/day for women and 10-20 mg/day for men) often results in improved mood, energy, memory, appetite, and skin color, sometimes after as little as two weeks. With continued treatment, the benefits may become even more pronounced and muscle wasting may be partially reversed.

Cancer Prevention

Administration of DHEA inhibited tumor formation in a strain of mice that develops spontaneous breast cancer.[5] DHEA also has been shown to prevent chemically-induced colon[6] and liver[7] cancers, as well as skin papillomas in mice.[8]

Premenopausal women with breast cancer had significantly lower plasma levels of DHEA than age-matched controls without breast cancer, whereas postmenopausal women with breast cancer had significantly higher DHEA levels than age-matched controls.[9] In another study, women with DHEA levels in the highest tertile were 60% less likely to develop breast cancer than were women in the lowest tertile.[10] In a prospective case-control study, serum DHEA and DHEA-S levels were significantly lower in individuals who subsequently developed bladder cancer than in those who did not.[11]

These findings suggest that DHEA has anti-cancer activity and that low DHEA levels might be a risk factor for cancer. However, additional research must be done before guidelines can be developed regarding DHEA therapy and cancer. The observation that some postmenopausal women with breast cancer have elevated DHEA levels, and the fact that DHEA is converted in part to estrogen and testosterone should be cause for concern. It is not known whether the possible anti-cancer effects of DHEA might be stronger than the prostate cancer-promoting effects of additional testosterone or the breast cancer-promoting effects of additional estrogen. Until those questions can be answered, DHEA therapy should be approached with caution in patients who are at risk for developing hormone-dependent cancers.

Effects on Immune Function

DHEA exerts a number of different effects on the immune system. Some of these effects appear to result from the anti-glucocorticoid actions of DHEA. For example, in mice DHEA antagonized the suppressive effects of dexamethasone on lymphocyte proliferation[12] and prevented glucocorticoid-induced thymic involution.[13] Administration of DHEA also has been shown to preserve immune competence in burned mice,[14] an effect that extends beyond its anti-glucocorticoid action.[15] Administration of DHEA also protected against acute lethal infections with coxsackie virus B4 and herpes simplex type 2 encephalitis in mice. DHEA appeared to act by preventing the suppression of immune competence caused by the viral infections.[16]

DHEA has also been shown to influence immune function in humans. In a double-blind study, administration of 50 mg/day of DHEA to postmenopausal women (mean age, 56.1 years) produced a two-fold increase in natural killer cell activity and a 6% decrease in the proportion of helper T cells.[17] While the increase in natural killer cell activity might be expected to enhance immune surveillance

against cancer and viral infections, the decline in helper T cells could have adverse consequences. On the other hand, since DHEA is known to mediate T cell responses,[18] the decline in helper T cells merely could be a reflection of enhanced T cell function. Although the implications of these changes in immune function are not entirely clear, it should be noted that 50 mg/day of DHEA has been shown to produce supraphysiologic serum levels in postmenopausal women.[19] Lower doses may therefore be more appropriate and might result in more clear-cut improvements in immune function.

Treatment of Autoimmune Diseases

The potential value of DHEA as a treatment for autoimmune disease was suggested by the observation that DHEA reduced the severity of renal damage in the NZB x NZW mouse, an animal model of spontaneous lupus. A clinical trial was therefore performed with ten women suffering from mild or moderate systemic lupus erythematosus (SLE).[20] Each patient received 200 mg/day of DHEA for 3-6 months. Eight of the 10 patients reported improvements in overall well-being, fatigue, energy, and/or other symptoms. For the group as a whole there was significant improvement in the physician's overall assessment of disease activity. After 3 months, the average prednisone requirement had decreased from 14.5 to 9.4 mg/day. Of three patients with significant proteinuria, two showed marked reductions and one a modest reduction in protein excretion. There was no significant correlation between changes in serum DHEA or DHEA-S levels and clinical response. In addition, pre-treatment levels of these hormones did not predict clinical response. Side effects were limited to mild or moderate acneiform dermatitis and mild hirsutism.

Administration of relatively large doses of DHEA has also been reported to increase stamina and improve the sense of well-being in patients with multiple sclerosis.[21]

During the past five years a number of practitioners have been prescribing DHEA for patients with autoimmune disease. Pre-treatment plasma levels of DHEA or DHEA-S are usually below normal in patients receiving prednisone or related drugs, because these medications cause adrenal suppression. However, in my experience, DHEA-S levels are also frequently low in patients with autoimmune disease who are not receiving corticosteroids.

I have treated a 76-year-old female patient with rheumatoid arthritis who was being maintained on 5 mg/day of prednisone. After taking 10 mg/day of DHEA for several weeks, her joint symptoms improved and she was able to wean off the prednisone. Another woman with poorly controlled dermatomyositis had marked clinical improvement and was able to reduce her prednisone by 50% after receiving 10 mg of DHEA, twice a day. A female patient with a 3-year history of persistent bleeding due to inflammatory bowel disease reported no further bleeding after taking 15 mg/day of DHEA. Two other women with SLE had clinical improvements with DHEA. However, low doses were not effective in these cases; results became apparent only after the dose was increased to around 100 mg/day or more.

Lamson has given DHEA to six patients with ulcerative colitis that had failed to respond to a combination of conventional therapy and nutritional treatments. In all six cases, the bleeding, diarrhea, and overall condition improved.[22]

Some patients with chronic fatigue syndrome (CFS) have also improved clinically with DHEA therapy. However, since cortisol deficiency appears to be the primary problem in some patients with CFS and, since DHEA can antagonize the effects of cortisol, DHEA therapy might actually cause some patients with CFS to worsen. It is important, therefore, to measure both DHEA and cortisol levels before treating CFS patients with DHEA.

Acquired Immunodeficiency Syndrome

Preliminary evidence suggests that DHEA might play a role in acquired immunodeficiency syndrome (AIDS). In one study, DHEA inhibited the replication of HIV, the virus believed to cause AIDS.[23] In addition, DHEA has been shown to enhance the immune response to viral infections. Furthermore, DHEA levels are low in people infected with HIV and these levels decline even more as the disease progresses to full-blown AIDS.[24] In a study of 108 HIV-infected men with marginally low helper T-cell counts (between 200 and 499), those with serum DHEA levels below normal were 2.34 times more likely to progress to AIDS than were men with normal DHEA levels.[25] These studies suggest that DHEA deficiency might be one of the factors contributing to immune system failure in HIV-infected patients.

To date, only one clinical trial has tested the effect of giving DHEA to HIV-infected patients. Although DHEA did not improve CD4 counts or serum p24 antigen levels,[26] the dosage used (750-2,250 mg/day) seems excessively large, possibly beyond the "therapeutic window" in which DHEA exerts its beneficial effects. The concept of a therapeutic window clearly has been demonstrated for cortisol (the other major adrenal steroid). For example, cortisol is known to enhance immune function at physiologic levels. However, both a deficiency and an excess of cortisol result in impaired immune function. Future trials of DHEA in HIV-infected patients should therefore use lower doses, perhaps 50-200 mg/day.

Allergic Disorders

Eight patients with severe attacks of hereditary angioedema were treated with 37 or 74 mg/day of DHEA-S (equivalent to 25 or 50 mg, respectively, of DHEA) every 1-3 days, for 3-29 months. DHEA-S treatment resulted in a dramatic clinical improvement in all eight patients.[27]

Practitioners who use DHEA have observed that treatment sometimes reduces the severity of food or chemical allergies. I have seen several patients with multiple chemical sensitivities who responded to physiologic doses of DHEA (5-15 mg/day for women, 10-30 mg/day for men). However, it is difficult to predict which patients will improve.

Subnormal serum levels of DHEA-S are common in asthmatics. DHEA deficiency might result in part from corticosteroid-induced adrenal suppression. However, low levels of DHEA-S were also found in 21% of asthmatics who were not taking steroids.[28] DHEA deficiency may also result from long-term administration of inhaled corticosteroids. In a study of 36 post-menopausal asthmatic women, those who were receiving at least 1 mg/day of beclomethasone dipropionate had nearly a 50% reduction in serum DHEA levels, compared with women who were not receiving the drug. Apparently, inhaled corticosteroids are absorbed in amounts sufficient to cause some degree of adrenal suppression.[29]

I have seen two female patients with long-standing asthma who had clinical

improvement after receiving 10 mg/day of DHEA. In one of these patients, chronic nasal polyps also disappeared, much to the surprise of her otolaryngologist.

Obesity

Administration of DHEA prevented the development of obesity in genetically obese mice.[30] However, studies in humans have so far failed to demonstrate a role for DHEA in the treatment of obesity.

Cardiovascular Disease

Administration of DHEA reduced the severity of atherosclerosis in cholesterol-fed rabbits.[31] DHEA-S also has been shown to have digitalis-like activity, accounting for 62-100% of the total plasma digitalis-like factors in 11 healthy adults.[32]

Mean plasma DHEA-S levels were significantly lower in men with a history of heart disease than in men without such a history. In men with no history of heart disease at baseline, a low plasma DHEA-S level (less than 140 mcg/dl) was associated with a more than 3-fold increase in the age-adjusted risk of death from cardiovascular disease.[33] Similar findings have been reported by others,[34] although another epidemiologic investigation found only a modest protective effect of DHEA.[35]

In women, no inverse association was found between DHEA-S levels and cardiovascular disease. In fact, cardiovascular death rates were highest in women in the upper tertile of DHEA-S levels and lowest in women in the middle tertile (a U-shaped distribution).[36]

Osteoporosis

At the time of menopause, the amount of DHEA manufactured by the ovaries declines. And, even though the ovaries are not the major source of DHEA, serum DHEA levels decline by more than 60% after menopause.[37]

The possible relationship between DHEA deficiency and osteoporosis was suggested by a study of women with Addison's disease (adrenal failure). In these patients, the onset of menopause was followed by an unusually rapid rate of bone loss. This accelerated bone loss was associated with marked reductions in plasma concentrations of DHEA and testosterone (94% and 63% lower, respectively, than those of healthy post-menopausal women).[38] These findings suggest that DHEA and/or testosterone is essential for the maintenance of bone mass in post-menopausal women.

In another study, bone mineral density was measured at the lumbar spine, hip, and radius in 105 women, aged 45-69. Fifty women had normal measurements, whereas 55 had low bone density. The average serum DHEA-S level was 60% lower in the women with low bone density than in those with normal bones. Women with low DHEA values were 40 times more likely to have osteoporosis than were women with normal DHEA levels. In contrast, there was no relationship between estrogen levels and bone density.[39] In a group of 29 post-menopausal women, there was a significant positive correlation between bone mineral content of the distal radius and ulna and age-adjusted serum DHEA levels.[40]

There are several mechanisms by which DHEA might prevent osteoporosis. First, one of the breakdown products of DHEA, a compound called 5-androstene-3ß, 17ß-diol, is known to bind strongly to estrogen receptors. Therefore, DHEA, like estrogen, might exert an inhibitory effect on bone

resorption. Second, there is evidence that androgens (a class of hormones that includes DHEA and testosterone) stimulate bone formation and calcium absorption.[41] Third, the partial conversion of DHEA to estrogen and testosterone would be expected to provide additional protection against bone loss.

I often recommend low doses of DHEA (usually 5-10 mg/day) for postmenopausal women whose serum DHEA-S levels are near or below the lower limit of normal. In some cases, DHEA relieves symptoms such as hot flashes that are usually attributed to estrogen deficiency. A combination of DHEA and identical-to-natural progesterone (usually given as a topical cream) may be more effective against hot flashes than either treatment alone.

Dementia

In one study, intracerebroventricular administration of DHEA or DHEA-S improved the results of certain memory tests in mice.[42] Some investigators have found low levels of DHEA in patients with Alzheimer's disease.[43] However, others have failed to confirm those observations.[44] In a small, uncontrolled trial, administration of DHEA appeared to produce modest improvements in cognition and behavior in a group of male patients with Alzheimer's disease.[45]

Diabetes

Administration of 0.4% DHEA in the diet reversed hyperglycemia, preserved beta-cell function, and increased insulin sensitivity in genetically diabetic mice.[46] Although DHEA has been reported to ameliorate insulin resistance in one patient with diabetes,[47] very large doses of DHEA (1,600 mg/day for 28 days) caused mild abnormalities of glucose metabolism.[48] The role of DHEA in the overall management of diabetes therefore remains unclear.

Toxicity of DHEA

For a steroid hormone, DHEA appears to be relatively safe. Administration of 1,600 mg/day for 28 days to healthy volunteers resulted in some degree of insulin resistance, but no other significant side effects occurred. In the SLE studies, 200 mg/day given for a number of months was well tolerated, with the exception of mild to moderate acne and occasional mild hirsutism.

Addition of 0.6% DHEA to the diet of rats reduced body weight and enhanced the development of chemically-induced pre-neoplastic pancreatic lesions.[49] Although that dose of DHEA is extremely large (the equivalent human dose would be approximately 2,000 mg/day), this report indicates that DHEA is by no means innocuous and therefore it should be used with caution.

Using DHEA Wisely and Safely

As this review suggests, DHEA shows promise for preventing age-related decline and as a treatment for certain diseases. Innovative practitioners, therefore, have begun prescribing DHEA for their patients and the public is becoming increasingly interested in this purported "anti-aging pill."

Although DHEA appears to be safe, its long-term effects are unknown. It is possible that adverse consequences will become evident with chronic use. It is therefore important that we use this hormone with care and err on the side of caution. Although some practitioners are routinely prescribing 50 mg/day for healthy women and 100 mg/day for healthy men, those doses may be supraphysiologic, raising legitimate concerns about the long-term safety of such dosages.

Unlike hydrocortisone (cortisol), for which the physiologic replacement dose is known, it is not clear what the physiologic dose of DHEA is. However, it may be lower than many practitioners believe. I have treated one patient with severe adrenal insufficiency who had a clear response to 15 mg/day of DHEA. She experienced marked clinical improvement at that dose, and her serum level of DHEA-S increased from barely detectable to well above the lower limit of normal. Another female patient with a history of bilateral adrenalectomy reported marked symptom relief with DHEA doses as low as 5-10 mg/day.

In my practice, I usually prescribe 5-15 mg/day for women and 10-30 mg/day for men. Many patients have obvious improvements with these doses. With some patients who have not improved I have prescribed larger doses, but in most cases, the larger doses were not helpful either. The one exception has been patients with lupus or other autoimmune diseases, who sometimes needed as much as 100 mg/day or more to obtain benefit. I typically prescribe DHEA in capsule form, in a base of hydroxymethylcellulose. In most cases, I recommend twice-a-day dosing, usually morning and evening.

Although serum measurements of DHEA and DHEA-S are available through most laboratories, it is not clear how closely one should rely on these measurements; nor is it clear whether DHEA or DHEA-S is the more reliable test. The normal range for DHEA-S as listed by my local laboratory is 350-4,300 ng/ml for women and 800-5,600 ng/ml for men. Many older individuals have values near or below the lower limit of normal. However, I prefer not to use an age-adjusted reference range (as published by some labs), since it seems that the age-related decline in serum DHEA-S is undesirable.

When DHEA therapy appears to be clinically indicated, I will consider treating a woman whose DHEA-S level is below 600 ng/ml and a man whose level is below 1,200 ng/ml. There are as yet no data on what constitutes an optimum serum level. Consequently, I continue to err on the side of caution by using low doses of DHEA.

There are also no data available concerning long-term administration of DHEA. While lifetime replacement therapy seems appropriate for patients with age-related DHEA deficiency, other patients should be assessed on a case-by-case basis.

I have found that about 10% of patients who are taking thyroid hormone develop symptoms of thyrotoxicosis after starting DHEA therapy. That observation is consistent with a report that DHEA potentiates the action of thyroid hormones.[50] Symptoms of thyroid over-treatment responded to a reduction in the thyroid-hormone dosage, and patients reported that they felt better on DHEA plus lower-dose thyroid hormone than they did on thyroid hormone alone.

In conclusion, DHEA appears to be one of the major therapeutic advances of the past twenty years. However, this powerful hormone must be utilized with caution in order to maximize its benefits and minimize its risks.

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