

DHEA: An Enigmatic Medicine

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Abstract

Dehydroepiandrosterone is an adrenal corticosteroid which is a precursor to sex hormones but acts by other independent mechanisms also. Serum levels are a function of age, falling off to very low levels by the age of 70. In epidemiological studies, a fall in activity is correlated with many disease states. Clinically it finds application in adrenal insufficiency, patients on corticosteroids, immunological diseases like SLE, psychiatric disorders and male and female sexual dysfunction. Side effects are mild and transient.

INTRODUCTION

Many a time a normal physiologic constituent find therapeutic potential quite apart from its normal physiological function. Dehydroepiandrosterone (DHEA) is one such agent. It is a paradox however, that on one hand it is widely sold as a wonder drug and the medical profession, on the other hand has not fully tapped its potential.

DHEA is a C19 corticosteroid secreted by the zona reticularis of adrenal cortex. DHEA and its sulfate ester are interconvertible through the enzymes sulfatase and sulfotransferase. DHEA is lipophilic. DHEAS is hydrophilic and circulates in the blood bound to albumin. They are both collectively termed DHEA(S). (1) Even though DHEA(S) and androstenedione are termed adrenal androgens, they are not true androgens, since they do not act on androgenic receptors. They are converted to potent metabolites including testosterone and estradiol. However, it would be too naïve to regard it as a simple precursor to the sex hormones. The process of intracrinology is invoked to explain their interesting metabolism. Peripheral conversion to testosterone and estradiol takes place depending on specific expression and local distribution of 17 beta hydroxysteroid dehydrogenase. (2) In men half the androgens are derived from adrenal precursor steroids, in premenopausal women 75% of oestrogen synthesis takes place in peripheral target cells and this figure becomes virtually 100% in postmenopausal women. (3) The sex steroids thus produced act mainly within the cells in which they are produced. DHEA administration leads to sexually dimorphic effects-androgenic in women (4) and oestrogenic in men. (5) Another peculiar characteristic of DHEA

metabolism is that of “metabolism on demand”. (6)

Administration of this molecule to men with normal DHEA levels did not lead to higher testosterone levels. On the other hand, when given to testosterone deficient elderly men, total testosterone levels did rise.

DISCUSSION

DHEA acts by mechanisms other than just as a precursor to sex hormones. Recently an endothelial receptor for DHEA has been discovered and it has been shown to activate endothelial nitric oxide synthase. (7) DHEA(S) act as neurosteroids by acting directly on neurotransmitter receptors in brain (8) including NMDA receptor, sigma receptor and GABA receptor. It has direct action on the immune cells and binding sites for it have been described on T lymphocytes. (9)

DHEA(S) activity is a function of age (10). Soon after birth levels are high due to synthesis by fetal adrenal gland. Levels rapidly drop thereafter and rise again between 6th and 10th year a phenomenon termed adrenarche. After reaching peak levels in the third decade of life, levels decline rapidly reaching 10-20% of maximum level by the age of 70. This phenomenon is termed adrenopause (even though cortisol levels do not change much). Adrenopause is independent of menopause and occurs in both men and women. It is related to reduction in the size of zona reticularis. Generally levels are lower in women than men of similar age.

DHEA continues to be less under-used and less understood by the medical profession. It is truly an enigmatic molecule.

Androgenic side effects may occur with DHEA even though

they are generally mild and transient. Hunt et al (₁₂) reported mild facial acne in 33% women and 7% men as compared to 17% women and 7% men on placebo. The same group reported mild excess facial growth in 4% females and 7% males.

Understandably, there would be concerns on the risk of prostate cancer. DHEA should not be given to men with history of prostate cancer. However, there is no data suggesting an increased incidence of prostate cancer in males receiving DHEA. A small increase in serum PSA (prostate specific antigen) may be detected at the beginning of therapy but levels return to baseline or below in a few months. In vitro and animal data paradoxically suggest a protective role for DHEA in prostate cancer (_{31,32}). Even though there is no data showing elevated risk of BPH (benign prostatic hypertrophy) in patients receiving DHEA, serum levels of DHEA(S) correlate with higher risk of BPH. Thus, DHEA should not be given to men with significant BPH related symptoms.

DHEA should also not be given to women with history of breast cancer. However, recently, Labrie (₃₃) recently proposed that DHEA be used in addition to selective estrogen receptor modulators (SERM) for secondary prevention in patients with breast cancer. DHEA could compensate for the important loss of androgens that accompanies aging and could also permit sex steroid formation and action in the brain while breast cancer prevention would be achieved by the SERM.

Epidemiological studies including the Ranch Bernardo Study have shown a correlation of low DHEA levels with increased mortality in men under 70 who smoke, depression in women and children, diminished bone mineral density in women, cancer in men, bladder cancer, rheumatoid arthritis and other inflammatory arthritides, increased risk of progression to AIDS, aggravation of HIV related lipodystrophy, lack of survival in sepsis, diminished sexual desire in women and congestive heart failure (₁).

Patients with adrenal insufficiency of any cause, often complain of persistent fatigue and lack of sense of well being despite optimum gluco-corticoid and mineralocorticoid replacement. These patients may show an improvement in mood, asthenia and possibly sexual function in women (_{11, 12, 13, 14, 15}). Most studies used a dose of 50 mg/day and most were performed in female patients. Patients on corticosteroid therapy have low DHEA levels because of adrenal suppression. It may therefore be useful to

administer DHEA to all patients on corticosteroids (Tom Geraciotti, personal communication). DHEA also has a synergistic anti-inflammatory effect with glucocorticoids. However; this idea has not been tested in a clinical trial.

Interaction of DHEA with the immune cells and their role in inflammatory, allergic and immunological disorders has been recently reviewed by Dillon (₁₆). Plasma levels of DHEA(S) are lower in inflammatory conditions like SLE (systemic lupus erythematosus), inflammatory bowel disease, rheumatoid arthritis and polymyalgia rheumatica. DHEA has been shown to influence various cytokines, TH1/TH2 balance etc. In animal models, while it has been shown to be useful in enhancing the response to vaccines, it has also been shown useful in animal models of autoimmune disease and atopy. A randomized double blind trial in SLE (₁₇) using 200 mg/day showed a significant reduction in number of flares and improved patients' global assessment of disease process. In another trial it was possible to document a reduction in steroid dose requirement (₁₈). Small studies have reported improvement in bone mineral density (₁₉) and joint pain (₂₀) in elderly. In a trial on influenza vaccination, a significant improvement in antibody titers was demonstrated with concomitant DHEA administration (₂₁).

DHEA(S) are synthesized in the brain independently of its secretion elsewhere. Their central nervous system concentration is 6-8 times greater than in the blood stream (₈). They have a modulatory role in stress response, sleep control and memory. (_{20,22}). Data is emerging to show its role in dementia, depression schizophrenia and anxiety (₆). In a 6 weeks double blind placebo controlled trial, it was shown to be effective for midlife onset depression (₂). High doses of DHEA (322 mg/day) were shown to improve depressed mood and fatigue in HIV positive patients. (₂₃).

Epidemiological work incriminates DHEA(S) among all hormones to have the strongest negative correlation with erectile dysfunction. (₂₄). A prospective double blind placebo controlled trial showed significant improvement in erectile function, intercourse satisfaction, sexual desire and orgasmic function. The improvement however was manifest only after 16 weeks of treatment (₂₅). In another study, where other comorbidities were present, patients with diabetes or neurological disorders did not show improvement (₂₆). The mechanism of action of DHEA(S) in erectile dysfunction is not well understood. It may involve effect on endothelial nitric oxide synthase or local formation of estrogens (₆).

DHEA has been studied for female sexual dysfunction. Women develop DHEA deficiency with adrenal dysfunction or age. Arlt et al⁽¹⁰⁾ in a placebo controlled cross over trial showed significant increase in sexual thoughts or fantasies, sexual interest and satisfaction in women with adrenal insufficiency. They used 50 mg of DHEA and improvement in sexual interest took place after a month of therapy and improvement in sexual satisfaction took 4 months. Baulieu et al⁽²⁷⁾ showed significant improvement in sexual parameters in women above 70 years of age but not in those below 70 and improvement took after 6 months of therapy, reaching statistical significance after 12 months.

Epidemiologic data shows a negative correlation between DHEA levels and cardiovascular risk. The Massachusetts Male Aging Study showed that men in the lowest quartile for DHEA had half the cardiovascular risk as compare to men in the highest quartile⁽²⁸⁾. Supplementation with DHEA was associated with decrease in total body weight, fat mass and trunk fat in men with DHEA deficiency⁽¹⁹⁾. Among the cardiovascular risk factors, a reduction in PAI-1, improvement in flow mediated dilation of brachial artery and improvement in insulin sensitivity have been demonstrated⁽²⁹⁾. An improvement in metabolic syndrome is therefore to be expected. Variable effects on blood lipids were noted. Small decrease in HDL cholesterol and total cholesterol was noted in some studies.⁽³⁰⁾

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