European Urology

European Urology 48 (2005) 724–733

Review

Dehydroepiandrosterone Treatment in the Aging Male – What Should the Urologist Know?

F. Saad[a,*], C.E. Hoesl[b], M. Oettel[c], J.-D. Fauteck[d], A. Römmler[e]

[a]*Gulf Medical College, P.O. Box 4184, Ajman, UAE*
[b]*Sailerstrasse 25, 80809 Munich, Germany*
[c]*Beethovenstrasse 30, 07743 Jena, Germany*
[d]*Proverum GmbH, Münsterstrasse 111, 48155 Münster, Germany*
[e]*Hormonzentrum München, Westendstraße 193-195, 80686 Munich, Germany*

Accepted 23 June 2005

Available online 18 July 2005

Abstract

Objective: Dehydroepiandrosterone (DHEA) has attracted considerable attention as a means against the decrements of aging. This review will summarize clinical studies evaluating DHEA as a treatment option for age-related conditions and diseases.

Methods: Literature search of PubMed documented publications and abstracts from meetings.

Results: The collected data indicate that DHEA supplementation to counteract its gradual decrease over age is beneficiary. Positive effects on the cardiovascular system, body composition, BMD, the skin, the CNS, and the immune system have been reported. Improvement of sexual function by DHEA has been demonstrated.

Conclusion: Although long-term clinical trials (applying the standards of evidence-based methods) are not available at present, the consistency of the data and the extensive practical experience may justify the use of DHEA in aging men given the rules of classical endocrinology are thoroughly followed including diagnosis based on clinical picture and biochemical evidence, compliance to periodic evaluations, and individual dose adjustment to maintain serum concentrations in the physiological range of young males. Being one among other important hormonal factors, DHEA can delay and correct age-related disorders only to a certain degree.

Keywords: Dehydroepiandrosterone; DHEA; Androgen deficiency; Adrenopause; Aging

1. Introduction

The secretion of the androgen dehydroepiandrosterone (DHEA) and its sulphate (DHEAS) from the corticoadrenal glands follows an intriguing age-related pattern. The serum concentration of DHEA(S) attains its highest level in the fetus during the 40th week of pregnancy. At birth, DHEA(S) levels are lowest and rise gradually to reach new peaks in early adulthood [1]. With increasing age, DHEA(S) in men declines progressively by 29% per decade, a phenomenon termed adrenopause [1–3].[1] DHEA, the most abundant steroid hormone in the body, acts through conversion to potent metabolites [4] including testosterone and estradiol in the peripheral intracrine tissues, which is dependent on the specific expression and local distribution of 17β-hydroxysteroid dehydrogenases [5]. The conversion of DHEA to DHEAS and vice versa occurs in vivo through the actions of the enzymes DHEAS

* Corresponding author. Tel. +971 6 743 1333; Fax: +971 6 743 1222.
E-mail addresses: gmcajman@emirates.net.ae, faridsaad@aol.com (F. Saad).

[1] Of note, while the International Society for the Study of the Aging Male defines the age-related decline of testosterone as ''late-onset hypogonadism'', some researchers refer to it as ''andropause''. We utilize ''andropause syndrome'' as a term including all anabolic deficiencies (adrenopause, late-onset hypogonadism and somatopause) to indicate that the decrease of testosterone is only one among other hormonal factors involved in age-related disorders.

0302-2838/$ – see front matter
doi:10.1016/j.eururo.2005.06.020

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sulfatase and DHEA sulfotransferase, respectively. DHEAS serves as transport vehicle and storage form of DHEA. Research data indicate that both, DHEA and DHEAS, have additional biological functions besides being precursors for testosterone. Recently, an endothelial receptor for DHEA has been discovered in human cell cultures [6]. As neurosteroids, DHEA and DHEAS exert direct action on neurotransmitter receptors in the brain [7]. Numerous reports have emerged stating that the age-related decline in serum DHEA(S) parallels the development and progression of a series of diseases and conditions associated with aging. In the USA, the hormone DHEA is marketed as a nutritional supplement available without prescription and control on its use by a physician. DHEA can be purchased from various sources at relatively low costs. Consequently, the financial incentive is small for the pharmaceutical industry to perform large-scale clinical trials and to obtain registration for DHEA, which may not crystallize into profound return on investment. Therefore, studies in humans on the effects of DHEA applying the standards of evidence-based methods are rare and limited in number, size, and duration of treatment. This lack of well-conducted, long-term human trials fuels an ongoing debate on the use of DHEA as a means against age-related conditions. Lately, the continuous efforts of individual investigators have converged to indicate that DHEA indeed may contribute to the improvement of health status and quality of life in aging men. The results from the Baltimore Longitudinal Study of Aging (BLSA) compared with caloric restriction trials in primates showed that DHEAS is one of the three most robust predictors of longevity [8]. This is consistent with findings from the Rancho Bernardo Study [9]. In this review, we will give an overview on the effects of DHEA in the aging male summarizing trials with acceptable study design.

2. Age-related DHEA deficiency

The urologist is generally faced with a high percentage of elderly patients. The incidence of various male urological diseases and conditions, such as erectile dysfunction (ED), prostate cancer, benign prostatic hyperplasia (BPH), and androgen deficiency increases with age [10]. Since evidence suggests that partial androgen deficit, along with other factors (Fig. 1), affects a wide range of body systems, the urologists should be aware of the potential benefits and the risks of DHEA supplementation to improve and sustain quality of life and health in aging men.

2.1. DHEA and sexual function

The Massachusetts Male Aging Study (MMAS) led to the finding that among 17 investigated hormones only DHEAS levels show a strong negative correlation to ED [11]. This result is corroborated by later studies on DHEA in ED patients with and without co-morbidities [12,13]. Prompted by this observation, Reiter [14] studied the effects of DHEA on erectile function in detail. In a prospective, randomized, double-blind, placebo-controlled trial, he demonstrated that DHEA significantly improves erectile function ($p < 0.001$), intercourse satisfaction ($p < 0.001$), sexual desire ($p < 0.001$), and orgasmic function ($p < 0.01$) as assessed by the IIEF (International Index of Erectile Function). Interestingly, all these effects were observed for the first time following 16 weeks of treatment, whereas after 8 weeks no significant changes could be found. This is in accordance with the general finding in men and women, that reversal of degenerative alterations requires hormone supplementation for a longer time dependant on the organ affected, while acute symptoms, e.g. neurotransmitter imbalances, often may be normalized within a few days [15–20]. In another study with men suffering from ED and various co-morbidities (hypertension: $N = 27$, diabetes: $N = 24$, neurological disorders: $N = 6$, no organic etiology: $N = 28$), a significant improvement ($p < 0.05$) in IIEF question 3 (frequency of penetration) was observed only in the patient groups with hypertension or no organic etiology [21]. Although the established effects of DHEA on endothelial nitric oxide synthase and local formation of estrogens may explain the improved blood flow, the explicit mode of action of DHEA in ED remains to be elucidated.

2.2. DHEA and the prostate

When administering androgenic compounds, it is absolutely mandatory that the prostate is carefully monitored. Androgen therapy can exacerbate preexisting prostate cancer and is therefore strongly contraindicated in men with a prior history of prostate malignancies or suspected prostate carcinoma. More than occasionally a small increase in serum levels of the prostate specific antigen (PSA) was detected at the beginning of DHEA treatment with levels returning to baseline or to concentrations below baseline after a few months [22]. Long-term treatment (25–50 mg/d DHEA for 12 months) in elderly men did not significantly increase mean PSA levels or suspect findings in ultrasound examination of the prostate [23,24]. Though seemingly a paradox, the theory was recently proposed that DHEA supplementation may be a means to prevent prostate cancer [25]. DHEA has been found to inhibit

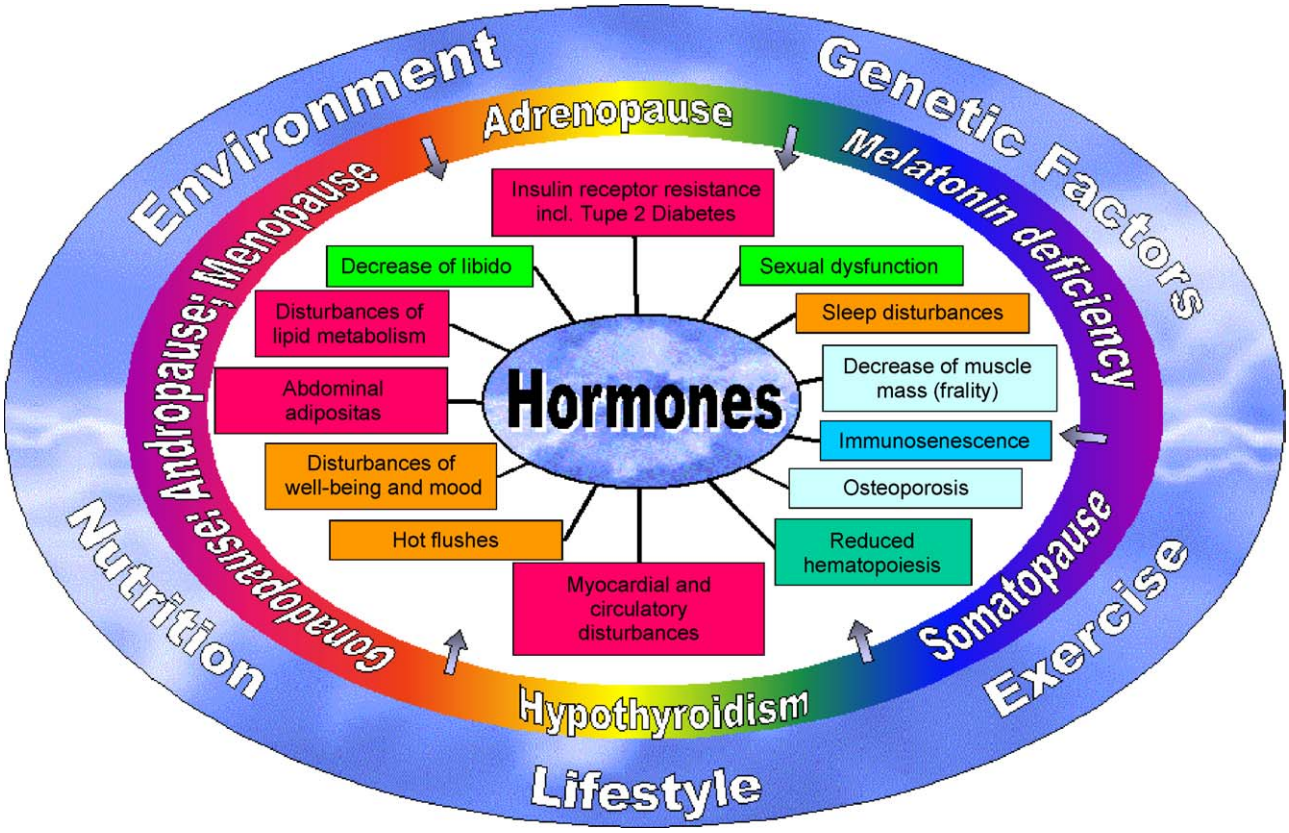

Fig. 1. Various factors influencing the aging process.

rat prostate carcinogenesis and the proliferation of human prostate cancer cell lines [26–29]. Thus far, the underlying mechanism remains unknown and the hypothesis of prostate cancer prevention by DHEA was not tested in human trials. Some researchers observed that DHEA and DHEAS levels are lower in patients with prostate cancer compared to matched healthy controls [30,31]. However, in a study with 52 patients having histologically confirmed BPH and 52 healthy controls matched according to age and town of residence, it was found that DHEAS is positively associated with the risk of BPH [odds ratio = 3.10 per standard deviation (60 micrograms/dl), 95% CI (1.28–7.50)] [32].

2.3. Effects on the cardiovascular system, the body composition and insulin resistance

Several epidemiological studies were reviewed by Muller to clarify the correlation between DHEAS levels and the risk of cardiovascular diseases [33]. The majority of studies revealed a negative correlation, i.e. higher endogenous DHEAS concentrations were associated with a lower incidence of coronary artery disease. However, in one study ($N = 867$), no correlation was observed and two studies ($N = 537$) even showed a positive correlation. Poršová-Dutoit concluded in a review that results of the analyzed epidemiological studies on the association between DHEAS levels and cardiovascular events are strongly dependent on the chosen cardiovascular endpoints [34]. A negative correlation was observed only for patients with fatal disease outcome. When compared to an age-matched healthy control group, non-obese men ($N = 109$) with coronary arteriosclerosis confirmed by coronary angiography showed significantly lower DHEAS levels ($p < 0.0001$), higher insulin, fibrinogen, tPA, PAI, PAI activity, and lipoprotein(a). Severity of the disease was related with the degree of DHEA deficiency [35]. Another study found lower DHEA and DHEAS levels in subjects with aortic calcification confirmed by chest X-ray [36]. In the Massachusetts Male Aging Study (MMAS), men in the lowest quartiles of both DHEA and DHEAS had the highest incidence of ischemic heart disease. The risk difference between the two quartiles amounted to almost 50% [11]. Due to the discrepancies noted in literature it is difficult to create a concise and conclusive picture of the cardioprotective effect exhibited by endogenous DHEA. The potential benefits of exogenous DHEA on the cardiovascular system were studied in several intervention trials. In a double-blind, placebo-controlled study with healthy men ($N = 34$), 18 men

received DHEA (3 × 50 mg p.o. for 12 days) to evaluate whether DHEA prevents heart disease by enhancing endogenous fibrinolytic potential. The atherosclerotic risk factors PAI-1 and tPA antigen were significantly reduced ($p < 0.0001$ for PAI-1 and $p < 0.0005$ for tPA) and diastolic blood pressure was lower in the DHEA group ($p < 0.05$). These results are corroborated by a randomized, double-blind, placebo-controlled study in Japan with men having mild hypercholesteremia. PAI-1 levels decreased when administering 25 mg of DHEA/d for 12 weeks ($p < 0.01$). Flow-mediated dilation of the brachial artery increased significantly and steadily ($p < 0.01$). Moreover, steady state plasma glucose was significantly lowered in the DHEA group whereas steady state plasma insulin was maintained indicating improved insulin sensitivity. Since testosterone levels did not change during the study, the authors attributed the observed results to direct physiological action of DHEA [20]. Blood levels of total, HDL and LDL cholesterol, and other lipids were significantly altered by DHEA administration. In an excellent review published recently by Tchernof and Labrie [37], the authors stated that the effects of DHEA on cardiovascular disease risk might be more modest than previously believed. According to their analysis, the association of low plasma levels of free DHEA with obesity, abdominal body fat, and serum lipid proteins is also debatable. Studies in women (mean age 42 ± 9.3 years) or men (mean age 59 ± 4.8 years) using 50–100 mg DHEA daily for 3–4 months did not reveal any significant changes in body composition [38–40]. However, in a randomized, double-blind, cross-over trial a decrease of fat body mass by 6.1% ($p = 0.02$) and an increase in knee extension/flexion strength, lumbar back strength and IGF-1 levels was observed when administering DHEA (100 mg p.o.) for 6 months to non-obese men ($N = 9$, age range: 50–65 years) [41]. In another trial with elderly men deficient of DHEA ($N = 6$, mean age: 72 years), a decrease of total body weight (0.9 kg), fat mass (1.4 kg), and trunk fat (1.2 kg) was determined following supplementation with DHEA (50 mg/d for 6 months) ($p \leq 0.01$). Fat-free mass (0.5 kg; $p \leq 0.05$) and IGF-1 levels (increase from 119 to 141 μg/L, $p < 0.01$) rose [42]. In an extended randomized, double-blind, placebo-controlled trial (28 men, mean age: 71 years) performed by the same research group, significant decreases in abdominal visceral fat by 7.4% ($p = 0.001$) and abdominal subcutaneous fat by 6% ($p = 0.003$) as measured by MRI were achieved [43]. DHEA deficiency may promote insulin resistance and type 2 diabetes mellitus suggested by two studies in patients with essential hypertension or obesity [44,45]. In a recently published, randomized, placebo-controlled study investigating the effects of DHEA (50 mg/d for 6 months in men and women, age range: 65 to 78 years), the insulin area under the curve (AUC) during the oral glucose tolerance test (OGTT) was significantly reduced in the DHEA group ($p = 0.007$). Despite the lower insulin levels, the glucose AUC remained unchanged resulting in a significant increase ($p = 0.005$) in insulin sensitivity index in response to DHEA [43]. These results indicate that DHEA may ameliorate characteristic features of the metabolic syndrome including central obesity, atherogenic dyslipidemia, high blood pressure, insulin resistance or glucose intolerance, and prothrombotic state.

2.4. Positive influence of DHEA on bones and joints

Supplementation with DHEA (50 mg/d for 6 months) significantly enhanced bone mineral density (BMD) for total body and lumbar spine ($p \leq 0.05$) in 8 healthy elderly men (mean age: 72 years) with low baseline DHEAS [42]. A similar trend was observed when administering DHEAS (100 mg for 6 months) to osteoporotic men (age range: 58–85 years) [46]. The intracrine conversion of DHEA to estrogens in human osteoblasts is one factor which may account for the protective effect of DHEA on the bone [47]. The osteoporosis and fracture risk was found to be almost doubled in patients with adrenal Morbus Cushing in comparison to patients with the pituitary type of the disease. Omori and Minetto demonstrated that adrenal Morbus Cushing encompasses profound suppression of adrenal type DHEA, whereas in patients with the pituitary type DHEA levels are normal [48,49]. Joint pain as assessed by the Kupperman questionnaire was significantly alleviated by DHEA (25 mg/d) given to 10 elderly men (age range: 58–69 years) over 1 year [22]. 5 out of 30 subjects (both men and women) had reported marked improvements of pre-existing joint pains and stiffness during DHEA treatment (50 mg/d for 12 weeks) in a double-blind, placebo-controlled, cross-over study [50].

2.5. DHEA and the central nervous system (CNS)

DHEA and DHEAS are synthesized in the brain independently of its secretion by the steroidogenic endocrine glands and its concentration in the CNS is 6–8 times greater than in the blood serum [51]. Evidence is accruing in support of DHEA supplementation in neurological disorders, such as Alzheimer's disease, age-related dementia, depression, anxiety and schizophrenia. DHEA appears to have a modulatory role in stress response, memory storage, and sleep control [52,50]. In accordance with several epidemiological studies, Alzheimer patients ($N = 14$, age range: 70–100

years) in the Berlin Aging Study were found to have significantly lower DHEAS levels as compared to two matched control groups [53]. In several trials, an improvement of depression, anxiety, and mood as assessed by various psychometric rating scales, such as the Cornell Dysthymia Scale (CDS), the Hamilton Depression Rating Scale (HDRS), the Beck Depression Inventory (BDI), the Bunney-Hamburg Global Depression scale (BH), the Kupperman score, and the Symptom Checklist-90 (SCL-90), was observed [54,55,22]. In one double-blind, cross-over study in 22 healthy men (mean age: 59.3 years), the global severity index of the Symptom Checklist 90 showed a significant improvement ($p < 0.05$) after 50 mg/d DHEA for four months. Anxiety and depression subscales were not significantly altered after DHEA administration when compared to placebo. The results of the study are difficult to interpret, since the volunteers had normal mood scales and no impaired well-being prior to DHEA treatment [56]. When 32 HIV positive patients (age range: 28–57 years) with depressed mood and persistent fatigue were treated with high doses of DHEA (mean dose: 322 mg/d for 8 weeks), HDRS, the Brief Symptom Inventory (BSI), Quality of Life, and the Chalder Fatigue Scale improved significantly ($p < 0.001$) [57]. In a double-blind, placebo-controlled study, effects of DHEA (100 mg/d for 6 weeks) in patients with long-term schizophrenia (age range: 18–70) were investigated. Significant improvements were observed in the mean values of the Scale for the Assessment of Negative Symptoms (SANS, $p < 0.001$), the Hamilton Scale for Anxiety (HAM-A, $p < 0.001$), the Hamilton Scale for Depression (HAM-D, $p < 0.05$), and the Clinical Global Impression Scale for Severity (CGI-S, $p < 0.001$) [58]. Recently, DHEA (90 mg/d and 450 mg/d, respectively) was found to be an effective treatment in a 6 weeks double-blind, randomized, placebo-controlled, crossover treatment study in men ($N = 23$) and women ($N = 23$) aged 45 to 65 years with midlife-onset major or minor depression. Significant improvements by DHEA were established in the 17-Item Hamilton Depression Rating Scale ($p < 0.01$) and Center for Epidemiologic Studies Depression Scale ratings ($p < 0.01$) [59].

2.6. DHEA and immune function

Clinical studies and in vitro experiments indicate that DHEA has a significant impact on immunological function. DHEA treatment was found to lead to 20% increase in IGF-1 ($p < 0.01$), a decreasing trend in IGF-1 binding protein-1 (IGFBP-1), and a 32% increase in the ratio IGF-1/IGFBP-1 ($p < 0.01$). The number of monocytes and B cells grew significantly. A 39% increase in cells expressing the interleukin-2 receptor (IL-2R) and 20% increase in serum IL-2R levels indicated a functional activation of T lymphocytes. In vitro stimulated release of interleukin-2 and interleukin-6 was enhanced by 50% and 30%, respectively. The natural killer cell number showed a 22–37% rise after an onset time of 18–20 weeks with a concomitant 45% increase ($p < 0.01$) in cytotoxicity [50,60–62]. In an influenza vaccination trial, 67 subjects (age > 65 years) received 50 mg of DHEAS or placebo for 2 consecutive days. Only 27.3% of the placebo group, but 41.2% of the DHEAS group showed at least a fourfold increase in hemagglutination inhibition (HAI) titers [63]. In a trial with 71 men, no improvement in the age-related declined response to immunization against influenza was observed [64]. DHEA was found to exhibit beneficiary effects in the management of ulcerative colitis and Crohn's disease [65,66]. Glucocorticoid treatment entails a significant blockade of DHEA secretion. To counteract this deleterious effect, DHEA supplementation may be fundamental in patients with chronic inflammatory diseases [67]. A fascinating facet of the steroid DHEA is its application against systemic lupus erythematosus, a potentially fatal autoimmune disease. Treatment with daily doses of 200 mg DHEA is now, at least in women, considered to be established. The interested reader is referred to the cited publications on the striking success of DHEA treatment in this debilitating disease [68–70].

3. Suggested mechanism of action

Up to now, a variety of mechanisms of action have been proposed (Fig. 2). The most evident mechanistic theory stems from the fact that DHEA is a precursor for testosterone and estrogens. However, results from studies measuring testosterone in men after DHEA administration, are controversial. In many studies the administration of DHEA did not cause higher testosterone concentrations in men with normal baseline DHEA levels. In hypophysectomized men or testosterone deficient elderly men total testosterone levels rose significantly with DHEA supplementation [43,71]. Accordingly, significant increments in free testosterone and DHT as well as estrone and estradiol were observed in androgen deficient men ($N = 100$) during an individually adjusted DHEA supplementation [22]. The contradictory observations gave rise to a concept called "metabolism on demand" meaning that testosterone is generated from DHEA preferentially when a lack of testosterone occurs. The mentioned methodological discrepancies between high and low baseline levels of

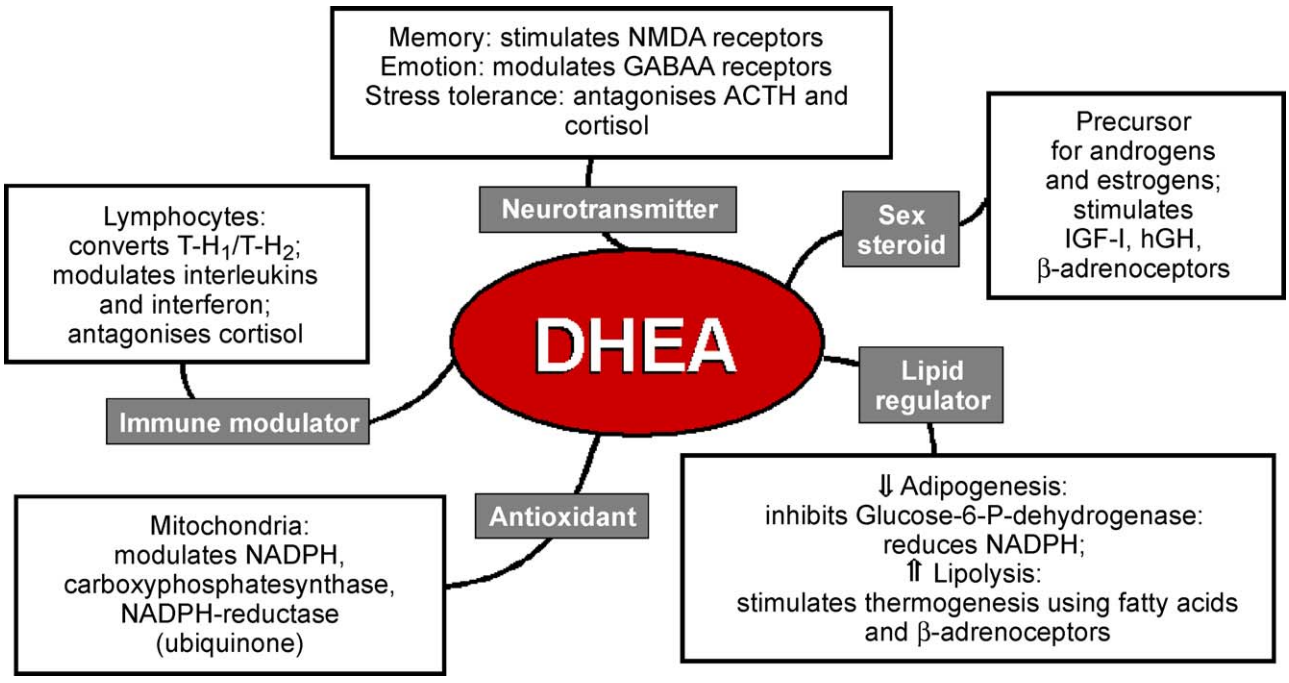

Fig. 2. Mechanisms of action of DHEA.

testosterone before DHEA treatment may provide an alternative, conceivable reason for conflicting findings. A severe reduction of DHEA in elderly subjects as a consequence of ACTH stimuli implies an impairment of adrenal reticularis zone activity due to aging processes [72]. Labrie suggested that DHT is only a poor indicator of androgenic activity in healthy young men as it is almost exclusively due to the contribution of the testes. Androstanediol glucuronide (ADG), an esterified metabolite of DHT, was proposed as a more reliable marker, since it directly mirrors the intracrine synthesis of androgens from DHEA in tissues possessing the required converting enzymes [5]. In elderly men, however, the serum increments of androgens including ADG are similar in quantity and time course following oral DHEA administration [23,73]. DHEA was found to exhibit various functions in addition to its role as a precursor for testosterone. Recently, an endothelial DHEA receptor was identified in endothelial cell cultures. Specific binding of DHEA was shown to significantly heighten the endothelial nitric oxide synthase activity thereby establishing a feasible mechanistic link between DHEA and vascular and erectile function [6,74,75]. DHEA-mediated inhibition of platelet activity may contribute to DHEA's putative protective action against atherosclerosis, thrombosis and cardiovascular mortality [76]. Antiatherogenicity attributed to DHEA possibly derives from its demonstrated antioxidative effect on LDL [77,78]. The mechanisms underlying the neuroprotective properties of DHEA are under investigation. Recently, it was shown that DHEA increases proliferation of human neural stem cells and positively regulates the number of neurons produced by these cultures. Raised proliferation induced by DHEA was completely blocked by the NMDA receptor antagonist MK801 and the sigma 1 opioid receptor antagonist haloperidol, whereas incubation with the $GABA_A$ receptor antagonist bicuculline did not lead to inhibition [79]. DHEA administration stimulates the production of both, allopregnanolone as well as β-endorphin [22], which are known as potent anxiolytic and mood elevating endogenous compounds. Of note, β-endorphin is a factor which has been found to inhibit sexual activity. However, Genazzani [24] observed that during DHEA supplementation in aging men testosterone, DHEAS, β-endorphin, and at the same time sexual scores increased. This indicates that there is no antagonistic effect of β-endorphin on sexual activity when DHEA is adjusted to the physiological levels of healthy young men. The positive results in the treatment of autoimmune diseases may be a consequence of the antagonization of corticosteroid induced side effects and direct modulation of inflammatory substances, e.g. Th1-Th2-cells, IL-2, IL-6, and TNFα.

4. Risk, side effects and precautions

All studies confirm that DHEA, even given experimentally in very high doses (1, 600 mg per day and

more), seems to be a safe compound. However, since sufficient long-term studies are not available, precaution is prudent. In most countries there are no pharmaceutical grade preparations available and production may not be carried out in compliance with the quality standards of Good Manufacturing Practice. Therefore, caution is strongly advised regarding the source of DHEA. Patients should be carefully informed about risks and side effects. The treatment with DHEA should be performed according to the established rules of endocrinology including continuous monitoring of the patient. In case of emerging adverse events or contraindications supplementation should be stopped immediately. Weight gain, oedema, impotence, and gynecomastia may be due to an abnormal increase of serum estrogens further aggravated by exogenous DHEA. Dose-related androgenic side effects such as oily skin, acne and odor have been reported in women [5]. In individual cases, androgenetic alopecia deteriorated due to an increase of DHT above normal levels. Nervousness, sleeping disorders and cardiac arrhythmia can be first signs of a DHEA overdose.

5. Discussion

The majority of the studies on DHEA come from academic institutions and must be considered pilot studies. The data collected from cross-sectional and longitudinal studies show that a decline in DHEA is indisputably involved in a variety of age-related degenerative diseases und functional impairments (cross-sectional: [80–86]; longitudinal: [87,88]). Intervention with DHEA can lead to significant improvement. Inconsistent study results may often be related to improper study designs and confounding factors. Furthermore, differences in dosage, duration of treatment and application mode, study population, sample size, statistical power and endpoints, as well as adjustments (e.g. for smoking, alcohol consumption, body weight) have an important influence. A variety of additional factors including gonadopause, hypothyroidism, somatotropin and melatonin deficiency, lifestyle, and genetics contribute to the aging process (Fig. 1). By correcting one of the various factors involved, DHEA supplementation can certainly only to some extent prevent or delay age-related pathophysiological developments. For instance, DHEA cannot replace appropriate testosterone therapy in men with hypogonadism. In healthy men, approximately 80% of testosterone is produced by the testes. Deficiency of testicular testosterone in hypogonadal men cannot be treated by supplementation with DHEA, since DHEA levels far above the normal physiological range would be required. DHEA and testosterone supplementation complement one another with DHEA administration being suitable for patients with DHEA deficiency and testosterone therapy being appropriate for men with late-onset hypogonadism [89–92]. In men having both, low testosterone and DHEA levels, a combination regimen may be considered. In analogy to recommendations for testosterone supplementation (ISSAM recommendations), a dosage should be selected which results in DHEA levels typical for healthy men aged 25–30 years (for DHEAS: 4–5 μg/ml). Initial doses of 15 to 50 mg oral DHEA given in the morning depending on the individual's height, weight, and baseline DHEAS concentrations have been suggested. Serum levels should be measured when time peak levels are to be expected (between 3 and 5 hours after intake). The dosage has to be adjusted if necessary. Supraphysiological concentrations, i.e. greater than 4–5 μg/ml, should be avoided [22,54]. The positive effects of DHEA supplementation generally take some time. After only a few weeks positive changes in mood, energy, vitality, and stress resistance have been seen as assessed by validated questionnaires such as the Psychological General Well-Being Index, the Beck Depression Inventory, Sabbatsberg Sexual Self-Rating Scale, Hamilton-Rating Score for Depression and Anxiety, Kupperman-Index, and Heinemann Score. Bone markers and skin parameters improve continuously and reach a plateau after 6 months. Significant changes in body composition and BMD have been observed following six month of supplementation [16,18,24,50,54,61,93].

DHEA should not be regarded as the only option to improve and maintain quality of life. However, strictly following the recommended precautions, the well aware responsible patient may benefit from the advantages of DHEA treatment anticipated on the basis of the information we have today.

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Editorial Comment

Emmanuele A. Jannini, *L'Aquila*, *Italy*
eaj@iol.it
jannini@univaq.it

There are two possibilities: DHEA is an inert precursor (about 5% of testosterone's biological potency) or a molecule with important biological function(s). The addition of more DHEA to the existing large pool of DHEA and DHEAS in unselected elderly individuals has limited clinical effects, suggesting the first possibility. However, the recent discovery of plasma membrane DHEA receptors in the endothelium may change this perspective. In this case, the presumed age-dependent DHEA deficiency requires endocrinological diagnosis and its supplementation requires endocrinological follow-up.

It is still not known whether long-term DHEA administration is safe with respect to development of ovarian, prostate, or other types of steroid-dependent cancers. But DHEA is currently widely used in the United States as an unapproved treatment against aging. With the scientific verdict still out, without further confirmation of its reported beneficial actions in humans, and without better understanding of its potential risks, it is premature to recommend its routine use to delay or prevent the physiological consequences of aging.