DHEA treatment: myth or reality?

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Dehydroepiandrosterone (DHEA) and its sulfate ester are major secretory products of the human adrenal. Serum DHEA concentrations decline with advancing age and DHEA supplementation in elderly people has been advertised as anti-aging medication. However, such claims are based on experiments in rodents with a fundamentally different DHEA physiology. In humans, DHEA is a crucial precursor of sex steroid biosynthesis and exerts indirect endocrine and intracrine actions following conversion to androgens and estrogens. In addition, it acts as a neurosteroid via effects on neurotransmitter receptors in the brain. DHEA has considerable effects on mood, well-being and sexuality in patients with adrenal insufficiency, and also neurotransmitter receptors in the brain. Because the role of DHEA in human health, in particular in adrenal insufficiency and mood disorders. Based mainly on the results of these clinical trials, we provide a substantiated overview on the current knowledge of the therapeutic potential of DHEA.

DHEA secretion and age

Secretion of DHEA in humans and in some non-human primates follows a characteristic age-related pattern [1]. DHEA is the major secretory product of the fetal adrenal, leading to high circulating DHEAS levels at birth. In parallel with the postnatal involution of the fetal zone of the adrenals, DHEA serum concentrations decrease to almost undetectable levels during the first year of life. Levels remain low until they gradually increase again between the sixth and tenth years of age, owing to increasing DHEA production in the adrenal zona reticularis, a phenomenon termed ‘adrenarche’ [2–5]. Peak DHEA(S) concentrations are reached in early adulthood, followed by a steady decline throughout adult life, so that at 70–80 years of age, peak concentrations are only 10–20% of those in young adults [1,6]. This age-associated decrease has been termed ‘adrenopause’ in spite of continued secretion of adrenal glucocorticoids and mineralocorticoids throughout life. The age-related decline in DHEA(S) concentrations shows high interindividual variability [6], and is accompanied by a reduction in the size of the zona reticularis [7]. By contrast, serum cortisol concentrations can even increase with aging [8], thereby contributing to an increase in the cortisol:DHEA(S) ratio that has been associated with cognitive impairment in elderly people [9]. However, a causal role of the increasing molar ratio of cortisol:DHEA(S) for components of individual aging remains uncertain.

Nevertheless, in an aging society, the age-related decrease in DHEA(S) secretion inevitably raised the question of whether aging is, in part, a consequence of DHEA deficiency, and potentially reversible by DHEA treatment. This idea has been strengthened by numerous animal experiments suggesting that DHEA is a multifunctional hormone with anti-cancer, immune-enhancing, neurotropic and general anti-aging effects (reviewed in Ref. [10]). However, most animal studies used pharmacological DHEA doses, yielding DHEA levels far beyond the physiological ones and, even more importantly, experiments were performed mainly in rodents, which, physiologically, have little circulating DHEA(S). Thus, these experiments cannot serve as a sound basis for promoting DHEA supplementation in humans.

Mechanisms of action

DHEA exerts its action either indirectly in peripheral target tissues of sex steroid action (following its conversion to androgens, estrogens or both) or directly, as a neurosteroid (via interaction with neurotransmitter receptors in the brain). Because the human steroidogenic enzyme P450c17 converts 17α-hydroxyprogesterone to androstenedione, the biosynthesis of all sex steroids in humans proceeds through DHEA. Thus, only DHEA can be converted to androstenedione by the activity of the 3β-hydroxysteroid dehydrogenase (3βHSD), and then further converted to testosterone and estradiol by isozymes of 17β-hydroxysteroid dehydrogenase (17βHSD) and by P450 aromatase, respectively (Fig. 1). Whereas DHEAS is the hydrophilic storage form that circulates in the blood,
only lipophilic DHEA can be converted intracellularly to androgens and estrogens. Thus, the tissue-specific synthesis of DHEA sulfotransferase and steroid sulfatase determines the ratio of DHEA activation (by conversion to sex steroids) to transient DHEA inactivation (by secretion of the sulfate ester back into the bloodstream). Analysis of the pharmacokinetics of DHEA and DHEAS following exogenous administration of DHEA reveals that DHEA and DHEAS undergo continuous interconversion [11,12]. Measured with a constant infusion technique, the conversion ratios for the conversion of DHEAS to DHEA were 0.006 for men and 0.004 for women, indicating that most of the DHEA produced arises from DHEAS [13].

In addition, almost ubiquitous production of 3β-HSD, 17β-HSD, 5α-reductase and P450 aromatase results in widespread peripheral conversion of DHEA to sex steroids [14–18]. It has been estimated that 30–50% of androgen synthesis in men and 50–100% of estrogen synthesis in pre- and postmenopausal women occurs in peripheral target cells [19]. For such synthesis, where action and metabolism occur within the same peripheral cell, the term 'intracrine' has been coined [19].

Studies on the pharmacokinetics and bioconversion of DHEA in humans with low serum DHEAS reveal that DHEA administration leads to a sexually dimorphic pattern of conversion: significant increases in circulating androgens in women [11] and in circulating estrogens in men [12]. In men with adrenal insufficiency and hypogonadism without androgen replacement, and thus total androgen depletion, DHEA administration results in a significant increase in circulating androgens, although it is still far from achieving normal male serum concentrations [20]. These findings suggest that DHEA administration causes androgenic and estrogenic effects and in women and men, respectively. However, circulating sex steroids do not correctly reflect the intracrine, tissue-specific action of DHEA. Men with an age-associated decline of DHEAS secretion and normal gonad function show no increase in circulating androgens after DHEA ingestion but do show a significant increase in circulating 5α-androstane-3α,17β-diol glucuronide (ADG) [12]. This reflects increased peripheral androgen synthesis in the DHEA-treated men, because ADG is the main metabolite of dihydrotestosterone [21,22], and its generation only occurs in peripheral androgen target tissues.

In addition to indirect endocrine and intracrine effects after its peripheral conversion to androgens and estrogens, DHEA exerts a direct action as a neurosteroid. Baulieu and co-workers were the first to provide compelling evidence for DHEA synthesis in the central nervous system (CNS), demonstrating steady DHEAS levels in brain tissue from adrenalectomized and gonadectomized rats [23]. Recent studies have demonstrated the synthesis of P450c17 and other steroidogenic enzymes in the brain [24–26]. Compagnone and Mellon [27] showed that DHEA and DHEAS have direct and differential effects on neuronal growth and development; in addition, they showed that DHEA signals via the N-methyl-D-aspartate (NMDA) receptor. This supports earlier findings describing DHEA as a modulator of the NMDA response via the sigma receptor [28] and as an allosteric antagonist of the γ-aminobutyric acid (GABA_A) receptor [29,30].

In spite of continuing efforts, the search for a specific DHEA receptor has not been fruitful. High-affinity binding sites for DHEA have been described in murine [31] and human [32] T cells, but these sites also effectively bind dihydrotestosterone. Recently, high-affinity binding sites for DHEA were identified on plasma membranes derived from bovine aortic cells, presenting evidence for the activation of endothelial nitric oxide synthase by DHEA via G proteins [33]. However, potential competition of binding by dihydrotestosterone was not tested. Similarly, it has been shown that DHEA activates extracellular-signal-regulated kinase 1 phosphorylation in human vascular smooth muscle cells, independently of androgen and estrogen receptors [34]. However, whether inhibition of downstream conversion of DHEA (e.g. by the 3β-HSD inhibitor trilostane) might alter these effects was not investigated. Thus, it seems possible that, particularly outside the CNS, effects of DHEA are only mediated indirectly after its bioconversion to other steroids.

**Epidemiological evidence**

In a prospective cohort study by Berr et al. [35] (622 subjects; >65 years of age), lower DHEAS in men (but not in women) was significantly associated with increased short-term mortality at two and four
DHEA replacement in adrenal insufficiency

The most rational approach to clarifying the physiological role of a putative hormone is to study the effects of replacement in the state of pathological hormone deficiency. For DHEA, patients with adrenal insufficiency represent such an ideal study population.

Oral administration of 25–50 mg DHEA in subjects with pathologically low serum DHEAS restores serum DHEA(S) to concentrations within the normal range of young adults, whereas 100–200 mg d⁻¹ DHEA leads to supra-physiological hormone concentrations. Owing to the long half-life of DHEAS and the ongoing interconversion of DHEA and DHEAS, a single morning dose is sufficient to maintain normal DHEA(S) concentrations throughout the day. Of note, further biotransformation of DHEA induced lasting increases in circulating androgens in women, suggesting that oral DHEA administration might be an attractive tool for androgen replacement in women [40]. Finally, patient compliance and adequacy of the DHEA replacement dose are easily assessed by determination of serum DHEAS during DHEA therapy.

Previous studies in patients with adrenal insufficiency have found impaired well-being in spite of adequate replacement of glucocorticoids and mineralocorticoids [41,42]. In addition, a landmark study by Morales et al. [43] in middle-aged subjects had suggested that DHEA administration might positively influence well-being. Thus, effects of DHEA on well-being and mood became a plausible target for studies in adrenal insufficiency.

In fact, as assessed by validated psychometric tools, DHEA replacement in women with either primary or secondary adrenal insufficiency significantly improved overall well-being and mood, specifically the subscale scores for depression, anxiety and their physical correlates [44] (Fig. 2a). There was no significant effect of DHEA on cognitive performance, which was found to be within the upper quartile already at baseline. A slight increase in serum insulin-like growth factor I (IGF-I) was seen in primary but not in secondary adrenal insufficiency, and was not related to improvements in well-being.

Another exciting finding in this study was that the increase in circulating androgens from very low levels was paralleled by a significant increase in both sexual interest and sexual satisfaction [44] (Fig. 2b). Also of note, significant changes in mood and well-being were only observed after four months of treatment, whereas after one month no significant difference from placebo was seen [44], suggesting complex neurosteroidal adaptation processes. Another randomized, double-blind study in men and women with primary adrenal insufficiency described similar effects of DHEA on mood and well-being, irrespective of the patient’s sex [45] (Fig. 3). Thus, it seems more probable that mood and well-being effects are
Mediated via the neurosteroidal properties of DHEA itself and not by the increase in the androgenic pool, which is seen in women only. A recent randomized, parallel trial, employing low doses of DHEA (20–30 mg) in women with secondary adrenal failure as a result of hypopituitarism, reported an increase in sexual interest and activity and significant improvements in alertness, stamina and initiative after six months of treatment, as judged by the patients’ spouses [46], thus supporting the previously reported effects of DHEA treatment in primary and secondary adrenal failure.

The metabolic effects of DHEA replacement in patients with adrenal insufficiency were less impressive: no change in insulin sensitivity, body composition or exercise capacity, a decrease in high-density lipoprotein cholesterol (HDL-C) in women, and heterogeneous changes in markers of bone metabolism [44,45,47]. Reliable evaluation of DHEA effects on bone mineral density (BMD) requires treatment for at least 12 months, whereas the published studies administered DHEA for only three to four months. The observed decrease in serum leptin [47] is most probably related to the conversion of DHEA to androgens, and possible long-term metabolic consequences remain to be determined.

Side effects of DHEA replacement are mild and mostly transient. They include mild facial acne and increased sebum production, reflecting increased androgenic action. Because the skin in women with adrenal insufficiency often appears to be dry, some patients welcome higher sebum secretion, and the observed re-growth of pubic and axillary hair is also generally considered positive [44]. Growth of axillary and pubic hair from Tanner stage I to stage III was also reported in a 24-year-old woman with Addison’s disease receiving a daily dose of 25–50 mg DHEA over two years [48], and substantiated in a recent double-blind trial in women with hypopituitarism [46]. Based on these findings, DHEA replacement in adrenal insufficiency has already been proposed for clinical routine practice [49,50]. However, to establish securely the role of DHEA in standard replacement therapy, long-term studies in patients with adrenal insufficiency are still needed.

DHEA treatment for impaired mood and well-being

Consistent with the effects on mood and well-being observed in patients with adrenal insufficiency, recent double-blind trials reported significant improvements after DHEA treatment in patients with major depression [51] and midlife dysthymia [52] (Fig. 4). By contrast, in perimenopausal women with complaints of altered mood and well-being, but without a clearly defined symptomatology, no specific effect of DHEA supplementation was seen, with all subjects significantly improving both after DHEA and placebo treatment [53]. DHEA significantly improved scores on an ADL scale in patients with myotonic dystrophy [54], whereas DHEA treatment induced no change in ADL scores in healthy elderly men [55]. The results of Morales et al. [43] had suggested a potential effect of DHEA on sleep, and in a study employing a single pharmacological dose of 300 mg DHEA in healthy volunteers an increase in rapid eye movement sleep was documented [56]. Reiter et al. [57] found a significant improvement in erectile function and other aspects of sexuality during DHEA treatment in 40–60-year-old men with erectile dysfunction and low endogenous DHEAS levels. However, low DHEAS levels served as an inclusion criterion in only some of the studies analyzing the effect of DHEA on impaired mood or well-being. Thus, DHEA administration might have the potential to improve impaired well-being, mood and sexuality, irrespective of endogenous DHEAS secretion.

DHEA supplementation in elderly subjects

Most of the studies using DHEA in healthy, elderly volunteers focused on metabolic effects and symptoms usually associated with aging, such as hyperlipidemia, decreased insulin sensitivity, increased fat mass, reduced muscle mass and decreased BMD. In studies administering DHEA in...
physiological (25–50 mg) or near physiological daily doses (100 mg) a significant decrease in apolipoprotein A1 [58,59] and HDL-C was seen in women [43,58–61] but not in men [43,58]. This corresponded to an increase in circulating androgen concentrations in women but not in men. In one study employing a dose of 100 mg d⁻¹ DHEA, a slight, but significant, HDL-C reduction was also seen in men [55], who concurrently showed an increase in both free testosterone and 17β-estradiol serum concentrations. Fasting glucose and insulin levels, in addition to insulin responses to oral and intravenous glucose loads, were consistently found to be unaltered by DHEA administration [43,55,58,60,62]. However, a recent study in postmenopausal women (n = 20) receiving 25 mg d⁻¹ DHEA reported significant improvement in insulin sensitivity, but not of glucose tolerance [61]. Of note, Yen et al. [63] observed an increase in lean body mass and muscular strength and a decrease in fat mass in age-advanced men receiving DHEA. This was also described in two open-label studies [60,62]. However, none of the other double-blind trials analyzing body composition found significant changes [43,55,59].

A slight but significant increase in serum IGF-I in response to oral DHEA treatment has been reported by some observers [43,58,62]. However, several others found no significant changes in parameters of the somatotropic axis [59,60,64]. Thus, the significance of these findings remains questionable.

Six months of DHEA supplementation had no effect on BMD in two placebo-controlled studies [58,59]. However, in a large-scale, placebo-controlled study involving 280 volunteers, Bauilleau et al. [64] described slight but significant BMD increases in 60–80-year-old women, but not in men receiving DHEA for 12 months. Slight increases in BMD observed in two open-label studies [62,65] are of considerably lower significance because comparison with placebo controls is crucial for the evaluation of drug effects on BMD.

An important target of DHEA action seems to be the skin. As in adrenal insufficiency, sebum secretion increased after DHEA administration in elderly people [64,65], suggesting androgenic activity of DHEA. Emphasizing the importance of tissue-specific bioconversion of DHEA, Labrie et al. [65] found androgenic effects of DHEA administration on the skin of postmenopausal women, but estrogenic effects on the vaginal epithelium. Interestingly, DHEA administration to elderly people also improved skin hydration [64].

Circulating interleukin 6 (IL-6) increases with ongoing age and several epidemiological studies have reported a negative correlation of serum DHEA and DHEAS with IL-6 [66,67]. In vitro evidence has been presented for DHEA-induced inhibition of IL-6 production by human peripheral mononuclear blood cells [67], suggesting a potential link between endocrinosenescence and immunosenescence. However, other studies reported a DHEA-induced increase in IL-6 secretion from human monocytes [68] or no effect on IL-6, but significant increases in IL-2 secretion, after DHEA treatment of human spleen mononuclear cells [69]. DHEA has also been reported to stimulate monocyte-mediated cytotoxicity [70], natural killer cell cytotoxicity [71,72] and IL-2 secretion from human T cells [73]. However, the clinical significance of these observations needs further clarification. Again, all immunomodulating effects of DHEA might be mediated by steroids derived from downstream conversion of DHEA, which effectively occurs in human macrophages [74].

An increase in self-perception of well-being was noted in a double-blind, placebo-controlled study in healthy elderly volunteers after three months of DHEA administration, although this was not assessed by validated psychometric questionnaires [43]. By contrast, no increase in well-being or sexuality was noted after four months of DHEA supplementation (50 mg d⁻¹) in healthy 50–70-year-old men with low, aging-related endogenous serum DHEAS [75]. This trial is particularly revealing because the methodology used was identical to that employed in a study on women with adrenal insufficiency, which had found pronounced effects of DHEA replacement on well-being, mood and sexuality [44] (Fig. 5). In spite of low endogenous DHEAS concentrations, these men had normal well-being and sexuality scores already at baseline, thereby clearly indicating that the age-associated decline in circulating DHEAS per se does not necessarily result in impaired well-being. This study, together with several other studies in elderly subjects suggests that DHEA supplementation could have the potential to improve impaired well-being, mood and sexuality, but that it is unlikely to enhance an already normal performance.
Conclusions and perspectives of future research

The past few years have seen exciting progress in the field of DHEA research. Replacement of DHEA in patients with adrenal insufficiency has demonstrated the important role of DHEA for well-being, mood and sexuality in humans, suggesting that the CNS is a major target of DHEA action. Multicenter studies in this patient population are under way and will further define the role of DHEA as part of the routine replacement therapy for adrenal failure.

Because chronic pharmacological glucocorticoid treatment almost invariably induces pronounced suppression of endogenous DHEA(S) secretion, patients on exogenous glucocorticoids will also probably benefit from DHEA treatment. This view is supported by beneficial effects of DHEA treatment in patients with systemic lupus erythematosus (SLE), leading to better overall performance and functional activity [76,77]. However, possible immunomodulating activities of DHEA in humans remain to be elucidated before DHEA replacement in patients receiving glucocorticoids for immune disorders other than SLE should be routinely considered.

Besides the replacement of a pathophysiological defined DHEA deficiency, as in adrenal insufficiency or chronic glucocorticoid-treated patients, DHEA treatment seems to be most promising in patients with impaired well-being, mood or sexuality, possibly irrespective of endogenous DHEA(S) serum concentrations. For example, women with sexual dysfunction not sufficiently explained by distinct physical or psychological factors might benefit from DHEA administration.

By contrast, an increasing number of studies in elderly men and women do not substantiate the myth of DHEA as a ‘fountain of youth’. Instead, biotransformation of exogenously administered DHEA into potent androgens and estrogens in excess of normal baseline levels might carry the risk of promoting sex hormone-dependent neoplasia [78], a matter that is still unsettled and that clearly requires more scientific attention.

Although some studies in aging men and women have revealed favorable effects of DHEA treatment on body composition, slight increases in BMI and improved skin hydration, which might be regarded as an anti-aging activity of DHEA, at present there is not enough evidence to recommend DHEA supplementation in advanced age.

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