Dehydroepiandrosterone – Is the Fountain of Youth Drying Out?

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Summary
Dehydroepiandrosterone (DHEA) and its sulphate-bound form (DHEAS) are important steroids mainly of adrenal origin. Their physiological and pathophysiological functions are not yet fully identified, although a number of various possible features have been hypothesized. Most popular is the description of the “hormone of youth” as the long-term dynamics of DHEA levels are characterized by a sharp age-related decline in the late adulthood and later. Low levels of DHEA are, however, associated not only with the ageing process but also with diabetes mellitus, cardiovascular diseases and some neurological or immunological entities. In the past decade, a number of brief studies have concentrated on these relationships and also on the role of exogenous DHEA in health, disease and human well-being. This article tries to summarize some of the most important facts achieved recently.

Key words
Dehydroepiandrosterone • Intracrinology • Hormone replacement therapy • Steroids

Introduction
In 1934 Butenandt and Dannenbaum isolated dehydroepiandrosterone (DHEA) from urine and in 1944 Munson and colleagues identified its 3β-sulphate (DHEAS). Even now, nearly 70 years later, we still do not fully understand the physiological function of DHEA and its importance in human life. It has even been hypothesized that high levels of DHEA (and melatonin), typical for human primates, are important for the evolution of hominids, bipedal locomotion and brain development (Howard 1996, 2000). There are two important reasons for this scientific delay of the general information about DHEA functions: 1) DHEA is an endogenous metabolite that cannot be patented so that pharmaceutical companies are not interested in supporting research in this field. 2) DHEA can be described as a “human molecule” because other investigated species have much lower concentrations. Especially the classical rodent laboratory animals are not suitable for experiments with DHEA. Moreover, even non-human primates produce only about 10 % of the “human amounts” of DHEA. Nevertheless, despite these and other problems the view on DHEA has changed dramatically in the late 90-ties and in the recent decade. The original enthusiasm has been replaced by sober skepticism.
Intracrinology

DHEA (3β-hydroxy-5-androsten-17-α) reaches serum concentrations of about 30 nmol/l in young healthy probands. DHEAS, on the other hand, is found in concentrations of more than 10 µmol/l. This makes DHEA and its sulphate-bound form the main adrenal steroid in humans. The classic biosynthetic pathway goes through pregnenolone and 17α-hydroxy-pregnenolone (Fig. 1). However, only about 50 % of the serum DHEA is of adrenal origin (Pieper and Lobocki 2000). The rest comes from the gonads, adipose tissue and particularly, from the brain. Cytochrome P450c17 plays an important role in the production within these locations.

Especially astrocytes, but not oligodendrocytes, have been revealed to be the cellular producer in the central nervous tissue (Zwain and Yen 1999). Till today, no specific receptor has been found for DHEA. This fact strongly supports the hypothesis that DHEA is more a metabolic precursor of other steroid molecules than a real hormone, or that it exerts its activity via non-genomic mechanisms. The ingestion of DHEA results in an immediate increase of androstenedione (Brown et al. 1999). In peripheral tissues, DHEA is converted to testosterone, dihydrotestosterone or estradiol. A scheme of the relevant metabolic pathways is shown in Figure 2.

Even after bilateral castration when testosterone concentrations in serum drop to almost immeasurable values, there is still about 50 % of the normal concentration of dihydrotestosterone in the prostate (Labrie et al. 2001), which is formed from circulating precursors as DHEA.

Similar to other products of the adrenal cortex, DHEA is also under strong regulation of ACTH from the pituitary. The adrenal response to ACTH stimulation is very inconsistent – the interindividual variability was estimated at 60-70 % for DHEAS while a range of 15-40 % was determined for cortisol (Azziz et al. 2001). Thus, a possible co-regulation by LH and other regulators like prolactin and gonadal steroids cannot be excluded. An “adrenal androgen-stimulating hormone” is hypothesized to take part in DHEA regulation, but has not yet been clearly identified. One of the candidates is β-endorphin – an oligopeptide derived from pro-opiomelanocortin (Alesci and Bornstein 2001). Some studies have shown a possible association of DHEAS with insulin, particularly in men. About 120-150 min after the last meal – during the hyperinsulinemic phase – DHEAS reaches the lowest concentrations. A gender difference is reported in cortisol/DHEAS ratio (with
higher values for women) when adjusted for BMI and age (Laughlin and Barrett-Connor 2000). Moreover, it has been shown that long-lasting caloric restriction of 30% in monkeys could slow the age-related decline of DHEAS levels (Lane et al. 1997) while, on the contrary, exogenous DHEA reduced the caloric intake in some mouse strains (Bradlow 2000). However, the presumed negative dependence between insulin and DHEAS was not confirmed in a large study on more than 2400 healthy participants (Nestler et al. 2002). Another intracrinological relationship seems to exist between DHEAS and the growth hormone, while a positive correlation was found to IGF-1 in men (Tissandier et al. 2001).

**Pathophysiology**

An important argument for the precursor hypothesis of DHEA is the discovery of biological importance of hydroxylated DHEA metabolites, such as 16α-hydroxy or 7α- and 7β-hydroxy derivatives. Although the physiological function of these compounds is everything but clear, they seem to be associated with different local and systemic pathophysiological processes like cancerogenesis (breast cancer) and autoimmune diseases (rheumatic arthritis) (Hampl and Stárka 2000).

DHEAS itself is often reported to have antidiabetic effects. Although the causal relationship is discussed, the main pathophysiological explanation is not known. Nevertheless, a higher grade of albuminemia in diabetic nephropathy is related to significantly lower endogenous DHEAS levels (Kanauchi et al. 2001). Furthermore, obese Zucker rats suffering from diabetic nephropathy benefit from DHEA treatment as assessed by the glomerular filtrate rate, creatinine levels and expression of α-smooth muscle actin in renal interstitium. The effect was similar to the action of ACE inhibitors, which belong to standard therapy in diabetic nephropathy. Combined administration of both had an additive effect (Richards et al. 2001). Leptin levels and weight increase were reduced and local lipid metabolism was altered in rats by the administration of DHEA (Richards et al. 2000, Abadie et al. 2001). However, clinical studies regarding this therapeutic possibility are necessary. Stroke, a frequent complication of diabetes, is associated with an enormous production of reactive oxygen species. Hyperglycemia and reperfusion injury contribute mostly to this oxidative stress. DHEA is able to inhibit its effects at various sites (Aragno et al. 2000). The first survey dealing with the metabolic effects of long-term (12 months) replacement of DHEA in postmenopausal women showed improved insulin sensitivity and a preferable effect on lipid metabolism (Lasco et al. 2001).
In a subgroup of women over 70 years the administration for such long time even improved bone turnover, which could indicate a possible relationship of low DHEA and a high risk for osteoporosis (Baulieu et al. 2000). In an animal model administration of DHEA after ovariectomy reversed the loss of bone mineral density due to local androgen production (Martel et al. 1998). In middle-aged and elderly men this effect was not seen despite 12 months of DHEA administration (Kahn and Halloran 2002). Lower levels of DHEAS correlate with the incidence of depressive symptoms and poor results in the Mini Mental State Examination (MMSE) test in elderly population (Berr et al. 1996).

Chronic heart failure is another civilization disease reported to be related to DHEAS. Patients with heart failure have indeed lower levels of DHEAS, that are also associated with increased oxidative stress parameters and natriuretic peptides (Moriyama et al. 2000). In rabbits, the administration of DHEA slows down the atherogenic process. Local conversion of DHEA to estradiol and its effect on nitric oxide formation seems to be involved in this effect (Hayashi et al. 2000). Studies on risk factors of atherosclerosis in cell cultures and animals were, however, not verified in clinical studies. DHEA values do not basically differ in patients developing or not developing atherosclerotic changes (Kiechl et al. 2000, Aminian et al. 2000). Similarly, there is no marked relationship to cardiovascular risk factors in women (Barrett-Connor and Goodman-Gruen 1995). Lower levels of DHEA are found in various clinical diagnoses, but their role in their pathogenesis remains dubious. Moreover, it seems that instead of being the cause, they are a consequence of the whole process. On the other hand, exogenous administration of DHEA is beneficial in patients with advanced HIV infection (Piketty et al. 2001), in cerebral ischemia (Li et al. 2001) and in different forms of physical injury (Araneo and Daynes 1995). These effects are attributed either to the modulatory action on neuronal receptors or to the antiglucocorticoid action that causes changes in the local and systemic immune system (Jarrar et al. 2001).

**In vitro studies**

As a neurosteroid DHEA is produced in the brain, however its function in the central nervous tissue is not clear. It is likely that its role is mainly immunomodulatory (Canning et al. 2000). Pretreatment of glial cultures with DHEA resulted in a reduction of expression of NO synthase induced by addition of lipopoly-saccharides. As DHEA is produced in the brain by neurons and the astroglia, a regulative effect on immune processes of the microglia is discussed. In high concentrations DHEA even increases the total antioxidative status of glial cells and this supports the aforementioned hypothesis (Wang et al. 2001). The results obtained suggest that DHEA protects hippocampal neurons in a glutamate neurotoxic environment, at least in part, by its antiglucocorticoid action via decreasing nuclear glucocorticoid receptor levels in hippocampal cells (Cardounel et al. 1999). The antiglucocorticoid activity of DHEA is not caused by its competition with cortisol on glucocorticoid receptors as it was confirmed by further experiments. Another neuroprotective mechanism has been studied. In the in vitro model of brain ischemia on cerebellar granule cell cultures, the DHEA effect on the cells was mediated through negative modulation of GABA receptors. Moreover, a positive modulatory effect was shown on NMDA receptors (Kaasik et al. 2001). These important results strengthen the assumption that GABA and NMDA receptors and their modulations are the targets for DHEA, particularly in the brain and these may be the cellular mechanisms of DHEA effects seen in the results of in vivo studies. It was demonstrated that metabolites of DHEA, especially 7-hydroxylation products have an even more potent effect in the brain tissue than the precursor (Morfin and Stárka 2001). Taken together, evidence has been collected that neurosteroids like DHEA act particularly through metabolites mainly via other pathways than the classic concept of activation of the nuclear receptor proposed (Puia and Belelli 2001).

DHEA is also linked to obesity. Human adipose tissue decreases the production of leptin when under the influence of DHEAS. Thus, the information coming from adipocytes to the brain may be decreased by the steroid (Pineiro et al. 1999). Diabetes mellitus manifested by high glycemia is associated with glucose induced oxidative stress. Mesangial cells are protected by DHEA from this impairment. The mechanism is not clear (Brignardello et al. 2000). It is speculated that the enhanced insulin secretion by the pancreatic β cells may be related to the antioxidant activity (Dillon et al. 2000).

With progressing age, some specific cytokines – interleukin 6 and tumor necrosis factor α are elevated. These immunity changes are called immunosenescence. This may also be associated with the age-dependent DHEA decline, as in vitro studies have shown that DHEA inhibits the interleukin 6 production of mononuclear cells (Straub et al. 1998). Furthermore, DHEA inhibits the
proliferation of vascular smooth muscle cells. An antiatheroslerotic effect of DHEA is thus presumed (Williams et al. 2002). From the physiological point of view, DHEA and its metabolites can also participate in the regulation of body temperature as has been shown recently (Catalina et al. 2002) and the sulphate bound form affects circadian rhythm of melatonin as it increases the level of its light nadir (San Martin and Toutou 2000).

To replace or not to replace – in vivo veritas

There are two main indications for the replacement therapy of DHEA: 1) age-related decline of DHEA levels, and 2) primary or secondary adrenal insufficiency. The results of various studies were reviewed recently (Gurnell and Chatterjee 2001). DHEA has been described as the “hormone of youth”. The highest concentrations are reached during the third decade and are then followed by a subsequent decline of about 2 % per year. The continual decrease stops at the age of 70-80 years with DHEA levels being 10-15 % of the “normal young” concentration (Orentreich et al. 1992). However, shifts and sex differences have been found in the dynamics of DHEA and DHEAs and these should be taken into account in interventional studies (Šulcová et al. 1997, 2001). The reason is unknown, but enzymatic disturbances in the steroidogenic pathways and involution of the adrenal reticular zone are discussed. An important fact is that the cortisol production is not affected even at the highest age, some studies showed even an age-related rise in cortisol levels (Ravaglia et al. 1996). Minor pharmacokinetic studies have found that 25-50 mg DHEA per day are enough to establish levels within a normal range. Higher doses of DHEA, represented by 100-200 mg used in patients with Addison’s disease and other adrenal or pituitary insufficiencies result in supraphysiological levels of testosterone, particularly in women. A body of evidence exists for the relationship between endogenous testosterone levels and specific cognitive performance in either sex (Ostatníková et al. 2002, Celec et al. 2002). Adverse effects of DHEA replacement of 100 mg/day include especially dermatological complications, hot flashes and chest pain. These effects were dose-dependent and disappeared at the dose of 50 mg (Wolf et al. 1997). One of the first studies regarding the DHEA replacement therapy in adrenopause showed a clear increase in well-being and other psychological parameters in both sexes compared to placebo treatment. Biochemical parameters do not seem to be significantly affected by DHEA replacement except IGF-1 that was increased tightly correlating with the increase in serum DHEA (Morales et al. 1994). Normal levels were reached after 1-2 weeks of treatment. However, in other studies well-being as the main psychological outcome parameter did not change after such a short time period (Wolf et al. 1997, Kudielka et al. 1998). Interestingly, serum DHEA increased significantly in postmenopausal women with classic transdermal estrogen/progesterone replacement therapy (Kos-Kudla et al. 2001). A similar placebo-controlled study by Arlt et al. (2001), which was based on validated psychometric evaluation of DHEA effects, reported only a few improved partial mood parameters. Neither well-being, nor psychosexual parameters were changed by four months of DHEA treatment, although the dosage was the same as in the above mentioned study. In contrary, women suffering from adrenal insufficiency evidently profit from DHEA replacement (Oelkers 1999). Both, well-being and psychosexual parameters improved after four months of DHEA treatment (Arlt et al. 1999). Women with adrenal insufficiency due to hypopituitarism also benefit from the replacement, as determined by various psychological tests (Johannsson et al. 2002). Similar studies in men with adrenal insufficiency have not yet been completed.

Cortisol and DHEAs seem to be partial antagonists. Diverse dynamics in older age, reverse cellular responses and antagonistic actions on central nervous system support this statement (Kalmijn et al. 1998). The blood-brain barrier is permeable for DHEA but not for the sulphate bound form. The concentration of DHEAS is, however, still higher than the DHEA level in the cerebrospinal fluid. The ratio DHEA/cortisol is high especially during late childhood and early adulthood (Guazzo et al. 1996). An old premise of the correlation between cognitive performance and DHEAS levels was refuted by the results of a large scale study with more than 800 male participants. Moffat et al. (2000) determined the endogenous levels of DHEAS and related them to the quantified cognitive status. Although both DHEAS and cognitive performance declined with age, it seems that a causal relationship is not likely. Similarly, no consistent relationship has been found between DHEAS and general causes or cardiovascular mortality in elderly persons of both sexes (Trivedi and Khaw 2001). In another study, lowest DHEAS levels were associated with the highest mortality, but this finding was restricted to healthy men under 70 years (Mazat et al. 2001). The data concerning the question whether DHEA and DHEAS
DHEA is its function as a neurosteroid (Friess et al. 2000). Besides dehydroepiandrosterone deficiency, either age-dependent or of adrenal origin, DHEA has found its place in the treatment of various diseases. Its benefit is now generally accepted in the therapy of lupus erythematosus (Furie 2000, Doria et al. 2002, Petri et al. 2002, van Vollenhoven 2002) and in other autoimmune rheumathological diseases (Cutolo 2000). The DHEA replacement may represent a valuable concomitant or adjuvant treatment to be associated with other disease-modifying antirheumatic drugs in the management of rheumatoid arthritis.

Clinical results suggest that replacement therapy with dehydroepiandrosterone is a safe and effective treatment for female androgen insufficiency and female sexual dysfunction (Munarriz et al. 2002) as well as of erectile dysfunction. Oral DHEA treatment may be of benefit to patients with erectile dysfunction who have hypertension or to patients with erectile dysfunction without organic etiology. There was no impact of DHEA therapy on patients with diabetes mellitus or with neurological disorders, in hypertensive men or those with organic cause of impotence (Reiter et al. 1999). DHEA treatment was recommended for the therapy of AIDS and HIV positive patients (Rabkin et al. 2000), shock, trauma and hemorrhage (Kuebler et al. 2001, Jarrar et al. 2001) and chronic inflammatory diseases (Straub et al. 2000). Positive effects of DHEA on skin (Baulieu et al. 2000) and its androgenic potential were also adopted for the treatment of atrichia pubis (Wit et al. 2001).

A special chapter of the therapeutic use of DHEA is its function as a neurosteroid (Friess et al. 2000). In humans, cross-sectional and longitudinal studies have shown that DHEA might be associated with global measures of well-being and functioning, but positive effects on assessment of memory and attention could not be found. Studies investigating DHEA and DHEAS levels in dementia have produced controversial results. Short-term experimental studies have not shown significant improvement in global measures of well-being and functioning in healthy subjects but have reported preliminary evidence for mood enhancing and antidepressant effects of DHEA. There is no evidence that DHEA could induce addiction in human subjects (Huppert et al. 2000, Rigaud and Pellerin 2001).

Conclusions

In recent studies, DHEAS has been found to be a much more suitable marker of individual function of the adrenal cortex than cortisol. The long-term stability is much higher (Kendall’s coefficient of concordance for DHEAS – 92 % vs. cortisol – 51 %) and so is the interindividual variability (skewness coefficients for DHEAS – 1.0 vs. cortisol – 0.3). This makes DHEA a very interesting parameter for both scientific research and clinical diagnostics (Thomas et al. 1994). However, one should be cautious about the chronobiological aspects. The circadian rhythm and related variations make it difficult to evaluate “basal” levels (Ostrowska et al. 1998).

Is DHEA a suitable dietary supplement? It is difficult to give advice, either to patients, or to doctors. Placebo controlled clinical studies with a great number of participants and an “general” observations are rare. Especially patients with a known risk factor for hormone-dependent cancer (prostate, breast) should reconsider regular DHEA ingestion (Weksler 1996). This is of particular importance for commercial products containing DHEA are freely available on the market in the USA and will soon be available in the EU (Parasrampuria et al. 1998). As the pharmaceutical industry is not interested in this topic (for reasons mentioned above), governmental or private resources are needed to support such an expensive research. Till then, no clear statement on DHEA supplement value can be made.

In the 90-ties, DHEA was assumed to be a possible candidate for the hormone or “fountain” of youth in a classical editorial in Journal of Clinical Endocrinology and Metabolism (Baulieu 1996). Since then the attitude to this adrenal steroid has changed (Yen 2001). Although the original enthusiasm has waned, many questions remain unanswered. Their solution is a challenge for future research.

For medical practice it can be concluded in concordance with other reviews (Cogan 2001, Gurnell and Chatterjee 2001): the exact physiological role of DHEA remains unknown, but DHEA supplementation has recently been proven beneficial in typical deficient states such as adrenal insufficiency, autoimmune disorders or major depressive illnesses. The putative favorable effects of DHEA in other conditions remain as a challenge for future research. However, recent studies have confirmed the positive effects of DHEA administration in healthy elderly people, mostly in more than 70-years old women, on skin, bone density, muscle strength and several neuropsychological symptoms. Positive effects on sexual interest and satisfaction and sense of well-being are more consistent in elderly women than in men. The recommended administered dose is 25-50 mg once a day in women. The androgenic side
effects are minor and reversible. It is fully justifiable to prescribe DHEA in patients with adrenal insufficiency. Other possible indications are depression, prolonged glucocorticoid therapy and lupus erythematosus. In elderly people, DHEA administration might be considered in DHEA depleted-patients with skin dryness or atrophy, muscle weakness, low bone density or neuropsychological symptoms. The treatment should be taken under close medical supervision in order to detect a possible hormone-dependent cancer such as breast cancer in women and prostate cancer in men. The patients should be informed about the potential risks of DHEA administration and on the lack of definitively proven beneficial effects of DHEA, while waiting for the results of well-conducted controlled double-blind prospective studies.

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