Physiol. Res. 52: 397-407, 2003

MINIREVIEW

Dehydroepiandrosterone – Is the Fountain of Youth Drying Out?

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Received September 15, 2002
Accepted October 7, 2002

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 The original enthusiasm has been replaced by sober skepticism.

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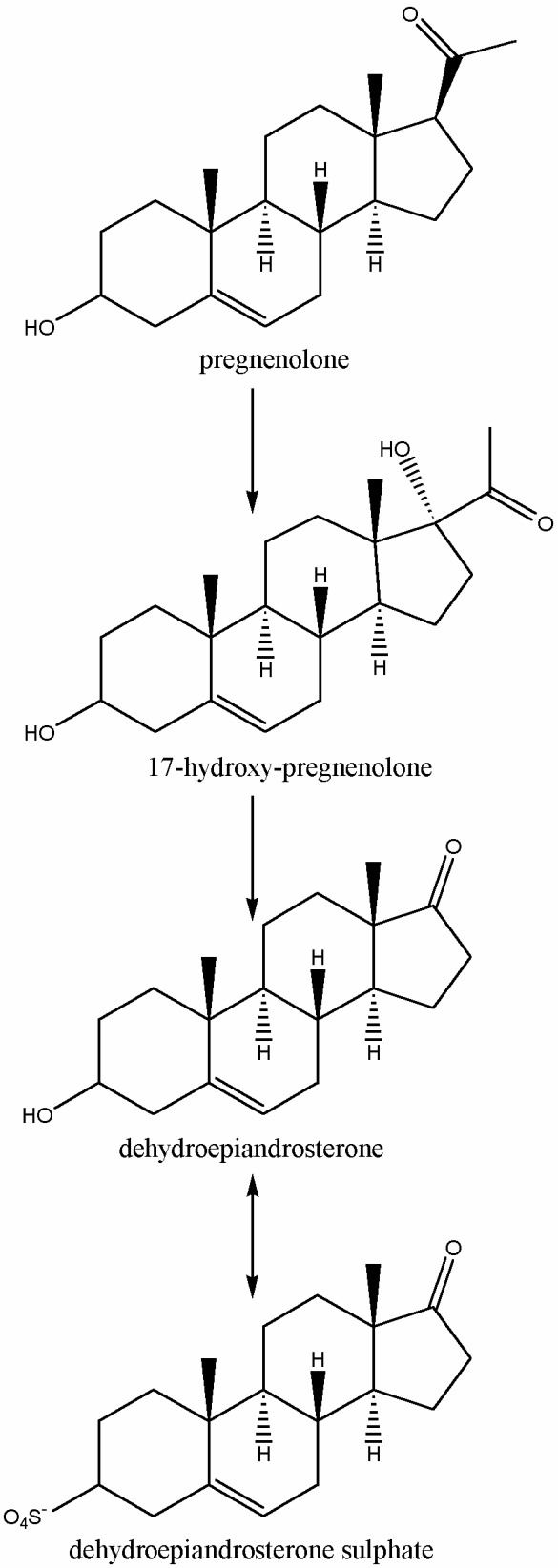

Fig. 1. *Metabolic pathway of DHEAS production*

Intracrinology

DHEA (3β-hydroxy-5-androsten-17-on) 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).

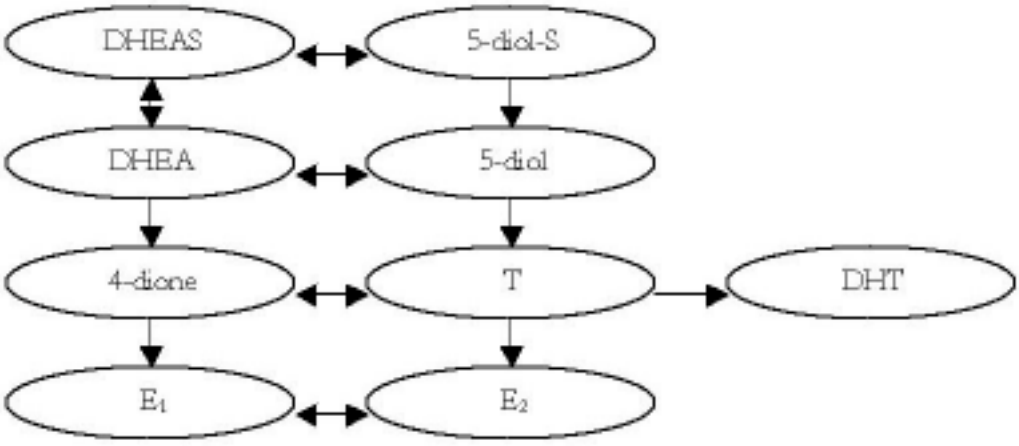

Fig. 2. *Scheme of the intracrinology of DHEAS in the peripheral tissue (adapted from Labrie et al. 2001). DHEAS – dehydroepiandrosterone sulphate, DHEA – dehydroepiandrosterone, 4-dione – androstenedione, E_1 – estrone, E_2 – 17β-estradiol, T – testosterone, 5-diol – androst-5-ene-3β; 17β-diol, 5-diol-S – androst-5-ene-3β; 17β-diol – sulphat; DHT – dihydrotestosterone.*

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 immuno-modulatory (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 Touitou 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

play a protective role in coronary heart disease was reviewed by Poršová-Dutoit *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 inflammative 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 DHEAS 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 praxis 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.

References

ABADIE JM, MALCOM GT, PORTER JR, SVEC F: Dehydroepiandrosterone alters Zucker rat soleus and cardiac muscle lipid profiles. *Exp Biol Med (Maywood)* **226**: 782-789, 2001.

ALESCI S, BORNSTEIN SR: Intraadrenal mechanisms of DHEA regulation: a hypothesis for adrenopause. *Exp Clin Endocrinol Diabetes* **109**: 75-82, 2001.

AMINIAN B, OSTOVAN MA, OMRANI GH: Correlation between dehydroepiandrosterone sulfate (DHEA-S) and coronary artery disease. *Arch Iran Med* **3**: http://www.sums.ac.ir/AIM/0034/aminian0034.html, 2000.

ARAGNO M, PAROLA S, BRIGNARDELLO E, MAURO A, TAMAGNO E, MANTI R, DANNI O, BOCCUZZI G: Dehydroepiandrosterone prevents oxidative injury induced by transient ischemia/reperfusion in the brain of diabetic rats. *Diabetes* **49**: 1924-1931, 2000.

ARANEO B, DAYNES R: Dehydroepiandrosterone functions as more than an antiglucocorticoid in preserving immunocompetence after thermal injury. *Endocrinology* **136**: 393-401, 1995.

ARLT W, CALLIES F, VAN VLIJMEN JC, KOEHLER I, REINCKE M, BIDLINGMAIER M, HUEBLER D, OETTEL M, ERNST M, SCHULTE HM, ALLOLIO B: Dehydroepiandrosterone replacement in women with adrenal insufficiency. *N Engl J Med* **341**: 1013-1020, 1999.

ARLT W, CALLIES F, KOEHLER I, VAN VLIJMEN JC, FASSNACHT M, STRASBURGER CJ, SEIBEL MJ, HUEBLER D, ERNST M, OETTEL M, REINCKE M, SCHULTE HM, ALLOLIO B: Dehydroepiandrosterone supplementation in healthy men with an age-related decline of dehydroepiandrosterone secretion. *J Clin Endocrinol Metab* **86**: 4686-4692, 2001.

AZZIZ R, FOX LM, ZACUR HA, PARKER CR, JR, BOOTS LR: Adrenocortical secretion of dehydroepiandrosterone in healthy women: highly variable response to adrenocorticotropin. *J Clin Endocrinol Metab* **86**: 2513-2517, 2001.

BARRETT-CONNOR E, GOODMAN-GRUEN D: Dehydroepiandrosterone sulfate does not predict cardiovascular death in postmenopausal women: the Rancho Bernardo Study. *Circulation* **91**: 1757-1760, 1995.

BAULIEU EE: Dehydroepiandrosterone (DHEA): a fountain of youth? *J Clin Endocrinol Metab* **81**: 3147-3151, 1996.

BAULIEU EE, THOMAS G, LEGRAIN S, LAHLOU N, ROGER M, DEBUIRE B, FAUCOUNAU V, GIRARD L, HERVY MP, LATOUR F, LEAUD MC, MOKRANE A, PITTI-FERRANDI H, TRIVALLE C, DE LACHARRIERE O, NOUVEAU S, RAKOTO-ARISON B, SOUBERBIELLE JC, RAISON J, LE BOUC Y, RAYNAUD A, GIRERD X, FORETTE F: Dehydroepiandrosterone (DHEA), DHEA sulfate, and aging: Contribution of the DHEAage Study to a sociobiomedical issue. *Proc Natl Acad Sci USA* **97**: 4279-4284, 2000.

BERR C, LAFONT S, DEBUIRE B, DARTIGUES JF, BAULIEU EE: Relationships of dehydroepiandrosterone sulfate in the elderly with functional, psychological, and mental status, and short-term mortality: a French community-based study. *Proc Natl Acad Sci USA* **93**: 13410-13415, 1996.

BRADLOW HL: Feeding DHEA to C57/B167 mice. *Proc Soc Exp Biol Med* **224**: 201-202, 2000.

BRIGNARDELLO E, GALLO M, ARAGNO M, MANTI R, TAMAGNO E, DANNI O, BOCCUZZI G: Dehydroepiandrosterone prevents lipid peroxidation and cell growth inhibition induced by high glucose concentration in cultured rat mesangial cells. *J Endocrinol* **166**: 401-406, 2000.

BROWN GA, VUKOVICH MD, SHARP RL, REIFENRATH TA, PARSONS KA, KING DS: Effect of oral DHEA on serum testosterone and adaptations to resistance training in young men. *J Appl Physiol* **87**: 2274-2283, 1999.

CANNING MO, GROTENHUIS K, DE WIT HJ, DREXHAGE HA: Opposing effects of dehydroepiandrosterone and dexamethasone on the generation of monocyte-derived dendritic cells. *Eur J Endocrinol* **143**: 687-695, 2000.

CARDOUNEL A, REGELSON W, KALIMI M: Dehydroepiandrosterone protects hippocampal neurons against neurotoxin-induced cell death: mechanism of action. *Proc Soc Exp Biol Med* **222**: 145-149, 1999.

CATALINA F, MILEWICH L, FRAWLEY W, KUMAR V, BENNETT M: Decrease of core body temperature in mice by dehydroepiandrosterone. *Exp Biol Med (Maywood)* **227**: 382-388, 2002.

CELEC P, OSTATNÍKOVÁ D., PUTZ Z, KÚDELA M: The circalunar cycle of salivary testosterone and the visual-spatial performance. *Bratisl Lek Listy* **103:** 59-69, 2002.

COGAN E: DHEA: orthodox or alternative medicine? (in French) *Rev Med Brux* **22**: A381-A386, 2001.

CUTOLO M: Sex hormone adjuvant therapy in rheumatoid arthritis. *Rheum Dis Clin North Am* **26**: 881-895, 2000.

DILLON JS, YANEY GC, ZHOU Y, VOILLEY N, BOWEN S, CHIPKIN S, BLISS CR, SCHULTZ V, SCHUIT FC, PRENTKI M, WAXMAN DJ, CORKEY BE: Dehydroepiandrosterone sulfate and beta-cell function: enhanced glucose-induced insulin secretion and altered gene expression in rodent pancreatic beta-cells. *Diabetes* **49**: 2012-2020, 2000.

DORIA A, CUTOLO M, GHIRARDELLO A, ZAMPIERI S, VESCOVI F, SULLI A, GIUSTI M, PICCOLI A, GRELLA P, GAMBARI PF: Steroid hormones and disease activity during pregnancy in systemic lupus erythematosus. *Arthritis Rheum* **47**: 202-209, 2002.

FRIESS E, SCHIFFELHOLZ T, STECKLER T, STEIGER A: Dehydroepiandrosterone - a neurosteroid. *Eur J Clin Invest* **30** (Suppl 3): 46-50, 2000.

FURIE R: Dehydroepiandrosterone and biologics in the treatment of systemic lupus erythematosus. *Curr Rheumatol Rep* **2**: 44-50, 2000.

GUAZZO EP, KIRKPATRICK PJ, GOODYER IM, SHIERS HM, HERBERT J: Cortisol, dehydroepiandrosterone (DHEA), and DHEA sulfate in the cerebrospinal fluid of man: relation to blood levels and the effects of age. *J Clin Endocrinol Metab* **81**: 3951-3960, 1996.

GURNELL EM, CHATTERJEE VK: Dehydroepiandrosterone replacement therapy. *Eur J Endocrinol* **145**: 103-106, 2001.

HAMPL R, STÁRKA L: 16α-hydroxylated metabolites of dehydroepiandrosterone and their biological significance. *Endocr Regul* **34**: 161-163, 2000.

HAYASHI T, ESAKI T, MUTO E, KANO H, ASAI Y, THAKUR NK, SUMI D, JAYACHANDRAN M, IGUCHI A: Dehydroepiandrosterone retards atherosclerosis formation through its conversion to estrogen: the possible role of nitric oxide. *Arterioscler Thromb Vasc Biol* **20**: 782-792, 2000.

HOWARD JM: Dehydroepiandrosterone, melatonin and testosterone in human evolution. http://www.naples.net/~nfn03605/, 1996.

HOWARD JM: Androgens in human evolution. A new explanation of human evolution. http://www.naples.net/~nfn03605/, 2000.

HUPPERT FA, VAN NIEKERK JK, HERBERT J: Dehydroepiandrosterone (DHEA) supplementation for cognition and well-being. *Cochrane Database Syst Rev* CD000304, 2000.

JARRAR D, KUEBLER JF, WANG P, BLAND KI, CHAUDRY IH: DHEA: a novel adjunct for the treatment of male trauma patients. *Trends Mol Med* **7**: 81-85, 2001.

JOHANNSSON G, BURMAN P, WIREN L, ENGSTROM BE, NILSSON AG, OTTOSSON M, JONSSON B, BENGTSSON BA, KARLSSON FA: Low dose dehydroepiandrosterone affects behavior in hypopituitary androgen-deficient women: a placebo-controlled trial. *J Clin Endocrinol Metab* **87**: 2046-2052, 2002.

KAASIK A, KALDA A, JAAKO K, ZHARKOVSKY A: Dehydroepiandrosterone sulphate prevents oxygen-glucose deprivation-induced injury in cerebellar granule cell culture. *Neuroscience* **102**: 427-432, 2001.

KAHN AJ, HALLORAN B: Dehydroepiandrosterone supplementation and bone turnover in middle-aged to elderly men. *J Clin Endocrinol Metab* **87**: 1544-1549, 2002.

KALMIJN S, LAUNER LJ, STOLK RP, DE JONG FH, POLS HAP, HOFMAN A, BRETELER MMB, LAMBERTS SWJ: A prospective study on cortisol, dehydroepiandrosterone sulfate, and cognitive function in the elderly. *J Clin Endocrinol Metab* **83**: 3487-3492, 1998.

KANAUCHI M, NAKAJIMA M, DOHI K: Dehydroepiandrosterone sulfate and estradiol in men with diabetic nephropathy. *Nephron* **88**: 95-96, 2001.

KIECHL S, WILLEIT J, BONORA E, SCHWARZ S, XU Q: No association between dehydroepiandrosterone sulfate and development of atherosclerosis in a prospective population study (Bruneck Study). *Arterioscler Thromb Vasc Biol* **20**: 1094-1100, 2000.

KOS-KUDLA B, OSTROWSKA Z, MAREK B, CIESIELSKA-KOPACZ N, KUDLA M, KAJDANIUK D, SIEMIDSKA L, STRZELCZYK J: Circadian serum levels of dehydroepiandrosterone sulphate in postmenopausal asthmatic women before and after long-term hormone replacement. *Endocr Regul* **35**: 217-222, 2001.

KUDIELKA BM, HELLHAMMER J, HELLHAMMER DH, WOLF OT, PIRKE KM, VARADI E, PILZ J, KIRSCHBAUM C: Sex differences in endocrine and psychological responses to psychosocial stress in healthy elderly subjects and the impact of a 2-week dehydroepiandrosterone treatment. *J Clin Endocrinol Metab* **83**: 1756-1761, 1998.

KUEBLER JF, JARRAR D, WANG P, BLAND KI, CHAUDRY IH: Dehydroepiandrosterone restores hepatocellular function and prevents liver damage in estrogen-deficient females following trauma and hemorrhage. *J Surg Res* **97**: 196-201, 2001.

LABRIE F, LUU-THE V, LABRIE C, SIMARD J: DHEA and its transformation into androgens and estrogens in peripheral target tissues: intracrinology. *Front Neuroendocrinol* **22**: 185-212, 2001.

LANE MA, INGRAM DK, BALL SS, ROTH GS: Dehydroepiandrosterone sulfate: a biomarker of primate aging slowed by calorie restriction. *J Clin Endocrinol Metab* **82**: 2093-2096, 1997.

LASCO A, FRISINA N, MORABITO N, GAUDIO A, MORINI E, TRIFILETTI A, BASILE G, NICITA-MAURO V, CUCINOTTA D: Metabolic effects of dehydroepiandrosterone replacement therapy in postmenopausal women. *Eur J Endocrinol* **145**: 457-461, 2001.

LAUGHLIN GA, BARRETT-CONNOR E: Sexual dimorphism in the influence of advanced aging on adrenal hormone levels: The Rancho Bernardo Study. *J Clin Endocrinol Metab* **85**: 3561-3568, 2000.

LI H, KLEIN G, SUN P, BUCHAN AM: Dehydroepiandrosterone (DHEA) reduces neuronal injury in a rat model of global cerebral ischemia. *Brain Res* **888**: 263-266, 2001.

MARTEL C, SOURLA A, PELLETIER G, LABRIE C, FOURNIER M, PICARD S, LI S, STOJANOVIC M, LABRIE F: Predominant androgenic component in the stimulatory effect of dehydroepiandrosterone on bone mineral density in the rat. *J Endocrinol* **157**: 433-442, 1998.

MAZAT L, LAFONT S, BERR C, DEBUIRE B, TESSIER JF, DARTIGUES JF, BAULIEU EE: Prospective measurements of dehydroepiandrosterone sulfate in a cohort of elderly subjects: relationship to gender, subjective health, smoking habits, and 10-year mortality. *Proc Natl Acad Sci USA* **98**: 8145-8150, 2001.

MOFFAT SD, ZONDERMAN AB, HARMAN SM, BLACKMAN MR, KAWAS C, RESNICK SM: The relationship between longitudinal declines in dehydroepiandrosterone sulfate concentrations and cognitive performance in older men. *Arch Intern Med* **160**: 2193-2198, 2000.

MORALES AJ, NOLAN JJ, NELSON JC, YEN SS: Effects of replacement dose of dehydroepiandrosterone in men and women of advancing age. *J Clin Endocrinol Metab* **78**: 1360-1367, 1994.

MORFIN R, STÁRKA L: Neurosteroid 7-hydroxylation products in the brain. *Int Rev Neurobiol* **46**: 79-95, 2001.

MORIYAMA Y, YASUE H, YOSHIMURA M, MIZUNO Y, NISHIYAMA K, TSUNODA R, KAWANO H, KUGIYAMA K, OGAWA H, SAITO Y, NAKAO K: The plasma levels of dehydroepiandrosterone sulfate are decreased in patients with chronic heart failure in proportion to the severity. *J Clin Endocrinol Metab* **85**: 1834-1840, 2000.

MUNARRIZ R, TALAKOUB L, FLAHERTY E, GIOIA M, HOAG L, KIM NN, TRAISH A, GOLDSTEIN I, GUAY A, SPARK R: Androgen replacement therapy with dehydroepiandrosterone for androgen insufficiency and female sexual dysfunction: androgen and questionnaire results. *J Sex Marital Ther* **28** (Suppl 1): 165-173, 2002.

NESTLER JE, WHITFIELD JB, WILLIAMS TY, ZHU G, CONDON J, KIRK KM, HEATH AC, MONTGOMERY GW, MARTIN NG: Genetics of serum dehydroepiandrosterone sulfate and its relationship to insulin in a population-based cohort of twin subjects. *J Clin Endocrinol Metab* **87**: 682-686, 2002.

OELKERS W: Dehydroepiandrosterone for adrenal insufficiency. *N Engl J Med* **341**: 1073-1074, 1999.

ORENTREICH N, BRIND JL, VOGELMAN JH, ANDRES R, BALDWIN H: Long-term longitudinal measurements of plasma dehydroepiandrosterone sulfate in normal men. *J Clin Endocrinol Metab* **75**: 1002-1004, 1992.

OSTATNÍKOVÁ D., LAZNIBATOVÁ J, PUTZ Z, MAŤAŠEJE A, DOHNˇANYIOVÁ M, PASTOR K: Biological aspects of intellectual giftedness. *Studia Psychologica* **44:** 3-13, 2002.

OSTROWSKA Z, ZWIRSKA-KORCZALA K, PARDELA M, DROZDZ M, KOS-KUDLA B, BUNTNER B: Circadian variations of androstenedione, dehydroepiandrosterone sulfate and free testosterone in obese women with menstrual disturbances. *Endocr Regul* **32**: 169-176, 1998.

PARASRAMPURIA J, SCHWARTZ K, PETESCH R: Quality control of dehydroepiandrosterone dietary supplement products. *JAMA* **280**: 1565, 1998.

PETRI MA, LAHITA RG, VAN VOLLENHOVEN RF, MERRILL JT, SCHIFF M, GINZLER EM, STRAND V, KUNZ A, GORELICK KJ, SCHWARTZ KE: Effects of prasterone on corticosteroid requirements of women with systemic lupus erythematosus: a double-blind, randomized, placebo-controlled trial. *Arthritis Rheum* **46**: 1820-1829, 2002.

PIEPER DR, LOBOCKI CA: Characterization of serum dehydroepiandrosterone secretion in golden hamsters. *Proc Soc Exp Biol Med* **224**: 278-284, 2000.

PIKETTY C, JAYLE D, LEPLEGE A, CASTIEL P, ECOSSE E, GONZALEZ-CANALI G, SABATIER B, BOULLE N, DEBUIRE B, LE BOUC Y, BAULIEU EE, KAZATCHKINE MD: Double-blind placebo-controlled trial of oral dehydroepiandrosterone in patients with advanced HIV disease. *Clin Endocrinol (Oxf)* **55**: 325-330, 2001.

PINEIRO V, CASABIELL X, PEINO R, LAGE M, CAMINA JP, MENENDEZ C, BALTAR J, DIEGUEZ C, CASANUEVA F: Dihydrotestosterone, stanozolol, androstenedione and dehydroepiandrosterone sulphate inhibit leptin secretion in female but not in male samples of omental adipose tissue in vitro: lack of effect of testosterone. *J Endocrinol* **160**: 425-432, 1999.

PORŠOVÁ-DUTOIT I, ŠULCOVÁ J, STÁRKA L: Do DHEA/DHEAS play a protective role in coronary heart disease? *Physiol Res* **49** (Suppl 1): S43-S56, 2000.

PUIA G, BELELLI D: Neurosteroids on our minds. *Trends Pharmacol Sci* **22**: 266-267, 2001.

RABKIN JG, FERRANDO SJ, WAGNER GJ, RABKIN R: DHEA treatment for HIV+ patients: effects on mood, androgenic and anabolic parameters. *Psychoneuroendocrinology* **25**: 53-68, 2000.

RAVAGLIA G, FORTI P, MAIOLI F, BOSCHI F, BERNARDI M, PRATELLI L, PIZZOFERRATO A, GASBARRINI G: The relationship of dehydroepiandrosterone sulfate (DHEAS) to endocrine-metabolic parameters and functional status in the oldest-old. Results from an Italian study on healthy free-living over-ninety-year-olds. *J Clin Endocrinol Metab* **81**: 1173-1178, 1996.

REITER WJ, PYCHA A, SCHATZL G, POKORNY A, GRUBER DM, HUBER JC, MARBERGER M: Dehydroepiandrosterone in the treatment of erectile dysfunction: a prospective, double-blind, randomized, placebo-controlled study. *Urology* **53**: 590-594, 1999.

RICHARDS RJ, PORTER JR, SVEC F: Serum leptin, lipids, free fatty acids, and fat pads in long-term dehydroepiandrosterone-treated Zucker rats. *Proc Soc Exp Biol Med* **223**: 258-262, 2000.

RICHARDS RJ, PORTER JR, INSERRA F, FERDER LF, STELLA I, REISIN E, SVEC F: Effects of dehydroepiandrosterone and quinapril on nephropathy in obese Zucker rats. *Kidney Int* **59**: 37-43, 2001.

RIGAUD AS, PELLERIN J: Neuropsychic effects of dehydroepiandrosterone. *Ann Med Interne (Paris)* **152** (Suppl 3): IS43-IS49, 2001.

SAN MARTIN M, TOUITOU Y: DHEA-sulfate causes a phase-dependent increase in melatonin secretion: a study of perifused rat pineal glands. *Steroids* **65**: 491-496, 2000.

STRAUB RH, KONECNA L, HRACH S, ROTHE G, KREUTZ M, SCHOLMERICH J, FALK W, LANG B: Serum dehydroepiandrosterone (DHEA) and DHEA sulfate are negatively correlated with serum interleukin-6 (IL-6), and DHEA inhibits IL-6 secretion from mononuclear cells in man in vitro: possible link between endocrinosenescence and immunosenescence. *J Clin Endocrinol Metab* **83**: 2012-2017, 1998.

STRAUB RH, SCHOLMERICH J, ZIETZ B: Replacement therapy with DHEA plus corticosteroids in patients with chronic inflammatory diseases-substitutes of adrenal and sex hormones. *Z Rheumatol* **59** (Suppl 2): II-108-II-118, 2000.

ŠULCOVÁ J, HILL M, HAMPL R, STÁRKA L: Age and sex related differences in serum levels of unconjugated dehydroepiandrosterone and its sulphate in normal subjects. *J Endocrinol* **154**: 57-62, 1997.

ŠULCOVÁ J, HILL M, MAŠEK Z, ČEŠKA R, NOVÁČEK A, HAMPL R, STÁRKA L: Effects of transdermal application of 7-oxo-DHEA on the levels of steroid hormones, gonadotropins amd lipids in healthy men. *Physiol Res* **50**: 9-18, 2001

THOMAS G, FRENOY N, LEGRAIN S, SEBAG-LANOE R, BAULIEU EE, DEBUIRE B: Serum dehydroepiandrosterone sulfate levels as an individual marker. *J Clin Endocrinol Metab* **79**: 1273-1276, 1994.

TISSANDIER O, PERES G, FIET J, PIETTE F: Testosterone, dehydroepiandrosterone, insulin-like growth factor 1, and insulin in sedentary and physically trained aged men. *Eur J Appl Physiol* **85**: 177-184, 2001.

TRIVEDI DP, KHAW KT: Dehydroepiandrosterone sulfate and mortality in elderly men and women. *J Clin Endocrinol Metab* **86**: 4171-4177, 2001.

VAN VOLLENHOVEN RF: Dehydroepiandrosterone for the treatment of systemic lupus erythematosus. *Expert Opin Pharmacother* **3**: 23-31, 2002.

WANG MJ, HUANG HM, CHEN HL, KUO JS, JENG KC: Dehydroepiandrosterone inhibits lipopolysaccharide-induced nitric oxide production in BV-2 microglia. *J Neurochem* **77**: 830-838, 2001.

WEKSLER ME: Hormone replacement for men. *Br Med J* **312**: 859-860, 1996.

WILLIAMS MRI, LING S, DAWOOD T, HASHIMURA K, DAI A, LI H, LIU JP, FUNDER JW, SUDHIR K, KOMESAROFF PA: Dehydroepiandrosterone inhibits human vascular smooth muscle cell proliferation independent of ARs and ERs. *J Clin Endocrinol Metab* **87**: 176-181, 2002.

WIT JM, LANGENHORST VJ, JANSEN M, OOSTDIJK WA, VAN DOORN J: Dehydroepiandrosterone sulfate treatment for atrichia pubis. *Horm Res* **56**: 134-139, 2001.

WOLF OT, NEUMANN O, HELLHAMMER DH, GEIBEN AC, STRASBURGER CJ, DRESSENDORFER RA, PIRKE KM, KIRSCHBAUM C: Effects of a two-week physiological dehydroepiandrosterone substitution on cognitive performance and well-being in healthy elderly women and men. *J Clin Endocrinol Metab* **82**: 2363-2367, 1997.

YEN SS: Dehydroepiandrosterone sulfate and longevity: new clues for an old friend. *Proc Natl Acad Sci USA* **98**: 8167-8169, 2001.

ZWAIN IH, YEN SSC: Dehydroepiandrosterone: biosynthesis and metabolism in the brain. *Endocrinology* **140**: 880-887, 1999.

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