Review Article (Mini-Review)

DEHYDROEPIANDROSTERONE (DHEA): PHARMACOLOGICAL EFFECTS AND POTENTIAL THERAPEUTIC APPLICATION

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ABSTRACT

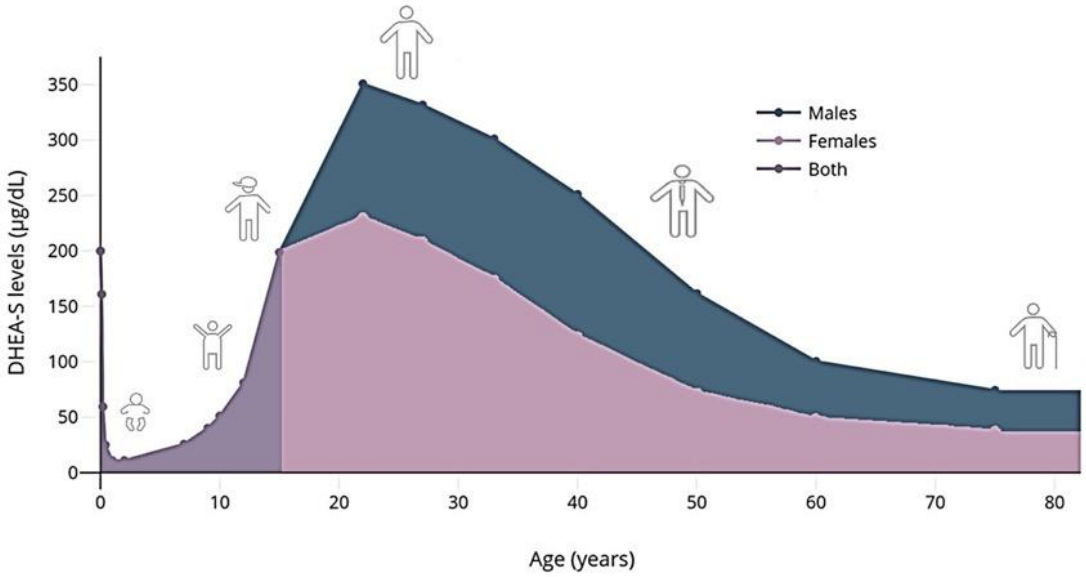
Dehydroepiandrosterone (DHEA) is the most abundant steroid hormone in primates, which is predominantly synthesized in the adrenal cortex. A characteristic curve of growth and decline of its synthesis during life was observed, together with the corresponding formation of its sulphate ester (DHEAS). High levels of plasma circulating DHEA are suggested as a marker of human longevity, and various pathophysiological conditions lead to a decreased DHEA level, including adrenal insufficiency, severe systemic diseases, acute stress, and anorexia. More recent studies have established importance of DHEA in the central nervous system (CNS). A specific intranuclear receptor for DHEA has not yet been identified; however, highly specific membrane receptors have been detected in endothelial cells, the heart, kidney, liver, and the brain. Research

shows that DHEA and DHEAS, as well as their metabolites, have a wide range of effects on numerous organs and organ systems, which places them in the group of potential pharmacological agents useful in various clinical entities. Their action as neurosteroids is especially interesting, due to potential neuroprotective, pro-cognitive, anxiolytic, and antidepressant effects. Evidence from clinical studies supports the use of DHEA in hypoadrenal individuals, as well as in the treatment of depression and associated cognitive disorders. However, there is also an increasing trend of recreational DHEA misuse in healthy people, as it is classified as a dietary supplement in some countries. This article aims to provide a critical review regarding the biological and pharmacological effects of DHEA, its mechanism of action, and potential therapeutic use, especially in CNS disorders.

Keywords: Dehydroepiandrosterone, biosynthesis, pharmacology, neurosteroid, supplementation, therapy.

GRAPHICAL ABSTRACT:

DHEAS concentrations during life



1. INTRODUCTION

Dehydroepiandrosterone (DHEA) is a steroid hormone secreted by the adrenal glands, the paired endocrine organs composed of the adrenal cortex and medulla. *Zona reticularis*, a part of the adrenal cortex, has been shown to be the main site of human DHEA origin; however, 10-20% of this steroid is produced by the gonads (ovarian theca cells, Leydig cells in the testes) [1]. Various studies have revealed other extra–adrenal sites of DHEA synthesis, primarily the central nervous system (CNS), where its concentrations are 6-8 times higher than in peripheral blood [2], which is the reason why DHEA is referred to as a neurosteroid [3, 4].

However, certain authors do not consider DHEA as a hormone, but as an essential prohormone of sex steroids that is excreted from the adrenal glands in humans and other primates [5]. The major tissues associated with DHEA metabolism include ovaries, testes, placenta, prostate, liver, adipose tissue, and CNS [6]. Specifically, enzymes necessary for the DHEA transformation into androgens and/or estrogens are present in the cells of many tissues, allowing androgen- and estrogen-sensitive tissues to regulate the concentrations of sex hormones depending on the local tissue needs [5]. This new area of endocrinology, named intracrinology, represents an important aspect to be considered in the pharmacokinetics of DHEA [7].

The observed age-related decline in DHEA has been associated with dysregulation in body composition, as well as in cognitive functions and mood [8, 9]. In addition, there is also a substantial body of evidence reporting that DHEA levels highly correlate with longevity of healthy primates [10]. The important role of DHEA is emphasized in a recently published meta-analysis, demonstrating an association of low levels of circulating DHEAS, a sulphated form of DHEA, with a general mortality risk in the older population [11].

PHYSIOLOGICAL CONCENTRATIONS OF DHEA LIFE

It has been estimated that plasma levels of DHEA and DHEAS (DHEA/S) in adult men and women are 100–500 times higher than testosterone levels and even 1000–10,000 times higher than estradiol levels [5]. The ratio of circulating DHEAS to DHEA is 1000:1 [12], but the levels of both steroids are gender- and age-dependent, demonstrating lower levels in women than in men [13]. Plasma DHEA/S concentrations are high during the fetal period, ranging from 100–200 μg/dL (3–7 μM), but drop rapidly after birth and remain low until adrenarche, an early stage in

sexual maturation, characterized by the rise in adrenal androgens [14]. Specifically, around 7–10 years of age, the levels of DHEA/S start to rise [15, 16], and they reach their maximum levels of approximately 10 μM for men and 5 μM for women between 20 and 30 years of age. Furthermore, the circulating levels of DHEA/S steadily decrease with a rate of 2% per year [17]. DHEA concentrations range from 1.33 ng/mL to 7.78 ng/mL between 18 and 40 years of age and between 0.63 ng/mL and 4.7 ng/mL after the age of 40, for both sexes [18]. At the age of 70, serum DHEA/S levels decline to approximately 20% of their highest values and can be reduced even by 95% at the age of 85-90 [5, 13]. This phenomenon of age-related DHEA/S decline with preserved cortisol secretion has been referred to as "adrenopause" [18].

Some authors suggest that a decrease in the activity of 17,20-lyase, which converts 17-hydroxypregnenolone to DHEA, may be responsible for a dramatic decrease of DHEA/S production during life [19]. The role of DHEA/S in the peripheral production of sex hormones is more important in women than in men, since androgen excretion by the testes remains at a high level throughout life, whereas estrogen excretion by the ovaries completely stops during menopause, leaving the adrenal glands as the only source of sex steroids in women. Specifically, in premenopausal women, approximately 75% of all estrogens are produced intracrine in peripheral tissues; however, their intracrine production reaches close to 100% in women after menopause [20].

High levels of plasma circulating DHEA are suggested as a marker of human longevity [10], since the longest life expectancy has been observed in the population with the highest DHEA levels, and healthier people have been demonstrated to express higher levels of DHEA [21]. In addition to ageing, various pathophysiological conditions can lead to a decrease in the DHEA levels in the circulation, including adrenal insufficiency, severe systemic diseases, acute stress, and anorexia. Specifically, in subjects with adrenal gland insufficiency there is a chronic deficit of DHEA; therefore, DHEA supplementation has been recommended following optimal glucocorticoid and mineralocorticoid substitution [22]. In contrast, DHEA levels may be elevated in individuals with hyperprolactinaemia [23].

DHEA BIOSYNTHESIS

DHEA and DHEAS are the two main steroids secreted by the adrenal gland's *zona reticularis*. They are, like the rest of the C19 steroids, products of cholesterol side-chain cleavage under the action of CYP11A1 (cytochrome P-450scc) [24]. To be specific, primates produce DHEA using the delta5-steroidogenic pathway (**Figure 1**). In this process, CYP11A1 catalyzes the transformation of cholesterol to pregnenolone, which is then hydroxylated into 17-hydroxypregnenolone, and converted to DHEA by CYP17A1 (cytochrome P450c17) [19, 25]. Some authors have suggested that an observed decrease in DHEA levels with age is associated with a lower activity of 17-alpha-hydroxyprogesterone aldolase [26]. However, this assumption has yet to be confirmed.

DHEA is mainly found in the circulation as DHEA-3beta-sulfate (DHEAS), which can be converted to DHEA by the action of DHEA-sulfotransferase and hydroxysteroid sulfatase [27]. Unlike DHEA, the active form used in the synthesis of steroid hormones, DHEAS is not bound to sex hormone binding globulin (SHBG) and represents the hydrophilic form that circulates free in the blood [21]. DHEA and DHEAS both bind to plasma albumin. Due to the weaker binding to albumin compared to DHEAS, DHEA is rapidly removed from the circulation with an elimination half-time ($t_{1/2}$) of 1 to 3 hours [21]. The metabolic clearance rate of DHEA (circa 2400 L/24h) is 240 times higher than the metabolic clearance rate of DHEAS (approximately 10 L/24h) [28]. Consequently, DHEAS is eliminated from the circulation very slowly, with a $t_{1/2}$ of 13.7 h. This slow elimination is mainly due to its strong binding to serum albumin and its renal tubular reabsorption, resulting in low variations of DHEAS levels in the plasma [29]. Although DHEA and DHEAS are often referred to as weak androgens, as they exhibit little or no androgenic activity, there is no clear evidence that they bind to androgen receptors [30].

HUMAN PHARMACOKINETIC STUDIES OF EXOGENOUSLY ADMINISTERED DHEA

Despite numerous research indicating multiple positive effects of DHEA/S as a potential therapeutic agent, as well as the fact that it is used as a supplement in some countries, there are not many studies that have addressed its pharmacokinetics. Studies in humans have shown different intracrine patterns in men and women after DHEA administration, with serum androgen levels in

women and estrogen levels in men generally increasing after DHEA administration [18]. However, it is almost impossible to precisely measure end hormone products after DHEA administration, since peripheral hormone levels do not always correspond to tissue levels of intracrine hormones. Besides, other DHEA-derived products, which may also have androgenic and estrogenic characteristics, are not taken into consideration when determining peripheral steroids [18].

A single-blind, placebo-controlled study conducted on healthy older subjects of both sexes, demonstrated pharmacokinetic differences of DHEA according to sex, after its single and repeated dose of 200 mg *per os* [31]. The application of DHEA resulted in higher values of C_{max} (maximum serum concentration) and AUC (area under the curve) in women in all periods of the study, probably due to the differences in body weight between males and females. The DHEAS concentrations achieved after DHEA administration were equivalent in women and men, even though women had only 25% of the values of endogenous DHEAS present in men, suggesting an increase in the DHEAS levels by 21 times in women and only 5 times in men. The concentrations of DHEA and DHEAS achieved after the first dose of DHEA were the same as after the 15^{th} dose in both sexes. However, during the 15-day application of DHEA, the middle $t_{1/2}$ of DHEA in women decreased from 11.7 to 6.9 hours, whereas in men the values of $t_{1/2}$ were stable and ranged around 8 hours [31].

Legrain et al. (2000) demonstrated that after the oral DHEA administration (50 mg and 25 mg) to persons of older age, the half-time of both DHEA and DHEAS elimination was longer than 20 hours, probably due to the reverse hydrolysis of large amounts of newly formed DHEAS. Moreover, the metabolic conversion of DHEAS to DHEA was significantly higher in women than in men. Since no steroid accumulation and no significant transformation of DHEA to androgens and estrogens were detected, the obtained results suggest that daily oral application of the investigated doses of DHEA is safe in elderly subjects [32].

The main metabolites of DHEA/S are androstenedione (Δ 4-androstenedine-3,17-dione), 5alpha-androstenedione, testosterone, 5alpha-dihydrotestosterone (DHT) and androstanediolglucuronide (ADG), as the final metabolic product. The enzymes involved in the metabolic pathway are 3β-hydroxysteroid dehydrogenase, 5alpha-reductase, 17β-hydroxysteroid oxidoreductase, 3α-hydroxysteroidoxidoreductase and glucuronotransferase. Furthermore, under the action of aromatase, androstenedione can be converted into estrone, and testosterone into

estradiol [32]. Mo et al. (2005) also included 7alpha-OH-DHEA, 7beta-OH-DHEA, and 7-oxo-DHEA as DHEA metabolites that show minimal androgenic activity [33].

In a prospective, randomized, double-blind, placebo-controlled study conducted on healthy young men, Acacio et al. (2004) measured serum levels of DHEA and its metabolite levels on day one, 3 months and 6 months after the administration of lower (50 mg/day) and higher (200 mg/kg) DHEA dose. Long-term daily oral intake of DHEA resulted in a significant and permanent increase of basal DHEA, DHEAS and 5-androstane-3-17-diol glucuronide (ADG) levels, but no changes in the levels of estradiol (E2), testosterone (T) and dihydrotestosterone (DHT). This is probably due to the transformation of DHEA into other metabolites (e.g., androsterone and etiocholanolone), and the rapid conversion of serum DHT into more stable ADG. During application of DHEA in a high dosage, a decrease in its basal levels has been observed from the third month of application onward, suggesting an adaptation to DHEA supplementation, which is reflected in the increased clearance of unconjugated steroid hormones by the activated sulfuryl- or glucuronyltransferase [34]. Unlike estrone and estradiol levels, daily serum concentrations of androstenedione, testosterone, DHEAS, estrone-S, androsterone glucuronide (ADT-G) and 3alpha-androstanediol-G (3alpha-diol-G) in serum increased during a 14-day administration of DHEA to postmenopausal women in different formulations (oral capsule, cream, and gel) [35].

In another study by Labrie et al. (2008), performed in healthy postmenopausal women, percutaneous administration of DHEA (3 g of 0.3% emulsion, twice a day) over a 12-month period resulted in an increased serum levels of DHEA and androst-5-en-3beta, 17beta-diol (5-diol) (by 203% and 178%, respectively). In addition, the sum of the concentrations of androgen metabolites, ADT-G, androstane-3alpha, 17beta-diol-3G and -17G, increased by 71% over a 12-month period of DHEA treatment, whereas the observed changes for estrone, estradiol and estrone-sulphate levels (30%, 17% and 20%, respectively) were not statistically significant. Therefore, the applied regimen of DHEA supplementation returned the serum DHEA concentration to its premenopausal levels and maintained its pharmacokinetics stable over a 12-month period, without significantly influencing the activity of enzyme systems that predominantly transform DHEA into androgens [36].

PHARMACOLOGICAL EFFECTS OF DHEA

Specific intranuclear receptor for DHEA has not yet been identified. However, the presence of peripheral highly specific membrane receptors on endothelial cells, heart, kidneys, and liver, to which DHEA binds with high affinity, has been detected [18]. Studies using animal and human models show that DHEA increases the production of nitrogen monoxide (NO) in endothelial cells *in vitro,* most likely through G-protein-dependent activation of endothelial NO-synthase (eNOS) and intracellular cyclic guanosine monophosphate (cGMP) (eNOS/cGMP pathway) [18]. In addition, some DHEA derivatives, such as 7alpha- and 7beta-hydroxylatedmetabolites, exert a direct effect on the nuclear receptor, although their function is still not clarified [37].

Numerous pharmacological effects of DHEA have been reported, **Table 1**. In cardiovascular disease (CVD), lower DHEA levels have been associated with greater coronary artery stenosis and fatal myocardial infarction in men [18]. Published evidence suggests that an increase in DHEA levels may reduce the process of atherosclerosis and coronary artery stenosis [17]. Some findings also demonstrate that DHEA and androgens, through genomic and/or non-genomic pathways, have a significant effect on endothelial cell proliferation and migration, vascular contractility, and endothelial pathological processes, such as inflammation, atherosclerosis, and clot formation [38]. In addition, Savineau et al. (2013) observed that DHEA acts as an anti-remodeling and vasorelaxant agent in CVD [39], whereas Wang et al. (2020) noted a neutral effect of DHEA supplementation on blood pressure [40]. These findings are in line with the results of a meta-analysis showing lower levels of DHEAS as a poor prognostic marker for patients with CVD [41].

Moreover, DHEA has been reported to reduce body fat, without significant changes in the diet. Specifically, the study by Wang et al. (2020) demonstrated that supplementation with DHEA increased muscle mass and reduced the percentage of fat tissue [40], possibly by blocking the glucose-6-phosphate dehydrogenase, an important enzyme in lipid synthesis, and affecting the usage of lipids and carbohydrates [17].

Low levels of DHEA have been associated with insulin resistance and type 2 diabetes [42]. DHEA/S beneficial effects on diabetes mellitus and obesity have been observed in animal models [43]. These steroids do not only increase insulin secretion, but also elevate the insulin sensitivity of the liver, adipose tissue, and muscle [43]. By using an animal model, Aoki et al. (2018) have

found reduced hepatic gluconeogenesis under the influence of DHEA [43]. In addition, one meta-analysis revealed that DHEA reduces the level of glycaemia, but no association has been determined between the use of DHEA and the level of insulin and insulin resistance [44].

There are reports regarding the link between DHEA and aging, and some studies even suggested that serum levels of DHEAS better reflect age than the health condition of the subjects [45, 46]. Various immunomodulatory and anti-inflammatory properties are often attributed to DHEA [47]. For instance, possible positive effects of DHEA on the course of bronchial asthma disease, especially when it was administered in combination with *Bacillus Calmette Guerin* (BCG) vaccine, have been observed in the study using an animal model [47]. There are also studies demonstrating that DHEA can improve immune function, especially in the elderly [17]. Specifically, available research suggests that DHEA may enhance the antibody production and activity of monocytes, NK, and immune cells, as well as anticancer function of T lymphocytes [17]. In older animals, DHEA has restored the cytokine levels characteristic of younger age and reduced auto-antibody production [17]. In addition, some studies have positively correlated 7-alpha-hydroxy-DHEA with the immune response, in terms of increased production of immunoglobulin G (IgG), and enhanced and prolonged immune response [48]. Furthermore, DHEA has increased antioxidant enzyme activity, improved NO content, and elevated the level of TNF-alpha expression in macrophages, as well as promoted a shift in the balance of Th1/ Th2 towards Th1-dominant immunity both *in vivo* and *in vitro* [49].

Based on the literature reporting a decrease in serum DHEAS levels with the progression of HIV infection [50], Piketty et al. (2001), in a double-blind, randomized, placebo-controlled study demonstrated that DHEA supplementation improved the score of mental function and mental health in patients with advanced HIV infection [50]. In this study, there was no change in the number of CD4 cells and no side effects, which were associated with the application of DHEA [50]. DHEA/S has also been studied in patients with malignant diseases [51]. The results of a recently published study showed that, when compared to healthy subjects, patients with non-microcellular lung cancer after chemotherapy had lower salivary concentrations of DHEA/S, which were associated with higher rates of patient fatigue and depression [51]. In addition, DHEA has been suggested to prevent the initiation and promotion of the carcinogenesis process, probably due to the inhibition of glucose-6-phosphate dehydrogenase [52].

Animal research demonstrated the immunomodulatory effects of DHEA [53], initiating the examination of its role in human autoimmune diseases [54, 55, 56]. Some studies reported that the application of DHEA in women with systemic lupus erythematosus (SLE) reduced the activity of the disease [54]. Moreover, serum DHEAS levels were lower in female patients with active SLE than in those with an inactive chronic form of the disease [55]. However, oral DHEA application at a dose of 200 mg per day did not affect the fatigue and the quality of life in patients with stable SLE; therefore, its use is not recommended in such cases [56].

In a mouse model of experimental colitis, DHEA reduced oxidative damage, inhibited the production of proinflammatory cytokines, protected colon barrier integrity, and influenced the regulation of the intestinal microbiota [57]. Lower DHEA levels observed in the serum of patients with inflammatory bowel disease (IBD) [58], as well as the positive effects of DHEA on disease remission in most patients with IBD [59], strongly link DHEA with this disease.

Certain hormones, whose secretion decreases with age, including DHEA, might be associated with the development of sarcopenia, characterized by the progressive and generalized loss of skeletal muscle mass [60]. Similarly, lower serum DHEAS levels were detected in patients with myotonic dystrophy, suggesting that DHEA substitution could improve muscle weakness [61]. Indeed, the use of DHEA has been shown to significantly increase muscle and bone mass [62]. Specifically, skeletal muscle can synthesize androgens and estrogens from circulating DHEA, which then increase muscle mass and strength [63]. This is supported by the findings on the existence of two DHEA binding sites on skeletal muscle cells [61]. In addition, the study by Villareal et al. (2006) indicated that in the elderly, DHEA substitution has a beneficial effect on the rate of increase in muscle mass and strength, when used together with the physical activity [64].

Studies have shown a significant association between DHEA and increased bone mineral density (BMD), probably due to the ability of DHEA to increase osteoblast activity and the expression of insulin-like growth factor-1 (IGF-1), which has a positive effect on BMD and bone fracture healing [65]. This is particularly important for women, who have a 51% higher risk of fracture after 50 years of age, in comparison to the 20% higher risk in men, and several studies have confirmed the positive, although relatively weak, effect of DHEA application on BMD [18]. Due to its chondroprotective effects in osteoarthritis (OA), DHEA has been suggested as a

potential disease-modifying OA drug (DMOAD) that slows the progression of the disease [66]. Specifically, DHEA positively modulates the balance between anabolic and catabolic factors in cartilage and chondrocytes, blocks catabolic signaling pathways, and suppresses the synovial inflammation mediated by proinflammatory cytokines [66].

The study by Rutkowski et al. (2014) demonstrated that DHEA improves sexual satisfaction and fertility in women and relieves vaginal atrophy often occurring in the older age [59]. Lin et al. (2021) reported that the serum DHEA levels are positively related to serum anti-mullerian hormone (AMH) [67], which represents one of the parameters indicating the ovary reserve [67]. In women with reduced ovarian reserve, DHEA administration improved ovulation, both in basal conditions and in the process of ovulation induction [68]. In addition, the results of the latest meta-analysis supported the use of DHEA supplementation to increase testosterone levels in older women [61], although this effect varies among different subgroups [69]. This effect of DHEA is especially important, considering the beneficial role of testosterone on the cardiovascular function, cognitive performance, musculoskeletal health, and libido in postmenopausal women [70]. On the other hand, in men, DHEA exerts positive effects on the ability to achieve an erection, and reduced serum DHEA levels have been observed in men with erectile dysfunction [17]. However, DHEA does not appear to improve erectile dysfunction caused by diabetes or neurological disorders [17].

DHEA AS A NEUROSTEROID

There are multiple effects of DHEA observed in the CNS [71]. DHEA/S possesses neuroprotective properties, improves neuronal “plasticity”, demonstrates antioxidative and anti-inflammatory effects, modulates mood, emotions, behavior, memory and cognitive functions, and exerts beneficial effects in the prevention and treatment of various aging-associated disorders and neuropsychiatric diseases [72]. In addition, some studies demonstrated that changes in serum DHEA concentrations might be involved in the pathophysiology of schizophrenia and some of its manifestations [73]. Significantly reduced levels of DHEA were found in female patients with schizophrenia and metabolic syndrome compared to healthy female subjects; however, these findings were not observed in male subjects [74]. Furthermore, the role of neurosteroids such as pregnanolone, allopregnanolone, pregnenolone, dehydroepiandrosterone, and their sulphate esters in anxiety and emotional disturbances, as well as learning and memory, has been suggested [75].

DHEA/S anti-amnestic and anxiolytic properties have been reported [17], and decreased DHEA levels have been associated with depressive symptomatology [18]. Recent animal study has shown that DHEA may have a beneficial effect in the treatment of depression and associated cognitive disorders [76]. However, the administered dose should be taken into consideration, due to the lack of effect at very low, as well as too high doses of DHEA [76]. The importance of administered DHEA dose is also emphasized in the work of Fedotova and Sapronov (2004), demonstrating significantly decreased locomotor activity and increased anxiety-like behavior in male rats treated with low dose of DHEA, whereas administration of DHEA in high doses produced an anxiolytic effect [77].

Recent findings suggested that DHEA could play an important role in the development of specific areas of the human brain, especially between the 4^{th} and 12^{th} years of life [78]. However, to date, studies investigating the role of DHEA in neurodegenerative diseases have yielded conflicting results [17, 72]. Specifically, some authors observed a decrease in the serum DHEA levels and the beneficial effect of administered DHEA in Alzheimer disease (AD), whereas other studies have not confirmed these findings [17, 72]. *In vitro* studies using human neural cells have shown a neurotrophic and neuroprotective effect of DHEA and its metabolites [18], whereas in clinical studies, DHEA levels have been associated with better executive function and a higher score on the *Mini Mental State Examination* (MMSE) scale [18]. Moreover, decreased concentrations of DHEAS have been suggested as an important indicator of AD, but their use as a diagnostic parameter for this disease requires further research [72, 79].

Various *in vivo* and *in vitro* studies investigating prolonged DHEAS treatment have been described in the literature [80]. It should be emphasized that *in vivo* methodology is essential to assess the pharmacological effect of DHEAS and its possible application in clinical studies [81]. From the aspect of studying DHEAS as a neurosteroid, special mention should be made of its effect on gamma-amino butyric acid (GABA) and glutamate neurotransmission, whose balance plays an important role in the normal functioning of the brain [82]. Considering the antagonistic effect of DHEAS on $GABA_A$ receptors, and its facilitating action on the glutamatergic system, which both may result in an increased brain excitability and seizures, a recent animal study demonstrated that treatment with DHEAS might be safe in adult and older mice of both sexes [83]. This was also suggested by the findings that DHEAS does not induce adaptive changes in $GABA_A$

receptor expression and functional coupling, which underlie the development of tolerance and dependence [84].

In addition to binding to $GABA_A$ receptors, DHEA is an agonist of central sigma-1 receptors, whose activation indirectly positively modulates the N-methyl-D-aspartate (NMDA) receptors and potentiates glutamatergic activity [85]. Moreover, DHEA/S interacts with the serotonin and dopamine neurotransmitter systems [86] and attenuates norepinephrine function [87]. In addition, this neurosteroid binds to the microtubule-associated protein 2 (MAP2) [88], but also to other receptors, such as the membrane DHEA binding sites (mDBS) [89], plasma membrane receptor tropomyosin receptor kinase (Trk) -A and p75 neurotrophin receptor (p75NTR) [90].

DHEA/S positive effect on neurogenesis, neuronal survival, and neuroplasticity has been probably achieved by acting on amino acid ionotropic receptors (glutamate, $GABA_A$ and sigma-1 receptors), which together with cytoskeleton proteins (such as MAP) affect neuroplasticity [91, 92]. Administration of DHEA/S has been suggested to stimulate the mobility and growth of neurons [93], with DHEA inducing the growth of axonal neurites, and DHEAS of neurites with dendritic markers [94].

Research on DHEA demonstrated that its antioxidative action is both dose- [95] and tissue-dependent [96]. Slightly elevated concentrations of this neurosteroid neutralize lipid peroxidation [95], reflecting an oxidative stress in the CNS [97], while a physiological dose of DHEA has a pro-oxidative effect [95]. The type of tissue to which DHEA is administered might also influence whether it will exhibit anti- or pro-oxidative action [96]. By acting on sigma receptors, DHEA/S reduces excitotoxicity [98, 99], resulting from an excessive intracellular calcium overload through NMDA receptors [100]. Other potential mechanisms of DHEA/S neuroprotective effects include modulation of GABA activity [84], reduction of proinflammatory cytokines levels [101], and increase in a glucose uptake [102].

Analysis of post-mortem brains from patients with AD found elevated levels of DHEA, predominantly in the hippocampus, but also in other parts of the brain, including the prefrontal cortex and hypothalamus [103]. Such a finding was also obtained in cerebrospinal fluid (CSF) [103]. Elevated DHEA in the brain of AD patients might be related to the presence of amyloid-beta plaques and increased oxidative stress [103]. On the other hand, some postmortem studies

demonstrated reduced concentrations of DHEAS in the brain and CSF of patients with AD, while its negative relationship with hyperphosphorylated tau levels was observed in the hypothalamus [104]. In cell culture experiments, DHEA/S was shown to increase specifically both synthesis and secretion of the amyloid precursor protein (APP) [105], and therefore might be involved in the regulation of the relative utilization of different APP processing pathways affecting the accumulation of amyloid-beta plaques in AD. Moreover, DHEA has been suggested to exert a protective effect against amyloid-beta protein-induced toxicity via the sigma-1 receptor [106].

The ability of DHEA and DHEAS to maintain the redox homeostasis allows them to affect the phosphorylation of tau protein [107], whose abnormal hyperphosphorylation and aggregation in AD lead to neurodegeneration and destabilization of microtubules structures [108, 109]. Cognition impairment in AD might be due to a decreased acetylcholine (ACh) synthesis and choline acetyltransferase activity [110, 111]. Specifically, neuronal degeneration in the hippocampus and cortex, which correlates with the number of amyloid-beta plaques and tau protein hyperphosphorylation, reduces the function of choline acetyltransferase in these brain regions [111, 112]. Several findings indicated that DHEA/S improves memory and cognition by acting as a $GABA_A$ receptor inhibitor, given the ability of GABA to modulate the ACh system [72]. However, the role of DHEA/S in cognitive function remains unclear. Some studies have not observed DHEA/S pro-cognitive effects in healthy non-dementia individuals [113, 114, 115], or perimenopausal women [116]. On the other hand, Wolf et al. [117] demonstrated improved attention, but not memory after the administration of DHEA in elderly subjects. Increased DHEA levels in the morning and evening have been correlated with a lower confusion and anxiety, respectively, whereas elevated morning cortisol/DHEA ratio was associated with a higher confusion and decreased visual spatial memory [118]. Although in AD patients, treatment with DHEA had no significant effect on cognition [119], in women with mild and moderate cognitive impairment, an improvement in cognitive scores has been observed after DHEA supplementation [120]. Considering that most studies to date have limitations due to a small sample size, frequent dropout, and small statistical power, large controlled randomized clinical trials are needed in the future to elucidate the benefits of DHEA/S as a potential therapeutic agent in AD.

CONCLUSION

DHEA is the most abundant steroid hormone in primates, which is predominantly synthesized in the adrenal cortex, while more recent studies have established its importance in the CNS. A characteristic curve of growth and decline in DHEA synthesis during life has been observed, together with the characteristic formation of its sulphate ester, which represents a "depot" of this steroid in the circulation. Isoenzymes from the human 3beta- and 17beta-hydroxysteroid dehydrogenase systems, as well as the catabolic enzyme UDP-glucuronyltransferase, are involved in the process of DHEA biosynthesis and catabolism. In previous studies, elevated DHEA and DHEAS levels were observed in both sexes after DHEA application. However, various studies recorded different values of the indicated increase, due to variations in the study design, dose, duration, and route of DHEA administration, as well as the monitoring method.

Previous research has shown that DHEA and DHEAS, as well as their metabolites, possess a wide range of pharmacological effects, such as anti-inflammatory, and pro-immune actions, as well as anti-diabetic, anti-obesity, anti-carcinogenic, anti-atherosclerosis, anti-osteoporosis, anti-aging, and various other effects. Due to these properties, they belong to the group of potential pharmacological agents targeting different clinical entities. DHEA/S exerts positive effects in various health conditions, including ischemic heart disease, disturbed endothelial function and atherosclerosis process, insulin resistance, type 2 diabetes and obesity, loss of muscle mass and bone mineral density, bronchial asthma, SLE and IBD, as well as during the process of the carcinogenesis. Their role as neurosteroids is particularly interesting, and it is manifested by neuroprotective, pro-cognitive, anxiolytic and antidepressant effects, suggesting their therapeutic potential in a variety of neuropsychiatric and neurodegenerative disorders, including depression, anxiety, schizophrenia, PTSD, addiction and AD.

Therefore, the evidence provided by clinical studies supported the application of DHEA in hypoadrenal individuals. In addition, a rising trend of recreational (mis)use of DHEA in healthy individuals has been observed, especially by bodybuilders aiming to increase their muscle mass. However, it should be emphasized that to date most studies investigating DHEA/S were performed *in vitro* or using animal models, and usually recorded responses to supra-physiological doses of DHEA. Finally, the quality of DHEA preparations on the market does not undergo the strict control

prescribed for the medicines, as they are considered as dietary supplements. Therefore, making a final position on the potential use of DHEA supplementation in the prevention or treatment of various health conditions requires extensive clinical studies in the future.

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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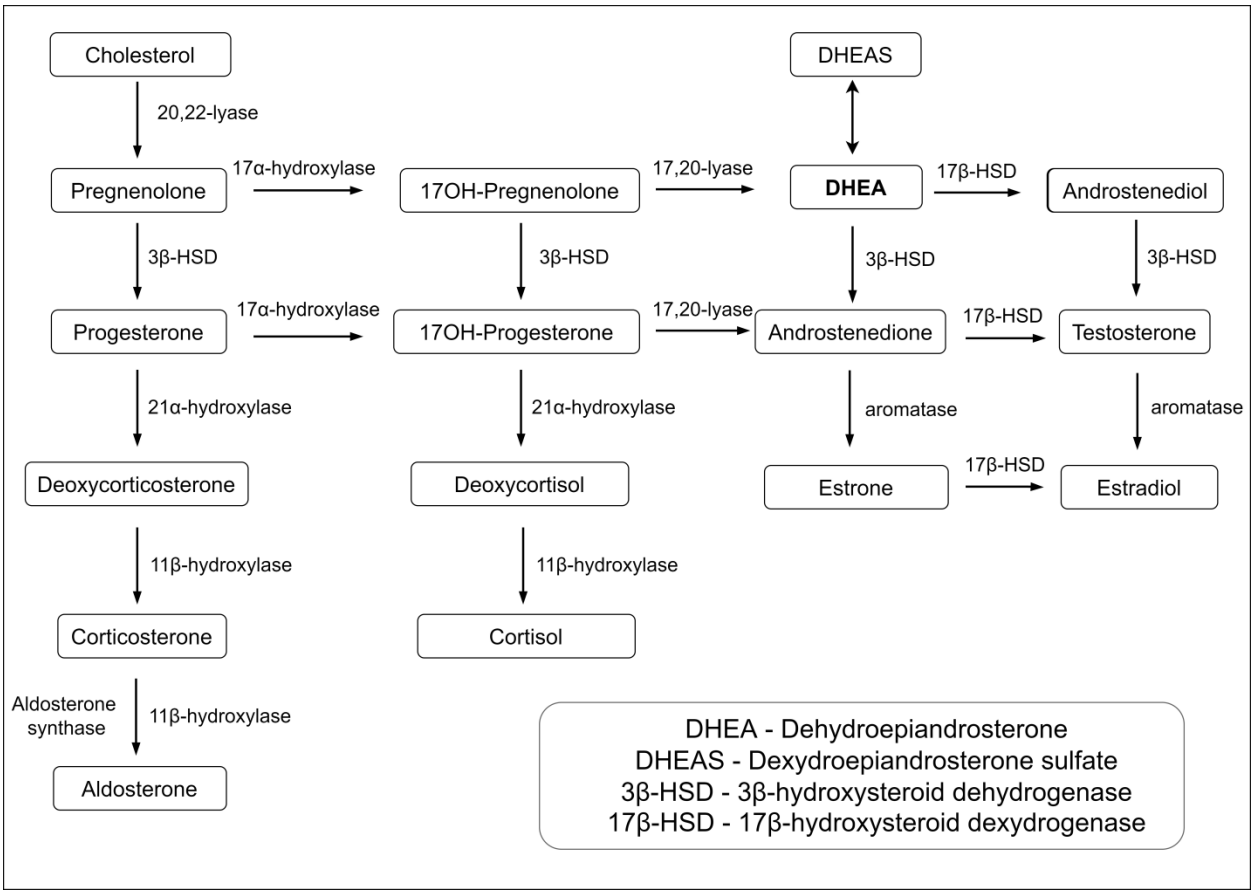

Figure 1. DHEA biosynthesis

Table 1. Effects of DHEA/S on certain pathological entities and target organs/tissues/cells

PATHOLOGICAL ENTITIES OR TARGET ORGANS/TISSUES/CELLS	TYPE OF THE STUDY	MAIN FINDINGS	DATA SOURCE
Cardiovascular diseases (CVD)	Review article	lower DHEA levels associated with greater coronary artery stenosis and fatal myocardial infarction in men	Samaras et al., 2013 [18]
	Review article	increased DHEA levels reduce atherosclerosis and coronary artery stenosis	Sahu et al., 2020 [17]
	Review article	DHEA effect on endothelial cell proliferation and migration, vascular contractility, endothelial pathological processes (inflammation, atherosclerosis, clot formation)	Cai et al., 2016 [38]
	Review article	DHEA as an anti-remodeling and vasorelaxant agent in CVD	Savineau et al., 2013 [39]
Insulin resistance and type 2 diabetes	Review article	DHEA may increase insulin secretion, elevates insulin sensitivity of the liver, adipose tissue, and muscle, reduce hepatic gluconeogenesis	Aoki et al., 2018 [43]
	Meta-Analysis	DHEA reduces glycaemia level	Wang et al., 2020 [44]
Immune system	Review article	DHEA enhances antibody production and activity of monocytes, NK, immune cells, and anticancer function of T lymphocytes	Sahu et al., 2020 [17]
Autoimmune diseases	Review article	in women with systemic lupus erythematosus (SLE), DHEA reduces disease activity	Meyer et al., 2005 [54]
	Review article	DHEA positive effects on disease remission in patients with inflammatory bowel disease (IBD)	Rutkowski et al., 2014 [59]
Bone mineral density (BMD)	Review article	DHEA increases bone mineral density (BMD)	Kirby et al., 2020 [65]
Muscle mass and fat tissue	Meta-Analysis	DHEA supplementation increased muscle mass and reduced fat tissue percentage	Wang et al., 2020 [44]
Carcinogenesis	Review article	DHEA prevents initiation and promotion of the carcinogenesis	Williams et al., 2000 [52]
Inflammation	Animal model	DHEA positive effects on the course of bronchial asthma	Lin et al., 2009 [47]

Sexual function and fertility	Clinical study	DHEA improves fertility in women	Elprince et al. 2020 [68]
	Review article	DHEA improves sexual satisfaction in women and relieves vaginal atrophy in older age	Rutkowski et al., 2014 [59]
	Review article	DHEA positive effects on erection	Sahu et al., 2020 [17]
Ageing	Clinical study	DHEA better reflects age than the health condition	Nagaya et al., 2012 [45]; Stomati et al., 2000 [46]
Central nervous system (CNS)	Review article	DHEA exerts neuroprotective and anti-inflammatory effects, modulates mood, emotions, behavior	Strac et al., 2020 [72]
	Clinical study	Reduced DHEA levels in female patients with schizophrenia and metabolic syndrome	Boiko et al., 2020 [74]
	Review article	DHEA exerts anti-amnestic effects	Sahu et al., 2020 [17]
	Animal model / Review article	DHEA exerts anxiolytic effects	Fedotova et al., 2004 [77]; Sahu et al., 2020 [17]
	Animal model	DHEA beneficial effects in depression and cognitive disorders	Samardzic et al., 2017 [76]
	Review article	DHEA role in development of specific areas of the human brain	Campbell et al., 2020
	Review article	DHEA positives effect in neurodegenerative diseases	Strac et al., 2020 [72]; Sahu et al., 2020 [17]
	Review article	DHEA positive effect on neurogenesis, neuronal survival, and neuroplasticity	George et al., 2006 [91]; Schverer et al., 2018 [92]
	Review article	DHEA stimulates mobility and growth of neurons	Mellon et al., 2007 [93]
	In vitro study	dose- and tissue-dependent DHEA anti-oxidative action	Gallo et al., 1999 [95]; Tamagno et al., 1998 [96]
	Animal model	DHEA protective effect against amyloid-beta protein- toxicity in Alzheimer's disease (AD)	Li et al., 2010 [106]

	In vitro study	DHEA maintains redox homeostasis and affects tau protein phosphorylation in AD	Grimm et al., 2016 [107]
	Review article	DHEA improves memory and cognitive functions in AD	Strac et al., 2020 [72]
	Clinical study	DHEA improves attention in elderly subjects	Wolf et al., 1998 [117]