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RESEARCH ARTICLE

Dehydroepiandrosterone (DHEA) and its Sulphate (DHEAS) in Alzheimer's Disease

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Abstract: ***Background*:** Neurosteroids dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulphate (DHEAS) are involved in many important brain functions, including neuronal plasticity and survival, cognition and behavior, demonstrating preventive and therapeutic potential in different neuropsychiatric and neurodegenerative disorders, including Alzheimer's disease.

***Objective*:** The aim of the article was to provide a comprehensive overview of the literature on the involvement of DHEA and DHEAS in Alzheimer's disease.

***Method*:** PubMed and MEDLINE databases were searched for relevant literature. The articles were selected considering their titles and abstracts. In the selected full texts, lists of references were searched manually for additional articles.

***Results*:** We performed a systematic review of the studies investigating the role of DHEA and DHEAS in various *in vitro* and animal models, as well as in patients with Alzheimer's disease, and provided a comprehensive discussion on their potential preventive and therapeutic applications.

***Conclusion*:** Despite mixed results, the findings of various preclinical studies are generally supportive of the involvement of DHEA and DHEAS in the pathophysiology of Alzheimer's disease, showing some promise for potential benefits of these neurosteroids in the prevention and treatment. However, so far small clinical trials brought little evidence to support their therapy in AD. Therefore, large-scale human studies are needed to elucidate the specific effects of DHEA and DHEAS and their mechanisms of action, prior to their applications in clinical practice.

Keywords: Dehydroepiandrosterone, Dehydroepiandrosterone sulphate, Alzheimer's disease, *In vitro* studies, Animal models, Patients, Treatment.

1. INTRODUCTION

1.1. Alzheimer's Disease

Alzheimer's disease (AD) is the most prevalent form of dementia that accounts for 60 to 80% of all cases [1]. The etiology of AD still remains unknown, but there are many known risk factors, including both genetic predisposition and various environmental factors [2]. It is often misdiagnosed or diagnosed too late, which significantly reduces the efficacy of subsequent pharmacological treatments. AD develops years before the first signs of dementia with gradual accumulation of characteristic AD pathology and cognitive impairment symptoms, and progresses from preclinical phase of the disease, through mild cognitive impairment (MCI) to AD.

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AD pathology is characterized by intracellular accumulation of hyperphosphorylated tau proteins [3], which form neurofibrillary tangles (NFT), and extracellular aggregation of amyloid β (Aβ) peptide into plaques [4]. These pathological processes lead to neurodegeneration, destruction and atrophy of the specific brain regions, with hippocampus and neocortex being most affected [5]. However, theories that emphasize the importance of neuroinflammation and mitochondrial dysfunction are attracting growing interest of the scientific community [6]. In the last two decades, a lot of effort was put into researching the amyloid and tau hypotheses of AD with the goal to develop more effective drug treatments. However, dissatisfaction with the results of clinical trials has led the scientists to search for new potential targets in AD therapy [7].

Different studies showed that neurosteroids, like dehydroepiandrosterone (DHEA) and its sulphate (DHEAS), together often referred as DHEA(S), could have a beneficial effect on cognition, and might reduce some negative behavioral symptoms [8]. It has also been demonstrated that

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DHEA(S) protect neurons from the degeneration [9], which is a major characteristic of AD, emphasizing the potential of these neurosteroids in the treatment of dementia.

2. DHEA(S) SYNTHESIS AND METABOLISM

In humans, DHEA and DHEAS are among the most abundant endogenous steroid hormones [10]. DHEA is synthesized *de novo* from the precursor cholesterol, by its conversion first into pregnanolone, and then into DHEA [11]. Specific enzymes convert DHEA into more stable and major circulating form, DHEAS, and back into DHEA [11]. DHEA can be metabolized into active androgenic and estrogenic compounds, and serves as an intermediate for the human sex steroids biosynthesis [12]. The major tissues associated with DHEA(S) metabolism are placenta, ovary, testes, prostate, adipose, liver, and brain [13]. DHEA and DHEAS are secreted mainly by the reticularis zone of the adrenal cortex; however, 10-20% of these steroids are produced by the gonads [14]. Moreover, they are also formed *de novo* in the brain [15] by both neurons and glial cells (astrocytes and oligodendrocytes). As DHEA(S) concentrations are 6-8 times higher in human brain than in peripheral blood [16], DHEA and DHEAS were designated as neurosteroids [17]. Circulating DHEAS to DHEA ratio is 1000:1 [18], but levels of both neurosteroids are gender- and age-dependent, with lower DHEA(S) levels in women than in men [19].

High fetal DHEA(S) concentrations steeply fall after birth and remain low until adrenarche. At around 8–10 years of age, serum DHEA(S) levels start to rise [20], reaching maximum at 20–30 years of age, after which they steadily decrease with age. In individuals aged between 60–80 years, DHEA(S) levels are only at 10-20% of their maximum values [19]. This age-related DHEA(S) decline has been associated with dysregulations in the body composition, fitness, mood and cognition [21,22]. Various studies also reported changes in DHEA(S) serum concentrations in patients with different neuropsychiatric disorders, such as anxiety, depression, post-traumatic stress disorder, schizophrenia and AD, but also with cardiovascular problems [23,24]. This prompted the idea of restoring DHEA(S) levels as a potential treatment for aging-associated disorders and resulted in the designation of DHEA(S) as a "fountain of youth" [25].

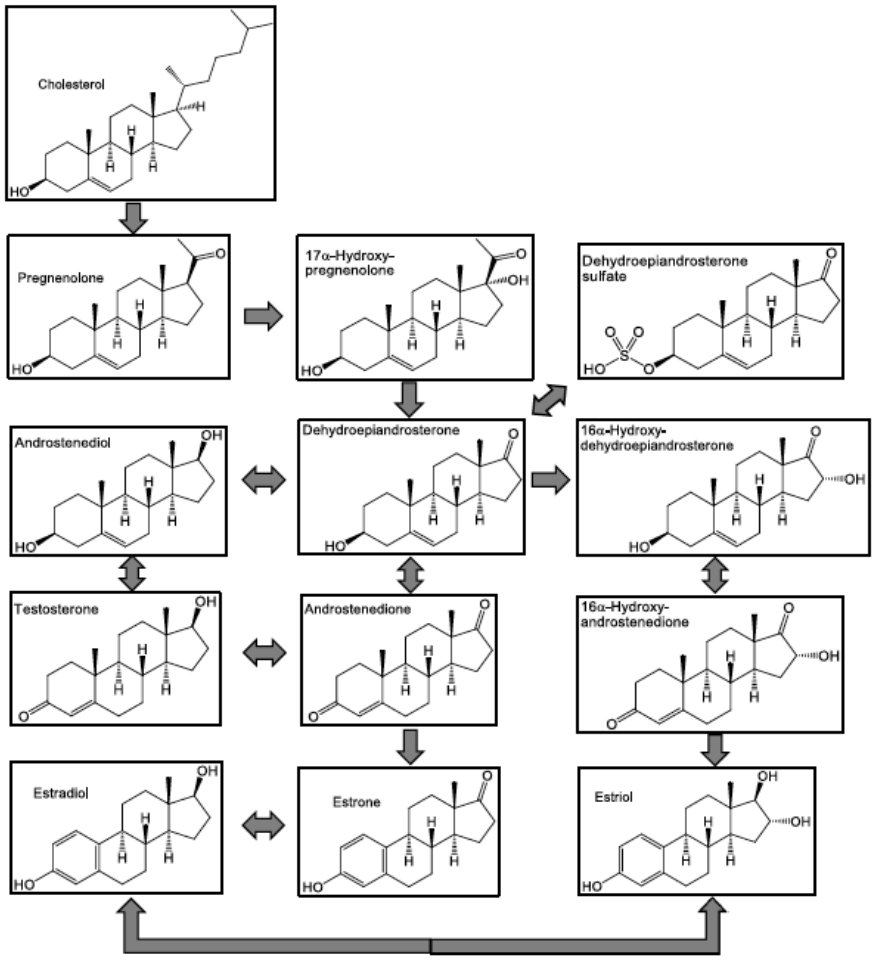

Fig. (1). Simplified DHEA(S) biosynthesis and metabolism pathways. The cleavage of the side chain of cholesterol produces pregnenolone, which is further converted first to 17α-hydroxypregnenolone, and then to DHEA. DHEA can be sulfonated into DHEAS and vice versa. DHEA serves as a precursor for weak androgens, androstenedione and androstenediol, which are both, precursors for the synthesis of sex hormones testosterone and estrogens, such as estradiol. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

3. DHEA(S) FUNCTIONS AND MECHANISMS OF ACTION

Although steroids mostly act via genomic pathways, DHEA and DHEAS have no specific nuclear receptor identified and act on non-genomic targets [26]. However, DHEA as a precursor acts through metabolic conversion into androgen and estrogen derivatives [27,28]. DHEA(S) bind various steroid hormone receptors [29,30] and their genomic mechanisms might be exerted via androgen receptors located in the peripheral androgen-dependent tissues [29,31]. In addition, DHEA activates mineralocorticoid receptors (MR), although it is not a direct ligand of MR [32]. Moreover, in the hypothalamus and hippocampus, DHEA affects genes involved in the regulation of the appetite, energy utilization, alertness, cell survival and apoptosis [33].

DHEA and DHEAS also activate specific G-protein coupled receptors in plasma membrane [34,35], and induce rapid activation of miR-21 expression via G-protein estrogen receptor (GPER) [36]. In addition, Liang *et al.* [37] demonstrated that DHEA increases insulin like growth factor (IGF-1)-receptor. The direct effects of DHEA(S) in the brain involve several neurotransmitters, primarily glutamate and γ-aminobutyric acid (GABA) systems [38,39]. DHEAS acts as a positive modulator of N-methyl-D-aspartate (NMDA) receptors and potentiates glutamatergic neurotransmission, probably indirectly by the activation of the central sigma 1 (σ1) receptors [40] as their agonist [41]. DHEA exerts neuroprotective effects in α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) induced toxicity, but without direct binding to AMPA receptors [42]. Most reported effect has been DHEA(S) allosteric modulation of the GABA-A receptor [9, 43], with DHEAS acting as an antagonist [16, 44, 45], although without identified binding site [46].

Moreover, DHEA and DHEAS have been found to interact with dopaminergic and serotoninergic systems [47] and potentiate the release of norepinephrine [48]. Microtubule-associated protein 2 (MAP2) also represents DHEA(S) receptor [49], whereas other potential DHEA receptors include membrane DHEA binding site (mDBS) [50], plasma membrane receptors tropomyosin receptor kinase (Trk)-A and p75 neurotrophin receptor (p75NTR) [51]. Interaction of DHEAS with the nitric oxide biosynthesis and ion channel function has been observed [52]. In the heart, DHEA inhibits voltage-gated T-type Ca^{2+} channels [53]. Various effects of DHEA on mitochondrial function have also been reported; however, no exact mechanism was elucidated [54].

Above reviewed mechanisms of action, emphasize different functions of DHEA(S) in various physiological systems, including central nervous system [43], immune systems [55], as well as body growth and development [56]. Many observed actions of DHEA(S) include anti-dementia, anti-aging, pro-immune, anti-diabetic, anti-obesity, anti-carcinogenic, anti-atherosclerosis, anti-osteoporosis, and various other effects [57,58].

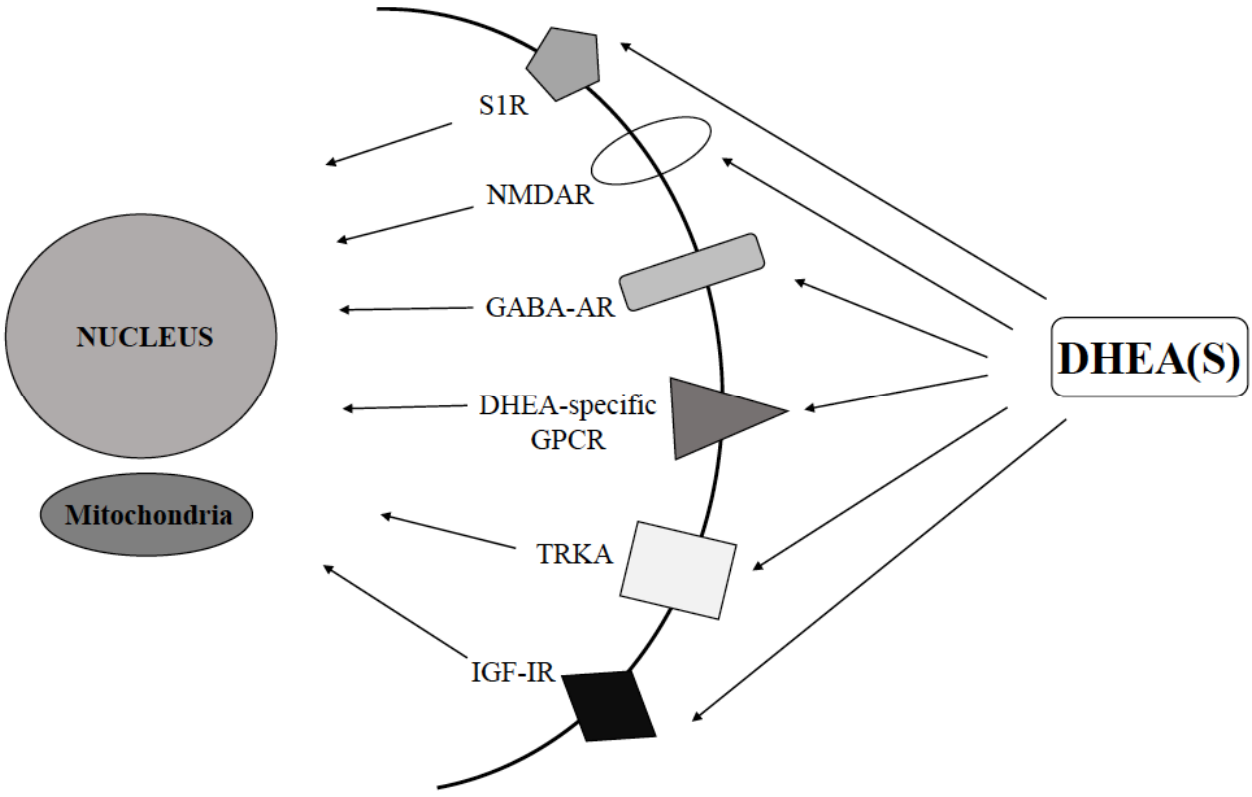

Fig. (2). Simplified summary of DHEA(S) actions via various plasma membrane receptors. DHEA and DHEAS activate different receptors in plasma membrane, including NMDA and GABA-A receptors, central σ1 receptors, IGF-1 receptors, Trk-A receptors, as well as various specific G-protein coupled receptors, affecting gene expression and mitochondrial function of the cell. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

DHEA(S) have been involved in neuronal plasticity modulation by influencing death and survival of neurons [59-61], especially during brain development [62]. Moreover, many studies reported neuroprotective [60,63-65], antioxidative and anti-inflammatory effects of DHEA(S) [66]. In addition, DHEA(S) have been shown to play a significant role in modulating mood, emotions and behavior [67-69], as well as memory and cognitive functions [70,71]. All these actions make DHEA and DHEAS potential targets for the prevention and treatment of a variety of neuropsychiatric and cognitive disorders, including AD [9,43,72-75].

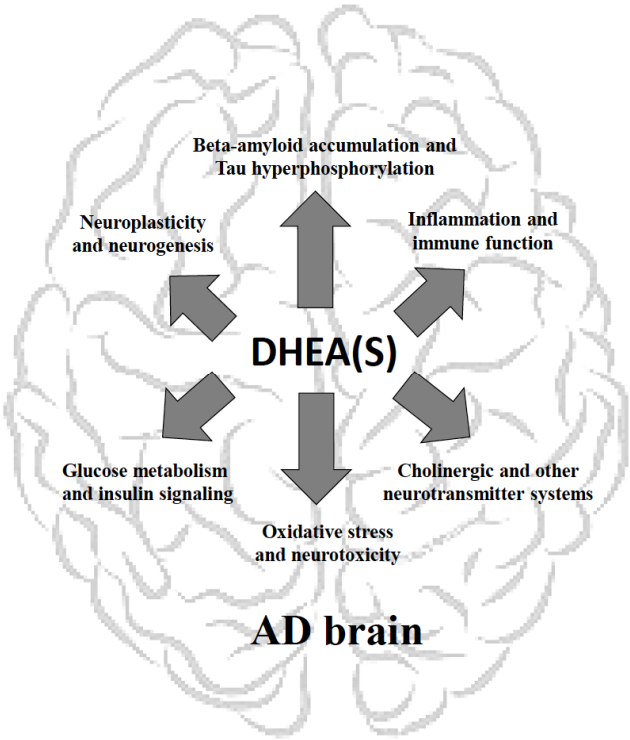

Fig. (3). Observed actions in the brain potentially involved in the beneficial effects of DHEA(S) in AD. Literature data suggest beneficial actions of DHEA(S) in AD brain, such as modulation of neuroplasticity and neurogenesis, β-amyloid accumulation and tau hyperphosphorilation, immune function and inflammatory responses, glucose metabolism and insulin signaling, neurotransmission via various neurotransmitter systems, as well as oxidative stress and neurotoxicity. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

4. DHEA(S), COGNITION AND MEMORY IN AGING

A number of findings support the role of DHEA(S) in aging and memory decline. As already mentioned, DHEA and its sulphate are secreted in age-specific manner, and their concentrations in plasma rapidly decrease after the age of 80 [76]. The decline in the cortisol/DHEA ratio could also be associated with age-related deterioration of cognitive function [77]. Since the decline in DHEA levels correlates with the decrease of IGF-1 concentration [78], the imbalance between higher cortisol levels and reduced DHEAS and IGF-1 concentration might underlie age-related cognitive decline and development of dementia [79]. It has been suggested that DHEA(S) could modulate brain function, deteriorated in old age, by affecting various neurotransmitter systems [27,43]. DHEA(S) could also affect cognitive function by modulating inflammatory mechanisms [80,81]. Age-related decline in DHEA(S) levels could lead to elevated levels of proinflammatory cytokines, resulting in neuroinflammation and consequent neurodegeneration. Some studies also reported a relationship between DHEA, glucose and insulin concentrations [82]. Since hyperglycemia [83] and hyperinsulinemia [84] can result in cognitive impairment, this could represent another potential mechanism of DHEA(S) effects on cognition. However, complex interactions between DHEA(S) and cognition still need further research, taking into account multiple factors and gender-specific effects of DHEAS on cognitive function [85]. DHEA supplementation can restore the calcium-phospholipid-dependent protein kinase C (PKC) signal transduction mechanism by affecting the levels of the receptor for activated C kinase (RACK-1) [86], a protein whose expression is reduced in the brain affected by aging [87], and neurodegeneration [88]. Some studies reported an association of cognitive decline with low levels of DHEA(S) [89], whereas others observed an opposite trend [90]. However, there are studies that found no association between cognition and DHEA(S) concentration in human subjects [91,92]. In the review of Grimley Evans *et al.* (2006) [93], authors concluded that so far, little evidence gathered from controlled trials does not indicate a beneficial effect of DHEA supplementation on cognitive function in non-demented elderly people. However, they emphasize a need for trials with longer DHEA treatment and a larger number of participants.

5. DHEA(S) LEVELS IN ALZHEIMER'S DISEASE

Post-mortem brain analysis in AD patients suggested elevated DHEA levels in several brain regions, including prefrontal cortex, hypothalamus and hippocampus [94], with the highest concentration in the hippocampus [94]. The increase in DHEA levels could be triggered by the presence of Aβ and increased oxidative stress and might represent an adaptive or compensatory mechanism in AD brain [94]. The higher levels of DHEA in the brain tissue of AD patients could originate from the periphery or from an alternative pathway of DHEA synthesis present only in CNS [95]. There is also evidence of elevated CSF DHEA levels in AD patients, in contrast to decreased serum DHEA concentration [94]. Some findings [96] suggested a correlation between CSF DHEA levels and DHEA levels in the temporal cortex and their relationship with neuropathological stages of AD. On the other hand, other clinical studies have reported decreased DHEAS concentration in *post-mortem* AD brain and CSF [97] and observed a negative correlation with the concentrations of hyperphosphorylated tau proteins in the hypothalamus [97]. These data suggest potential neuroprotective effect of DHEAS, and highlight the importance of DHEA-to-DHEAS ratio in the brain of AD patients rather than changes in individual steroid levels.

Lower DHEA and DHEAS levels were detected in plasma and serum samples of AD patients in comparison to healthy elderly individuals [75,89,94,97,98], possibly as a result of the pathological process, or as a potential risk factor for AD. The systematic review and meta-analysis by Pan and colleagues [99], collected and summarized the results from 31 studies that compared the concentration of DHEA(S) in

patients diagnosed with AD with the one in healthy control subjects, using plasma, serum or CSF samples. The results suggested no association between the concentration of DHEA and AD, except in the studies, which enrolled individuals aged 80 years or older. However, the results of this study showed lower DHEAS concentration in patients diagnosed with AD compared to healthy individuals [99]. These results highlight the importance of further studies that should investigate the mechanisms behind reduced DHEAS levels in AD and evaluate the effects of their supplementation. The various DHEA(S) mechanisms of action that might result in beneficial effects of these neurosteroids on the brain functions, impaired in AD, are reviewed in detail in subsequent chapters.

6. BETA-AMYLOID PATHOLOGY AND DHEA(S)

The major pathological hallmark of AD, accumulation of β-amyloid plaques, which are mainly composed of 4-kDa amyloid β peptide, is a result of disruption in amyloid precursor protein (APP) metabolism [6,100]. Recent evidence suggests a possible alternative pathway for DHEA(S) synthesis in the brain associated with oxidative stress and β-amyloid plaques formation. It is assumed that elevation of β-amyloid plaques could cause increment of DHEA(S) in the brain. Increased DHEA levels in the AD brain, especially in the hippocampus, may be a result of the oxidative stress caused by the Aβ formation [94]. Experiments in cultured cells showed that DHEA(S) might affect metabolism of APP, whose dysregulation leads to the accumulation of Aβ plaques [101]. It is also assumed that DHEA exhibit a protective role against toxicity caused by Aβ protein by the inhibition of the Aβ-induced elevation through a sigma (1) receptor-mediated modulation of PI3K-Akt-mTOR-p70S6k signaling [102].

Several studies demonstrated that DHEA, DHEAS and its precursor, pregnenolone affect augmentation of calcium ions induced by β-amyloid protein and in that way exert their neuroprotective effects [103]. In addition, experiments using AD animal models demonstrated that DHEA administration reduces cognitive impairments in animals previously treated with β25-35-amyloid peptide [104]. The role of DHEA in Aβ formation has been correlated with cholinergic system through desensitization of the muscarinic receptors in PC12 cells, which might have an influence on APP metabolism. Namely, DHEA causes elevation of APP secretion from PC12 cells, while APP levels are also increased inside the cells. Therefore, it is assumed that the age-dependent decrease in DHEA serum and plasma levels can lead to APP metabolism deficits and later to Aβ formation and development of AD [105].

7. PHOSPHORYLATION OF TAU PROTEINS AND DHEA(S)

In addition to β-amyloid plaques, one of the hallmarks of AD are intracellular NFT containing hyperphosphorylated tau protein. Abnormal phosphorylation of tau proteins causes their aggregation and leads to neurodegeneration due to destabilization of microtubule structure [106,107]. According to "Alzheimer mitochondrial cascade hypothesis", it is assumed that mitochondrial impairments, which are characteristic for aging, cause bioenergetics alterations that can lead to Aβ formation and hyperphosphorylation of tau proteins. Levels of tau proteins are higher in almost all brain areas in AD patients compared to healthy controls [97]. Animal studies, which included administration of Aβ25–35, suggested significant influence of many biochemical pathways in hyperphosphorylation of tau protein and consequently NFT formation. Kinases that participate in Akt signaling pathway, more precisely GSK-3β activation, are crucial in tau phosphorylation and alterations found in AD. Inactivation of these kinases cause decrease in tau phosphorylation, while increase in GSK-3β phosphorylation induces hyperphosphorylation of tau proteins [108].

Neurosteroids, such as DHEA and DHEAS might modulate phosphorylation of tau proteins due to their role in maintaining redox homeostasis [109]. Concentration of tau proteins was negatively and significantly correlated with concentration of DHEAS in the hypothalamus, which suggests potential neuroprotective role of DHEAS in AD [27,97,110]. Connections between tau proteins and neurosteroids were also observed in neuroblastoma cells [107]. Elevation of neurosteroids has been followed by hyperexpression of the wild type tau protein, and decrease of hyperphosphorylated tau [111]. DHEA(S) also improve memory, stimulate neurogenesis and have beneficial effect on neuron survival, possibly by binding to MAP2 [112]. In cultured cells, both DHEAS and DHEA cause an increase in neurites that contain either MAP2 or tau proteins, while this process is mediated through NMDA receptor [113].

8. CHOLINERGIC SYSTEM AND DHEA(S)

The hypothesis about involvement of cholinergic system in the development of AD has been established more than 50 years ago. Cholinergic impairment was confirmed by the several studies that observed alterations in acetylcholine (ACh) release and uptake due to degenerations of cholinergic neurons in different areas associated with cognition, memory and learning [114,115]. Impairments in AD related to cognition could develop due to the reduction of ACh synthesis and activity of choline acetyltransferase [114,115]. It is assumed that alterations in cholinergic neurotransmission begin in the early stage of AD. Reduction of choline acetyltransferase in hippocampus and cortex is due to neuronal degeneration, which is correlated with the number of β-amyloid plaques [115,117].

Pyramidal neurons are mostly degenerated in AD and represent a risk for dysregulated APP metabolism that leads to formation of β-amyloid plaques, and these processes are regulated by ACh [114,118]. One study showed decreased concentration of APP in CSF of depressed patients after receiving anticholinergic drugs [114,115]. On the other side, phosphorylation of tau protein is also associated with cholinergic system [114,115]. Stimulation of muscarinic cholinergic receptors and consequently, activation of downstream protein kinases leads to phosphorylation of tau protein and later formation of neurofibrillary tangles, one of the main symptom of AD [114,115]. Several studies have suggested that DHEA(S) act as GABA-A receptor inhibitors and improve memory and cognition, due to the role of GABA in modulating ACh system. The effects of 7-oxo DHEA ace-

tate, derivative of DHEA were tested by using Morris water task, which reveals spatial memory deficits due to cholinergic blockade, and it is especially sensitive to impaired cholinergic hippocampal function [118]. The administration of 7-oxo DHEA acetate and DHEA had beneficial effects on memory in young mice treated with scopolamine, an anticholinergic agent, as well as in old mice [118]. Drugs that stimulate cholinergic system, such as tacrine and nicotine, were shown to significantly improve attentional function in patients with AD [117]. The knowledge about the involvement of cholinergic system in the cognitive impairments of AD patients contributed to drug development, and therefore, today the inhibitors of acetylcholinesterase still represent the main AD treatment. Donepezil, galantamine and rivastigmine are drugs that belong to second, newer generation of cholinesterase inhibitors. Most of the patients show improvement in cognitive response after the treatment with these drugs.

In addition to cholinergic system, other neurotransmitter systems are also involved in AD pathology, such as serotonergic, GABAergic and glutamatergic systems, which can interact with cholinergic system. Reduction in glutamate and uptake of D-aspartate was observed in different brain areas among AD subjects [114], resulting in introduction of memantine, uncompetitive NMDA receptor antagonist in the treatment of AD. However, further investigations are necessary to improve knowledge on the potential novel treatments that should be used earlier in the prodromal phases of AD, and should include findings about relationship between ACh and metabolic dysregulation of tau and APP proteins [114,117].

9. THE ROLE OF DHEA(S) IN NEUROPLASTICITY AND NEUROGENESIS

Brain steroids, DHEA and DHEAS, affect neurogenesis and survival of neurons, the brain processes important during the developmental and aging phases of life. These neurosteroids have been characterized as neuroplasticity modulators. Main DHEA(S) targets are amino acid ionotropic receptors (glutamate, GABA-A and σ1 receptors), which, together with cytoskeleton proteins such as MAP, represent the main components of neuroplasticity regulation system [116,119]. Additionally, there are indications, confirmed by *in vitro* and animal model study, that DHEA can act as a neurotrophin binding to neuronal growth factor (NGF) receptors, and can protect neurons against apoptosis [51] Apart from this neuroprotective role, it has been shown that administration of both DHEA and DHEAS stimulates mobility and growth of neurons during CNS development [62]. DHEA stimulated the growth of axonal neurites, while DHEAS was effective in growth stimulation of neurites containing the dendritic marker [113]. Moreover, DHEA potentiated synaptic efficacy and neurogenesis through σ1 receptor in the hippocampal dentate gyrus [120]. Besides, a subcutaneous administration of DHEA in ovariectomized rats increased CA1 spine synapse density by around 50% [121]. Chronic DHEAS treatment in rats resulted in facilitated long-term potentiation (LTP) and amplification of Src-dependent NMDA receptor signaling in the hippocampal CA1 area [122]. Besides affecting LTP, DHEAS can also modify a short-term potentiation *in vitro* [123]. The study performed *in vitro* and *in vivo* in mice showed that DHEAS stimulates neurite outgrowth and prevents its decrease induced by Aβ25-35 [124]. As it seems that after crossing the blood brain barrier, sulfated DHEA undergoes desulfation and transformation into metabolites [125], most of the observed effects might be due to its metabolites and not DHEAS itself.

Considering all the promising observations about DHEA and DHEAS as neuroprotective, neurotrophic and neuroplasticity modulating neurosteroids, they have potential for applications as positive modulators of learning and memory, as well as therapeutic targets in neurodegenerative conditions. However, the synaptic and molecular mechanisms underlying their biological effects need to be further investigated.

10. OXIDATIVE STRESS IN AD AND NEUROPROTECTIVE PROPERTIES OF DHEA(S)

Oxidative stress emerges when homeostasis between physiological production of reactive oxygen species (ROS) and antioxidative power of cell is disrupted [126]. Although ROS production represents a byproduct of metabolism and is essential to normal cell signaling, the damage in nucleic acids, proteins and lipids, resulting from its its excessive abundance, has been associated with premature aging and various autoimmune, cardiovascular, metabolic, intestinal and brain degenerative conditions [127]. Cell's defense system against oxidative damage includes several antioxidant enzymes that act as scavengers of ROS and other highly reactive radicals, which damage biological macromolecules, as well as enzymes included in DNA base excisions and strand repair [128]. Brain cells, due to their high oxygen intake and metabolism, high lipid and metal (particularly Fe^{2+}) content, as well as relatively small amount of antioxidants, are especially sensitive to ROS damage [129]. One of the main manifestations of the oxidative stress in CNS is lipid peroxidation and formation of its highly pro-inflammatory product 4-hydroxynonenal (HNE), which can promote additional ROS production [130]. Studies on animal models and in human post-mortem brain samples showed that interplay between mitochondrial dysfunction and excessive ROS production leads to elevated Aβ aggregation and deposition in brain tissue, as well as formation of NFT, both hallmarks of AD [131].

Although the initiating event in AD development is still unknown, AD pathophysiology probably includes several pathways including inflammation, ischemia, excitotoxicity, decreased energy metabolism and oxidative damage [132], which eventually lead to neuronal cell death. It has been shown that local oxidative stress and consequently, neuroinflammation, play an important role in AD pathogenesis, especially in hippocampus, a region responsible for memory formation [133,134]. Therefore, antioxidant therapy has been proposed to be beneficial in treating AD [135]. Observed anti-oxidative, anti-apoptotic, anti-glucocorticoid and anti-inflammatory properties of DHEA could be involved in its mechanisms of neuroprotection [136]. Numerous studies demonstrated anti-oxidative properties of DHEA [137-139], but some of them noticed its pro-oxidant property depending on the dose, tissue and time of administration [137,140,141]. Slightly higher concentrations of DHEA diminished lipid peroxidation, while DHEA in pharmacological doses showed

a pro-oxidant activity [140]. It has been demonstrated that not only the dose, but also the tissue of administration could influence whether DHEA will exert its anti- or pro-oxidant actions [137].

One of the main signaling pathways of DHEA probably includes phosphatidylinositol 3-kinase (PI3K)/Akt signaling cascade. Akt is a serine/threonine kinase that can be stimulated by ROS and insulin, but also as a response to chronic DHEA treatment [138,139]. Other recent *in vitro* studies showed that pre-treatment with DHEA inhibited OH ion production by stimulating the peroxidase (POD) activity, and decreased the expression of Bax, caspase-9 and caspase-3 mRNA, which leads to a lower apoptosis rate [139]. DHEA could also exert its antioxidative effects indirectly by inhibitory effect on glucose-6-phosphate dehydrogenase (G6PDH), resulting in lower NADPH levels and reduced NADPH-dependent oxygen-free radical production [142], as well as by acting as a metal chelator [137], thus preventing the activation of ROS generating enzymes. Therefore, it could be concluded that DHEA is not an anti-oxidant or pro-oxidant molecule per se, but it rather interferes with signaling cascade involved in the metabolism of ROS and other non-oxygen radicals.

Additionally, it has been reported that both DHEA and DHEAS can stimulate sigma receptors and lower the calcium flux in mitochondria in response to excitotoxicity [60,143]. Excitotoxicity as a consequence of excessive intracellular Ca^{2+} overload through NMDA receptors, which is present during ischemia, is one of the first events in neuronal degradation [144]. Other mechanisms by which these neurosteroids could exert their neuroprotective properties include modulation of GABA activity seen after DHEAS administration [45], reduction of pro-inflammatory cytokines [145] or increase of glucose uptake, noticed following DHEA treatment [146], as well as their actions through metabolite estradiol. Neuroprotective properties of DHEA have been observed in different models including animal models of neurodegeneration [147], ischemia rat model [148], aged rat model [149], but also in cell models of ischemia, neurotoxicity and neurodegeneration [54,146]. In addition, neuroprotective action of DHEAS has been reported against the Aβ25-35-induced toxicity in B104 cells [124], where it prevented cells from entering the late apoptosis and necrosis phases.

11. DHEA(S) AND IMMUNE SYSTEM IN AD

Pathological changes in AD, besides the formation of Aβ plaques and intracellular NFT, also include neuroinflammation [150]. In the early phases of AD, Aβ peptides are co-localized with complement factors, acute-phase proteins, and pro-inflammatory cytokines [151]. Deposition of Aβ induces a pro-inflammatory cascade and increased synthesis and release of the pro-inflammatory cytokines via activated microglia, and all these processes contribute to tau hyperphosphorylation and accumulation in the brain, resulting in destruction of neurons, neuronal death and impairment of the synaptic function [152]. However, some pro-inflammatory cytokines activating their signaling pathways might also have neuroprotective roles in AD [152], offering a possible therapeutic target that needs to be explored.

Patients with AD had increased levels of IL-1β, IL-2, IL-6, IL-18, interferon-γ, homocysteine, high-sensitivity C-reactive protein [151], as well as elevated levels of C-X-C motif chemokine-10, epidermal growth factor, vascular cell adhesion molecule-1, tumor necrosis factor (TNF)-α converting enzyme, soluble TNF receptors 1 and 2, α1-antichymotrypsin, but reduced IL-1 receptor antagonist in comparison to age matched healthy subjects [151]. Significant elevation of the cytokines and receptors of the IL-1 family in subjects with AD may differentiate these subjects from subjects with MCI and normal healthy subjects and could be used as biomarkers for the prediction of progression of MCI to AD [153]. Various findings suggest that DHEA also modulates the immune function [154,155]. In pro-oxidative conditions, such as those occurring in AD, DHEA biosynthesis in the brain is induced by pro-oxidant agents, such as Fe^{2+} and β-amyloid peptide [156,157]. During acute stress, DHEA in combination with other hormones, especially cortisol, mediates immunological responses [154]. Lower DHEA and DHEAS levels are found in older age [21], that are usually related to disturbances of the immune system (termed immunosenescence), altered endocrine functions (termed endocrinosenescence), increased inflammation [136], and cognitive decline [99,158]. Cognitive disturbances are major characteristics of AD, and increased serum DHEAS levels were associated with better working memory [158], while there was a negative trend for association of pro-inflammatory cytokine TNF-α and working memory [158].

Since AD is associated with increased pro-inflammatory cytokines and decreased DHEAS levels, reduced DHEAS levels in AD might lead to a dysregulated immune system, increased oxidative stress and cognitive decline, as DHEAS shows antioxidative and anti-inflammatory effects [99]. However, the exact molecular mechanism by which DHEA and DHEAS affect the immune system in AD is far from clear [99,155]. DHEA can exert direct effects on immune system via binding to steroid hormone receptors, located on B cells, T cells, monocytes, and natural killer cells [155]. Anti-inflammatory properties of DHEA, presumably mediated by the inhibition of the NF-kappa B activation were detected, since DHEA decreased T cell proliferation and secretion of pro-inflammatory cytokines (IL-1β, IL-5, IL-6, IL-10, IL-12, TNF-α, and IFN-γ) *in vitro* [155], inhibited the activation and translocation of NF-kappa B *in vivo* in mice [159], and increased the secretion of IL-2 and IL-4 [155], probably acting via the intracellular binding site in murine T cells [160]. In addition, DHEAS was shown to regulate pro-inflammatory cytokines in neuritic plaques [99]. The effects of DHEA might be modulated also by its binding via a receptor-dependent process on monocytes [161]. In *in vitro* model, using T lymphocytes (i.e. in fresh CD4+ T cells and CD4+ clones) from healthy adults, the addition of the physiological concentration of DHEA increased the transcription of IL-2 mRNA and enhanced cytotoxicity [162], suggesting that DHEA regulates human immune response via increased IL-2 transcription. In a rat model of AD, DHEA treatment decreased oxidative stress biomarkers and acetylcholinesterase activity, but increased antioxidant enzyme activities, brain-derived neurotrophic factor (BDNF) and ACh levels, revealing that its anti-inflammatory effects in AD might be mediated via different pathways [163].

On the other hand, DHEA and DHEAS are precursors of many hormones, bioactive steroid metabolites and downstream molecules that might also modulate immune responses. Some metabolites of DHEA (androstenediol and androstenetriol) were reported to elevate lymphocyte activity and were shown to possess more potent protective effects from lethal bacterial and viral infections in mice in comparison to DHEA [164]. Therefore, the modulation of the immune response by DHEA might be achieved through its metabolites, and not by binding to a specific receptor [164,165]. Independently of their metabolites and active hormones, DHEA and cortisol, and their delicate balance, are not only responsible for modulation of immunity and inflammation, but also for neurotransmission, neurogenesis and neuronal survival [166]. DHEA when used as a supplement, generally shows improvement in humans with autoimmune diseases, bacterial/viral or parasite infections, and beneficial effects as adjuvant to various vaccines or in rodent models with experimental infections [155].

DHEA also demonstrates antiglucocorticoid activity [167,168]. Although the mechanism of anti-glucocorticoid effect of DHEA is not yet fully understood, DHEA blocks glucocorticoid-induced elevations of tyrosine aminotransferase, ornithine decarboxylase 1, and IL-4 gene expression and inhibition of IL-2 induced by glucocorticoids *in vivo* [168]. *In vitro* studies, using cell models of pre-adipocytes to mature adipocytes, also revealed antiglucocorticoid activity of DHEA, since it inhibited differentiations of pre-adipocytes and blocked the expression and activity of 11β-hydroxysteroid dehydrogenase type 1 [167]. In the hippocampal cell line, the addition of DHEA in a dose-dependent manner, protected neurons from glutamate-induced toxicity, presumably by the reduction of the glucocorticoid receptor nuclear localization in the hippocampal cells [168].

12. DHEA(S) EFFECTS ON GLUCOSE METABOLISM AND INSULIN SIGNALING

According to some studies, there are indices that diabetes and insulin resistance are risk factors for AD [169]. Indeed, an impaired uptake of glucose [170], as well as an impaired glucose metabolism due to reduced glycolytic flux [171], were found in different brain regions of AD patients. Additionally, some AD-related abnormalities were reported in genes encoding insulin, insulin growth factors and their receptors [172]. These AD abnormalities were even proposed to be categorized as "type-3 diabetes" [173]. However, it is still not clear whether brain glucose dysregulation is a feature or a symptom of AD [174]. DHEA(S) could have beneficial effects in the regulation of glucose metabolism. DHEAS levels decrease not only with cognitive and physical impairments related to aging, but they also decrease in diabetes [175]. There are *in vitro* and animal model studies indicating that both DHEA and DHEAS increase insulin secretion and sensitivity [176]. Furthermore, administration of DHEA in mouse model for type 2 diabetes (db/db mice) results in beneficial suppression of the increased activity [177] and mRNA expression [178] of gluconeogenic enzyme glucose-6-phosphatase (G6Pase), as well as increased glucose production in liver [179]. Besides, pancreatic β-cell lines secrete more glucose-stimulated insulin after treatment with DHEA *in vitro* [176] or *in vivo* [180] in rats. Human studies observed no effect of DHEA on glucose metabolism in elderly men [181] or postmenopausal women [182], probably because expected effects are usually associated with the conversion of DHEA into androgens, estrogens and other metabolites.

Administration of DHEA or DHEAS in patients with type 2 diabetes did not yield clear findings. Studies reported improved insulin sensitivity after taking the supplements of DHEA [183] or observed no effect of DHEA on plasma glucose, glycated hemoglobin, body mass index or homeostatic model assessment index [184]. A study conducted on peripheral blood mononuclear cells of elderly subjects with AD showed that DHEAS stimulated production of neuroprotective growth factors including IGF-1 [185]. This finding becomes particularly important if we take into account the fact that a few years later the reduction in insulin and IGF-1 sensitivity was reported in postmortem brain tissues from AD patients [186]. However, although DHEA(S) can influence insulin and IGF-1 sensitivity, it seems that it is more effective in AD than in diabetes. In a study in which DHEAS was administered orally in mouse models for AD and diabetes type 2, improvements were observed in learning and memory in AD mice, but not in diabetic mice [187].

13. RANDOMIZED CONTROL TRIALS OF DHEA(S) TREATMENT FOR COGNITIVE FUNCTION AND ALZHEIMER'S DISEASE

Several clinical studies were conducted and some of them are still ongoing in order to provide novel effective treatment for cognitive impairment and AD or to improve already known medicines that are mainly used as symptomatic therapy [188]. Few clinical trials examined DHEA or DHEAS supplementation on cognition, since preclinical and preliminary studies indicated their beneficial role for memory. Some studies [189] reported no significant effects of DHEA on cognition in perimenopausal women compared with placebo at 3 months, using three cognitive measures. Another study investigating the effect of DHEA on cognitive impairment induced by stress enrolled 75 healthy volunteers [190]. After two weeks of DHEA treatment, the effects on memory and attention after stress exposure were heterogeneous: the recall of previously learned material was impaired, whereas attention was enhanced [190]. One clinical study was conducted on 46 elderly nonclinical participants and investigated cognition after DHEA treatment for 13 weeks, followed by 13 weeks of placebo, or the reverse [162]. Salivary cortisol and DHEA levels were measured in the morning and in the evening. High DHEA levels in the evening were associated with low anxiety, while high DHEA levels in the morning correlated with low confusion. In addition, a higher morning cortisol/DHEA ratio was also associated with higher confusion and lower visuo-spatial memory performance. However, no effect of DHEA supplementation on cognitive function was observed [77]. Moreover, DHEA administration for one year to 225 healthy older people showed no benefits on cognition performance [191]. Another clinical trial of DHEA supplementation on non-smokers, non-demented subjects showed no significant difference in cognitive function compared with placebo control group [192]. The review of Grimley Evans *et al.* (2006) [93] reported that so far evidence from controlled trials does not

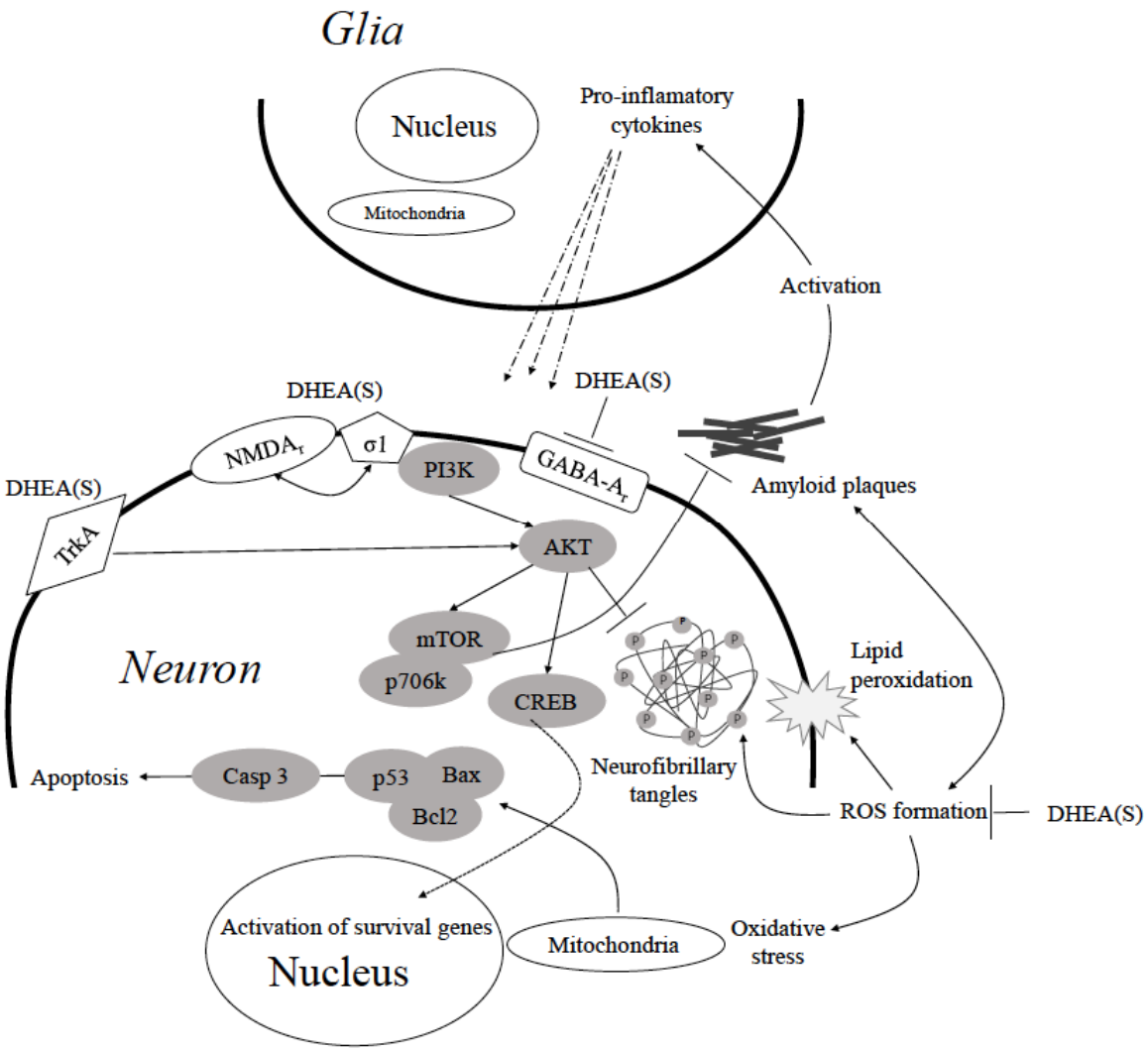

Fig. (4). Main proposed molecular mechanisms of DHEA(S) interactions with AD pathogenesis. DHEA(S) act as antagonists of GABA-A receptors, agonists of TrkA receptors, as well as positive modulators of NMDA receptors, probably indirectly by the activation of the central σ1 receptors. Through plasma membrane receptors, DHEA(S) show neuroprotective properties by modulating PI3K-Akt-mTOR-p70S6k signaling, and influencing accumulation of Aβ plaques, hyperphosphorylation of tau proteins and formation of neurofibrillary tangles. Moreover, DHEA(S) exert anti-oxidant activity, by preventing ROS generation, diminishing lipid peroxidation and protecting mitochondrial function. DHEA(S) also inhibit apoptosis by increasing the expression of anti-apoptotic Bcl-2 and other pro-survival genes, as well as by decreasing levels of Bax, caspase-9 and caspase-3 mRNA. In addition, DHEA(S) demonstrate beneficial effects on neuroinflammation by decreasing the secretion of various pro-inflammatory cytokines. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

support a beneficial effect of DHEA supplementation on cognitive function in non-demented middle-aged or elderly people.

A clinical study that investigated DHEA vs. placebo effect on 58 AD subjects was the first randomized, double-blind study of DHEA in AD [193]. No significant difference was observed in scores for Clinicians Interview Based Impression of Change with Caregiver Input and Alzheimer's disease Assessment Scale-Cognitive subscale after 3 and 6 months of DHEA administration [193]. In addition to small sample size, large dropout and small statistical power, limitation of this study also included paranoid reaction, agitation and confusion in DHEA-treated subjects. Another nonrandomized clinical trial [194] examined the role of DHEA supplementation on cognition among woman with mild and moderate cognitive impairment. Cognitive function was measured with Hasegawa Dementia Scale-Revised, Mini-Mental Status Examination and Barthel Index scales at the beginning of the administration, after 3 and 6 months. Better cognitive scores were observed in the treatment group after 6 months of administration compared with scores obtained at the beginning of the administration [192]. Limitation of the study was a non-randomized, small number of samples, with uncertain results [192]. Although, so far evidence from controlled trials has not supported a beneficial effect of DHEA supplementation on cognitive function, it is obvious that in the future, larger clinical trials are necessary to determine the

role of DHEA or DHEAS as a possible therapy in AD subjects.

14. DISCUSSION

Various findings from epidemiology, animal models, and *in vitro* systems reviewed in this article, led to the interest in DHEA(S) treatment for AD patients. Despite many encouraging preclinical findings of various DHEA and DHEAS biological actions, clinical trials found that beneficial cognitive effects of these neurosteroids in AD patients are mild, if present at all, bringing little evidence to support DHEA(S) therapy in improving cognitive function in AD [195]. However, beneficial effects of DHEA(S) treatment are more likely to be seen in patients with AD, than in healthy subjects, although treatment response is not merely due to replenishing DHEA(S) deficiency syndrome. Data suggest that DHEA-to-DHEAS ratio, as well as DHEA(S)-to-cortisol ratio, rather than the absolute concentrations of each steroid may be important.

The reason for failure of DHEA(S) clinical studies to replicate the findings seen in preclinical experiments may lie in the global phenomenological approach of assessing outcomes such as cognitive function, and not the core biochemical abnormalities or neuroanatomical and neurophysiological measures of AD, which are the focus of basic research. In addition, DHEA(S) clinical studies conducted in AD patients had small samples sizes with low power to detect significant effects. Much of inconsistency in clinical findings is also due to the methodological differences. Moreover, gender and age of enrolled subjects have to be considered in hormone studies like these, in addition to the fact that stress and glucocorticoids may play an important role in memory and cognitive performance of patients with AD.

So far clinical studies generally employed DHEA as a solitary treatment, and further studies are needed to investigate the effects of DHEA(S) as an adjunct therapy to standard AD medications such as cholinesterase inhibitors, or in the combination with other promising treatments. Additionally, larger-scale and longer-term studies, as well as studies employing a broad range of DHEA(S) doses are needed in order to investigate their potential clinical benefit. Future studies in AD should also screen for subtypes of patients, which might respond more favorably than others, for example patients with MCI, mild AD or AD patients with specific genetic predisposition, such as carriers of Apo E3 allele.

CONCLUSION

This article provided a comprehensive overview of the literature on the involvement of DHEA and DHEAS in AD. Despite mixed results, the findings of the most preclinical studies dealing with the effects of DHEA(S) on cognitive functions and other pathophysiological characteristics of AD, including accumulation of β-amyloid protein, tau hyperphosphorylation, changes in cholinergic and other neurotransmitter systems, neuroplasticity and neurogenesis, oxidative stress, glucose metabolism and insulin signaling, immune system function, and many other alternations are quite promising. However, clinical trials so far brought little evidence to support DHEA(S) therapy in AD. Therefore, this review also highlights the need for further studies, which are necessary to elucidate their exact mechanisms and all possible benefits, risks and applications. In addition, it has to be emphasized that although most of the studies reported DHEA(S) as a beneficial supplement, smaller number also demonstrated some neurotoxic and pro-oxidant characteristics [104,196]. This might be due to the fact that DHEA and DHEAS may act through distinct and different mechanisms. Therefore, the significance of this review is also in underlining that special concern should be focused on the time, dose and tissue specific administration, as well as on carefully designed clinical studies in humans, for a detailed investigation into preventive and therapeutic potential of both DHEA and DHEAS in AD. Final clarification of the DHEA(S) replacement potential, in age-related cognitive decline and dementia, including AD, will need additional well-designed and conducted human studies, with sufficiently large sample size.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are base of this research.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

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CONFLICT OF INTEREST

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

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