
Dehydroepiandrosterone (DHEA) and DHEA Sulfate: Roles in Brain Function and Disease

Tracey A. Quinn, Stephen R. Robinson and
David Walker

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/intechopen.71141>

Abstract

Among the neuroactive steroids, dehydroepiandrosterone (3 β -hydroxyandrost-5-ene-17-one, [DHEA]) and its sulfated metabolite DHEA sulfate (DHEAS) have been shown to be potent modulators of neural function, including neurogenesis, neuronal growth and differentiation, and neuroprotection. Highlighting the potential health significance of DHEA and DHEAS in humans, serum concentrations decrease steadily with age, with lowest concentrations present at the time many diseases of aging and neurodegeneration become apparent. This temporal association has led to the suggestion that pathology associated with cognitive decline, age-related neurological disorders such as Alzheimer's disease, dementia, amyotrophic lateral sclerosis (ALS), and adult onset schizophrenia may, in part at least, be attributed to decreased secretion of DHEA. Animal studies suggest neuroprotective functions for DHEA and DHEAS through reduction of glutamate-induced excitotoxicity. Reduced myelin loss and reactive gliosis after spinal cord injury by DHEA treatment also suggest a role for DHEA in the treatment of white matter pathologies such as multiple sclerosis. In this chapter, we discuss the physiological roles of DHEA and DHEAS in the central nervous system (CNS), their potential as neuroprotective hormones with reference to documented effects on excitotoxicity and oxidative stress, and their anti-glucocorticoid actions during chronic stress. The potential for metabolic derivatives of DHEA, such as estrogens and testosterone on brain function, and their contribution to neurodevelopment and neurodegenerative conditions are also discussed.

Keywords: adrenal zona reticularis, adrenarche, adrenopause, aging, Alzheimer's disease, amyotrophic lateral sclerosis, androgens, C19 steroids, glucocorticoids, neurocognitive decline, neurogenesis, neuroprotection, estrogens, schizophrenia, steroid biosynthesis

1. Introduction

Dehydroepiandrosterone (DHEA) is the principal carbon (C)-19 steroid produced by the adrenal gland in humans and mammals [1]. DHEA and its sulfated derivative DHEAS are multifunctional steroids with actions in a wide variety of physiological systems, with effects on the brain [2], immune systems [3], and somatic growth and development [4, 5]. Although DHEA and DHEAS were identified more than 50 years ago, there remains some uncertainty as to their physiological significance, full mechanisms of action [6–9], and their roles in human disease.

In humans, DHEA is a crucial precursor of sex steroid biosynthesis and exerts indirect endocrine and intracrine actions following conversion to androgens and estrogens. In addition, DHEA acts as a neurosteroid via its effects on neurotransmitter receptors in the brain. The potential health significance of DHEA in humans is highlighted by the observation that serum concentrations decrease steadily with age, approaching lowest concentrations around the time at which many diseases of aging, particularly neurocognitive decline, become apparent. The age-related decline in DHEA levels [10] has led to the suggestion that this is associated with a decrease in cognitive function as well as the increased rates of neuronal degeneration and dysfunction that occur during aging [11, 12]. Other studies have reported altered DHEA serum concentrations in patients with conditions such as schizophrenia [13], dementia [14], and Alzheimer's disease (AD) [13, 15–18]. Due to these associations, DHEAS has been widely publicized both in the lay press [19, 20] and in the scientific literature [21, 22] for their putative anti-aging and neuroprotective effects. This has sparked controversial speculation that DHEA treatment might be a remedy for neuropsychiatric and neurodegenerative disorders [7, 23–27] and, even more optimistically, that it is a hormone with the potential to increase the life span [28].

As promising as these speculations may seem, there are many contradictions about the roles of DHEA in normal and degenerative brain function. This is especially evident when comparing preclinical and clinical data. For example, studies in animals show a myriad of neuroprotective and trophic effects of DHEAS in development and disease, while clinical studies show inconsistent, and sometimes highly conflicting, results. Clinical studies of neurodegenerative diseases have variously reported increased or decreased DHEAS concentrations in serum, cerebrospinal fluid, and brain tissue, leading to doubt as to the role of DHEA in the neuropathology of aging. It has been suggested that the incongruity in measured DHEAS concentrations may lie in the methodological differences used to sample DHEAS; however, it is possible that these changes are indicative of a more nuanced and multifaceted role. There is consistent evidence that DHEA is neuroprotective with respect to oxidative stress, neuroinflammation, and excitotoxicity, and thus it is possible that DHEA assists the defense of the brain and has a beneficial effect on cognition in healthy brains. Therefore, it is the aim of this review to briefly discuss the physiology of DHEA and its synthesis and secretion during development and aging and to discuss the relationship between alterations in DHEA concentrations and cognition. We further discuss the possible role of DHEAS in a variety of disease states, including AD, and acute illnesses such as schizophrenia, with focus on the fact that these conditions are characterized by imbalances in oxidative stress, neuroinflammation, and excitotoxicity.

2. The physiology of DHEA

In humans, DHEA is one of the most abundant hormones synthesized and secreted by the adrenal cortex. This C19 steroid displays an episodic and diurnal rhythm of synthesis and release that parallels that of cortisol [29, 30]. The major synthetic pathways for DHEA and DHEAS are shown in **Figure 1**. The *de novo* synthesis of DHEA from cholesterol depends on the presence and activity of the mitochondrial enzyme steroidogenic acute regulatory protein (StAR), the microsomal enzyme cytochrome P450 enzyme 17 α -hydroxylase /17,20 lyase (P450c17), and the accessory hemoprotein cytochrome b5 (Cytb5) [32]. Importantly, P450c17 and Cytb5 need to be colocalized, because the function of Cytb5 is to selectively enhance the 17,20-lyase activity of P450c17 [33–35].

DHEAS is the precursor of approximately 50% of androgens in adult men, 75% of active estrogens in premenopausal women, and almost 100% of active estrogens after menopause [36]. DHEA has a 3- to 10-fold predominance of androgenic over estrogenic activity [37], and although a small portion of the circulating pool of DHEA is of gonadal origin in men and women, the majority of DHEA, and virtually all DHEAS, is produced by the adrenal cortex [1]. However, DHEA is also synthesized in the brain, from cholesterol and other hormonal precursors, primarily by astrocytes and oligodendrocytes; indeed, much higher concentrations of DHEAS are found in the brain than in the serum, suggesting that the DHEAS is primarily synthesized *in situ*, rather than being transported across the blood-brain barrier [38].

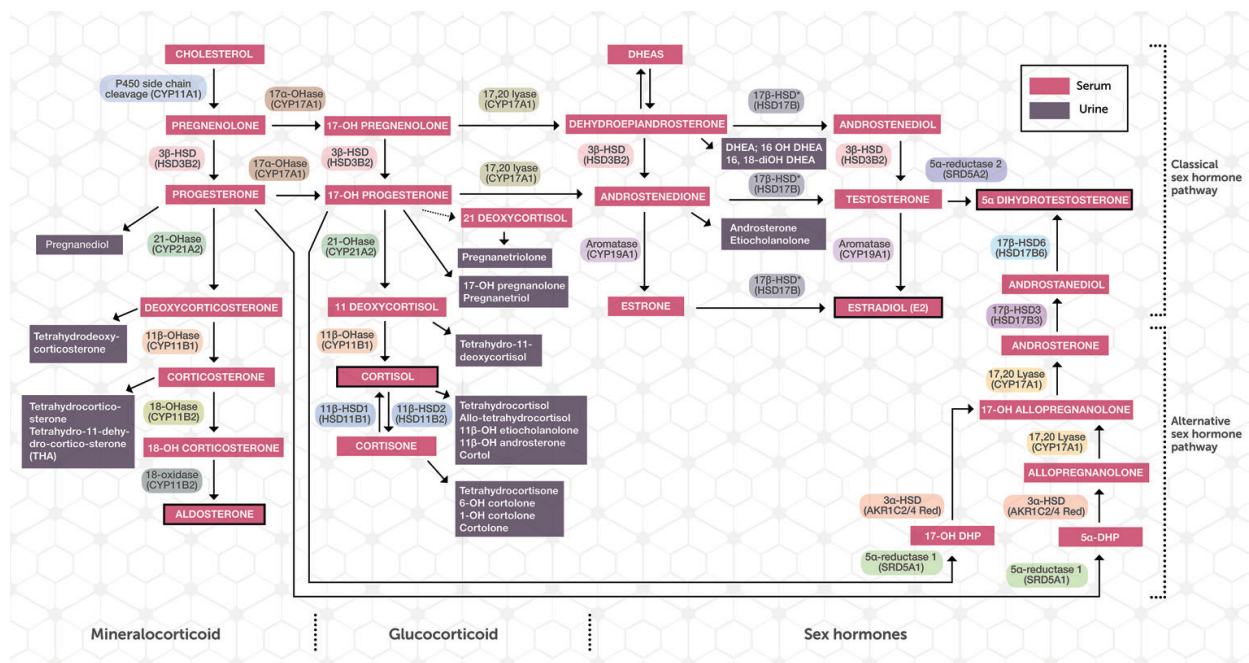


Figure 1. The complete steroid pathway showing the formation of DHEA from pregnenolone and 17OH-pregnenolone, and its reversible sulfation, and disposition via androstenes to estradiol and 5 α -dihydroxytestosterone. Steroid metabolites identified in serum and urines are shown in light gray boxes and dark gray boxes, respectively. From Greaves et al. [31].

The specific receptors that bind DHEA as a ligand have been of great interest for over 20 years. The biological actions of DHEA and its metabolites are mediated through androgen receptors or estrogen receptors, which belong to the nuclear receptor steroid-receptor subfamily [39]. DHEA has been found to exert both agonistic and antagonistic effects on the androgen receptor, and it acts as an agonist at both the estrogen receptor- α and estrogen receptor- β sites, with a binding preference for estrogen receptor- β [40, 41]. In the brain, DHEA is thought to affect neuronal excitability by modulating the *N*-methyl-D-aspartate (NMDA) [42–44] and sigma receptors [45], and as a positive allosteric modulator of the Gamma-aminobutyric acid type A (GABA_A) receptor [46–49]. In addition to this, DHEA has been shown to be a selective antagonist of the glucocorticoid receptor (GR) [50].

2.1. DHEA and DHEAS synthesis during development and aging

In humans, the patterns of DHEA synthesis and secretion change markedly throughout life. In the last months of gestation, the fetal adrenal can synthesize and release considerable amounts of DHEA and DHEAS, which together with estrogen and progesterone produced by the placenta play pivotal roles in the maintenance and endocrine control of pregnancy [51]. Although the plasma concentrations of DHEAS remain high in the newborn, they decrease quickly as the fetal zone of the adrenal gland involutes after birth. From 1 to 6 years of age, the adrenal gland secretes very low concentrations of DHEAS and androstenedione [52]. However at approximately 7–8 years of age, the adrenal zona reticularis increases the production of DHEAS and androstenedione, all of which are C₁₉ steroids that exert androgenic activity in several tissues by converting into potent androgens [36]. This pre-pubertal phenomenon is known as adrenarche, a biochemical, endocrine, and morphological event hypothesized to have evolved only in humans and higher primates. From an evolutionary point of view, adrenarche may be related to the highly coordinated events associated with human growth and organ maturation, particularly of the brain [53–55].

Following the onset of adrenarche, plasma concentrations of DHEAS differ between the sexes, with levels of DHEAS being about 2-fold higher in males than in females (**Figure 2**). This difference may reflect secretion of these androgens by the testes [10, 57], but it has also been proposed that the higher concentration of DHEAS in men may be attributable to steroid sulfatase, which degrades androgens. The gene for steroid sulfatase is located on the X chromosome, and in having only one copy of the gene, men may have less steroid sulfatase and consequently higher DHEAS concentrations [58].

Maximal plasma concentrations of DHEAS normally occur at 20–30 years of age (**Figure 2**), followed by a progressive decline in adrenal production in both males and females, until serum concentrations of DHEAS return to pre-adrenarche levels in persons over 80 years of age [59, 60]. The magnitude of this decline is such that serum levels of DHEAS in elderly adults are only around 10–20% of those in young adults [1, 61]. The diminution in adrenal androgens with aging is often termed ‘adrenopause.’ It has been suggested that adrenopause is associated with a generalized reduction in the 17,20 lyase activity of P450c17 in the zona reticularis of the adrenal gland [62]. Interestingly, it has been shown that the zona reticularis of older men is reduced in size when compared to the adrenals of young men [63], suggesting that at least part of the age-associated

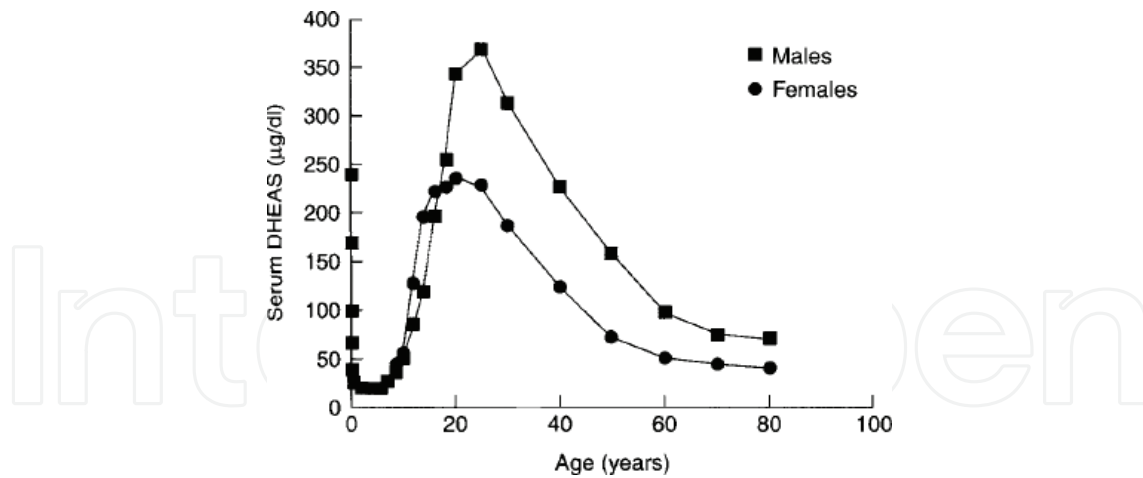


Figure 2. Concentrations of serum DHEAS as a function of age in females and males. Values are high in cord blood and immediately after birth, fall in the first months of life as the fetal adrenal zone involutes, and remain low until the onset of adrenarche at about age 8 years in girls and age 9 years in boys. Peak DHEAS concentrations are usually higher in males than in females. In both sexes, the concentrations of DHEAS decline slowly during the adult years. From Miller [56].

decrease in adrenal androgens might relate to a reduction in the number of DHEA-secreting cells in the zona reticularis itself. Although the underlying mechanisms regarding this change must be further elucidated, the temporal association between falling DHEA concentrations and the onset of age-related diseases has led many investigators to suggest that some age-related neurological disorders such as AD and dementia may be partly attributable to the decrease in systemic DHEA concentrations [11].

2.2. DHEA and cognition

The gradual decline in serum concentrations from the peak at 20–30 years of age has led to speculations that low DHEA concentrations could have a negative effect on cognitive function in later life. It has been hypothesized that rise in DHEA concentrations from 6 to 8 years until 20–30 years of age might be associated with the extended period of cortical maturation in humans [55]. While numerous animal studies have shown that DHEA can modulate cognitive performance, the outcomes of such studies in humans are less clear. For example, one study reported that DHEA supplementation improves cognitive performance in young men [64], whereas other studies detected no benefit in an older group who were predominantly male and were HIV-1 seropositive [65]. DHEA supplementation does not appear to improve cognition in the elderly [66].

A study evaluating the cognitive domains of working memory, executive function, and word processing speed in men and women aged between 60 and 88 years with low serum DHEAS concentrations found a positive association between serum DHEAS and working memory [67]. However, the relationship was sex-specific, with a trend toward a better executive function in men only. Other studies in males have shown that increased endogenous androgen concentrations (following cessation of chemical castration in males) resulted in improved performance on the Cambridge Cognitive Examination (part of the Cambridge Examination

for Mental Disorders of the Elderly, a global measure of cognition and memory) and verbal recall tests [68]. A study in a population of older healthy women (aged 21–77 years) further indicated that women with high serum concentrations of DHEAS had increased performance on a variety of cognitive tests, including better verbal, visual, and spatial abilities; working memory; attention; concentration; and accuracy [69]. In older men and women in an Italian cohort, low DHEAS levels were significant predictors of accelerated decline in Mini-Mental State Examination score during the 3-year follow-up period [70]. Despite these associations, Mazat et al. [71] reported no significant role for serum DHEAS concentrations as a predictor of cognitive decline in an elderly population, while other studies conducted in frail elderly patients and nursing home residents found an inverse relationship between DHEAS levels and cognitive abilities [72, 73].

While the reasons for the conflicting data on DHEAS and cognition require further investigation, the changes in cognition are likely to be reflective of interactions with both the GABAergic and glutamatergic pathways, and possibly through the mediator brain-derived neurotrophic factor (BDNF). Neurosteroids have contrasting effects on GABA_A receptors, which when activated result in chloride entry into the cell, hyperpolarization, and reduced membrane excitability [48]. Reduced metabolites of progesterone and deoxycorticosterone have an agonistic effect on GABA_A receptors, resulting in chloride ion movement into the cell. In contrast, DHEAS is a GABA_A antagonist and thus increases the likelihood of membrane depolarization [48, 74]. Animal studies have shown that acute exposure to DHEAS may facilitate basal synaptic transmission in the CA1 region of the hippocampus through the non-competitive potentiation of GABA_A receptors [75–77]. In terms of learning and memory, studies have shown that acute administration of DHEAS facilitates primed-burst potentiation, but not the induction of long-term potentiation [78], whereas long-term potentiation is stimulated by the chronic administration of DHEAS [79].

In addition to GABA_A receptor modulation, neurosteroids have been found to interact in a structure-specific manner with glutamatergic NMDA receptors. DHEAS potentiates the neuronal response to NMDA in the rat hippocampus [80]. These steroids also act as non-selective sigma-1 receptor antagonists [81], thus suppressing the activity of NMDA receptors, which are central to the process of excitotoxicity [82]. In addition, DHEAS may reduce the cytoplasmic Ca²⁺-induced loss of mitochondrial membrane potential by preventing Ca²⁺ influx into the mitochondrial matrix [83]. The neuroprotective effect of DHEA against NMDA-induced excitotoxicity may also involve the calcium/nitric oxide signaling pathway, since DHEA has been shown to inhibit NMDA-induced nitric oxide synthase activity and the production of nitric oxide in primary cultures of hippocampal neurons [84].

The potential of DHEAS to modulate the activity of NMDA receptors through a variety of mechanisms is likely to underpin their capacity to protect neurons from excitotoxicity when high levels of extracellular glutamate are present. Of note, glutamate excitotoxicity has been implicated in AD [85] (discussed further below), where a reduction in neurosteroid production may compromise the intrinsic defense mechanisms of the central nervous system (CNS). Another possible mechanism by which DHEAS could promote neurogenesis and neuronal survival in the CNS is through the mediation of the neurotrophin BDNF [86, 87].

BDNF is expressed in several areas of the CNS and is necessary for cell proliferation and differentiation [88, 89]. In addition, BDNF plays a vital role in neural plasticity, enhances long-term potentiation, and promotes learning and memory [90, 91]. As such, a mutation or deletion of the BDNF gene in mice results in learning deficits and long-term potentiation impairment [92, 93], as well as decreased learning and memory in behavioral paradigms [90]. In humans, low plasma BDNF is associated with impairments in memory and general cognitive function in aging women [94].

A recent study investigated the effect of DHEA on cognition and learning in a rat model of vascular dementia [86] and found that DHEA treatment significantly preserved working and reference memory, which was accompanied by a significant increase in the levels of acetylcholine, norepinephrine, and dopamine in the brain. Of note was a significant increase in the hippocampal expression of BDNF after DHEA treatment [86]. In a rodent model, Naert et al., [95] showed that DHEAS treatment can lead to biphasic increases in BDNF in the hippocampus and amygdala, but decreased BDNF concentrations in the hypothalamus. It is interesting to note that glucocorticoids are also involved in BDNF regulation [27, 96], where stress has been found to decrease the expression of BDNF, leading to neuronal atrophy and degeneration in the hippocampus and the cortex, a process that may be common to both development and aging [97, 98]. These findings are important, considering, that BDNF expression is also altered in acute psychiatric disorders such as major depression [99, 100] and schizophrenia [101], as well as in neurodegenerative diseases such as AD [102].

2.3. DHEA and AD

AD is a chronic neurodegenerative disorder characterized by progressive memory loss and cognitive deterioration. It is the most common form of dementia, affecting about 50 million people worldwide [103], with the majority of cases in the elderly population, which presents global health and economic challenges [104]. Currently, there are no disease-modifying therapies available to treat AD [105], and it represents a major unmet need in neurological research and patient management. The neuropathological hallmarks of AD include neurofibrillary tangles, which are formed when the neuronal cytoskeletal protein tau becomes hyperphosphorylated and precipitates, and also amyloid plaques, which are abnormal deposits of extracellular protein that accumulate after cleavage of the β -amyloid precursor protein [106]. Other degenerative changes include cerebral amyloid angiopathy, glial inflammatory responses, and synaptic loss. These processes ultimately lead to neuronal atrophy, white matter loss, and a reduction in the volumes of the entorhinal, temporal, and frontal cortices as well as the hippocampus [107], followed by devastating clinical sequelae and resultant morbidity and mortality [108].

Sporadic AD is the predominant form of the disease, present in more than 95% of patients, and it usually occurs after 65 years of age [109]. The etiology of sporadic AD is multifactorial and may be associated with a number of risk factors including advancing age [110, 111], increased oxidative stress [112, 113], autoimmunity [114], and excess glucocorticoids [115–117]. Although serum DHEA levels decrease with age, the majority of studies have reported that serum DHEAS levels in AD patients are even lower than in age-matched healthy controls. For

instance, Yanase et al. [18] found that patients with AD or cerebrovascular dementia had lower concentrations of serum DHEAS and a lower DHEAS/DHEA ratio when compared to controls. Several other clinical studies have reported lower serum concentrations of DHEAS in patients with AD [14, 118–120], a reduction paralleled by decreases in the brain and cerebral spinal fluid [121, 122]. For instance, Weill-Engerer and colleagues [108] reported that not only are brain levels of DHEAS significantly lower in AD, but also the lower levels are inversely correlated with the presence of phosphorylated tau and β -amyloid. A few studies have not detected differences in serum DHEAS concentrations between AD patients and controls [120, 123], and there is one report that serum DHEAS levels are increased in mild-moderate AD [124]. The reasons for these differences between studies have not yet been elucidated.

In contrast to the majority of studies, Naylor and colleagues [125] reported that cerebral spinal fluid levels of DHEA are significantly elevated in AD, as are tissue levels in the temporal cortex, with the extent of elevation being correlated with disease severity, as assessed by the burden of β -amyloid plaques. Similarly, Brown and colleagues [126] reported increased DHEA concentrations in the brains and cerebral spinal fluid of patients with AD when compared with controls, even though mean serum concentrations of DHEA did not differ. Interestingly, in this study, DHEA concentrations were highest in the hippocampus of AD patients, a region that does not express P450c17. Brown and colleagues speculated that the higher concentrations of DHEA in the hippocampus may have been produced by an as-yet-unknown pathway that involved the oxidation of an unknown precursor. This speculation has been given support by the finding that the addition of redox-active ferrous iron to serum samples causes a significant increase in the amount of detectable DHEA [127]. It is also supported by the demonstration that oxidative stress associated with the presence of β -amyloid treatment induces DHEA synthesis in human and rodent cells *in vitro* [126–129]. In this context, it is interesting that the brain regions containing the higher concentrations of DHEA [126] also have higher burdens of neuritic plaques and β -amyloid immunoreactivity, features that are generally associated with AD progression [130]. It may be significant that DHEA protects HT-22 cells (an immortalized mouse hippocampal cell line) against amyloid β protein toxicity in a dose-dependent manner [131].

Another link to the pathogenesis and progression of AD comes from the anti-inflammatory properties of DHEA [132]. Hence, the local production of DHEA in the AD brain may function, at least in part, to reduce the level of inflammation that would otherwise be injurious to neurons if left unchecked. Serum levels of DHEAS have been shown to negatively correlate with serum interleukin-6 (IL-6), to inhibit IL-6 secretion from human mononuclear cells [133], and to inhibit cytokine-stimulated, NF- κ B-mediated transcription, partly through an antioxidant property [134]. Interestingly, elevated levels of IL-6 are consistently detected in the brains of AD patients, but not in the brains of non-demented elderly persons [135]. Several studies have suggested that an increase of circulating IL-6 in AD patients indicates immune activation and may be related to the pathophysiology of AD [136–138].

Perhaps the most intriguing link between DHEA and AD comes from its association with systemic stress and glucocorticoid production, which has led to the hypothesis that chronic stress is an important factor in AD pathogenesis [139]. Epidemiological evidence supports a role for stress in AD because elderly individuals prone to psychological distress are more

likely to develop the disorder than age-matched, nonstressed individuals [117]. Cortisol is the most prominent stress-related glucocorticoid in human serum. Serum cortisol levels are elevated in patients with AD [140], as are the levels of urinary cortisol [141]. It is pertinent that the overactivation of GABA_A receptors plays a central role in anxiety disorders and consequently these receptors are the principal targets of anxiolytic drugs for the treatment of affective disorders [142]. Since DHEAS antagonizes GABA_A receptors, they are thought to act as endogenous anxiolytics, and hence a reduction in the availability of DHEAS in aging or AD could contribute to increased anxiety and stimulate the chronic production of cortisol.

Animal experiments have shown that excess concentrations of glucocorticoids during prolonged periods of stress can have deleterious effects on the brain, especially in aged animals, and particularly affecting the hippocampus [143]. Glucocorticoids exert several actions on the brain, including the stimulation of glutamatergic neurotransmission via the stimulation of glucocorticoid receptors (GR), which if left unchecked can lead to excitotoxicity. Several studies have shown that DHEA can protect against the effects of glucocorticoid-mediated neurotoxicity [144, 145]. The neuroprotective effects of DHEA have been modeled *in vivo* where the toxic effects of corticosterone in the dentate gyrus of male rats were suppressed by low concentrations of DHEA [146]. The protection conferred by DHEA may be via downregulating the expression of glucocorticoid receptors [147]. In cultured HT-22 cells, DHEA augmentation suppresses the nuclear localization of the GR in response to glutamate toxicity, as assessed by immunohistochemistry [131]. Thus, inhibition of GR translocation into the nucleus is a possible mechanism of DHEA's anti-glucocorticoid effects. DHEA administration reduces GR expression in hippocampal cells in the mouse [131] and reduces glucocorticoid receptors by 50% in the rat liver [145]. Furthermore, DHEA may act as a GR antagonist and can attenuate the translocation of stress-activated protein kinase-3 in rat hippocampal primary cultures [148].

DHEA may also attenuate the neurotoxic effects of cortisol by reducing the regeneration of active glucocorticoids. The 7 α -hydroxylated metabolite of DHEA (7 α -hydroxy-DHEA) has antiglucocorticoid effects in target tissues by competition with 11-keto glucocorticoids for access to 11 β -hydroxysteroid dehydrogenase-1 [149]. Enzyme kinetic data from yeast-expressed human 11 β -hydroxysteroid dehydrogenase imply that 7 α -hydroxysteroid substrates are preferred to cortisone by this enzyme [150]. Therefore, in tissues such as the brain, 7 α -hydroxy-DHEA may act as an endogenous inhibitor of 11 β -hydroxysteroid dehydrogenase, thereby reducing the regeneration of active glucocorticoids [151]. 7 α -hydroxy-DHEA may have more potent bioactivity and stronger neuroprotective and antiglucocorticoid effects than DHEA itself [152]. Interestingly, some investigators have hypothesized that the degree of metabolism of DHEA to 7 α -hydroxy-DHEA is related to the pathology of AD [122, 151, 153, 154]. This is evident in the study by Yau et al. [151], which found that gene expression for cytochrome P4507b (which converts DHEA into 7 α -hydroxy-DHEA) was significantly decreased in hippocampal dentate neurons from patients with AD when compared to controls [151]. Another study found lower plasma 7 α -hydroxy-DHEA concentrations in patients with AD when compared to controls [154].

Taken together, the preceding observations are generally supportive of the view that DHEAS levels in serum are reduced in AD when compared to those in healthy age-matched controls.

Given that DHEAS reduces oxidative stress and neuroinflammation, protects against glutamate excitotoxicity, and minimizes the negative effects of cortisol on the brain, the reduced levels of serum DHEAS are likely to increase the vulnerability of the brain to these factors. While limited evidence suggests that the brain may compensate by increasing the local production of DHEAS, this may not be sufficient to slow the pathogenesis of the disease.

2.4. DHEA in schizophrenia

In addition to neurodegenerative diseases, there is evidence that low levels of circulating DHEA with normal levels of glucocorticoids (cortisol) place the developing brain at risk for a range of acute neuropsychiatric disorders, including major depressive disorder, bipolar disorder, and anxiety [155–158]. It is further hypothesized that abnormalities of the hypothalamic-pituitary-adrenal (HPA) axis play a central role in the pathogenesis and etiology of schizophrenia [159–161]. Low ratios of DHEA to cortisol have been noted in patients with schizophrenia and are positively associated with the severity of depression, state and trait anxiety, anger, and hostility [155]. DHEA augmentation in affected patients has been seen to attenuate the severity of some negative symptoms associated with this mental illness, including lack of volition and drive, and social withdrawal [16, 162].

Previous studies have found evidence of abnormal dopaminergic activity [163] and deficits in GABAergic and glutamatergic activity [164] in the brain tissue of patients with schizophrenia. Neuroactive steroids such as DHEA modulate the activity of these neurotransmitter systems, both directly and indirectly, and therefore may contribute to the pathophysiology of the illness [82, 165–168]. A number of studies [169] have reported elevated plasma levels of DHEA and DHEAS in severely psychotic male subjects [170, 171], medicated patients with chronic schizophrenia [172], and nonmedicated first-episode patients [170, 173] compared with controls. Elevated DHEA levels have been detected in the *post-mortem* brain tissue of schizophrenic patients in both the posterior cingulate and parietal cortex [171]. In addition to this, the levels of allopregnanolone are significantly lower in the schizophrenic parietal cortex when compared with healthy controls, whereas pregnenolone levels are significantly higher [49]. Since both of these neurosteroids are downstream metabolites of DHEA, these data suggest that DHEA is preferentially metabolized to pregnenolone in patients with schizophrenia [49]. As DHEA is a positive modulator of excitatory NMDA receptors, and allopregnanolone is a positive modulator of the inhibitory GABA_A receptors, the shift in the ratio of DHEA:allopregnanolone could favor a net increase in neuronal excitation [49], similar to the alterations in brain neurotransmitter systems seen in schizophrenia patients.

As a result of the positive modulatory effects of DHEA on NMDA receptors [49], in addition to its capacity to enhance learning and memory in rodent models [174], it may be speculated that an elevation of DHEA levels reflects a compensatory process in the schizophrenic brain. It is possible that subjects with schizophrenia may be physiologically resistant to DHEA action in some manner (potentially resulting in the increased synthesis of this neurosteroid) or that there is dysregulation in a feedback system involving the HPA axis [175]. Specifically, DHEA increases following cortisol-releasing hormone [49] and adrenocorticotrophic hormone [176] administration in humans, and persistent DHEA elevations may reflect a prolonged upregulation of this axis [177].

As noted earlier, DHEA can protect neurons from glutamate excitotoxicity, β -amyloid toxicity, and oxidative stress [49, 131], and furthermore, oxidative stress can lead to increased DHEA formation [84, 178]. Oxidative stressors may therefore stimulate DHEA levels in schizophrenic patients [126], in an adaptive change to other precipitating disease factors.

However, other studies have found no difference in DHEA levels between schizophrenic and control subjects [49], and some studies have reported significantly reduced plasma DHEA concentrations [179–181], particularly in the morning [180, 182, 183], as well as abnormal DHEA diurnal rhythms [184] in schizophrenics compared with matched controls. Furthermore, DHEA augmentation has been found to be effective in the management of depressive and anxiety symptoms of patients with schizophrenia [185], suggesting that higher levels of circulating DHEA in schizophrenic populations may be associated with superior functioning [16]. The inconsistency between studies is understandable in view of the wide clinical polymorphism, variability of psychometric properties (distress and anxiety), drug treatment, and clinical responsiveness of schizophrenia patients to their antipsychotic treatment [169].

It may be difficult to interpret the significance of elevated or decreased DHEA levels in the absence of concentrations of other HPA axis hormones. Dysregulation of the HPA axis described in schizophrenia [13] includes increased basal cortisol levels [186], cortisol non-suppression on the dexamethasone suppression test [187], increased adrenocorticotrophic hormone and cortisol response to the dexamethasone/cortisol releasing hormone challenge test [188], and increases in glucocorticoid receptor mRNA as observed *post-mortem* [189]. DHEA and cortisol are both cleaved from 17-hydroxypregnenolone and are adrenocorticotrophic hormone regulated [190]. It is not clear, therefore, if an elevated DHEA concentration is specific to a particular disease state or due to a generalized overactivation of the HPA axis. This difference is of functional significance as DHEA possesses antiglucocorticoid properties and may protect against some of the deleterious effects of persistently elevated cortisol levels [145]. This can be clarified by determining the cortisol/DHEA ratio, which may be a more appropriate measurement than DHEA alone [191]. If the biological response to stress is impaired among schizophrenia patients, it is possible that the cortisol/DHEA ratio would be elevated as a result of stress associated with the illness [192].

There is also evidence for oligodendrocyte and myelin dysfunction in neuropathologies such as schizophrenia and bipolar affective disorder, where alterations in the cortisol/DHEA ratio have been observed [16, 17, 155]. Some key oligodendrocyte and myelination genes (such as proteolipid protein 1 and myelin-associated glycoprotein), and transcription factors that regulate the expression of these genes, are downregulated in brains of schizophrenia and bipolar subjects [193]. Together, these studies indicate that common pathophysiological pathways may govern the disease phenotypes of schizophrenia, as well as other neurodegenerative diseases that specifically involve oligodendrocytes.

3. Conclusion

A significant body of preclinical research investigating the biological actions of DHEA have shown that this steroid, and its sulfated congener DHEAS, has a multifunctional role in a

variety of physiological systems, including in the developing and aging brain. A summary of the actions of DHEA relevant to the discussion above is shown in **Table 1**. The present review has highlighted the involvement of DHEAS in glutamatergic and GABAergic

DHEA	Effects/function
Receptor interactions:	Agonistic and antagonistic effects on AR, agonist at ER α and ER β [40, 41] Modulates the NMDA receptor [42–44] Positive allosteric modulator of the GABA-A receptor [46–49] Nonselective sigma-1 receptor antagonist [81] Selective antagonist of the GR [50]
Development & regeneration:	Maintenance and endocrine control of pregnancy [51] Associated with human growth and organ maturation, particularly of the brain, during adrenarche [53–55] Promotes neurogenesis and neuronal survival in the CNS through the mediation of BDNF [86, 87]
Memory and learning:	DHEAS may facilitate basal synaptic transmission in the CA1 region of the hippocampus [75–77] Acute DHEAS administration facilitates primed-burst potentiation [78] and chronic administration of DHEAS stimulates LTP [79] DHEA treatment significantly preserves working and reference memories and increases acetylcholine, norepinephrine, and dopamine concentrations in the rat brain [86]
Neuroprotection: <i>Anti-excitatory actions</i>	Reduces the cytoplasmic Ca ²⁺ -induced loss of mitochondrial membrane potential by preventing Ca ²⁺ influx into the mitochondrial matrix [83] Inhibits NMDA-induced nitric oxide synthase activity and the production of nitric oxide in primary cultures of hippocampal neurons [84] Protect neurons from glutamate excitotoxicity, β -amyloid toxicity, and oxidative stress [49, 131]
<i>Anti-inflammatory actions</i>	Inhibits IL-6 secretion from human mononuclear cells [133] Inhibits cytokine-stimulated, NF- κ B-mediated transcription, partly through an antioxidant property [134]
<i>Antiglucocorticoid actions</i>	GR antagonist and can attenuate the translocation of stress-activated protein kinase-3 in rat hippocampal primary cultures [148] Suppresses the nuclear localization of the GR in response to glutamate toxicity and inhibition of GR translocation into the nucleus [131] Downregulation of the expression of glucocorticoid receptors [147] Reduces the regeneration of active glucocorticoids [149]

Abbreviations: AR, androgen receptor; BDNF, brain-derived neurotrophic factor; CNS, central nervous system; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate; ER, estrogen receptor; GABA-A, Gamma-aminobutyric acid receptor A; GR, glucocorticoid receptor; IL-6, interleukin 6; LTP, long-term potentiation; NMDA, N-methyl-D-aspartate.

Table 1. Summary of functions of DHEA related to development and aging.

neurotransmission, where this neurohormone acts as an important modulator of neuronal excitability. Consequently, perturbations in the level of DHEA can affect cognition and mood. DHEAS has also been shown to respond to stress and to modulate the effects of cortisol on the brain. Reductions in the availability of DHEAS can increase the likelihood of glutamate excitotoxicity as well as exacerbate the deleterious effects of cortisol. Evidence indicates that the brain is not dependent on serum levels of DHEA as it is able to synthesize DHEAS *in situ*. Indeed, there appears to be a capacity to produce DHEA in direct response to oxidative stress. We have shown that in AD, the levels of DHEA are depleted, and the subsequent loss of protection from glutamate, cortisol, and oxidative stress may contribute to the pathogenesis of the disease. Conversely, in schizophrenia, there appears to be an elevation in the availability of DHEA, and this may act to decrease the influence of the GABAergic inhibitory pathways in favor of excitatory neurotransmission. While these emerging roles for DHEA are exciting, the present review also highlighted the discordant findings in the clinical literature, and it is clear that much remains to be learned about the contribution of DHEAS to brain function in both health and disease.

Acknowledgements

The authors are grateful for support and many discussions from Dr. Udani Ratnayake, Dr. Stacey Ellery, Dr. Margie Castillo-Melendez, and Dr. Hayley Dickinson from The Ritchie Centre, Hudson Institute of Medical Research, and from Professor Jonathan Hirst, University of Newcastle, New South Wales, Australia. Tracey Quinn received support from an Australian Post-graduate Award (APA) postgraduate scholarship for some of the studies reported above. Tracey Quinn and David Walker are grateful for funding from National Health & Medical Research Council of Australia and Cerebral Palsy Alliance. We also acknowledge generous support from the Victorian Government Infrastructure Fund to the Hudson Institute of Medical Research.

Author details

Tracey A. Quinn¹, Stephen R. Robinson² and David Walker^{2*}

*Address all correspondence to: david.walker@rmit.edu.au

1 The Ritchie Centre, Monash University, Melbourne, Australia

2 School of Health and Biomedical Sciences, RMIT University, Melbourne, Australia

References

- [1] Parker CR. Dehydroepiandrosterone and dehydroepiandrosterone sulfate production in the human adrenal during development and aging. *Steroids*. 1999;**64**:640-647

- [2] Kroboth PD, Salek FS, Pittenger AL, Fabian TJ, Frye RF. DHEA and DHEA-S: A review. *Journal of Clinical Pharmacology*. 1999;**39**:327-348
- [3] Chen CC, Parker Jr CR. Adrenal androgens and the immune system. *Seminars in Reproductive Medicine*. 2004;**22**:369-377
- [4] Arquitt AB, Stoecker BJ, Hermann JS, Winterfeldt EA. Dehydroepiandrosterone sulfate, cholesterol, hemoglobin, and anthropometric measures related to growth in male adolescents. *Journal of the American Dietetic Association*. 1991;**91**:575-579
- [5] Zemel BS, Katz SH. The contribution of adrenal and gonadal androgens to the growth in height of adolescent males. *American Journal of Physical Anthropology*. 1986;**71**:459-466
- [6] Johnson M, Bebb R, Sirrs S. Uses of DHEA in aging and other disease states. *Ageing Research Reviews*. 2002;**1**:29-41
- [7] Allolio B, Arlt W. DHEA treatment: Myth or reality? *Trends in Endocrinology & Metabolism*. 2002;**13**:288-294
- [8] Eberling P, Koivisto V. Physiological importance of dehydroepiandrosterone. *The Lancet*. 1994;**343**:1479-1481
- [9] Widstrom RL, Dillon JS. Is There a Receptor for Dehydroepiandrosterone or Dehydroepiandrosterone Sulfate?: *Seminars in Reproductive Medicine*. New York, NY, USA: Thieme Medical Publishers, Inc.; 2004;**22**:289-298
- [10] Rainey WE, Carr BR, Sasano H, Suzuki T, Mason JI. Dissecting human adrenal androgen production. *Trends in Endocrinology & Metabolism*. 2002;**13**:234-239
- [11] 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. *Proceedings of the National Academy of Sciences of the United States of America*. 1996;**93**:13410-13415
- [12] Krug A, Ziegler C, Bornstein S. DHEA and DHEA-S, and their functions in the brain and adrenal medulla. In: Ritsner M, Weizman A, editors. *Neuroactive Steroids in Brain Function, Behavior and Neuropsychiatric Disorders*. The Netherlands: Springer; 2008. p. 227-239
- [13] Ritsner M, Gibel A, Maayan R, Ratner Y, Ram E, Biadsky H, Modai I, Weizman A, Ritsner M, Gibel A, Ram E, Maayan R, Weizman A. Alterations in DHEA metabolism in schizophrenia: Two-month case-control study. *European Neuropsychopharmacology*. 2006;**16**:137-146
- [14] Aldred S, Mecocci P. Decreased dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEA-S) concentrations in plasma of Alzheimer's disease (AD) patients. *Archives of Gerontology and Geriatrics*. 2010;**51**:e16-e18
- [15] Ritsner M, Maayan R, Gibel A, Weizman A. Differences in blood pregnenolone and dehydroepiandrosterone levels between schizophrenia patients and healthy subjects. *European Neuropsychopharmacology*. 2007;**17**:358-365

- [16] Strous RD, Maayan R, Lapidus R, Stryjer R, Lustig M, Kotler M, Weizman A. Dehydroepiandrosterone augmentation in the management of negative, depressive, and anxiety symptoms in schizophrenia. *Archives of General Psychiatry*. 2003;**60**:133-141
- [17] Gallagher P, Watson S, Smith MS, Young AH, Ferrier IN. Plasma cortisol-dehydroepiandrosterone (DHEA) ratios in schizophrenia and bipolar disorder. *Schizophrenia Research*. 2007;**90**:258-265
- [18] Yanase T, Fukahori M, Taniguchi S, Nishi Y, Sakai Y, Takayanagi R, Haji M, Nawata H. Serum dehydroepiandrosterone (DHEA) and DHEA-sulfate (DHEA-S) in Alzheimer's disease and in cerebrovascular dementia. *Endocrine Journal*. 1996;**43**:119-123
- [19] Wick G. Anti-aging'medicine: Does it exist? A critical discussion of 'anti-aging health products'. *Experimental Gerontology*. 2002;**37**:1137-1140
- [20] Jaroff: New age therapy. *Time* 1995;**23**:52
- [21] Morales AJ, Nolan JJ, Nelson JC, Yen S. Effects of replacement dose of dehydroepiandrosterone in men and women of advancing age. *Journal of Clinical Endocrinology and Metabolism*. 1994;**78**:1360-1367
- [22] Nawata H, Yanase T, Goto K, Okabe T, Ashida K. Mechanism of action of anti-aging DHEA-S and the replacement of DHEA-S. *Mechanisms of Ageing and Development*. 2002;**123**:1101-1106
- [23] Sands DE, Chamberlain GH. Treatment of inadequate personality in juveniles by dehydroisoandrosterone: preliminary report. *British Medical Journal*. 1952;**2**:66-68
- [24] Strauss EB, Sands DE, Robinson AM, Tindall WJ, Stevenson WA. Use of dehydroisoandrosterone in psychiatric treatment: A preliminary survey. *British Medical Journal*. 1952;**2**:64-66
- [25] Watson RR, Huls A, Araghinikuan M, Chung S. Dehydroepiandrosterone and diseases of aging. *Drugs & Aging*. 1996;**9**:274-291
- [26] Bastianetto S, Ramassamy C, Poirier J, Quirion R. Dehydroepiandrosterone (DHEA) protects hippocampal cells from oxidative stress-induced damage. *Molecular Brain Research*. 1999;**66**:35-41
- [27] Evans JG, Malouf R, Huppert F, van Niekerk JK: Dehydroepiandrosterone (DHEA) supplementation for cognitive function in healthy elderly people. *Cochrane Database of Systematic Reviews* 2006
- [28] Olshansky SJ, Hayflick L, Carnes BA. No truth to the fountain of youth. *Scientific American*. 2004;**14**:98-102
- [29] Rosenfeld R, Hellman L, Roffwarg H, Weitzman ED, Fukushima DK, Gallagher T. Dehydroisoandrosterone is secreted episodically and synchronously with cortisol by normal man. *The Journal of Clinical Endocrinology and Metabolism*. 1971;**33**:87-92

- [30] Lejeune-Lenain C, Van Cauter E, Desir D, Beyloos M, Franckson J. Control of circadian and episodic variations of adrenal androgens secretion in man. *Journal of Endocrinological Investigation*. 1987;**10**:267
- [31] Greaves RF et al. *Clinical Chemistry and Laboratory Medicine*. 2017;**55**(4):522-529
- [32] Parker CR, Staton B, Grilliot M. Ontogeny of cytochrome b-5 and cytochrome p450c17 in the human fetal adrenal gland during normal development. *Endocrine Research*. 2004;**30**:541-542
- [33] Kominami S, Ogawa N, Morimune R, Huang DY, Takemori S. The role of cytochrome-b5 in adrenal microsomal steroidogenesis. *Journal of Steroid Biochemistry and Molecular Biology*. 1992;**42**:57-64
- [34] Katagiri M, Kagawa N, Waterman MR. The role of cytochrome b5 in the biosynthesis of androgens by human p450c17. *Archives of Biochemistry and Biophysics*. 1995;**317**:343-347
- [35] Nguyen AD, Corbin CJ, Pattison JC, Bird IM, Conley AJ. The developmental increase in adrenocortical 17,20-lyase activity (biochemical adrenarche) is driven primarily by increasing cytochrome b5 in neonatal rhesus macaques. *Endocrinology*. 2009;**150**:1748-1756
- [36] Labrie F, Bélanger A, Luu-The V, Labrie C, Simard J, Cusan L, Gomez J-L, Candas B. DHEA and the intracrine formation of androgens and estrogens in peripheral target tissues: Its role during aging. *Steroids*. 1998;**63**:322-328
- [37] Labrie C, Flamand M, Belanger A, Labrie F. High bioavailability of dehydroepiandrosterone administered percutaneously in the rat. *The Journal of Endocrinology*. 1996;**150**:S107-S118
- [38] Maninger N, Wolkowitz OM, Reus VI, Epel ES, Mellon SH. Neurobiological and neuropsychiatric effects of dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEA-S). *Frontiers in Neuroendocrinology*. 2009;**30**:65-91
- [39] Mangelsdorf DJ, Thummel C, Beato M, Herrlich P, Schütz G, Umesono K, Blumberg B, Kastner P, Mark M, Chambon P. The nuclear receptor superfamily: The second decade. *Cell*. 1995;**83**:835-839
- [40] Chen F, Knecht K, Birzin E, Fisher J, Wilkinson H, Mojena M, Moreno CT, Schmidt A, Harada S-i, Freedman LP. Direct agonist/antagonist functions of dehydroepiandrosterone. *Endocrinology*. 2005;**146**:4568-4576
- [41] Arnold JT, Blackman MR. Does DHEA exert direct effects on androgen and estrogen receptors, and does it promote or prevent prostate cancer? *Endocrinology*. 2005;**146**:4565-4567
- [42] Holsboer F, Grasser A, Friess E, Wiedemann K. Steroid effects on central neurons and implications for psychiatric and neurological disorders. *Brain Corticosteroid Receptors*. 1994;**746**:345-361
- [43] Baulieu EE. Neurosteroids: Of the nervous system, by the nervous system, for the nervous system. *Recent Progress in Hormone Research*. 1997;**52**:1-32

- [44] Rupprecht R. The neuropsychopharmacological potential of neuroactive steroids. *Journal of Psychiatric Research*. 1997;**31**:297-314
- [45] T-P S, London ED, Jaffe JH. Steroid binding at sigma receptors suggests a link between endocrine, nervous, and immune systems. *Science*. 1988;**240**:219-221
- [46] FS W, Gibbs TT, Farb DH. Pregnenolone sulfate – A positive allosteric modulator at the N-methyl-D-aspartate receptor. *Molecular Pharmacology*. 1991;**40**:333-336
- [47] Irwin RP, Lin SZ, Rogawski MA, Purdy RH, Paul SM. Steroid potentiation and inhibition of N-methyl-D-aspartate receptor-mediated intracellular Ca⁺⁺ responses – structure-activity studies. *Journal of Pharmacology and Experimental Therapeutics*. 1994;**271**:677-682
- [48] Compagnone NA, Mellon SH. Dehydroepiandrosterone: A potential signalling molecule for neocortical organization during development. *Proceedings of the National Academy of Sciences of the United States of America*. 1998;**95**:4678-4683
- [49] Marx CE, Stevens RD, Shampine LJ, Uzunova V, Trost WT, Butterfield MI, Massing MW, Hamer RM, Morrow AL, Lieberman JA. Neuroactive steroids are altered in schizophrenia and bipolar disorder: Relevance to pathophysiology and therapeutics. *Neuropsychopharmacology*. 2006;**31**:1249-1263
- [50] Sacco M, Valenti G, Corvi Mora P, FCW W, Ray DW. DHEA, a selective glucocorticoid receptor antagonist: Its role in immune system regulation and metabolism. *Journal of Endocrinological Investigation*. 2002;**25**:81-82
- [51] Ishimoto H, Jaffe RB. Development and function of the human fetal adrenal cortex: A key component in the fetoplacental unit. *Endocrine Reviews*. 2011;**32**:317-355
- [52] de Peretti E, Forest MG. Pattern of plasma dehydroepiandrosterone sulfate levels in humans from birth to adulthood: Evidence for testicular production. *The Journal of Clinical Endocrinology and Metabolism* 1978;**47**:572-577
- [53] Cutler GB, Glenn M, BUSH M, Hodgen GD, Graham CE, Loriaux DL. Adrenarche: A survey of rodents, domestic animals, and primates. *Endocrinology*. 1978;**103**:2112-2118
- [54] Smail PJ, Faiman C, Hobson WC, Fuller GB, Winter JSD. Further studies on adrenarche in nonhuman primates. *Endocrinology*. 1982;**111**:844-848
- [55] Campbell B. Adrenarche and the evolution of human life history. *American Journal of Human Biology*. 2006;**18**:569-589
- [56] Miller WL. The molecular basis of premature adrenarche: An hypothesis. *Acta Paediatrica. Supplementum*. 1999;**433**:60-66
- [57] Goto M, Hanley KP, Marcos J, Wood PJ, Wright S, Postle AD, Cameron IT, Mason JJ, Wilson DI, Hanley NA. In humans, early cortisol biosynthesis provides a mechanism to safeguard female sexual development. *Journal of Clinical Investigation*. 2006;**116**:953-960
- [58] Miller WL. Androgen synthesis in adrenarche. *Reviews in Endocrine and Metabolic Disorders*. 2009;**10**:3-17

- [59] Bates K, Harvey AR, Carruthers M, Martins R. Androgens, andropause and neurodegeneration: Exploring the link between steroidogenesis, androgens and Alzheimer's disease. *Cellular and Molecular Life Sciences*. 2005;**62**:28
- [60] Labrie F, Bélanger A, Cusan L, Gomez J-L, Candas B. Marked decline in serum concentrations of adrenal c19 sex steroid precursors and conjugated androgen metabolites during aging. *Journal of Clinical Endocrinology & Metabolism*. 1997;**82**:2396-2402
- [61] Havelock JC, Auchus RJ, Rainey WE. The rise in adrenal androgen biosynthesis: Adrenarche. *Seminars in Reproductive Medicine*. 2004;**22**:337-347
- [62] Dharia S, Slane A, Jian M, Conner M, Conley AJ, Brissie RM, Parker CR. Effects of aging on cytochrome b5 expression in the human adrenal gland. *The Journal of Clinical Endocrinology and Metabolism*. 2005;**90**:4357-4361
- [63] Parker C, Mixon R, Brissie R, Grizzle W. Aging alters zonation in the adrenal cortex of men. *The Journal of Clinical Endocrinology and Metabolism*. 1997;**82**:3898-3901
- [64] Alhaj HA, Massey AE, McAllister-Williams RH. Effects of DHEA administration on episodic memory, cortisol and mood in healthy young men: A double-blind, placebo-controlled study. *Psychopharmacology*. 2006;**188**:541-551
- [65] Bradley M, McElhiney M, Rabkin J. DHEA and cognition in hiv-positive patients with non-major depression. *Psychosomatics*. 2012;**53**:244-249
- [66] Grimley Evans J, Malouf R, Huppert FA, Van Niekerk JK. Dehydroepiandrosterone (DHEA) supplementation for cognitive function in healthy elderly people. *The Cochrane Library*. 2006
- [67] Hildreth KL, Gozansky WS, Jankowski CM, Grigsby J, Wolfe P, Kohrt WM. Association of serum dehydroepiandrosterone sulfate and cognition in older adults: Sex steroid, inflammatory, and metabolic mechanisms. *Neuropsychology*. 2013;**27**:356
- [68] Almeida OP, Waterreus A, Spry N, Flicker L, Martins RN. One year follow-up study of the association between chemical castration, sex hormones, beta-amyloid, memory and depression in men. *Psychoneuroendocrinology*. 2004;**29**:1071-1081
- [69] Davis SR, Shah SM, McKenzie DP, Kulkarni J, Davison SL, Bell RJ. Dehydroepiandrosterone sulfate levels are associated with more favorable cognitive function in women. *Journal of Clinical Endocrinology & Metabolism*. 2008;**93**:801-808
- [70] Valenti G, Ferrucci L, Lauretani F, Ceresini G, Bandinelli S, Luci M, Ceda G, Maggio M, Schwartz R. Dehydroepiandrosterone sulfate and cognitive function in the elderly: The inchianti study. *Journal of Endocrinological Investigation*. 2009;**32**:766-772
- [71] Mazat L, Lafont S, Berr C, Debuire B, Tessier J-F, Dartigues J-F, Baulieu E-E. Prospective measurements of dehydroepiandrosterone sulfate in a cohort of elderly subjects: Relationship to gender, subjective health, smoking habits, and 10-year mortality. *Proceedings of the National Academy of Sciences*. 2001;**98**:8145-8150

- [72] Morrison MF, Katz IR, Parmelee P, Boyce AA, TenHave T. Dehydroepiandrosterone sulfate (DHEA-S) and psychiatric and laboratory measures of frailty in a residential care population. *The American Journal of Geriatric Psychiatry*. 1998;**6**:277-284
- [73] Breuer B, Martucci C, Wallenstein S, Likourezos A, Libow LS, Peterson A, Zumoff B. Relationship of endogenous levels of sex hormones to cognition and depression in frail, elderly women. *The American Journal of Geriatric Psychiatry*. 2002;**10**:311-320
- [74] Demirgören S, Majewska M, Spivak CE, London E. Receptor binding and electrophysiological effects of dehydroepiandrosterone sulfate, an antagonist of the gaba a receptor. *Neuroscience*. 1991;**45**:127-135
- [75] Park-Chung M, Malayev A, Purdy RH, Gibbs TT, Farb DH. Sulfated and unsulfated steroids modulate γ -aminobutyric acid a receptor function through distinct sites. *Brain Research*. 1999;**830**:72-87
- [76] Majewska MD. Neuronal actions of dehydroepiandrosterone possible roles in brain development, aging, memory, and affect. *Annals of the New York Academy of Sciences*. 1995;**774**:111-120
- [77] Meyer J, Lee S, Wittenberg G, Randall R, Gruol D. Neurosteroid regulation of inhibitory synaptic transmission in the rat hippocampus in vitro. *Neuroscience*. 1999;**90**:1177-1183
- [78] Diamond DM, Branch BJ, Fleshner M. The neurosteroid dehydroepiandrosterone sulfate (DHEA-S) enhances hippocampal primed burst, but not long-term, potentiation. *Neuroscience Letters*. 1996;**202**:204-208
- [79] Chen L, Dai X-N, Sokabe M. Chronic administration of dehydroepiandrosterone sulfate (DHEAs) primes for facilitated induction of long-term potentiation via σ_1 (σ_1) receptor: Optical imaging study in rat hippocampal slices. *Neuropharmacology*. 2006;**50**:380-392
- [80] Maurice T, Roman FJ, Privat A. Modulation by neurosteroids of the in vivo (+)-[3h] skf-10,047 binding to σ_1 receptors in the mouse forebrain. *Journal of Neuroscience Research*. 1996;**46**:734-743
- [81] Maurice T, Grégoire C, Espallergues J. Neuro (active) steroids actions at the neuromodulatory σ_1 (σ_1) receptor: Biochemical and physiological evidences, consequences in neuroprotection. *Pharmacology Biochemistry and Behavior*. 2006;**84**:581-597
- [82] Konradi C, Heckers S. Molecular aspects of glutamate dysregulation: Implications for schizophrenia and its treatment. *Pharmacology & Therapeutics*. 2003;**97**:153-179
- [83] Kaasik A, Safiulina D, Kalda A, Zharkovsky A. Dehydroepiandrosterone with other neurosteroids preserve neuronal mitochondria from calcium overload. *The Journal of Steroid Biochemistry and Molecular Biology*. 2003;**87**:97-103
- [84] Kurata K, Takebayashi M, Morinobu S, Yamawaki S. Beta-estradiol, dehydroepiandrosterone, and dehydroepiandrosterone sulfate protect against N-methyl-D-aspartate-induced neurotoxicity in rat hippocampal neurons by different mechanisms. *Journal of Pharmacology and Experimental Therapeutics*. 2004;**311**:237-245

- [85] X-x D, Wang Y, Qin Z-h. Molecular mechanisms of excitotoxicity and their relevance to pathogenesis of neurodegenerative diseases. *Acta Pharmacologica Sinica*. 2009;**30**:379-387
- [86] Sakr H, Khalil K, Hussein A, Zaki M, Eid R, Alkhateeb M. Effect of dehydroepiandrosterone (DHEA) on memory and brain derived neurotrophic factor (BDNF) in a rat model of vascular dementia. *Journal of Physiology and Pharmacology*. 2014;**65**:41-53
- [87] Pluchino N, Russo M, Santoro A, Litta P, Cela V, Genazzani A. Steroid hormones and BDNF. *Neuroscience*. 2013;**239**:271-279
- [88] Numakawa T, Suzuki S, Kumamaru E, Adachi N, Richards M, Kunugi H. BDNF function and intracellular signaling in neurons. *Histology and Histopathology*. 2010;**25**:237-258
- [89] Mattson MP. Glutamate and neurotrophic factors in neuronal plasticity and disease. *Annals of the New York Academy of Sciences*. 2008;**1144**:97-112
- [90] Lu Y, Christian K, Lu B. BDNF: A key regulator for protein synthesis-dependent LTP and long-term memory? *Neurobiology of Learning and Memory*. 2008;**89**:312-323
- [91] Korte M, Staiger V, Griesbeck O, Thoenen H, Bonhoeffer T. The involvement of brain-derived neurotrophic factor in hippocampal long-term potentiation revealed by gene targeting experiments. *Journal of Physiology-Paris*. 1996;**90**:157-164
- [92] Patterson SL, Abel T, Deuel TA, Martin KC, Rose JC, Kandel ER. Recombinant BDNF rescues deficits in basal synaptic transmission and hippocampal LTP in BDNF knockout mice. *Neuron*. 1996;**16**:1137-1145
- [93] Monteggia LM, Barrot M, Powell CM, Berton O, Galanis V, Gemelli T, Meuth S, Nagy A, Greene RW, Nestler EJ. Essential role of brain-derived neurotrophic factor in adult hippocampal function. *Proceedings of the National Academy of Sciences of the United States of America*. 2004;**101**:10827-10832
- [94] Komulainen P, Pedersen M, Hanninen T, Bruunsgaard H, Lakka TA, Kivipelto M, Hassinen M, Rauramaa TH, Pedersen BK, Rauramaa R. BDNF is a novel marker of cognitive function in ageing women: The Dr's extra study. *Neurobiology of Learning and Memory*. 2008;**90**:596-603
- [95] Gl N, Maurice T, Tapia-Arancibia L, Givalois L. Neuroactive steroids modulate hpa axis activity and cerebral brain-derived neurotrophic factor (BDNF) protein levels in adult male rats. *Psychoneuroendocrinology*. 2007;**32**:1062-1078
- [96] Barbany G, Persson H. Regulation of neurotrophin mRNA expression in the rat brain by glucocorticoids. *European Journal of Neuroscience*. 1992;**4**:396-403
- [97] Roceri M, Cirulli F, Pessina C, Peretto P, Racagni G, Riva MA. Postnatal repeated maternal deprivation produces age-dependent changes of brain-derived neurotrophic factor expression in selected rat brain regions. *Biological Psychiatry*. 2004;**55**:708-714
- [98] Murakami S, Imbe H, Morikawa Y, Kubo C, Senba E. Chronic stress, as well as acute stress, reduces BDNF mRNA expression in the rat hippocampus but less robustly. *Neuroscience Research*. 2005;**53**:129-139

- [99] Tamatam A, Khanum F, Bawa AS. Genetic biomarkers of depression. *Indian Journal of Human Genetics*. 2012;**18**:20-33
- [100] Karege F, Perret G, Bondolfi G, Schwald M, Bertschy G, Aubry J-M. Decreased serum brain-derived neurotrophic factor levels in major depressed patients. *Psychiatry Research*. 2002;**109**:143-148
- [101] Toyooka K, Asama K, Watanabe Y, Muratake T, Takahashi M, Someya T, Nawa H. Decreased levels of brain-derived neurotrophic factor in serum of chronic schizophrenic patients. *Psychiatry Research*. 2002;**110**:249-257
- [102] Connor B, Young D, Yan Q, Faull R, Synek B, Dragunow M. Brain-derived neurotrophic factor is reduced in Alzheimer's disease. *Molecular Brain Research*. 1997;**49**:71-81
- [103] Scheltens P, Blennow K, Breteler MM, de Strooper B, Frisoni GB, Salloway S, Van der Flier WM: Alzheimer's disease. *Lancet (London, England)* 2016;**388**:505-517
- [104] Wimo A, Jönsson L, Bond J, Prince M, Winblad B. International AD: The worldwide economic impact of dementia 2010. *Alzheimer's & Dementia*. 2013;**9**:1-11.e13
- [105] Citron M. Alzheimer's disease: Strategies for disease modification. *Nature Reviews. Drug Discovery*. 2010;**9**:387-398
- [106] Serrano-Pozo A, Frosch MP, Masliah E, Hyman BT. Neuropathological alterations in Alzheimer disease. *Cold Spring Harbor Perspectives in Medicine*. 2011;**1**:a006189
- [107] Arnold SE, Hyman BT, Flory J, Damasio AR, Van Hoesen GW. The topographical and neuroanatomical distribution of neurofibrillary tangles and neuritic plaques in the cerebral cortex of patients with Alzheimer's disease. *Cerebral Cortex*. 1991;**1**:103-116
- [108] Nuovo G, Panicia B, Mezache L, Quiñónez M, Williams J, Vandiver P, Fadda P, Amann V. Diagnostic pathology of Alzheimer's disease from routine microscopy to immunohistochemistry and experimental correlations. *Annals of Diagnostic Pathology*. 2017;**28**:24-29
- [109] Bekris LM, C-E Y, Bird TD, Tsuang DW. Genetics of Alzheimer disease. *Journal of Geriatric Psychiatry and Neurology*. 2010;**23**:213-227
- [110] Hebert LE, Scherr PA, Bienias JL, Bennett DA, Evans DA. Alzheimer disease in the us population: Prevalence estimates using the 2000 census. *Archives of Neurology*. 2003;**60**:1119-1122
- [111] Launer L, Andersen K, Dewey M, Letenneur L, Ott A, Amaducci L, Brayne C, Copeland J, Dartigues J-F, Kragh-Sorensen P. Rates and risk factors for dementia and Alzheimer's disease results from EURODEM pooled analyses. *Neurology*. 1999;**52**:78-78
- [112] Markesbery WR. Oxidative stress hypothesis in Alzheimer's disease. *Free Radical Biology and Medicine*. 1997;**23**:134-147
- [113] Lin MT, Beal MF. Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. *Nature*. 2006;**443**:787-795

- [114] Sardi F, Fassina L, Venturini L, Inguscio M, Guerriero F, Rolfo E, Ricevuti G. Alzheimer's disease, autoimmunity and inflammation. The good, the bad and the ugly. *Autoimmunity Reviews*. 2011;**11**:149-153
- [115] Green KN, Billings LM, Roozendaal B, McGaugh JL, LaFerla FM. Glucocorticoids increase amyloid- β and tau pathology in a mouse model of Alzheimer's disease. *Journal of Neuroscience*. 2006;**26**:9047-9056
- [116] Stein-Behrens B, Mattson M, Chang I, Yeh M, Sapolsky R. Stress exacerbates neuron loss and cytoskeletal pathology in the hippocampus. *Journal of Neuroscience*. 1994;**14**:5373-5380
- [117] Wilson R, Barnes L, Bennett D, Li Y, Bienias J, de Leon CM, Evans D: Proneness to psychological distress and risk of Alzheimer disease in a biracial community. *Neurology* 2005;**64**:380-382
- [118] Sunderland T, Merrill C, Harrington M, Lawlor B, Molchan S, Martinez R, Murphy D. Reduced plasma dehydroepiandrosterone concentrations in Alzheimer's disease. *The Lancet*. 1989;**334**:570
- [119] Näsman B, Olsson T, Bäckström T, Eriksson S, Grankvist K, Viitanen M, Bucht G. Serum dehydroepiandrosterone sulfate in Alzheimer's disease and in multi-infarct dementia. *Biological Psychiatry*. 1991;**30**:684-690
- [120] Leblhuber F, Windhager E, Reisecker F, Steinparz F, Dienstl E, Cuckle H, Stone R, Smith D, Wald N, Brammer M. Dehydroepiandrosterone sulphate in Alzheimer's disease. *The Lancet*. 1990;**336**:449-450
- [121] Weill-Engerer S, David J-P, Sazdovitch V, Liere P, Eychenne B, Pianos A, Schumacher M, Delacourte A, Baulieu E-E, Akwa Y. Neurosteroid quantification in human brain regions: Comparison between Alzheimer's and nondemented patients. *The Journal of Clinical Endocrinology & Metabolism*. 2002;**87**:5138-5143
- [122] Kim S-B, Hill M, Kwak Y-T, Hampl R, Jo D-H, Morfin R. Neurosteroids: Cerebrospinal fluid levels for Alzheimer's disease and vascular dementia diagnostics. *The Journal of Clinical Endocrinology & Metabolism*. 2003;**88**:5199-5206
- [123] Schneider LS, Hinsey M, Lyness S. Plasma dehydroepiandrosterone sulfate in Alzheimer's disease. *Biological Psychiatry*. 1992;**31**:205-208
- [124] Rasmuson S, Näsman B, Carlström K, Olsson T. Increased levels of adrenocortical and gonadal hormones in mild to moderate Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders*. 2002;**13**:74-79
- [125] Naylor JC, Hulette CM, Steffens DC, Shampine LJ, Ervin JF, Payne VM, Massing MW, Kilts JD, Strauss JL, Calhoun PS, Calnido RP, Blazer DG, Lieberman JA, Madison RD, Marx CE. Cerebrospinal fluid dehydroepiandrosterone levels are correlated with brain dehydroepiandrosterone levels, elevated in Alzheimer's disease, and related to neuropathological disease stage. *The Journal of Clinical Endocrinology and Metabolism*. 2008;**93**:3173-3178

- [126] Brown RC, Han ZQ, Cascio C, Papadopoulos V. Oxidative stress-mediated DHEA formation in Alzheimer's disease pathology. *Neurobiology of Aging*. 2003;**24**:57-65
- [127] Rammouz G, Lecanu L, Papadopoulos V. Oxidative stress-mediated brain dehydroepiandrosterone (DHEA) formation in Alzheimer's disease diagnosis. *Frontiers in Endocrinology*. 2011;**2**:69
- [128] Cascio C, Brown RC, Liu Y, Han Z, Hales DB, Papadopoulos V. Pathways of dehydroepiandrosterone formation in rat brain glia. *The Journal of Steroid Biochemistry and Molecular Biology*. 2000;**75**:177-186
- [129] Brown RC, Cascio C, Papadopoulos V. Pathways of neurosteroid biosynthesis in cell lines from human brain: Regulation of dehydroepiandrosterone formation by oxidative stress and beta-amyloid peptide. *Journal of Neurochemistry*. 2000;**74**:847-859
- [130] Gella A, Durany N. Oxidative stress in Alzheimer disease. *Cell Adhesion & Migration*. 2009;**3**:88-93
- [131] Cardounel A, Regelson W, Kalimi M. Dehydroepiandrosterone protects hippocampal neurons against neurotoxin-induced cell death: Mechanism of action. *Proceedings of the Society for Experimental Biology and Medicine*. 1999;**222**:145-149
- [132] Straub RH, Scholmerich J, Zietz B. Replacement therapy with DHEA plus corticosteroids in patients with chronic inflammatory diseases – substitutes of adrenal and sex hormones. *Zeitschrift für Rheumatologie*. 2000;**59**(Suppl 2):Ii/108-Ii/118
- [133] Straub RH, Konecna L, Hrach S, Rothe G, Kreutz M, Schölmerich 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. *The Journal of Clinical Endocrinology & Metabolism*. 1998;**83**:2012-2017
- [134] Iwasaki Y, Asai M, Yoshida M, Nigawara T, Kambayashi M, Nakashima N. Dehydroepiandrosterone-sulfate inhibits nuclear factor-kappaB-dependent transcription in hepatocytes, possibly through antioxidant effect. *The Journal of Clinical Endocrinology and Metabolism*. 2004;**89**:3449-3454
- [135] Hüll M, Fiebich BL, Lieb K, Strauss S, Berger M, Volk B, Bauer J. Interleukin-6-associated inflammatory processes in Alzheimer's disease: New therapeutic options. *Neurobiology of Aging*. 1996;**17**:795-800
- [136] Singh VK, Guthikonda P. Circulating cytokines in Alzheimer's disease. *Journal of Psychiatric Research*. 1997;**31**:657-660
- [137] Cojocaru IM, Cojocaru M, Miu G, Sapira V. Study of interleukin-6 production in Alzheimer's disease. *Romanian journal of internal medicine = Revue roumaine de medecine interne*. 2011;**49**:55-58
- [138] Rubio-Perez JM, Morillas-Ruiz JM. A review: Inflammatory process in Alzheimer's disease, role of cytokines. *The Scientific World Journal*. 2012;**2012**:756357

- [139] Machado A, Herrera AJ, de Pablos RM, Espinosa-Oliva AM, Sarmiento M, Ayala A, Venero JL, Santiago M, Villarán RF, Delgado-Cortés MJ: Chronic stress as a risk factor for Alzheimer's disease. *Reviews in the Neurosciences* 2014;**25**:785-804
- [140] Lei J. Change of serum acth and cortisol levels in Alzheimer disease and mild cognition impairment. *Zhonghua Yi Xue Za Zhi*. 2010;**90**:2894-2896
- [141] Curto M, Martocchia A, Ferracuti S, Comite F, Scaccianoce S, Girardi P, Nicoletti F, Falaschi P. Increased total urinary cortisol (TUC) and serum brain-derived neurotrophic factor (BDNF) ratio in Alzheimer disease (AD)-affected patients. *Alzheimer Disease & Associated Disorders*. 2017;**31**(2):173-176
- [142] Nuss P. Anxiety disorders and gaba neurotransmission: A disturbance of modulation. *Neuropsychiatric Disease and Treatment*. 2015;**11**:165-175
- [143] Sapolsky RM, Krey LC, McEWEN BS. Prolonged glucocorticoid exposure reduces hippocampal neuron number: Implications for aging. *Journal of Neuroscience*. 1985;**5**:1222-1227
- [144] Hu Y, Cardounel A, Gursoy E, Anderson P, Kalimi M. Anti-stress effects of dehydroepiandrosterone: Protection of rats against repeated immobilization stress-induced weight loss, glucocorticoid receptor production, and lipid peroxidation. *Biochem Pharmacol*. 2000;**59**:753-762
- [145] Kalimi M, Shafagoj Y, Loria R, Padgett D, Regelson W. Anti-glucocorticoid effects of dehydroepiandrosterone (DHEA). *Molecular and Cellular Biochemistry*. 1994;**131**:99-104
- [146] Karishma KK, Herbert J. Dehydroepiandrosterone (DHEA) stimulates neurogenesis in the hippocampus of the rat, promotes survival of newly formed neurons and prevents corticosterone-induced suppression. *European Journal of Neuroscience*. 2002;**16**:445-453
- [147] Saponaro S, Guarnieri V, Pescarmona GP, Silvagno F. Long-term exposure to dehydroepiandrosterone affects the transcriptional activity of the glucocorticoid receptor. *The Journal of Steroid Biochemistry and Molecular Biology*. 2007;**103**:129-136
- [148] Kimonides VG, Spillantini MG, Sofroniew MV, Fawcett JW, Herbert J. Dehydroepiandrosterone antagonizes the neurotoxic effects of corticosterone and translocation of stress-activated protein kinase 3 in hippocampal primary cultures. *Neuroscience*. 1999;**89**:429-436
- [149] Muller C, Hennebert O, Morfin R. The native anti-glucocorticoid paradigm. *The Journal of Steroid Biochemistry and Molecular Biology*. 2006;**100**:95-105
- [150] Muller C, Pompon D, Urban P, Morfin R. Inter-conversion of 7 α - and 7 β -hydroxy-dehydroepiandrosterone by the human 11 β -hydroxysteroid dehydrogenase type 1. *The Journal of Steroid Biochemistry and Molecular Biology*. 2006;**99**:215-222
- [151] Yau J, Rasmuson S, Andrew R, Graham M, Noble J, Olsson T, Fuchs E, Lathe R, Seckl J. Dehydroepiandrosterone 7-hydroxylase cyp7b: Predominant expression in primate hippocampus and reduced expression in Alzheimer's disease. *Neuroscience*. 2003;**121**:307-314

- [152] Morfin R, Starka L. Neurosteroid 7-hydroxylation products in the brain. *International Review of Neurobiology*. 2001;**46**:79-95
- [153] Attal-Khemis S, Dalmeyda V, Michot JL, Roudier M, Morfin R. Increased total 7 alpha-hydroxy-dehydroepiandrosterone in serum of patients with Alzheimer's disease. *The journals of gerontology Series A, Biological sciences and medical sciences*. 1998;**53**: B125-B132
- [154] Bicikova M, Ripova D, Hill M, Jirak R, Havlikova H, Tallova J, Hampl R. Plasma levels of 7-hydroxylated dehydroepiandrosterone (DHEA) metabolites and selected amino-thiols as discriminatory tools of Alzheimer's disease and vascular dementia. *Clinical Chemistry and Laboratory Medicine*. 2004;**42**:518-524
- [155] Ritsner M, Maayan R, Gibel A, Strous RD, Modai I, Weizman A. Elevation of the cortisol/dehydroepiandrosterone ratio in schizophrenia patients. *European Neuropsychopharmacology*. 2004;**14**:267-273
- [156] Goodyer I, Park R, Netherton C, Herbert J. Possible role of cortisol and dehydroepiandrosterone in human development and psychopathology. *The British Journal of Psychiatry*. 2001;**179**:243-249
- [157] Wolkowitz OM, Reus VI. Neuropsychiatric effects of dehydroepiandrosterone (DHEA). In: Kalimi M, Regelson W, editors. *Dehydroepiandrosterone (DHEA): biochemical, physiological and clinical aspects*. Berlin: Walter De Gruyter, 2000;271-298
- [158] Harris DS, Wolkowitz OM, Reus VI. Movement disorder, memory, psychiatric symptoms and serum DHEA levels in schizophrenic and schizoaffective patients. *The World Journal of Biological Psychiatry*. 2001;**2**:99-102
- [159] Kunugi H, Nanko S, Murray RM. Obstetric complications and schizophrenia: Prenatal underdevelopment and subsequent neurodevelopmental impairment. *The British Journal of Psychiatry*. 2001;**40**:S25-S29
- [160] Barker DJP. The developmental origins of adult disease. *Journal of the American College of Nutrition*. 2004;**23**:588S-595S
- [161] Gilmore JH, Jarskog LF, Vadlamudi S. Maternal poly i:C exposure during pregnancy regulates TNF-alpha, BDNF, and NGF expression in neonatal brain and the maternal-fetal unit of the rat. *Journal of Neuroimmunology*. 2005;**159**:106-112
- [162] Strous RD, Stryjer R, Maayan R, Gal G, Viglin D, Katz E, Eisner D, Weizman A. Analysis of clinical symptomatology, extrapyramidal symptoms and neurocognitive dysfunction following dehydroepiandrosterone (DHEA) administration in olanzapine treated schizophrenia patients: A randomized, double-blind placebo controlled trial. *Psychoneuroendocrinology*. 2007;**32**:96-105
- [163] Raison CL, Miller AH. When not enough is too much: The role of insufficient glucocorticoid signaling in the pathophysiology of stress-related disorders. *American Journal of Psychiatry*. 2003;**160**:1554-1565
- [164] Seeman P, Kapur S. Schizophrenia: More dopamine, more d-2 receptors. *Proceedings of the National Academy of Sciences of the United States of America*. 2000;**97**:7673-7675

- [165] Blum BP, Mann JJ. The gabaergic system in schizophrenia. *International Journal of Neuropsychopharmacology*. 2002;**5**:159-179
- [166] Coyle JT, Tsai G, Goff D. Converging evidence of nmda receptor hypofunction in the pathophysiology of schizophrenia. *Glutamate and Disorders of Cognition and Motivation*. 2003;**1003**:318-327
- [167] Wassef A, Baker J, Kochan LD. Gaba and schizophrenia: A review of basic science and clinical studies. *Journal of Clinical Psychopharmacology*. 2003;**23**:601-640
- [168] Costa E, Davis JM, Dong E, Grayson DR, Guidotti A, Tremolizzo L, Veldic M. A gabaergic cortical deficit dominates schizophrenia pathophysiology. *Critical Reviews in Neurobiology*. 2004;**16**:1-23
- [169] MacKenzie EM, Odontiadis J, Le Melledo JM, Prior TI, Baker GB. The relevance of neuroactive steroids in schizophrenia, depression, and anxiety disorders. *Cellular and Molecular Neurobiology*. 2007;**27**:541-574
- [170] Oades RD, Schepker R. Serum gonadal-steroid hormones in young schizophrenic-patients. *Psychoneuroendocrinology*. 1994;**19**:373-385
- [171] Strous RD, Maayan R, Lapidus R, Goredetsky L, Zeldich E, Kotler M, Weizman A. Increased circulatory dehydroepiandrosterone and dehydroepiandrosterone-sulphate in first-episode schizophrenia: Relationship to gender, aggression and symptomatology. *Schizophrenia Research*. 2004;**71**:427-434
- [172] Howard JS. Severe psychosis and the adrenal androgens. *Integrative Physiology and Behavioral Sciences*. 1992;**27**:209-215
- [173] di Michele F, Caltagirone C, Bonaviri G, Romeo E, Spalletta G: Plasma dehydroepiandrosterone levels are strongly increased in schizophrenia. *Journal of Psychiatric Research* 2005;**39**:267-273
- [174] Debonnel G, Bergeron R, deMontigny C. Potentiation by dehydroepiandrosterone of the neuronal response to N-methyl-D-aspartate in the Ca(3) region of the rat dorsal hippocampus: An effect mediated via sigma receptors. *Journal of Endocrinology*. 1996;**150**:S33-S42
- [175] Flood JF, Morley JE, Roberts E. Memory-enhancing effects in male mice of pregnenolone and steroids metabolically derived from it. *Proceedings of the National Academy of Sciences of the United States of America*. 1992;**89**:1567-1571
- [176] Genazzani AR, Petraglia F, Bernardi F, Casarosa E, Salvestroni C, Tonetti A, Nappi RE, Luisi S, Palumbo M, Purdy RH, Luisi M. Circulating levels of allopregnanolone in humans: Gender, age, and endocrine influences. *Journal of Clinical Endocrinology and Metabolism*. 1998;**83**:2099-2103
- [177] Rasmusson AM, Vasek J, Lipschitz DS, Vojvodal D, Mustone ME, Shi QH, Gudmundsen G, Morgan CA, Wolfe J, Charney DS. An increased capacity for adrenal DHEA release is associated with decreased avoidance and negative mood symptoms in women with ptsd. *Neuropsychopharmacology*. 2004;**29**:1546-1557

- [178] Kimonides VG, Khatibi NH, Svendsen CN, Sofroniew MV, Herbert J. Dehydroepiandrosterone (DHEA) and DHEA-sulfate (DHEAs) protect hippocampal neurons against excitatory amino acid-induced neurotoxicity. *Proceedings of the National Academy of Sciences of the United States of America*. 1998;**95**:1852-1857
- [179] Brophy MH, Rush AJ, Crowley G. Cortisol, estadiol and androgens in acutely ill paranoid schizophrenics. *Biological Psychiatry*. 1983;**18**:583-590
- [180] Harris DS, Wolkowitz OM, Reus VI. Movement disorder, psychiatric symptoms and serum DHEA levels in schizophrenic and schizoaffective patients. *World Journal of Biological Psychiatry*. 2001;**2**:99-102
- [181] Shirayama Y, Chen ACH, Nakagawa S, Russell DS, Duman RS. Brain-derived neurotrophic factor produces antidepressant effects in behavioral models of depression. *Journal of Neuroscience*. 2002;**22**:3251-3261
- [182] Tournay G, Hatfield L. Plasma androgens in male schizophrenics. *Archives of General Psychiatry*. 1972;**27**:753
- [183] Oertel GW, Benes P, Schirazi M, Holzmann H, Hoffmann G. Interaction between dehydroepiandrosterone, cyclic adenosine-3',5'-monophosphate and glucose-6-phosphate-dehydrogenase in normal and diseases subjects. *Experientia*. 1974;**30**:872-873
- [184] Tournay G, Erb JL. Temporal variations in androgens and stress hormones in control and schizophrenic subjects. *Biological Psychiatry*. 1979;**14**:395-404
- [185] Erb JL, Kadane JB, Tournay G, Mickelsen R, Trader D, Szabo R, Davis V. Discrimination between schizophrenic and control subjects by means of plasma dehydroepiandrosterone measurements. *Journal of Clinical Endocrinology and Metabolism*. 1981;**52**:181-186
- [186] Cotter D, Pariante CM. Stress and the progression of the developmental hypothesis of schizophrenia. *The British Journal of Psychiatry*. 2002;**181**:363-365
- [187] Ryan MCM, Sharifi N, Condren R, Thakore JH. Evidence of basal pituitary-AD renal overactivity in first episode, drug naive patients with schizophrenia. *Psychoneuroendocrinology*. 2004;**29**:1065-1070
- [188] Dewan MJ, Pandurangi AK, Boucher ML, Levy BF, Major LF. Abnormal dexamethasone suppression test-results in chronic-schizophrenic patients. *American Journal of Psychiatry*. 1982;**139**:1501-1503
- [189] Lammers CH, GarciaBorreguero D, Schmider J, Gotthardt U, Dettling M, Holsboer F, Heuser IJE. Combined dexamethasone/corticotropin-releasing hormone test in patients with schizophrenia and in normal controls. *Biological Psychiatry*. 1995;**38**:803-807
- [190] Webster MJ, Knable MB, O'Grady J, Orthmann J, Weickert CS. Regional specificity of brain glucocorticoid receptor mRNA alterations in subjects with schizophrenia and mood disorders. *Molecular Psychiatry*. 2002;**7**:985-994
- [191] Young AH, Gallagher P, Porter RJ. Elevation of the cortisol-dehydroepiandrosterone ratio in drug-free depressed patients. *American Journal of Psychiatry*. 2002;**159**:1237-1239

[192] Hechter O, Grossman A, Chatterton RT. Relationship of dehydroepiandrosterone and cortisol in disease. *Medical Hypotheses*. 1997;**49**:85-91

[193] Tkachev D, Mimmack ML, Ryan MM, Wayland M, Freeman T, Jones PB, Starkey M, Webster MJ, Yolken RH, Bahn S. Oligodendrocyte dysfunction in schizophrenia and bipolar disorder. *Lancet (London, England)*. 2003;**362**:798-805

IntechOpen

IntechOpen