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

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<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.

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

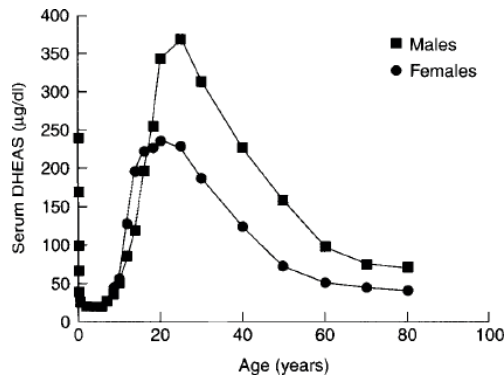


Figure 2. Concentrations of serum DHEAS as a function of age in females and males. Values are high in cord blood and immediately after birth, fall in the first months of life as the fetal adrenal zone involutes, and remain low until the onset of adrenarche at about age 8 years in girls and age 9 years 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.

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