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Neurobiology of DHEA and effects on sexuality, mood and cognition

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ABSTRACT

Dehydroepiandrosterone (DHEA) and its sulfate ester, DHEAS, are the most abundant steroid hormones in the humans. However, their physiological significance, their mechanisms of action and their possible roles as treatment are not fully clarified.

Biological actions of DHEA(S) in the brain involve neuroprotection, neurite growth, neurogenesis and neuronal survival, apoptosis, catecholamine synthesis and secretion, as well as anti-oxidant, anti-inflammatory and antiglucocorticoid effects. In addition, DHEA affects neurosteroidogenis and endorphin synthesis/release. We also demonstrated in a model of ovariectomized rats that DHEA therapy increases proceptive behaviors, already after 1 week of treatment, affecting central function of sexual drive. In women, the analyses of clinical outcomes are far from being conclusive and many issues should still be addressed. Although DHEA preparations have been available in the market since the 1990s, there are very few definitive reports on the biological functions of this steroid. We demonstrate that 1 year DHEA administration at the dose of 10 mg provided a significant improvement in comparison with vitamin D in sexual function and in frequency of sexual intercourse in early postmenopausal women. Among symptomatic women, the spectrum of symptoms responding to DHEA requires further investigation, to define the type of sexual symptoms (e.g. decreased sexual function or hypoactive sexual desire disorder) and the degree of mood/cognitive symptoms that could be responsive to hormonal treatment. In this regard, our findings are promising, although they need further exploration with a larger and more representative sample size.

This article is part of a Special Issue entitled: Essential role of DHEA.

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1. Introduction

The growth, differentiation, normal physiology and aging of the central nervous system (CNS) are all now recognized to be influenced by gonadal steroid hormones. Dehydroepiandrosterone (DHEA) and its sulfate ester, DHEAS, represent the most abundant steroid hormones in the human body. However, their physiological significance, their mechanisms of action and their possible roles in disease remains to be defined in different tissues. DHEA and DHEAS concentrations in humans typically decrease steadily with age, approaching a nadir at about the time many diseases of aging become more prevalent. Observations such as these, coupled with basic and preclinical demonstrations of DHEA's biological effects, fostered hope that restoring DHEA to youthful levels might, conservatively, increase well-being and, optimistically, extend life, protect the brain, ameliorate sex function and retard the ravages of aging, as recently reported by Maninger et al. [1].

Though a large attention has been given to the study of postmenopause and to the options in hormone replacement therapy (HRT), relative attention and awareness has been focused on the activity of endogenous or exogenous androgens in women. In fact the middle age of women life is characterized by the coexistence of menopause and adrenopause that sometimes both participate to create an androgen-deficiency syndrome. In these terms, the field of inquiry into the neurobiological actions of DHEA and DHEAS is rapidly growing.

The aims of present article are (1) to review briefly basic and preclinical studies of DHEA(S) biological actions in the brain and their supposed mechanisms of action, (2) to evaluate DHEA(S) specific effects on brain function including sexual function in vivo, and (3) the therapeutic potential of DHEA(S) in postmenopausal women using measures of mood, sexuality and cognition.

2. DHEA(S) synthesis and metabolism

A detailed description of synthesis and secretion of DHEA and DHEAS is beyond the scope of the present article and reviews have recently been published [1]. However specific aspects of DHEA/S synthesis, metabolism and action in the brain are described in the present review.

Pregnenolone is converted into DHEA by the enzyme cytochrome P450c17; this single enzyme catalyzes both the 17α-hydroxylation reaction converting pregnenolone to 17-OH pregnenolone and the 17,20-lyase reaction converting 17-OH pregnenolone to DHEA [2]. The sulfation of DHEA into its more stable sulfate ester DHEAS is catalyzed by the enzyme hydroxysteroid sulfotransferase (HST, SULT2A1), commonly known as DHEA sulfotransferase. DHEAS can be converted back into DHEA by steroid sulfatase (STS). P450c17 is encoded by a single gene (cyp17) and mutations can cause either 17α-hydroxylase or 17,20-lyase deficiency or both [3]. In addition to its expression in human adrenals and gonads, P450c17 is also expressed in the brain [4], where it may synthesize DHEA from pregnenolone.

Adrenal secretion of DHEA and DHEAS increases during adrenarche in children at the age of 6–8 years. Maximal values of circulating DHEAS are reached between the ages of 20 and 30 years. Thereafter, serum DHEA and DHEA-S levels decrease markedly [5,6]. The marked reduction in the formation of DHEAS by the adrenals during aging results in a fall in the formation of androgens and estrogens in peripheral target tissues. Despite most animal models used in the laboratory, where the secretion of sex steroids takes place exclusively in the gonads with no significant amount excreted by adrenals [6], humans peripheral target tissues have the capacity to transformate the adrenal precursor steroids DHEAS and DHEA into androgens and/or estrogens [7].

Higher concentrations of DHEA are found in brain in comparison with plasma values with a brain-to-plasma ratio of ~6.5 [8]. In a study of 10 postmortem human brains, DHEA concentrations were 29.4 nmol/kg in prefrontal lobe, 16.3 nmol/kg in parietal lobe, 13.1 nmol/kg in temporal cortex, 16.9 nmol/kg in cerebellum, and 18.7 nmol/kg in corpus callosum [9]. These data were derived from nine women and one man (76–93 years old), and it is worth noting that large individual differences in DHEA brain concentrations were observed.

Analyses of sulfated steroids also confirmed high concentrations of DHEAS and pregnenolone sulfate in rodent and human brains [10,11].

Humans and rodents differ in the pathways through which sex steroids are synthesized. Whereas DHEAS is the most abundant circulating steroid hormone in the human body [12], rats and mice have low circulating concentrations of DHEA(S) in the periphery [13–16]. Brain DHEA in rat is derived from local synthesis and not from peripheral synthesis. In humans, brain DHEA concentration is the result of from both local synthesis and peripheral synthesis.

2.1. DHEA as neurosteroid

Although adrenal cortex is considered to be the primary source of DHEAS in the brain, it was reported that DHEAS did not disappear or decrease in the brain 15 days neither after orchiectomy, adrenalectomy, or both, nor after the inhibition of adrenal secretion by dexamethasone. DHEA and DHEAS were among the first neurosteroids identified in rat brains. Cytochrome P450c17 was found in a subset of neurons of embryonic rodent brains [17]. While P450c17 protein was readily detected in the brain, the abundance of P450c17 mRNA transcripts in the embryonic mouse brain [18] or hippocampus of adult male rats was low, and was approximated to be 1/200th of the expression in testis.

In addition DHEA can be synthesized in vivo in rat brains. Rat brains were capable of converting pregnenolone into DHEA and this may be activity-dependent [19]. Basal P450c17 steroidogenic enzyme activity was low, but could be enhanced by exposing neurons to N-methyl-D-aspartate (NMDA) [19]. In addition immunohistochemical studies localized P450c17 in both neuros and glial cells in the spinal rat cord, showing evidence that the spinal cord tissue is another region of CNS that express P450c17. Frog brains also were found to synthesize DHEA from pregnenolone, and this enzymatic activity was reduced in a concentration-dependent manner by ketoconazole, an inhibitor of P450c17 [20].

DHEAS may be synthesized in the brain from DHEA [21]. Sulfation of DHEA has been observed in the brains of rhesus monkeys in vivo and in human fetal brain slices in vitro [21]. DHEA sulfotransferase (HST or SULT2A1) is an enzyme that sulfonates DHEA (in addition to pregnenolone) [22,23]. Western blotting and immunohistochemistry showed protein expression of an HST in adult Wistar rat brain [3]. In addition SULT2A1 mRNA expression has been shown in rat brains.

DHEAS is predominately transported out of the brain across the blood–brain barrier and DHEAS found in the brain is most likely due to local synthesis [1,24,25].

3. Mechanisms of DHEA action in the brain

The mechanisms by which DHEA(S) operate his action are not fully understood [25]. DHEA(S) may mediate some of its actions through conversion into more potent sex steroids and activation of androgen or estrogen receptors in tissue (i.e. skin, bone,