Brain Research Reviews 30 (1999) 264–288

www.elsevier.com/locate/bres

Full length review

Actions of dehydroepiandrosterone and its sulfate in the central nervous system: effects on cognition and emotion in animals and humans

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Accepted 17 August 1999

Abstract

Dehydroepiandrosterone (DHEA) and its sulfate ester, DHEAS, exert multiple effects in the rodent central nervous system (CNS). Most of them seem to be mediated through their non-genomic action on several neurotransmitter receptors. DHEA(S) increases neuronal excitability, enhances neuronal plasticity and also has neuroprotective properties. In line with these observations DHEA(S) treatment in rodents enhances memory in several paradigms. Even more studies show antiamnestic effects of the steroids. However, DHEA(S) has also anxiolytic and anti-aggressive properties. In humans cross-sectional and longitudinal studies suggest that DHEAS might be associated with global measures of well-being and functioning; however, a relationship with cognition could not be detected to date. Moreover, studies investigating DHEAS levels in neurodegenerative diseases have produced conflicting results. Experimental studies in elderly humans have revealed preliminary evidence for mood enhancing and antidepressant effects of DHEA treatment, while positive effects on measures of memory and attention could not be found. However, electrophysiological studies demonstrated that DHEA treatment has effects on the human CNS. Several reasons for the discrepancy between data obtained in rodents and humans are discussed and research perspectives are outlined which might help to improve interpretation of results obtained in the two species.

Keywords: Hormone; Cognition; Emotion

Contents

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0165-0173/99/$ - see front matter
PII: S0165-0173(99)00021-1

1. Introduction

In this decade dehydroepiandrosterone (DHEA) and its sulfated ester dehydroepiandrosterone sulfate (DHEAS) has regained significant interest in science and in the lay public mainly caused by two discoveries: the strong age-associated decline of the steroid in humans and the demonstration of DHEA(S) metabolism and action in the rodent brain. The current review will, after a brief outline of some basic endocrinological characteristics, describe DHEA(S)' effects in the central nervous system (CNS) and thereafter discuss in detail results of studies which investigated the effects of DHEA(S) on cognition and emotion in rodents and humans.

2. DHEA secretion and metabolism

2.1. Blood concentration, half-life and circadian rhythm of DHEA and DHEAS

DHEAS is the most abundant product of the adult human adrenal cortex (and of the fetal adrenal gland) with concentrations in the microgram per milliliter range [3]. Only a small fraction (less than 1%) is circulating in the unsulfated form (as DHEA) [307]. DHEA has a short half-life (30 min or less) and a marked circadian rhythm (300% variation) while the sulfated form has a longer biological half-life (7–10 h) and therefore displays only a weak circadian rhythm (20% variation) [13,17,86,141,260]. Most of DHEAS (60–80%) entering the blood gets interconverted to DHEA by steroid sulfatase, while a small amount of DHEA (5–7%) gets converted by hydroxysteroid sulfotransferase in liver and kidney to DHEAS, thereby creating an equilibrium between the two forms of the steroid [141,254].

2.2. Site of biosynthesis

The human adrenal cortex is divided into three histologically distinct zones which produce different classes of steroid hormones. The inner layer (zona reticularis) produces the so-called adrenal androgens (AA) with DHEA and its sulfate ester DHEAS being the most prominent. The middle layer, the zona fasciculata is responsible for glucocorticoid (GC) production (cortisol in humans and corticosterone in rodents). The outer layer (zona glomerulosa) mainly secretes mineralocorticoids [3,96,205,206]. In addition to its adrenal origin DHEA is also produced in small amounts (10–20% of the circulating hormone) by the gonads [76,187]. Moreover there is now good evidence that DHEA(S) is also produced in the CNS (see Section 2.5).

2.3. Factors controlling adrenal DHEA(S) synthesis

There is an ongoing discussion about the factors which are responsible for the regulation of adrenal DHEA(S) secretion. It is generally accepted that ACTH from the pituitary stimulates DHEA synthesis; however, there are several hypotheses which try to explain the dissociation between adrenal cortisol and DHEA secretion in certain conditions. One of the main differences between cortisol and DHEA is their strikingly different developmental pattern as described below (Section 2.4). However, such a dissociation is also seen in several medical conditions (e.g., burn trauma [202], severe illness [207,282], anorexia nervosa [286], Cushing's disease [44]).

One hypothesis put forward by Parker and Odell is the existence of an additional pituitary factor which controls AA secretion (an AA stimulating hormone, AASH) [209]. However, initial reports of a discovery of such a factor [208] could not be confirmed by others (e.g., [170]) so that

the idea of an AASH seems to be rejected by most authors [96]. Adams [3] suggests that instead of an AASH there may be a factor involved in the stimulation of adrenarche (as suggested in Ref. [228]) and the resulting differentiation of the zona reticularis. However, after the establishment of a zona reticularis AA secretion may be regulated solely by ACTH [3]. A dissociation between cortisol and DHEA secretion could also be mediated by an ACTH-induced stimulation of 3 beta-hydroxysteroid dehydrogenase (3-β HSD), which would lead to a shift away from androgen towards glucocorticoid production as suggested by a study in patients with congenital adrenal hyperplasia [306].

There is still little knowledge about how the adrenal cortex becomes zoned, and what determines when the different zones develop. One hypothesis mentioned above is the existence of an adrenarche factor; another one is that the blood flow through the capillary bed (starting at the zona glomerulosa and ending at the adrenal medulla) creates a gradient of an autocrine or paracrine factor which may signal cells to adopt a particular zonal characteristic [6,96].

Another interesting phenomenon in the control of AA secretion is that there seems to be no feedback action of DHEA(S) on the pituitary or the hypothalamus [96], which is in sharp contrast to the very sensitive feedback control of the hypothalamus pituitary adrenal system for cortisol [24,46,47,102,111].

2.4. Developmental pattern of DHEA(S) in humans

One of the most intriguing facts about DHEA(S) is its strong and almost unique developmental pattern. While DHEA is produced in the fetal adrenals, its concentration sharply drops after birth and is almost undetectable 6 months thereafter [48]. One or two years before puberty (in the so-called adrenarche) a strong rise in DHEA production occurs, with peak levels obtained in the third decade of life [3,205,206]). This pattern is observed in women and men, with men having higher DHEAS levels in adulthood. Thereafter, a marked continuous decline in DHEA(S) secretion is observed with elderly subjects secreting only 20% compared to young subjects [48,82,169,196].

This strong age-associated pattern is not observed for cortisol, the primary human GC secreted from the zona fasciculata, whose basal levels remain unchanged or slowly increase throughout the life-span [144,252]. Elevated basal cortisol levels at older age were recently described at the circadian nadir [62,112,278]. A number of studies which found a reduced DHEA (but not cortisol) response in elderly subjects after ACTH [204,280] or CRH challenge [140,211] suggest that the decline in DHEA production is caused by changes at the level of the adrenal. These alterations may include a reduction in the numbers of functional cells in the zona reticularis [64], a reduced ACTH sensitivity of these cells [204], an altered zonation in the adrenal cortex [203], or a decreased 17,20-desmolase activity [140].

While DHEA(S) is abundant in large concentrations in man and other primates (and to some degree in rabbits and dogs) its concentrations are very low in rats and mice (e.g., Refs. [45,69,93,285]), due to the missing or very low expression of the adrenal enzyme P 450-17α (17 α hydroxylase; the enzyme which converts pregnenolone into DHEA) [279]; for slightly divergent results see Ref. [97]. In addition, only in humans and nonhuman primates is a strong developmental pattern of DHEA(S) secretion (with adrenarche and a continuous decline with aging) observed [45,129,247]. These species differences might be one reason for some of the conflicting results reported for DHEA effects in rodents and humans, respectively (see below).

2.5. DHEA(S) as a neurosteroid

There is now good evidence that DHEA and DHEAS (together with several other steroids) are produced in the CNS. Therefore, these steroids have been termed 'neurosteroids' [10]. DHEA(S) concentrations in the rodent brain by far exceeds its low concentrations in the periphery and are independent from adrenal synthesis as shown after adrenalectomy and gonadectomy (see for recent reviews [9,11]). However, the exact metabolic pathways of DHEA metabolism in the (rodent) brain are still not fully understood, since P 450-17α seems only to be present in the fetal rodent brain, but not in the adult [35]. Therefore an alternative pathway was suggested and first evidence for such an P 450-17α independent pathway has recently been published [29] (see for discussion Ref. [11]). The presence of small amounts of hydroxysteroid sulfotransferase activity in the rodent brain has recently been demonstrated in two studies [4,219]. These findings suggest that DHEA (which much more readily passes the blood–brain barrier) could be locally converted to DHEAS. However, since the activities measured in brain cytosols were 300 times lower than those measured in liver cytosols the physiological significance of the hydroxysteroid sulfotransferase activity in the brain remains to be established [219]. Sulfatase activity, in contrast, is widely present in the CNS [127, 137,176,201,225] and its pharmacological inhibition has effects on memory (see Section 4.1).

With respect to primates or humans the empirical evidence for DHEA synthesis in the brain is sparse. One study in monkeys reported high DHEAS levels in the brain which were not strongly suppressed by dexamethasone treatment, suggesting local biosynthesis [231]. One small postmortem study in humans observed higher levels of DHEA and DHEAS in brain tissue compared to blood values, which again could suggest local biosynthesis [126]. Studies measuring DHEA(S) in the cerebrospinal fluid reported DHEA concentrations to be 5% of those in serum while DHEAS concentrations (due to its low lipophilicity [116]) were only 0.1% of serum levels [84,251]. However, serum and CSF DHEA(S) concentrations were nevertheless highly correlated [84].

3. Action of DHEA(S) in the CNS

3.1. Effects on neurotransmitter receptors

After the discovery of high DHEA and DHEAS concentration in the rat brain [40] substantial effort has been undertaken to elucidate their mechanisms of actions. It appears that DHEA(S) (as well as most other neurosteroids) act primarily through interactions with neurotransmitter-receptors on the cell surface (so-called non-genomic action). This is in contrast to the classic action of steroids which includes binding to an intracellular receptor, translocation into the nucleus, binding to a steroid response element resulting in a changed protein synthesis (see for review Refs. [12,83,104,249].

The best-documented effects of DHEA(S) in the CNS are on the GABA-A receptor complex. This ligand gated ion channel is a hetero-oligomeric protein composed of several distinct polypeptides which upon activation by agonists, increase Cl^- influx into the cell. Benzodiazepines as well as barbiturates act as GABA agonist [41,134], while several convulsants show GABA antagonistic action [195,250].

Majewska showed that DHEA(S) are negative noncompetitive modulators of the GABA-receptor. DHEAS and DHEA noncompetitively inhibit the GABA-induced currents in cultured rat neurons with DHEAS being 3–4 times more potent than DHEA. Moreover it was suggested that DHEAS may interact with the sites of barbiturate actions at the GABA-A receptor complex (reviewed in Ref. [149]). However, other researchers suggested TBPS/picrotoxin as the DHEAS binding domain and failed to find any effects for DHEA [262], but see for recent data in support of Majewska's initial findings Ref. [98].

In addition to effects on the GABA-A receptor DHEAS also has effects on sigma receptors. These receptors are present in high density in the CNS [283], and several antipsychotic as well as antidepressant drugs have high affinity for the sigma receptor [52]. Selective sigma ligands potentiate the response of rat CA3 dorsal hippocampal neurons to *N*-methyl-D-aspartate (NMDA) which (in addition with other evidences) suggest a functional link between sigma and NMDA receptors [50,52,268,269]. There are at least two types of sigma receptors termed sigma 1 and sigma 2 receptor [218].

The first report of a modulatory role of DHEA on the sigma receptor was an in vitro study which investigated the effects of DHEAS on norepinephrine (NE) release induced by NMDA from preloaded hippocampal slices [172]. DHEAS at doses of 30 nM or higher enhanced the response to NMDA. This effect was blocked by sigma antagonists as well as by prior infusion of pertussis toxin (PTX) which suggests that DHEAS acted on the sigma 1 receptor [172]. This conclusion is supported by a recent in vivo binding study in mice [157]. Another study reported that DHEA (not DHEAS as in the other experiments) induced a significant increase of the response of hippocampal CA3 pyramidal neurons to NMDA [14]. This effect was again blocked by sigma antagonists. Taken together these studies show that DHEA(S) acts as sigma 1 receptor agonist and via this mechanism potentiates NMDA-induced neuronal excitability. In addition to its effect via the sigma receptor DHEAS might also directly potentiate the NMDA receptor response, although this effect seems to be relatively small [23,100].

In addition to action on the GABA-A and sigma receptor there is also evidence that DHEAS depresses CA^{2+} voltage-gated currents in freshly isolated hippocampal pyramidal CA1 neurons of the guinea pig [67]. This is to our knowledge the only experimental demonstration of a DHEAS action that leads to a reduced neuronal excitability. This is therefore in contrast to the effects on GABA (antagonistic) and sigma (agonistic) receptors which both lead to an enhanced neuronal excitability. The latter observations resulted in DHEA(S) being named an excitatory neurosteroid [149].

3.1.1. The role of GABA, sigma, and NMDA receptors in memory

The previous paragraph documented that DHEA(S) seems to modulate primarily two types of neurotransmitter receptors in the CNS. On one hand DHEA(S) acts as a GABA-A antagonist and on the other hand DHEA(S) acts as a sigma receptor agonist. Through the latter mechanism DHEA(S) enhances NMDA-induced neuronal excitability. Since the main focus of the present review is on the effects of DHEA(S) on cognition we will briefly summarize the knowledge about the role of these neurotransmitter receptors in learning and memory.

There are several studies in rodents, which in general show that GABA-A agonists impair learning and memory while GABA-A antagonists enhance memory (e.g., Refs. [31,99]). Moreover in humans benzodiazepines (as GABA agonists) impair cognition as indicated by changes in the EEG (e.g., Refs. [122,152]) as well as in performance (e.g., Ref. [65]). With respect to the sigma receptor animal studies document that sigma agonists enhance memory performance in several paradigms in young rodents (e.g., Refs. [153,154,253]) as well as in a rodent model of cognitive aging [158] (see for review Ref. [156]). NMDA receptor involvement in memory (and especially in the storage of new information) is suggested by its important role in the development of long-term potentiation (LTP) [101,230]. Studies using NMDA receptor antagonists reported on amnestic effects in humans (e.g., Refs. [150,235]) as well as in rodents (e.g., Refs. [21,33,66,139,200]). Taken together there is very good evidence that GABA-A antagonists as well as sigma agonists can enhance memory in rodents as well as in humans.

3.2. Is there a DHEA receptor?

There are some reports of a DHEA specific receptor complex in the rat liver [105], in murine T cells [166] and

in activated human T lymphocytes [194], which might suggest that DHEA can directly and specifically influence the immune system. However, only the study in murine T cells could demonstrate a biological action, which was correlated with DHEA binding [166], while the other studies failed to observe a biological response [105,194]. Moreover, to the best of our knowledge there have been no reports about a DHEA specific receptor or binding site in the CNS.

3.3. Effects on steroid hormone receptors

DHEA(S) is a precursor hormone for several bio-active sex steroids like estradiol and testosterone [206]. Therefore, some effects of DHEA treatment might be caused by these metabolites with known intracellular receptors. Indeed Labrie and coworkers suggest that most of the DHEA effects in the periphery are the result of an intracellular conversion of DHEA into bioactive sex steroids, a mechanism of action, which they termed intracrinology [123,125].

Some studies have reported that DHEA(S) binds with low affinity to the estradiol receptor and can induce nuclear translocation as well as transcription of the estrogen responsive element (ERE) [2,215], although the required concentrations were supraphysiological, suggesting that these effects do not occur under normal conditions [2,119,215]. However, 5-androstene-3 β,17 b-diol (ADIOL) a DHEA metabolite exerts estrogenic activity in physiological conditions [2,119,215].

In addition, there is first experimental evidence from a study using transiently transfected hypothalamic neurons that DHEA itself can stimulate the ERE, probably through activation of the estradiol receptor. However, this study could not completely rule out the possibility that metabolized estradiol or ADIOL caused the observed effects [26]. Nevertheless, it is important in discussing possible effects of DHEA to keep in mind the known effects of estradiol and testosterone to be able to compare them with reported DHEA effects.

3.4. Effects on neurotransmitters

In one study the effects of DHEAS on hippocampal acetylcholine (ACh) release was investigated in rats [226]. DHEAS administered i.p. enhanced the ACh release as measured by in vivo microdialysis at all doses tested (10–100 mg/kg). The authors suggest that this response may be the results of a GABA antagonistic action of DHEAS on neurons in the medial septal nucleus which are involved in hippocampal ACh utilization [5,120]. However, sigma-receptor-mediated effects should also be considered [153].

Svec et al. investigated the effects of a DHEA-supplemented diet in an animal model of youth onset obesity (the Zucker rat). A first study showed that 7 days of DHEA treatment induced a decrease in food intake and body weight which was accompanied by increased serotonin levels in the hypothalamus [1]. No effects were observed on dopamine, epinephrine and norepinephrine concentrations [1]. DHEA treatment influences food selection towards a reduced intake of fat in these animals [271,274]. Additional research showed that obese Zucker rats have reduced dopamine and serotonin levels in the lateral hypothalamus and reduced dopamine concentration in the paraventricular nucleus, when compared to lean rats. DHEA given i.p. 24 h before analysis reversed these neurotransmitter reductions and in addition enhanced epinephrine (in the ventromedial nucleus) and norepinephrine (in the paraventricular nucleus) concentrations [273,300]. However, similar effects on hypothalamic neurotransmitters were not observed after long-term (28 days) DHEA treatment, suggesting that the effect might be transient [272].

3.5. Effects on neuronal electrophysiology

The first study, which investigated effects of DHEA and DHEAS on neuronal electrophysiology was carried out in guinea pigs [28]. DHEA(S) has excitatory effects (on spontaneous and glutamate-induced activity of single units) when applied iontophoretically or by pressure to neurons in the septo-preoptic area. Meyer and Gruol performed an in vitro study on the influences of DHEAS on neuronal properties and synaptic transmission in the CA1 area of the hippocampus [171]. DHEAS had no effects upon cell membrane resistance or active cell responses to intracellular current pulses. However, DHEAS increased the excitability of CA1 neurons in response to Schaffer collateral synaptic stimulation by increasing the amplitudes of the excitatory postsynaptic potentials (EPSPs). Steffensen [266] investigated the effects of microelectrophoretically applied DHEAS on electrophysiological parameters in the hippocampal CA1 region and in the dentate gyrus. DHEAS increased population excitatory postsynaptic potentials (pEPSP) and population spike amplitudes in CA1 but not in the dentate gyrus. Moreover DHEAS increased the spontaneous firing rate of dentate hilar interneurons, CA1 pyramidal cells and CA1 interneurons and synchronized their firing to hippocampal theta rhythm [266]. Hippocampal theta rhythm is observed if rats show exploratory behavior and is thought to be involved in memory consolidation (e.g., Ref. [27]).

Diamond et al. [55] tested the effects of DHEAS on primed burst potentiation (PBP) and long-term potentiation (LTP) in hippocampal CA1 region of rats. Four DHEAS doses (6, 24, 48, 96 mg/kg) injected s.c. 30 min before recording were tested and the two intermediate doses significantly enhanced PBP while having no effects on LTP, thereby suggesting an inverted U-shaped dose–response curve. Diamond and Fleshner obtained similar results giving DHEAS in the drinking water 5 days before recording. The medium dose (0.1 mg/ml) enhanced PBP while the higher dose (0.4 mg/ml) did not [57]. Another

study documented a DHEAS-induced increase in LTP in the dentate gyrus [304]. In this study all three DHEAS doses tested (10, 20, 30 mg/kg) increased LTP with the medium and higher dose having larger effects. These results might suggest, that DHEAS increases LTP in the dentate gyrus but not in CA1 [55,304].

3.6. Antiglucocorticoid effects in the CNS

Several disease states are characterized endocrinologically by increased cortisol levels accompanied by reduced DHEA(S) levels. Examples are burn trauma [202], severe illness [207,282], short-term GC treatment [25], anorexia nervosa [286], and Cushing's disease [44]. In general a shift away from AA production towards GC production seems to be associated with disease or chronic physical stress. Whether this phenomena represents an adaptive response to the disease or might rather be responsible for the initiation or progression of the disease is still a matter of debate. Several authors have speculated that an imbalance between DHEA and cortisol might be causally related to physical diseases [90] or psychiatric disorders (especially depression and Alzheimer's disease (see Section 5.2–Section 5.3) [63].

Immunological studies in rodents have repeatedly demonstrated that DHEA(S) has antiglucocorticoid actions (see for review Ref. [106]), and there is now some evidence for a similar effect in the rodent CNS. This is especially relevant for the present review, since animal and human studies have demonstrated modulatory effects of glucocorticoids on cognition and neuronal integrity mediated via the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR) [47,146,164]. Several studies in rodents have observed memory-enhancing effects of glucocorticoids in tasks measuring emotional memory (e.g., active or passive avoidance training) [73,118,244]. The results regarding hippocampus-mediated spatial memory as assessed with maze tasks are more complex. An endogenous rise in corticosterone while learning the task [38] or immediate posttraining corticosterone injection enhances retention [236,242]. However, stress during the consolidation period [59] or before retention [49] impairs performance. Studies using selective MR or GR antagonists have shown performance impairments after i.c.v. injection [192], while injection of a GR antagonist into the hippocampus enhanced spatial memory [193]. In addition to the timing and localization of the drug administration there is also evidence for an inverted U-shaped function between glucocorticoid concentrations and memory performance [118,217,243]. Very low as well as very high levels seem to result in memory impairments, which is in agreement with electrophysiological data (PBP and LTP) [54,210]. Human studies found that glucocorticoid administration or acute stress before the learning phase or between the learning and the recall phase impairs hippocampus-mediated declarative memory [115,145,186,298]. Memory-enhancing effects of glucocorticoids have not been reported in humans, although the timing of the drug administration and/or the difference in the used tasks probably explain these species differences.

While the relationship between acute stress and cognition is rather complex, the detrimental effects of chronic stress or hypercortisolemia seem to be generally accepted. Chronic stress leads to dendritic atrophy in the hippocampus [147,148,299] and to spatial memory impairments [37,190,191], which may be more pronounced in older animals [20]. However, the idea that long-term severe stress or glucocorticoid treatment leads to neuronal death in the hippocampus, as suggested by studies in rodents [245,246] has recently been challenged by studies in tree shrews [281] and monkeys [136]. In humans high basal cortisol levels due to disease or aging are associated with hippocampal atrophy and memory impairments [142,143,265], although the mechanisms for this phenomenon awaits to be determined [160].

DHEA given i.c.v. or into the amygdala before stress exposure blocked the stress-induced increase in tryptophan hydroxylase (TH) activity (the rate-limiting enzyme in the synthesis of serotonin) observed in midbrain and cortex but had no effect on TH activity in a control group. Coadministration of a glucocorticoid agonist (RU 28362) completely blocked the DHEA effect, which suggests that DHEA exerted its action by antagonizing the effects of glucocorticoid [259]. In an extension of their previous electrophysiological work, Diamond et al. demonstrated that DHEAS enhanced PB potentiation when administered 10 min before, but not 20 min after, the rats were stressed [56,58]. These studies suggest that DHEA(S) can enhance hippocampal plasticity and prevent the stress-induced increase in TH activity only if glucocorticoid levels are low at the time of DHEA(S) injection. This would suggest that DHEA(S) might have neuroprotective but not neurocurative properties with respect to hypercortisolemia. However, two recent behavioral studies do not correspond with the PBP data. In rodents [69] as well as humans [289], DHEA(S) treatment for several days before testing impaired (and not protected) hippocampus-mediated memory in a stressful test situation (see Sections 4.2 and 5.4).

3.7. Neuroprotective and neurodevelopmental effects

Two studies investigated the effects of DHEA and DHEAS on cell survival in cultures of embryo mouse brains. DHEA(S) added for 4 days enhanced neuronal and glial survival and/or differentiation [22,233]. Another experiment suggests an involvement of DHEA(S) in neurodevelopment. In primary cultures of mouse embryonic neocortical neurons, DHEA increased the length of neurites containing Tau-1 (an axonal marker) while DHEAS increased the length of neurites containing the dendritic marker microtubule-associated protein-2 (MAP-2) [36]. In hippocampal slice cultures from adult gonadectomized male

rats DHEA(S) induced a transformation of astroglial cells into hypertrophic and highly glial fibrillary acidic protein (GFAP) immunoreactive cells, with the appearance of reactive astroglia [53]. The physiological relevance of this observation, however, is not understood so far. Kimonides et al. [113] demonstrated that DHEA and DHEAS protected hippocampal neurons against excitatory amino acid (NMDA, AMPA and kainic acid)-induced neurotoxicity in vitro (neuronal cell cultures) and in vivo (NMDA infusion into the CNS of animals with or without a DHEA pellet). This study suggests, that DHEA(S) might be protective against cerebral ischemia, which is in agreement with the known neuroprotective effects of sigma receptor agonists [156].

4. DHEA(S) effects on cognition in rodents

4.1. Effects on memory

Several studies tested the memory-enhancing and/or antiamnestic properties of DHEA and DHEAS in rodents (see Tables 1 and 2 for summary). Flood et al. were the first to show that DHEA and DHEAS had memory-enhancing effects in young [70,72,233] and old [71] mice using an active as well as passive foot shock paradigm. In their extensive studies several routes of administration (i.c.v, s.c., oral) were used, all leading to memory-enhancing effects although the doses required for these were rather high. The observed dose–response curve was inverted U-shaped. Melchior and Ritzmann investigated the effects of DHEA and DHEAS on short-term working memory as assessed with a T maze. Both steroids given i.p. enhanced memory [168]. Again an inverted U-shaped dose–response curve was found. In another series of experiments by Reddy and Kulkarni DHEAS enhanced memory when given before or directly after training, but not when given before retention testing, demonstrating that DHEAS enhanced the storage and/or consolidation of the learned material, but could not improve retrieval [223]. Again an inverted U-shaped dose–response curve was observed. Moreover DHEAS effects were blocked by a sigma receptor antagonist, suggesting a role of the sigma receptor in DHEAS-induced memory enhancement [223]. In a similar set of experiments DHEAS also enhanced memory in old mice, although the dose needed was slightly higher [224].

Even more studies have investigated antiamnestic properties of DHEA(S) in mice using a wide variety of amnestic agents. Flood et al. were again the first to show antiamnestic effects of the neurosteroid using several routes of administration [70,72,233]. Their results were extended to a different memory paradigm by others [168]. Maurice et al. documented antiamnestic effects of DHEA and DHEAS in mice using multiple memory paradigms (Y maze, watermaze, step down passive avoidance) as well as several amnestic agents. However, the authors failed to observe a memory-enhancing effect when DHEAS was given alone [155,159,277]. In their studies Maurice et al. also accumulated evidence that the sigma agonistic properties of DHEAS are responsible for the observed antiamnestic properties [155,159,277]. Moreover, they demonstrated that DHEAS had effects on learning and/or storing information but had no effects on recall [159]. These studies therefore match the results from Reddy and Kulkarni mentioned above [223].

Only three studies published so far investigated the memory-enhancing effects of DHEA(S) in rats. Frye and Sturgis tested the effects of several neurosteroids including DHEAS on memory in ovariectomized rats using the Morris water maze and the Y maze. Subcutaneous injection had no effects on performance in the water maze, while it had opposing effects (impairing as well as enhancing) effects on the Y maze, depending on the dose used. However, if the steroid was given i.c.v. it enhanced memory in both tasks [78]. Diamond and Fleshner observed that DHEAS given into the drinking water for 5 days enhanced retention in the Morris water maze at the intermediate doses tested, again demonstrating an inverted U-shaped dose–response curve [57].

There is only one study published so far which reported a memory impairment after DHEAS treatment. DHEAS given for 5 days into the drinking water of rats selectively impaired hippocampal-dependent contextual fear conditioning, while having no effects on auditory cue fear conditioning [69]. Since the authors observed similar effects after adrenalectomy [217] they suggested that their findings might provide evidence for an antiglucocorticoid action of DHEA. However, it is known that low as well as high levels of GC can impair hippocampal plasticity (see Section 3.6) and the authors indeed observed an inverted dose–response curve between corticosterone levels and performance in their experiments [217]. Therefore the results of Fleshner and coworkers could also be explained by a DHEAS-induced potentiation of the corticosterone response to the stressful test paradigm, which might shift the optimal corticosterone range to the ‘right’ rather than to the ‘left’ side of the inverted U-shape. This interpretation is supported by a recent study in humans (Ref. [289]; see Section 5.4) but other explanations are possible. Moreover the identical DHEAS treatment enhanced memory performance in the Morris water maze (a less stressful task of hippocampus-mediated memory in rodents) [57], thereby demonstrating that the impairing effects of DHEAS are only observed if hippocampus-mediated memory is tested under very stressful conditions.

Another series of studies investigated the effects of several steroid sulfatase inhibitors on memory and their interaction with DHEAS. These studies demonstrated that the steroid sulfatase inhibitor enhanced memory, increased hippocampal acetylcholine release and potentiated the effects of DHEAS on memory [137,138,225]. These data suggest that DHEAS rather than DHEA is responsible for

Table 1
Effects of DHEA(S) on memory in rodents

Ref.	Test paradigm	Animals tested	Memory type	Administration time	Administration route	Effective doses
[72]	Footshock active avoidance training (FAAT). Memory testing 1 week later	Male mice	Emotional memory	Directly after training	i.c.v.	DHEAS: 108–271 ng enhanced memory; higher or lower doses had no effect
				Directly after training	s.c.	DHEAS: 10–24 mg/kg enhanced memory; higher or lower doses had no effect
				1 week before training and during the week between training and testing	Drinking water	DHEAS: 21–41 mg/kg/day enhanced memory; higher or lower doses had no effect
[72]	Footshock passive avoidance training. Memory testing 1 week later	Male mice	Emotional memory	Directly after training	i.c.v.	DHEAS: 54–216 ng enhanced memory; higher or lower doses had no effect
[71]	Footshock active avoidance training (FAAT). Memory testing 1 week later	Old male mice	Emotional memory	Directly after training	s.c.	DHEAS: 20 mg/kg brought the performance back to the level of young mice
[168]	Win shift paradigm in a T maze	Male mice	Short-term working memory	Injection 30 min before testing	i.p.	DHEA: 0.005 and 0.05 mg/kg; DHEAS: 0.05 mg/kg enhanced memory, higher or lower doses had no effect
[223]	Passive avoidance task. Memory testing 24 h later	Male mice	Emotional memory	Injection 60 min before training, directly after training, or 60 min before retention testing	s.c.	DHEAS: 0.5, 1 and 5 mg/kg enhanced memory when given before or after training, but not when given before retention; higher or lower doses had no effect
[224]	Passive avoidance task. Memory testing 24 h later	Old male mice	Emotional memory	Injection 30 min before training	s.c.	DHEAS: 5 and 10 mg/ kg enhanced memory; higher or lower doses had no effect
[224]	Memory version of the elevated plus maze. Memory testing 24 h later	Old male mice	Long-term memory	Injection 30 min before training	s.c.	DHEAS: 5 and 10 mg/ kg enhanced memory; higher or lower doses had no effect
[78]	Watermaze	Ovariectomized female rats	Spatial long-term memory	Injection 30 min before to testing	s.c.	DHEAS: no effect of both doses tested, 3.2 and 6.4 mg/kg
	Y maze	Ovariectomized female rats	Short-term working memory	Injection 30 min before testing	s.c.	DHEAS: 3.2 mg/kg s.c. impaired while 6.4 mg/kg enhanced performance
	Watermaze	Ovariectomized female rats	Spatial long-term memory	Injection 30 min prior to testing	i.c.v.	DHEAS: 1.2 mg/rat enhanced performance (only one dose tested)
[78]	Y maze	Ovariectomized female rats	Short-term working memory	Injection 30 min prior to testing	i.c.v.	DHEAS: 1.2 mg/rat enhanced performance (only one dose tested)
[57]	Watermaze	Male rats	Spatial long-term memory	5 days prior to testing	Drinking water	0.05 and 0.1 mg/ml but not 0.2 or 0.4 m/mg DHEAS enhanced recall, while no treatment effects were obvious on initial learning
[69]	Contextual and auditory cue fear conditioning	Male and female rats	Emotional spatial and emotional nonspatial memory	5 days prior to testing	Drinking water	0.1 mg/ml DHEAS selectively *impaired* hippocampus dependent contextual fear conditioning (only one dose tested)

the memory enhancement, which would be in agreement with the stronger GABA antagonistic action of DHEAS [149]. However, since in all these experiments the sulfatase inhibitor was given i.p., it is unclear whether the observed

Table 2
Antiamnestic effects of DHEA(S) in rodents

Ref.	Test paradigm	Animals tested	Memory type	Administration time	Administration route	Effective doses
[72]	Footshock active avoidance training (FAAT). Memory testing 1 week later	Male mice	Emotional memory	Directly after training dimethyl sulfoxide (DMSO) together with DHEA or saline	i.c.v.	DHEA: 1–120 ng prevented the DSMO-induced amnesia; higher or lower doses had no effect
				Directly after training Anisomycin (ANI) or scopolamine (SCO) together with DHEAS or saline	i.c.v.	DHEAS: 160 ng prevented the ANI- or SCO-induced amnesia (only one dose tested)
[168]	Win shift paradigm in a T maze		Short-term working memory	Steroid or saline injection 30 min before testing; ethanol injection 10 min before testing	i.p.	DHEA and DHEAS: 0.05 mg/kg (only one dose tested) prevented the ethanol-induced amnesia
[155]	Spontaneous alternations in the Y maze	Male mice	Short-term working memory	Injection 30 min before testing	i.p. or s.c.	DHEAS: 20 mg/kg prevented dizoclipine-induced amnesia, but did not improve performance when given alone. Lower doses were not effective
	Footshock passive avoidance training. Memory testing 24 h later	Male mice	Emotional memory	Injection 30 min before training	i.p. or s.c.	DHEAS: 10 and 20 mg/kg prevented dizoclipine-induced amnesia, but did not improve performance when given alone. Lower doses were not effective
[277]	Spontaneous alternations in the Y maze	Male mice	Short-term/ working memory	Injection 30 min before testing	i.p. or s.c.	DHEAS: 20 mg/kg prevented SCO-induced amnesia, but did not improve performance when given alone. Lower doses were not effective
[277]	Water maze	Male mice	Spatial/long-term memory	Injection 30 min before testing	i.p. or s.c.	DHEAS: 20 mg/kg prevented SCO-induced amnesia, but did not improve performance when given alone. Lower doses were not effective
[159]	Spontaneous alternations in the Y maze	Male mice	Short-term/working memory	Injection 30 min before testing	i.p. or s.c.	DHEA and DHEAS: 20 mg/kg prevented amyloid-induced amnesia, but did not improve performance when given alone. Lower doses were not effective
	Footshock passive avoidance training. Memory testing 24 h later	Male mice	Emotional memory	Injection 30 min before training	i.p. or s.c..	DHEA: 20 mg/kg and DHEAS: 10 and 20 mg/kg prevented amyloid-induced amnesia, but did not improve performance when given alone. Lower doses were not effective
	Footshock passive avoidance training. Memory testing 24 h later	Male mice	Emotional memory	Injection 30 min before *retention* testing	i.p. or s.c..	DHEAS: 20 mg/kg did not prevented amyloid-induced amnesia. Lower doses were not effective
[224]	Passive avoidance task. Memory testing 24 h later	Male mice	Emotional memory	Injection 30 min before training	s.c.	DHEAS: 5 and 10 mg/kg prevented dizocilpine-induced amnesia. Higher or lower doses had no effect

Table 2 (continued)

Ref.	Test paradigm	Animals tested	Memory type	Administration time	Administration route	Effective doses
[224]	Memory version of the elevated plus maze. Memory testing 24 h later	Male mice	Long-term memory	Injection 30 min before training	s.c.	DHEAS: 5 and 10 mg/kg prevented dizocilpine-induced amnesia. Higher or lower doses had no effect

effects are caused by action of the inhibitor at a peripheral or central level. Given the weak blood–brain barrier penetration of DHEAS one might speculate that the central sulfatase inhibition was causing the memory-enhancing effects; however, the sulfatase inhibition was much more pronounced in the liver than in the brain [137,138,225].

Taken together, all but one study observed memory-enhancing effects of DHEA(S) in several test paradigms. The dose needed to see a memory enhancement varied considerably between the different studies making a conclusion on an optimal steroid range difficult. While the effective i.c.v. doses were often rather low, the effective peripheral doses (i.p. or s.c.) varied considerably and were sometimes higher (10–24 mg/kg; Ref. [72]) but also sometimes lower (0.05 mg/kg; Ref. [168]) than those used as a physiologically replacement dose in elderly humans (approx. 0.5–1 mg/kg [174]). But at least in the studies by Reddy and Kulkarni the most effective dose was identical to those commonly used in humans [223]. It is very interesting that all studies which investigated a wide range of DHEA(S) doses observed an inverted U-shaped dose–response curve with very low and very high doses having no effect [57,72,168,223]. One reason for the different effective dose ranges might be the time interval between training and testing. When comparing the effects of s.c. or i.p. DHEAS injection very low doses were effective in a short-term memory task [168], while intermediate doses were necessary for memory enhancement when retention was tested 24 h later [223], while even higher doses were needed for proamnestic effects when retention was tested 7 days later [72]. This comparison might suggest that depending on the delay between learning and retention, a specific dose (e.g., 1 mg/kg) could be too high, too low or exactly right. On a neuronal level this might be reflected in an optimal range of DHEA(S)-enhanced neuronal excitability with less or more excitability actually being without a beneficial effect.

While the memory-enhancing properties of DHEA(S) are remarkable, the antiamnestic effects are even more impressive. The studies by Maurice et al. [155,159] and Urani et al. [277] suggest that the antiamnestic effects of DHEA(S) are stronger than the memory-enhancing effects. Notably DHEA(S) prevents amnesia induced by a large variety of agents with apparently different mechanisms of actions (see Table 2).

Last but not least, DHEA(S) has memory-enhancing and antiamnestic effects on several distinct memory domains suggestive of a rather global effect of DHEA(S) which is not limited to a specific brain structure. When taking a look at the paradigms used one might at least anticipate DHEA(S) effects on the hippocampus, the amygdala as well as frontal regions (see Tables 1 and 2).

4.2. Effects on emotional behavior

Haug et al. assessed the effects of DHEA and a structural analogue which cannot be further metabolized (3 β-methyl-androst-5-ene-17-one (CH3-DHEA) on a model of aggressiveness in mice [89]. In this paradigm a lactating female intruder is placed into the home-cage of a castrated male. Chronic administration of either substance to the male animal significantly reduced its aggressiveness. The use of CH3-DHEA excludes the possibility that the anti-aggressive effect of DHEA was due to the action of one of its metabolites. Similar effects were observed in androgenized female mice. Further research revealed that DHEA treatment surprisingly did not increase brain DHEAS levels but reduced the concentration of pregnenolone sulfate (PS) in the brain by almost 50% [305]. The time course of the DHEA-induced PS decrease in the brain (becoming significant after 15 days) paralleled its anti-aggressive action [232]. The authors speculate that DHEA, by reducing PS levels in the brain (another excitatory neurosteroid with GABA-antagonistic activity [149]), actually increases the GABA-ergic tone, which has been implicated in the control of aggressiveness [232]. If long-term DHEA treatment would indeed reduce PS concentration in the brain (a substance known to improve memory in rodents at lower concentrations than DHEA(S) [70]), then one would expect that long-term DHEA treatment actually has impairing effects on cognition. These results have been largely ignored by researchers who have investigated the effects of DHEA on memory. However, all rodent studies performed so far (see previous point) only tested the effects of acute rather than long-term treatment effects of DHEA on memory.

In addition to their anti-aggressive effects DHEA as well as DHEAS have anxiolytic effects in the elevated plus maze [167] which were blocked by a benzodiazepine antagonist, as well as a GABA channel blocker. This study suggests that these effects might be caused by a GABA agonistic rather than a GABA antagonistic action of these steroids [167], which is in contrast to the receptor binding data from Majewska (Ref. [149] and see Section 3.1). Two

studies showed that DHEA decreased behavioral despair as measured in the Porsolt swim test [216,221] which fits to the above reported anxiolytic effects of the steroid [167]. However, a fourth study actually found anxiogenic effects of DHEAS in the mirrored chamber test [222]. These conflicting results might be caused by the higher DHEAS doses used by the latter study [222], when compared to the elevated plus maze study [167] and/or by the different test paradigms used.

Anxiolytic, antidepressant as well as anti-aggressive effects seem to contradict the GABA antagonist action of DHEA(S) described in the previous chapter which suggests that DHEA might have additional, yet undiscovered, mechanisms of action. One example would be the effects of DHEA treatment on PS CNS concentrations, as suggested by Robel et al. [232]. Another mechanism might be the effects on the serotonergic system [1,300], which is known to play a key role in depression [229]. In addition the known effects of DHEA(S) on the sigma receptor might also explain the anxiolytic and antidepressant effects (e.g., Refs. [108,240,241], although the role of sigma receptors in psychopathology is still poorly understood [50,51].

5. DHEA effects on mood and cognitive functions in humans

Since DHEA and DHEAS concentration decrease so dramatically with age in humans and multiple beneficial effects of DHEA in the CNS have been observed in rodents, several studies were conducted to investigate the relationship between DHEA and CNS functions in healthy elderly humans and elderly patients with psychiatric disorders. This section will first summarize studies which investigated associations between DHEA and markers of CNS functions and/or pathologies, the second section discusses data from experimental trials.

5.1. Studies investigating associations in healthy elderly subjects

Studies trying to relate DHEAS levels and global and/or cognitive functioning in elderly humans in a cross-sectional or longitudinal design are summarized in Table 3. Two studies report on a positive relationship between DHEAS levels and global measures of functional abilities (activities of daily living; ADL [110]) in nursing home residents [238] or healthy subjects 90 years of age and older [220]. A third study observed that high-functioning community-dwelling elderly people, as defined after a broad cognitive and functional evaluation, had higher DHEAS levels compared to subjects in the median or lower-functioning group [15]. No difference between these groups was observed for any of the other hormones measured (cortisol, norepinephrine, epinephrine, dopamine). A fourth study assessed the relationship between DHEAS levels and several measures of functional, psychological and mental status in a large population-based study [16]. Low DHEAS levels tended to be associated with limitations in activities of daily living and mobility as well as with dyspnea, depressive symptomatology, subjective health and reduced life satisfaction in women. In men only the association with subjective health reached statistical significance [16]. No strong relationship was found between DHEAS levels and several cognitive measures [16]. A fifth study observed that lower DHEAS levels were associated with poorer functional status in men but not in women [175], which is in line with results mentioned above [220]. In women, however, lower DHEAS levels were surprisingly associated with better cognitive performance [175].

Three studies evaluated the predictive properties of DHEAS levels. Barrett-Connor and Edelstein investigated whether DHEAS levels would predict cognitive test performance assessed approximately 16 years later. No predictive value for DHEAS levels could be detected [8]. Similar negative results were obtained in another study, where DHEAS levels were related to changes in cognitive performance over 4–6 years [302]. The only significant finding in the latter study was that women in the lowest DHEAS quartile were more frail. In addition those women with DHEAS levels below the assay detection limit had higher depression scores. This study therefore matches previous findings that DHEAS levels are probably not a good predictor of cognitive changes in elderly humans [8], but may be a marker of the general health status of an individual [16,220]. A third study investigated cross-sectionally as well as longitudinally the relationship between DHEAS levels and a global measure of cognitive functioning (the Mini Mental Status Exam, MMSE; Ref. [75]). There was a trend for lower DHEAS levels to increase the odds for being cognitively impaired at baseline or showing some signs of cognitive decline over the 2-year follow-up period. Again, this relationship did not reach statistical significance [107].

Taken together these studies demonstrate that low DHEAS levels seem to be associated with poorer health, impaired global functioning, or psychological well being, while there seems to be no specific relationship to cognition and/or changes in cognition over time.

5.2. DHEA(S) in depression

Since DHEA(S) has memory-enhancing, anxiolytic, antidepressant and antiglucocorticoid effects in rodents (see above) abnormal DHEA(S) levels might be one factor in explaining some symptoms of psychiatric disorders. As of today the role of DHEA(S) in depression and dementia have been studied the most and only those two disorders are going to be discussed in this review.

Table 3
Summary of studies investigating the association between DHEAS levels and cognitive and/or general level of functioning

Ref.	Study design	Subject characteristics	Main outcome with respect to DHEAS
[238]	Group comparison between male nursing home residents and control subjects	Nursing home residents ($N = 61$, mean age 80) and community living controls ($N = 50$, mean age 73)	Lower DHEAS in nursing home men; inverse relationship to ADL and dementia
[15]	Group comparison between healthy high-, median-, and low-functioning community-dwelling elderly men and women	High-functioning ($N = 1192$, mean age 75), median-functioning ($N = 80$, mean age = 76) low-functioning ($N = 80$, mean age 76)	Higher DHEAS in the high-functioning group
[220]	Cross sectional study. Level of functioning assessed with ADL	Men ($N = 36$) and women ($N = 39$) (age range 90–103)	Higher DHEAS in men from the high-functioning group
[16]	Cross sectional study in healthy elderly community dwelling subjects. Several measurements of functional, psychological and cognitive status	Men ($N = 266$) and women ($N = 356$), mean age 75	In women: inverse relationship with functional limitations, dyspnea, depressive symptomatology, poor subjective health. In men only with subjective health.
[175]	Cross sectional study in healthy elderly nursing home residents. Several measurements of functional and cognitive status	Men ($N = 24$) and women ($N = 35$), mean age 87	In men: inverse relationship with functional status. In women: lower DHEAS levels were associated with better cognition.
[8]	Prospective study in healthy elderly community dwelling subjects: DHEAS levels as a predictor of cognitive performance 16 years later	Women ($N = 167$, age above 55 at study begin) and men ($N = 270$, age above 50 at study begin)	DHEAS is not a predictor of cognitive changes over time.
[302]	Prospective study in healthy elderly women. Cognitive and psychological assessment at baseline and 4–6 years later	Women ($N = 394$), mean age at baseline 72	Baseline levels were not associated with changes in cognition. Women without detectable DHEAS had higher depression scores.
[107]	Cross sectional and prospective study in healthy elderly women and men. Cognition assessed at baseline and 2 years later	Men and women ($N = 189$), mean age at baseline 67	Lower DHEAS levels tended to increase the odds of being cognitively impaired or becoming cognitively impaired

There are a few reports about DHEA(S) levels in depressive illness which are in contrast to the large literature about other HPA abnormalities in this condition. Depressed patients as a group show enhanced corticotropin releasing factor (CRF) in the CSF [181] as well as elevated basal cortisol levels (reviewed in Ref. [177]). Moreover depressed patients show abnormalities in several endocrine challenge tests, for example nonsuppression in the dexamethasone (DEX) suppression test [109,239] as well as an enhanced response in the combined DEX/CRH test [95]. One hypothesis is that a central CRF overdrive is responsible for the observed HPA alterations as well as for the majority of depressive symptoms (see for a recent review [180]). Indeed a normalization of HPA activity/reactivity is observed if pharmacological treatment is successful [7,94]. The elevated cortisol levels may also be responsible for the cognitive impairments associated with depression [151,237,294].

In teenagers with a first episode of major depression, higher evening cortisol levels as well as lower morning DHEA levels were independently associated with major depression [81]. Moreover a higher cortisol to DHEA ratio was associated with subsequent negative life events in those patients [80]. In adults, however, higher DHEAS levels were observed in depressed patients in three studies [87,275,276]. Moreover DHEAS levels significantly decreased in response to pharmacological treatment in two of those studies [275,276]. Another report documented that in hypercortisolemic depressed patients DHEA levels were also elevated in comparison to healthy controls [92]. A fifth study reported on a loss in diurnal DHEA rhythmicity in hypercortisolemic patients while no difference between DHEA and cortisol levels were found in 24-h urine excretion [197]. Taken together low DHEA levels seem to be associated with depressive symptoms in teenagers, but adults with clinical depression and hypercortisolemia have higher DHEAS and DHEA levels than normal controls. However, in old subjects without clinical depression low DHEAS levels might be again associated with more depressive mood disturbances (see Section 5.1) [16,302].

Wolkowitz et al. had reported preliminary evidence for beneficial DHEA effects from an open labeled DHEA trial (30–90 mg/day) in six elderly subjects with major depression. Scores in several depression scales declined and automatic memory improved [297]. These authors just recently replicated their findings in a double-blind study. With a similar treatment protocol they observed a significant improvement in depression ratings (30%) in 11 depressed patients after 6 weeks of treatment, when compared to 11 depressed controls on placebo [293]. The subjects in this study were younger (mean age 44) than in the first open trial and most of them were on antidepressant medication. Effects on cognition were not assessed and/or not reported [293]. Another recent crossover double-blind study reported that DHEA treatment (30 mg/day for 3 weeks followed by 150 mg/day for another 3 weeks)

reduced depressive symptoms in 15 medication-free patients with midlife onset of dysthemia. No effects were observed on several neurospychological tests [19]. Interestingly the antidepressant effects were observed rather quickly (within 10 days).

These first two clinical studies provide evidence that DHEA treatment may decrease depressive symptomatology in age-advanced patients with major depression or dysthymia, while having no effects on cognition. Whether similar results could be obtained in patients with hypercortisolemia (which is often associated with high DHEAS levels (see above) seems unlikely but should be investigated in the future.

5.3. DHEA(S) in dementia

Sunderland et al. reported that 10 patients suffering from Alzheimer's disease (AD) had significantly lower DHEAS levels than healthy controls [270] but this preliminary finding could not be replicated in other small studies [133,263] and two larger studies [135,248]. However, two larger clinical investigation [178,303] and one smaller study [261] again reported on reduced DHEAS level in AD patients. One of those studies reported that the DHEAS reduction was AD-specific [178], while the other reported similar effects for patients with cardiovascular dementia [303]. The physiological relevance of the latter finding remains open, since concentrations of the unsulfated form (DHEA) which more easily passes the blood–brain barrier were not reduced in those patients [303]. Most other studies summarized above only measured DHEAS.

Similar conflicting results have been reported in studies which were not explicitly performed for the comparison of AD and healthy aged individuals. While one study [238] found reduced DHEAS level in patients with dementia due to several causes, two other studies failed to show predictive [8,16] or discriminative properties of DHEAS levels [16]. Adding to the confusion, higher basal as well as ACTH stimulated levels of the unsulfated form (DHEA) but not of cortisol were observed in early stages of AD [179].

From the above survey it becomes obvious that a reduction in DHEAS levels in AD is only observed in some studies, suggesting that low DHEAS levels cannot be regarded a key symptom of this disease. Reasons for the discrepant results could be the stage of the disease as well as other factors like gender, medication, body composition, or peripheral glucose regulation (see Ref. [182]).

Some researchers have suggested that the DHEAS/cortisol ratio might be a more appropriate and sensitive measure of adrenal abnormalities in psychiatric disorders [90,132,295,296]. This idea is based on the antiglucocorticoid effects of DHEA observed in rodents (see Section 3.6). Leblhuber et al. reported on a reduced DHEAS/cortisol ratio in female AD patients, while no such difference existed in male patients [131]. Whether the use of a DHEAS/cortisol ratio is a useful parameter in describing the endocrine milieu in patients or healthy subjects awaits further investigation.

Clinical trials which test the effects of DHEA administration to AD patients have not been published so far (but are currently under way). One preliminary study with two male AD patients reported subtle beneficial effects of DHEA treatment [234].

5.4. Experimental studies in humans investigating cognition and well-being

As obvious from the previous sections, results from studies investigating associations between DHEA(S) levels and cognition or well-being are conflicting. Only experimental trials in which the steroid is given to volunteers in a double-blind fashion are able to answer the questions, whether DHEA(S) effects in humans might be as strong as they are in rodents. As of today only a few experimental trials which measured cognitive performance or mood have been conducted and these will be discussed in this section.

Two studies investigated cognitive effects of a single high-dose DHEA application in young subjects with high endogenous DHEA(S) blood levels. The first one observed an increase in REM sleep after 500 mg of DHEA, leading the authors to speculate that this might be one mechanism by which DHEA could enhance cognition [77]. However, a second study, which tested cognitive performance and mood with a large test battery found no effects of a single although somewhat smaller (300 mg) DHEA dose on both parameters in young healthy men [287].

Elderly people who have low DHEA(S) levels and also often show some forms of mild cognitive decline naturally appear to be the prime target population for DHEA treatment in humans (see Table 4). Morales et al. reported that 3 months of DHEA replacement (50 mg/day) in age-advanced subjects (mean age 54) increased the sense of well-being in 82% of women and 67% of men in a placebo-controlled double-blind experiment [174]. This finding was accompanied by a significant increase in bioavailable IGF-I. In this study well-being was assessed only with an open interview and no standardized questionnaires or cognitive tests were used. Examples of specific statements given by the subjects were: improved sleep quality, more relaxed, more energy, less joint pain. This documents that the beneficial DHEA effects varied substantially between subjects. Another study mentioned a similar increase in well-being after transdermal DHEA replacement; however, the study was neither double-blind nor were the assessment of well-being or the specific effects observed described at all in the paper [61]. Flynn et al. performed a double-blind placebo-controlled crossover study with 39 elderly men who received 100 mg/day DHEA or placebo over a period of 3 months [74]. No changes in the satisfaction to perform activities of daily

Table 4
Summary of placebo-controlled double-blind DHEA replacement studies in humans, investigating psychological and/or cognitive measures

Ref.	Study design	Subject characteristics	Main outcome with respect to DHEAS
[174]	Crossover: 50 mg/day DHEA or placebo for 3 months. Well-being assessed with an open interview	Healthy volunteers: 17 women (mean age 55) and 13 men (mean age 54)	Increased sense of well being in women and men, increase in IGF-I, accompanied by a decrease in IGF-BP3
[291]	Crossover: 50 mg/day DHEA or placebo for 2 weeks. Mood questionnaires and neuropsychological tests	Healthy volunteers 15 women (mean age 69) and 25 men (mean age 69)	No changes in cognitive performance. In women a trend towards an increased mood.
[290]	Crossover: 50 mg/day DHEA or placebo for 2 weeks. EEG recording, mood questionnaires and neuropsychological tests	Healthy volunteers: 14 men (mean age 71)	Enhanced P 300 amplitude if the oddball task was performed for the second time. No changes in cognitive performance or mood.
[289]	Group comparison: 50 mg/day DHEA or placebo for 2 weeks. Attention and memory tests before and after exposure to a laboratory stressor (TSST)	Healthy volunteers: 37 women (mean age 67) and 38 men (mean age 67)	No difference between the groups before stress. After stress, DHEA group recalls fewer previously learned items (declarative memory), but shows enhanced attention.
[74]	Crossover: 100 mg/day DHEA or placebo for 3 months. Activity of daily living and libido questionnaire after each treatment period	Healthy volunteers: 39 men (mean age 72)	No changes in satisfaction with activities of daily living and no changes in libido.
[293]	Group comparison: 30–90 mg/day DHEA or placebo for 6 weeks. Depression questionnaire before and after treatment	Psychiatric outpatients: 12 men 10 women (mean age 44) with major depression; most on antidepressant medication	30% reduction in depression scores
[19]	Crossover: 30 mg/day and 150 mg/day DHEA (for 3 weeks each) or placebo for 3 weeks. Depression questionnaires and a large cognitive test battery after each treatment period	Psychiatric outpatients: 14 men 11 women (mean age 50) with midlife onset dysthymia; all medication free	30–40% reduction in depression scores, no effects on cognition.

living (ADL) as assessed with a questionnaire were detected. However, it has to be said that the questionnaire used in this study [213] is not well suited to detect mood changes in physically healthy subjects. Another recent placebo-controlled crossover study reported that subjects after 6 months of DHEA or placebo treatment were unable to guess which treatment they had received suggesting that they did not experience any strong effects of the steroid [30]. In age-advanced patients with depression DHEA treatment might have antidepressant effects as suggested by two recent double-blind trials [19,293] (see Section 5.3).

In a series of placebo-controlled double-blind experiments Wolf et al. investigated cognitive and psychological effects of a 2-week DHEA replacement (50 mg/day) in healthy elderly subjects (mean age 70). The authors found that DHEA had no effects on cognitive performance (as assessed with a large cognitive test battery) but tended to increase mood in women, but not in men [291]. Another experiment used event-related potentials (ERPs) derived from EEG recording as evidence of CNS effects of the steroid treatment. DHEA replaced subjects showed an enhanced P 300 amplitude (an electrophysiological index of information processing in short-term memory [214]) if the task was repeatedly presented [290]. Again no changes in memory test performance could be observed. This finding suggests that with more sensitive measurement techniques subtle effects of DHEA replacement on CNS stimulus processing can be observed, which do not seem to be strong enough to influence test performance or well-being [290]. Another study from the same laboratory investigated the effects of DHEA on cognition before and after exposure to a laboratory stressor (Trier Social Stress Test; TSST [114]). This experiment set out to investigate whether DHEA replacement would protect hippocampal mediated declarative memory from the impairing effects of psychosocial stress (Refs. [115,145] and see Section 3.6). DHEA-replaced women showed a significantly enhanced ACTH stress response, and both sexes tended to show an increased free cortisol response with DHEA treatment [121,289]. Subjects under DHEA recalled less previously learned items (hippocampal mediated declarative memory [264]) after stress but performed better in an attention task than subjects from the placebo group [289]. These findings document a complex DHEA by stress by cognitive domain interaction with impairing as well as protecting properties of the steroid. However, the results do not support the idea that DHEA replacement might protect hippocampal-dependent declarative memory from the impairing effects of psychosocial stress [289]. These results are similar to the report of a DHEA-induced impairment of hippocampal-mediated fear conditioning [69], but seems to be in contrast to the electrophysiological data from Diamond et al. [58] (see Section 3.6).

In summary, present human experimental studies on the effects of DHEA replacement on cognition and mood have not led to a clear picture. While Morales et al. reported positive effects [174], Wolf et al. failed to observe similar

results in their studies which employed a large battery of standardized tests and questionnaires [289–291]. Reasons for the observed differences might be the length of the treatment (3 months vs. 2 weeks) as well as the age of the subjects (55 vs. 70 years). However, the negative findings from Wolf et al. with respect to mood have recently been replicated in a 3-month trial in elderly men [74], suggesting that the treatment length might not be an explanation for the observed differences. Whether elderly people (over 60 years) differ in their response to DHEA when compared to age-advanced or mid-aged subjects (40–60 years) has not been addressed so far.

At least the EEG studies by Friess et al. in young subjects [77] as well as the ERP study by Wolf et al. in old subjects [290] demonstrate that with sensitive methods subtle DHEA effects on CNS functioning can be detected. Future studies are needed to clarify whether longer treatment and/or application to younger elderly subjects is needed to reveal beneficial effects on the behavioral or emotional level. Moreover, preliminary results in depressed patients suggest that DHEA might be helpful in treating age-advanced patients with depression [19,293]. Unfortunately most studies conducted in humans so far have not assessed changes in emotions and/or cognition, but rather focused on endocrine or immunological effects of the steroid.

6. Possible indirect long-term effects of DHEA replacement in humans

6.1. DHEA(S) interaction with insulin

Since DHEA(S) has antiobesity and antidiabetic effects in rodents (e.g., Ref. [85]), one suggested beneficial mechanism of DHEA(S) action in humans is its ability to enhance glucose tolerance, which is known to decrease with age [257]. Since poor glucose regulation is associated with cognitive impairments in humans with and without dementia [42,43,79,117], this would be a peripheral mechanism of DHEA(S) action with possible strong effects on the CNS. Several studies have documented that insulin administration decreases DHEA(S) levels [60,130] at least in men [185]. Moreover, pharmacological insulin reduction leads to increased DHEAS levels [183,184]. However, DHEA treatment seems neither to reduce insulin levels nor to enhance glucose tolerance (reviewed in Ref. [182]). DHEAS levels might therefore be a biomarker of insulin resistance in humans, but the steroid does not seem to have strong antidiabetic potential in humans [182].

6.2. DHEA effects mediated by conversion into estrogens and/or androgens

The present review has summarized the current evidence of DHEA(S) action in the brain and its resulting effects on emotions and cognition. DHEA(S), on one hand, acts via non-genomic mechanisms as an excitatory neurosteroid; however, metabolism into potent androgens and estrogens also occurs. Therefore it seems important to compare the observed DHEA effects with the currently available knowledge about estrogens and androgens.

Basically three major areas of DHEA effects in the CNS have been suggested: (a) neuroprotective properties, which might suggest a role of DHEA in neurodegenerative diseases like AD, (b) cognition and (c) mood-enhancing effects. This points to a role for DHEA in age-related cognitive decline as well as in depressive disorders in elderly people.

Recently, evidence has accumulated that estradiol replacement prevents or postpones the onset of AD [18,91, 198,199]. Moreover small clinical trials have been conducted with promising results (Refs. [68,188,189], but see Ref. [284]). With respect to memory in healthy elderly subjects the empirical situation is less clear. At least the studies by Philips and Sherwin [212] and Sherwin and Tulandi [256] suggest that estradiol enhances verbal memory performance specifically and there is now evidence to suggest that these effects occur rapidly [288]. However, other studies reported on enhanced attention after estradiol treatment or failed to find any positive effect. These conflicting results might be caused by the variability in cognitive tests and/or different estradiol compounds used (see for recent reviews Refs. [88,227,255]). In addition to its effects on memory antidepressant effects of estradiol replacement have been documented in several studies (see for review Ref. [308]). Possible underlying mechanisms of these beneficial effects of estradiol are summarized by McEwen et al. [161–163].

There are only a few testosterone replacement studies looking at cognitive outcome measures. Memory enhancement has been found in two studies [32,103], while two other studies failed to find beneficial effects [258,292]. However, mood and libido enhancement has been documented repeatedly (see for recent review Ref. [267]).

Several beneficial effects of estradiol replacement are now demonstrated in animals as well as humans, while testosterone replacement is still a neglected research area. Whether DHEA has additional benefits when given to women on estradiol replacement [173,174] or might exert similar effects with less harmful side-effects as suggested by Labrie at al. [125], has to be investigated in future studies comparing DHEA and estradiol replacement alone with a combination of the two. So far epidemiological as well as experimental evidence in humans certainly documents more positive effects of estradiol when compared to DHEA.

6.3. Effects mediated via a DHEA-induced increase in bioavailable IGF-I concentrations

Another possible mechanism of indirect DHEA action is the increase in bioavailable IFG-I (increase in IGF-I

and/or decrease of one of the binding proteins) after long-term DHEA replacement, as shown by several studies [30,61,173,174]. Since growth hormone (GH) and IGF-I concentrations sharply decrease with age [39], an increase in IGF-I might have positive effects on body composition and muscle strength. This may directly or through IGF-I action on the brain also have an impact on well-being or cognition [34,39,301]. Future studies are needed to clarify whether an increase in bioavailable IGF-I is a prerequisite for positive changes in well-being and cognition in elderly humans.

7. Summary and conclusion

The present review tried to document the broad and impressive range of beneficial effects of DHEA(S) treatment in rodents and to compare those effects to results obtained in clinical trails or experimental studies in humans. This comparison revealed profound differences in research strategies and related problems with interpretation of the findings.

First, on a more general note, DHEA concentrations are low in rodents compared to humans [45,69,279]. This raises the question of whether rodents can be adequate species to study DHEA effects relevant to humans. Extrapolation from data obtained in rodents to humans should be made with great caution. Research in nonhuman primates, which also show rather high DHEA(S) levels with similar developmental patterns [45,129,247], would be very valuable for future studies.

Second, beneficial effects on neuronal plasticity and survival as well as positive effects on memory and emotional behavior have been documented in several animal studies. Most of these studies have investigated the effects of rather acute DHEA(S) treatment, often with relatively high DHEA(S) doses (see Table 5). However, DHEA replacement in humans as a therapeutic strategy would consist of a rather long-term treatment of several years with low DHEA(S) doses to avoid negative side effects. Therefore, one goal of future DHEA(S) research in rodents should be the investigation of longer treatments on memory and CNS integrity in older animals. These studies could employ protocols like previous experiments on the relationship between glucocorticoids and CNS aging [128,165] and would thus correspond better to the human situation

Third, most animal studies have used DHEAS, probably due to its better solubility, while in humans DHEA is used more often. The pharmacokinetics of DHEA(S) in rodents is still poorly understood [93]. Since only a small fraction of DHEAS crosses the blood–brain barrier [84,116] it remains to be shown through which mechanisms peripherally administered DHEAS enhances memory. DHEAS could be converted into DHEA in the periphery, which can easily enter the brain. There it could be converted back into DHEAS by hydroxy sulfotransferase [4,219] or act as the unsulfated form. The dynamic role of the sulfotransferase and sulfatase has to be addressed in future studies which should monitor DHEA and DHEAS concentrations in blood and brain to be able to relate those measurements to observed behavioral effects.

Today the human research in this field is still relatively sparse, so that several areas of potentially beneficial long-term DHEA treatment have not been investigated so far (see Table 5). Beneficial effects on electrophysiological indices of CNS functioning have been obtained after acute or midterm DHEA treatment; however, studies looking at cognition have failed to find effects of DHEA. These studies document that the fast neuroactive effects of DHEA as observed in rodents can be detected with sensitive electrophysiological methods, but do not seem to be strong enough to improve cognition in healthy young and old adults. However, prolonged DHEA treatment has been reported to enhance well-being and to reduce depressive symptoms, although additional studies are clearly needed to support there findings. These long-term effects might not be caused by the neuroactive effects of DHEA(S) but may rather reflect effects mediated by conversion into estrogens or androgens [124,125], or mediated by a DHEA-induced increase in IGF-I [173,174].

Future studies in humans should investigate the effects of DHEA treatment over several months with multiple cognitive testing during the treatment period to be able to

Table 5
Effects of DHEA(S) treatment in rodents and humans: a comparison with respect to treatment length and domain investigated (1: in young subjects; 2: in elderly subjects; 3: in patients with major depression; 4: in patients with dysthymia)

Nature of observed effects	Treatment length					
	Rodents			Humans		
	Acute (single administration)	Midterm (days to weeks)	Long-term (1 month or more)	Acute (single administration)	Midterm (days to weeks)	Long-term (1 month or more)
Electrophysiological	yes	yes	not tested	yes (1)	yes (2)	not tested
Cognitive	yes	yes	not tested	no (1)	no (2)	no (4)
Emotional	yes	yes	not tested	no (1)	no (2)	yes (2,3,4)
Neuroprotective	not tested	yes	not tested	not tested	not tested	not tested

answer questions regarding the time course of DHEA action in humans. Another important avenue for future research are DHEA replacement studies in elderly adults with cognitive impairment.

Taken together the multiple beneficial effects of DHEA(S) as observed in rodents could, as of today, only in part be substantiated by similar effects in humans. However, it is still too early to dismiss the possibility of positive effects of DHEA replacement on human brain aging. Future experimental studies are required to identify human populations who might show favorable responses to DHEA(S) treatment.

Acknowledgements

The authors thank Bruce S. McEwen for most helpful comments on an earlier version of this manuscript. This work was supported by DFG grants Ki 537/6-1, He1013/13-1 and Wo 733/1-1.

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