1: Ann Endocrinol (Paris). 2003 Apr;64(2):158-61.

Cognitive functions and sex steroids.

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In humans, levels of adrenal (DHEA(S)) and gonadal (estradiol, testosterone) sex steroids decline with age. Studies in rodents have demonstrated that these hormones can have neuro-excitatory and neuro-protective effects in the central nervous system (CNS). Behavioural studies repeatedly have reported enhanced memory performance of rats and mice after acute or sub-chronic treatment with sex steroids. The current review summarizes human studies on this topic conducted by the author as well as other groups. Epidemiological as well as experimental studies have in general shown that estradiol replacement improves cognition, especially verbal memory in menopausal women. Similarly positive effects of testosterone replacement in older men have been reported in several, but not all studies. Cognition enhancing effects of DHEA replacement in older healthy humans in contrast could not be demonstrated with short (weeks) or prolonged (months) treatment regimes. Even though most results support the notion that estradiol in women and testosterone in men can enhance cognition in older healthy humans, more research is needed before recommendations for the clinical practice can be made.

PMID: 12773955 [PubMed - indexed for MEDLINE]

2: Brain Res Brain Res Rev. 1999 Nov;30(3):264-88.

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

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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.

PMID: 10567728 [PubMed - indexed for MEDLINE]

3: J Endocrinol Invest. 1999 Apr;22(4):316.

Comment on: J Endocrinol Invest. 1998 Sep;21(8):544.

Dehydroepiandrosterone replacement in elderly individuals: still waiting for the proof of beneficial effects on mood or memory.

Wolf OT, Kirschbaum C. PMID: 10342369 [PubMed - indexed for MEDLINE]
4: Psychoneuroendocrinology. 1998 Aug;23(6):617-29.

Opposing effects of DHEA replacement in elderly subjects on declarative memory and attention after exposure to a laboratory stressor.

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Aging is accompanied by a continuous decline of the adrenal steroid hormone DHEA and its ester DHEAS. Results from studies in rodents have demonstrated that DHEA(S) administration can enhance memory in several test paradigms. However studies from this laboratory did not find positive effects of DHEA treatment on cognitive performance in young and elderly humans. With respect to a possible mechanism of DHEA activity, effects on several neurotransmitter receptors as well as a possible antiglucocorticoid action are discussed. For high levels of glucocorticoids, a disruptive effect on hippocampal mediated memory is documented in rodents and humans. Therefore it was speculated that, if an antiglucocorticoid action of DHEA would underlie the observed beneficial effects of DHEA on memory, these effects might only be detectable if subjects are stressed (and therefore have high cortisol levels). To test this hypothesis 75 elderly women and men participated in a placebo-controlled experiment. Subjects took DHEA (50 mg/day) or placebo for 2 weeks (double blind). Thereafter they participated in a standardized psychosocial laboratory stressor (Trier Social Stress Test; TSST). Before and after stress exposure subjects completed two declarative memory tests (visual-verbal and spatial) as well as one attention test. In addition recall of visual material learned before stress was assessed after stress. Baseline DHEAS levels were significantly lower compared with young adults. DHEA replacement increased DHEAS levels into ranges found in young subjects. DHEA-substituted subjects showed a trend towards a larger cortisol stress response. In the visual memory test subjects under DHEA recalled less items after stress which they had learned before stress. In the attention test however subjects under DHEA performed better than subjects from the placebo group after stress. No interaction between stress and DHEA was found for the spatial memory task. The effects of DHEA substitution on memory and attention after stress exposure seem to be heterogenous. While recall of previously learned material seems to be impaired, attention is enhanced. These results do not support the idea of a direct antiglucocorticoid or anti-stress effect of DHEA on hippocampal mediated memory functions.

PMID: 9802132 [PubMed - indexed for MEDLINE]

5: J Gerontol A Biol Sci Med Sci. 1998 Sep;53(5):M385-90.

Effects of dehydroepiandrosterone replacement in elderly men on event-related potentials, memory, and well-being.

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BACKGROUND: In humans, concentrations of the adrenal steroid hormone dehydroepiandrosterone (DHEA) and its sulfate ester (DHEAS) decline with age. Results from studies in rodents have suggested that DHEA administration can improve memory performance as well as neuronal plasticity. However, a first study from our laboratory could not demonstrate beneficial effects of DHEA substitution on cognitive performance and well-being in elderly subjects. To further evaluate whether DHEA replacement has effects on the central nervous system, an experiment using event-related potentials (ERPs) was conducted. METHODS: In this placebo-controlled crossover study, 17 elderly men (mean age, 71.1 +/- 1.7 yr; range 59-81 yr) took placebo or DHEA (50 mg/day) for 2 weeks

(double blind). After each treatment period subjects participated in an auditory oddball paradigm with three oddball blocks. In the first two blocks subjects had to count the rare tone silently, whereas, in the third block they had to press a button. In addition, memory tests assessing visual, spatial, and semantic memory as well as questionnaires on psychological and physical well-being were presented. RESULTS: Baseline DHEAS levels were lower compared with young adults. After 2-week DHEA replacement, DHEAS levels rose 5-fold to levels observed in young men. DHEA substitution modulated the P3 component of the ERPs, which reflects information updating in short-term memory. P3 amplitude was increased after DHEA administration, and only selectively in the second oddball block. DHEA did not influence P3 latency. Moreover, DHEA did not enhance memory or mood. CONCLUSIONS: A 2-week DHEA replacement in elderly men results in changes in electrophysiological indices of central nervous system stimulus processing if the task is performed repeatedly. However, these effects do not appear to be strong enough to improve memory or mood.

PMID: 9754145 [PubMed - indexed for MEDLINE]

6: J Clin Endocrinol Metab. 1998 May;83(5):1756-61.

Sex differences in endocrine and psychological responses to psychosocial stress in healthy elderly subjects and the impact of a 2-week dehydroepiandrosterone treatment.

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Evidence from animal as well as human studies has suggested that significant sex differences exist in hypothalamus-pituitary-adrenal axis (HPA) activity. As gonadal steroids could be important modulators of HPA sex differences, stress responses were investigated in subjects of advanced age after dehydroepiandrosterone (DHEA) or placebo treatment. After a 2-week treatment with 50 mg DHEA daily or placebo, 75 men and women (mean age, 67.6 yr) were exposed to the Trier Social Stress Test (TSST). The TSST is a brief psychosocial stress that consists of a free speech and mental arithmetic task in front of an audience. The results show that the TSST induced significant increases in ACTH, salivary free cortisol, total plasma cortisol, norepinephrine, and heart rates (all $P < 0.0001$) as well as decreased positive affect in the elderly ($P = 0.0009$). Men showed larger stress responses in ACTH ($P = 0.004$), salivary free cortisol ($P = 0.044$), and plasma total cortisol ($P = 0.076$) compared to women. No sex differences were observed in norepinephrine, epinephrine, or heart rate responses. In contrast to ACTH and cortisol response differences, women reported that they were significantly more stressed by the TSST than men ($P = 0.0051$). Women treated with DHEA showed ACTH stress responses similar to those of men, but significantly enhanced compared to those of women taking placebos ($P < 0.009$). No other stress response differences emerged between DHEA and placebo groups. Finally, DHEA treatment did not result in an improvement of subjective well-being. We conclude that elderly men show larger HPA responses than women to psychosocial stress, as studied in the TSST. Estrogen effects on hypothalamic CRF-producing neurons might be responsible for these sex differences.

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7: J Endocrinol Invest. 1998 Feb;21(2):133-5.

Comment in: J Endocrinol Invest. 1998 Sep;21(8):544. | J Endocrinol Invest. 2000 Dec;23(11):782-3.

Wishing a dream came true: DHEA as a rejuvenating treatment?

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PMID: 9585389 [PubMed - indexed for MEDLINE]

8: Biol Psychiatry. 1997 Nov 1;42(9):845-8.

A single administration of dehydroepiandrosterone does not enhance memory performance in young healthy adults, but immediately reduces cortisol levels.

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PMID: 9347134 [PubMed - indexed for MEDLINE]

9: J Clin Endocrinol Metab. 1997 Jul;82(7):2363-7.

Effects of a two-week physiological dehydroepiandrosterone substitution on cognitive performance and well-being in healthy elderly women and men.

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The levels of dehydroepiandrosterone (DHEA) and its sulfate ester DHEAS decrease with age after a peak around 25 yr. Animal studies as well as the first studies in humans have generated the idea that DHEA replacement in elderly subjects may have beneficial effects on well-being and cognitive functions. In the present experiment 40 healthy elderly men and women (mean age, 69 yr) participated in a double blind, placebo-controlled DHEA substitution study. For 2 weeks subjects took 50 mg DHEA daily, followed by a 2-week wash-out period and a 2-week placebo period. The treatment sequence was randomized in a cross-over design. After 2 weeks of DHEA or placebo, psychological and physical well-being as well as cognitive performance were assessed using several questionnaires and neuropsychological tests. All subjects had low DHEAS baseline levels. DHEA substitution lead to a 5-fold increase in DHEAS levels in women (from 0.67 +/- 0.1 to 4.1 +/- 0.4 micrograms/mL; $P < 0.001$) and men (from 0.85 +/- 0.1 to 4.5 +/- 0.4 micrograms/mL; $P < 0.001$). DHEA, androstenedione, and testosterone levels also increased significantly in both sexes (all $P < 0.001$). No significant changes were observed in insulin-like growth factor I or insulin-like growth factor-binding protein-3 levels. DHEA replacement had no strong beneficial effect on any of the measured psychological or cognitive parameters. Only women tended to report an increase in well-being ($P = 0.11$) and mood ($P = 0.10$), as assessed with questionnaires. They also showed better performance in one of six cognitive tests (picture memory) after DHEA. However, after Bonferroni alpha adjustment, this difference was no longer significant. No such trend was observed in men ($P > 0.20$). Likewise, no beneficial effects of DHEA substitution could be observed in any of the other tests of the neuropsychological test battery in either sex (all $P > 0.20$). In conclusion, the present data do not support the idea of strong beneficial effects of a physiological DHEA substitution on well-being or cognitive performance in healthy elderly individuals.

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