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OPINION

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

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Several endocrine changes occur with aging, and the idea that substitution of a certain hormone may be able to reverse some of the age associated physical or mental impairments has a long history. In this respect the adrenally derived steroid hormone dehydroepiandrosterone (DHEA) and its sulfate ester DHEAS, which both sharply decline with age (1) have received increasing attention recently. Among a multitude of effects, DHEA treatment has been reported to bolster the immune system (2), act against cancer processes (3) and enhance memory performance (4, 5). However, clear-cut experimental evidence for these effects has only been shown in rodents so far. While DHEAS is the most abundant steroid hormone in humans (1) the adrenals of mice and rats do not produce DHEA (or only very small amounts) and serum concentrations of this steroid are very low in these animals (6). Extrapolation from data obtained in rodents should thus be made with great caution (7).

To date the empirical evidence in favor of beneficial effects of DHEA treatment in humans is less convincing. Epidemiological data which had suggested that low DHEAS levels in elderly individuals may be associated with cardiovascular diseases, cancer, or dementia could not be replicated by other laboratories resulting in rather inconclusive data (e.g. 8-12). Placebo-controlled double blind replacement studies are therefore needed to test the potential beneficial effects of DHEA treatment.

With respect to psychological parameters, the first of such studies was published in 1994 with startling results. Following three months of DHEA replacement (50 mg/day), Morales et al. (13) reported an increase in well-being in 84% (women) and in 67% (men), respectively. Unfortunately, these results were derived from open interviews, i.e., no standardized test material was employed. This publication was welcomed news for the lay press and received considerable attention among endocrinologists, too.

The reported increase in well-being could have been induced by a direct effect of DHEA on the brain. In fact, DHEA acts in a nongenomic fashion on several neurotransmitter receptors and increases neuronal excitability in the rodent central nervous system (CNS). It is therefore called an "excitatory neurosteroid" (14).

Stimulated by the Morales et al. (13) study, studies from our laboratory were launched to test the hypothesis that DHEA might affect cognition and mood via its nongenomic actions in humans. Since both in rodent (15) as well as in human studies (16), neuroactive effects of DHEA occurred within minutes to hours, we chose to administer DHEA for no more than two weeks. A first study in young subjects with a single dose of 300 mg DHEA failed to reveal any effect on memory or mood (17). Next, the effects of a two-week DHEA replacement with 50 mg per day on cognitive performance and well-being in elderly humans were investigated. Several well-standardized neuropsychological tests and questionnaires were employed. While comparable increases in sex steroid levels as reported by Morales et al. (13) were obtained, we were unable to demonstrate any beneficial effect of the hormone on cognitive performance or well-being (18). This suggested that the DHEA-treatment had no strong effects on these parameters. However, these negative findings did not exclude the possibility of more subtle effects on the CNS not 'translated' to overt behavioral or cognitive changes.

In fact, an additional study showed DHEA-induced changes in EEG parameters in an oddball paradigm, but again failed to reveal positive effects on memory or mood (19). Moreover, no evidence for an "anti stress" or "antiglucocorticoid" action (20, 21) of this

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steroid could be detected. Elderly subjects replaced for two weeks with 50 mg DHEA daily did not differ in their psychological responses to a laboratory stressor (e.g., rated stressfulness of the test situation). Women showed a significantly larger ACTH increase under DHEA and both sexes tended to show a larger free cortisol response compared with placebo treated controls (22).

Taken together these studies clearly demonstrate that DHEA replacement in elderly subjects has no strong direct (i.e., neuroactive) effects on well-being or cognition in humans. To the best of our knowledge these experiments are the only published studies investigating well-being and cognition in placebo-controlled, double blind protocols employing well-standardized test material.

It has to be considered, however, that more indirect effects of DHEA substitution may exist. One interesting finding of the Morales et al. study (13) was an increase in IGF-I which was accompanied by a decrease in IGF-BP1. Increased bioavailable IGF-I appears to exert beneficial effects similar to the proposed DHEA induced changes (23). Morales et al. suggested that DHEA may be able to reverse some of the age-associated catabolic processes and increase well-being via this mechanism. However, an enhancement of bioavailable IGF-I is not necessarily induced by DHEA. While 12 months of percutaneous DHEA administration in postmenopausal women resulted in positive effects of DHEA on body composition, bone density and vaginal cytology (24, 25), no increase in IGF-I was observed (24). These authors proposed yet another mechanism to explain longer-term effects of DHEA replacement, suggesting that DHEA may enhance intracrine derived bio-active sex-steroids (26).

With respect to possible immune enhancing effects of DHEA the available data are also contradictory. A first placebo-controlled study reported on large increases in natural killer cell activity (NKCA) after three weeks of DHEA treatment in women (27). This is in contrast to a study of DHEA effects on NKCA in men (28). Here, NKCA was unaltered until 18 weeks of DHEA treatment.

Another important point to mention is that possible negative side effects of DHEA treatment have not been evaluated carefully so far, which is especially worth considering given the fact that DHEA is sold and consumed in large amounts in some countries. Studies looking at changes in prostate specific antigen or other markers of tumor growth are definitely needed. Also the risk of DHEA-induced liver tumors, as suggested from rodent studies (29, 30), has to be considered in long-term DHEA treatment.

In conclusion the scientific evidence in favor of a routine DHEA replacement in elderly humans is sparse at best. While numerous anecdotal evidences may exist, none of the several proposed beneficial effects of DHEA have been shown by replicated placebo-controlled double blind studies. Until convincing results from carefully performed long-term studies are presented, we feel that the dream of an 'endocrine fountain of youth' still awaits materialization.

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