COMMENTARY

DHEA deficiency syndrome: a new term for old age?

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Abstract

Dehydroepiandrosterone (DHEA) is a steroid secreted by the adrenal cortex, with a characteristic, age-related, pattern of secretion. The decline of DHEA concentrations with age has led to the suggestion that old age represents a DHEA deficiency syndrome and that the effects of ageing can be counteracted by DHEA 'replacement therapy'. DHEA is increasingly being used in the USA, outside medical supervision, for its supposed anti-ageing effects. This commentary weighs the evidence for the existence of a DHEA deficiency syndrome and considers the value of DHEA 'replacement therapy'.

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Introduction

DHEA has been an endocrine paradox for many years: it was found to circulate in extremely high quantities, yet appeared to have no significant biological function and the regulation of its secretion was a matter of speculation. Recently, there has been a resurgence of interest in DHEA, because it has been suggested that it might have anti-ageing effects. In the USA, DHEA is widely available without prescription, and the increase in unsupervised self-administration of this hormone is a cause for concern to many physicians. There have been, however, many claims for its effects as a preventive medication for the diseases associated with older age. So, should we now describe old age as a DHEA deficiency syndrome?

DHEA secretion declines with age

There is certainly a far lower plasma concentration of DHEA seen in older individuals compared with younger people (Vermuelen 1980, Orentreich *et al.* 1984). DHEA has a characteristic pattern of secretion through life (Fig. 1). It is the major product of the foetal adrenal (Shackleton 1984), and circulates in high concentrations, but declines rapidly after birth, as the foetal zone atrophies and disappears in the first year of life (de Peretti & Forest 1976). During childhood, DHEA concentrations remain low, but, 2 years before the onset of puberty, there is a dramatic increase in DHEA secretion, termed the 'adrenarche' (Albright 1947). Peak DHEA concentrations are seen in early adulthood, and this is followed by a gradual decline throughout adult life, termed 'adrenopause'. By the age of 70–80 years, circulating DHEA is only 5–10% of peak values (Orentreich *et al.* 1984). This is in contrast to the other adrenocortical hormones, which do not exhibit significant age-related changes. Thus there appears to be a prima facie case for old age representing a state of relative

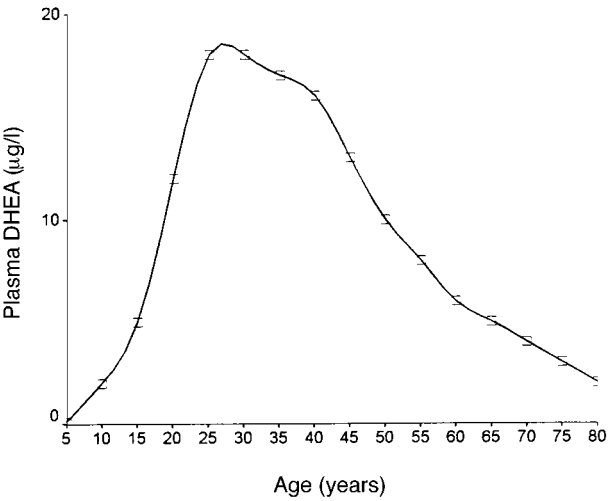

Figure 1 Age-related changes in plasma DHEA concentrations in men. Data taken from de Peretti & Forest (1976) and Vermuelen (1980).

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DHEA deficiency. Is there, though, any evidence that diminished blood concentrations of DHEA have any associated pathology?

Low plasma DHEA is associated with disease

Most of the DHEA circulating in blood is in the sulphated form (DHEAS) reflecting the adrenocortical secretion (Van de Weile *et al.* 1963). Conventional wisdom dictates that only the free DHEA is biologically active, although recent studies on the putative DHEA receptor call this into question. It has been suggested that DHEAS may act as a large plasma reservoir of hormone (Shealy 1995), thus obviating the need for tight regulation of adrenocortical production of DHEA. The long half-life of DHEAS in blood supports this hypothesis (Poortman *et al.* 1980). Most studies measuring serum hormone concentrations do not make a particular distinction between DHEA and DHEAS. This may be appropriate, as DHEA and DHEAS appear to be freely interconverted by extra-adrenal sulphotransferase and sulphatase activity (Arlt *et al.* 1998). However, it does not take into account the possibility of active regulation of these enzymes.

There have been many studies that have looked at either plasma DHEA or DHEAS concentrations in a range of disease states. There are difficulties presented by such studies, the major of these being the great range of 'normal' DHEA concentrations found, even within a single age and sex grouping (Orentreich *et al.* 1984). Despite this, there is a remarkable consistency to the data obtained from these studies; DHEA concentrations were found to be significantly decreased in all the conditions investigated, including various cancers, inflammatory diseases, type II diabetes mellitus and cardiovascular disorders (for review, see Shealy 1995). The only exception appears to be Major Depression, a disorder with significant adrenocortical involvement, in which both increased (Heuser *et al.* 1998) and decreased (Goodyer *et al.* 1996) DHEA concentrations have been reported. Two recent studies have been carried out on DHEA and cardiovascular disease: the first, on a cohort of 1700 men in New England, suggests that low serum DHEAS may be associated with a greater risk of heart disease, independently of other risk factors (Feldman *et al.* 1998); the second was a prospective study in Sweden, which found that low serum DHEAS was a predictor of cardiovascular mortality, in a 10-year follow-up of survivors of myocardial infarction (Jansson *et al.* 1998).

In some conditions, measuring crude changes in serum DHEA or DHEAS has not proved useful and so variations to this approach have been used. For example, in elderly people with cognitive impairment, no correlation has been demonstrated between serum DHEA(S) and the cognitive testing scores (Ravaglia *et al.* 1998), and in a larger study of normal older women there was no relationship found between serum DHEAS and cognitive performance (Yaffe *et al.* 1998). However, when DHEA is expressed in relation to cortisol concentrations, a pattern emerges of a low DHEA/cortisol ratio associated with increasing cognitive impairment (Kalmijn *et al.* 1998). This observation is supported by findings of a prospective study of premenopausal women, in which it was found that DHEAS and cortisol concentrations became dissociated, with lower DHEAS concentrations, in women who later developed rheumatoid arthritis before the age of 50 years (Masi *et al.* 1998). Also, in inflammatory bowel disease, an inverse relationship between DHEAS and cortisol concentrations appears to be a predictor of inflammatory activity (Straub *et al.* 1998).

There does appear to be an abundance of data suggesting that there are a range of disease states associated with decreased serum DHEA(S) concentrations relative to cortisol. Although it may be argued that low serum DHEA may result from certain illnesses, the data obtained from the prospective studies, in which serum DHEA was significantly decreased before the onset of symptoms, would support the hypothesis of a DHEA deficiency syndrome. Clearly, this putative deficiency syndrome is not exclusively a condition of old age, but is associated with a range of pathologies, involving, most obviously, the immune system.

How can DHEA concentrations be increased?

The above findings inevitably lead to the question of the regulation of DHEA secretion. While corticotrophin (ACTH) is undoubtedly capable of stimulating DHEA secretion, the dissociation between cortisol and DHEA in a variety of physiological and pathological conditions suggests that ACTH is not the sole regulator of adrenal androgen secretion (for review, see Parker & Odell 1980). Thus, in the late 1970*s*, there began a quest to find the 'adrenal androgen stimulating hormone'. The quest was unsuccessful. Various candidates and regulatory mechanisms were proposed, then discounted because they failed to account for some aspect of the characteristic pattern of DHEA secretion seen throughout life (McKenna & Cunningham 1991). The physiological regulation of DHEA secretion therefore remains unclear and fails to give any clues about the possible causes of DHEA deficiency. Despite our lack of understanding of the regulation of DHEA, two patents have recently been taken out in the USA on different methods for increasing serum DHEA concentrations. The earlier patent (number 5609 617; issued March 1997) bypasses the adrenal gland, and involves the topical application of progesterone, accompanied by electronic stimulation of specific acupuncture points on the body. The more recent patent (number 5753 696; issued May 1998), however, is for a cocktail that is purported to enhance serum DHEA concentrations.

The cocktail comprises three substances, none of which is a steroid: methyl sulphonyl methane, vitamin C and β-1,3-glucan. The mechanism by which the combination of these agents might affect DHEA remains obscure and, as yet, unpublished in the scientific literature. Both these patented methods seem bizarre, but clearly there is much interest in increasing serum DHEA concentrations. This is most easily achieved by taking oral DHEA, as many Americans are currently doing. Is there, however, any evidence that correcting 'DHEA deficiency' has a beneficial effect?

DHEA 'replacement' studies

There have been several studies looking at the effects of DHEA administration, both in animals and in people (for review, see Svec & Porter 1998). Some studies have been designed to determine whether DHEA may be useful in the treatment of the various different disorders in which a decreased serum DHEA has been demonstrated. One condition in which DHEA treatment appears to have clear beneficial effects is systemic lupus erythematosus (SLE), in which DHEA has been shown to cause an improvement in the condition and allow a reduction in concurrent glucocorticoid doses (vanVollenhoven *et al.* 1998, Barry *et al.* 1998). It has also been suggested that DHEA may protect against the osteoporosis seen with glucocorticoid treatment in SLE (Formiga *et al.* 1997). When administered topically, as a skin cream, to healthy postmenopausal women, DHEA was also found to cause an increase in bone density (Labrie *et al.* 1997). The authors suggest that DHEA may be a useful form of hormone replacement therapy (HRT) in postmenopausal women, as it had oestrogenic effects on the vagina, without the unwanted endometrial actions of oestrogen HRT (Labrie *et al.* 1997).

The one study that looked at the effects of 3-month oral DHEA 'replacement' in older, healthy people found that the only significant change in biochemical markers was an increased serum IGF-1. However, the group receiving DHEA reported a greatly increased sense of physical and psychological well-being compared with the placebo control group (Morales *et al.* 1994). Shorter-term studies have failed to demonstrate any beneficial effect on cognitive function or perceived well-being (Wolf *et al.* 1997). This perhaps is the crux of the problem with DHEA. It appears that the duration and timing of treatment is important. The route of administration of the DHEA may also be critical: when it was administered by injection, as an adjuvant to influenza vaccination, an increase in the number of responders to the vaccine was observed (Degelau *et al.* 1997). However, two studies on oral administration produced diametrically opposing results; one demonstrated that, when given orally for 4 days, commencing 2 days before influenza vaccination, no change in response was found (Dannenberg *et al.* 1997), whereas the other study, in which DHEA was administered at the same time as the vaccination, demonstrated an increased response (Evans *et al.* 1996).

Thus there is little consensus on the benefits of DHEA replacement therapy. Although low levels of DHEA may predispose to certain diseases, lack of DHEA does not, in itself, appear to cause the diseases. In even the most optimistic studies, DHEA administration did not result in cure, but just in a more effective treatment. Most of the studies to date have been relatively short-term, and not all have been appropriately placebo controlled. We await with interest the results from longer-term replacement studies. From the data available on serum DHEA concentrations in different disease states, it may be predicted that DHEA may have a more important role as a preventive agent than as a treatment for established disease.

Is DHEA 'deficiency' an endocrine disorder?

In order for DHEA deficiency to be classified as an endocrine disorder, DHEA would need a clear status as a hormone. Hormones are usually defined by three characteristics: their secretion by ductless glands, their transport in blood, and their action through specific receptors. Clearly, DHEA satisfies the first two criteria, but the question of a specific DHEA receptor is a matter of some controversy. There is evidence that DHEA can interact with several different classes of receptor, and there appears to be a considerable degree of tissue and species variation in the receptor type mediating the response to DHEA. In the rat mammary gland, for example, DHEA appears to interact with androgen receptors (Gatto *et al.* 1998, Sourla *et al.* 1998) to induce either growth or inhibition of growth, whereas, in the human breast cancer cell line, MCF-7, DHEA has been reported to act through either the oestrogen receptor (Liberato *et al.* 1993) or the androgen receptor (Boccuzzi *et al.* 1993). It has been suggested that the hormonal environment may influence the receptor type with which DHEA interacts (Ebeling & Koivisto 1994), which may explain some apparent discrepancies. Despite being widely reported to have anti-glucocorticoid effects, it does not appear that, in the liver, DHEA either binds to the glucocorticoid receptor (McIntosh *et al.* 1993) or changes glucocorticoid receptor expression (Browne *et al.* 1993). In the brain, DHEAS, but not DHEA, binds to the picrotoxin site of the gamma-amino butyric acid ($GABA_A$) receptor (Sousa & Ticku 1997). There is also evidence that DHEA binds to the *N*-methyl-D-aspartate (NMDA) receptor in the rat brain (Monnett *et al.* 1995).

Specific DHEA binding has been detected in a variety of species and tissues, including: mouse T cells (Meikle *et al.* 1992), the mouse B16 melanoma cell line (Kawai *et al.* 1995), a human T-lymphoid cell line (Okabe *et al.* 1995), and rabbit vascular smooth muscle cells (Furutama

et al. 1998). This would suggest the possibility of a specific DHEA receptor, although, to date, this has not been confirmed. DHEA and its sulphate therefore appear to have the capacity to bind to several different receptor types. It is noteworthy that DHEA and DHEAS appear to have different binding properties at the $GABA_A$ receptor, and there may also be a DHEAS-specific receptor in rat liver (Yamada *et al*. 1994). Clearly, a great deal of research is still needed to be carried out on the mechanism of action of DHEA and DHEAS at the receptor level.

Perhaps the most compelling evidence against the existence of a syndrome of DHEA deficiency comes from the apparent absence of significant pathology in patients receiving cortisol and fludrocortisone after bilateral adrenalectomy. From the studies outlined above, it might be expected that this group of patients would have a high prevalence of cardiovascular or immunological diseases. However, this does not appear to be the case.

Conclusion

Despite the lack of a base of evidence to support the concept of DHEA replacement therapy, a massive, uncontrolled and unregulated experiment is currently under way in the United States. There, DHEA is classified as a food supplement and is not only easily available, but is being marketed with unsubstantiated claims for its anti-ageing properties. The explosion in the use of DHEA has been partly due to the new medium of the internet, which has increased available outlets. It can only be a matter of time before widespread DHEA self-administration reaches Europe. As we have seen, the short-term effects of DHEA administration remain controversial, the mechanism of its action is poorly understood and possible adverse effects of its long-term use are, as yet, unrecorded. It is time that science took a lead in informing public opinion.

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