



DHEA and DHEA-S: An Introduction to their Function and Measurement

Background

Dehydroepiandrosterone (DHEA) and its sulfated analog (DHEA-S) are steroid hormones made principally in the adrenal cortex; smaller amounts of DHEA are also secreted from the testis and ovary. DHEA-S is the most abundant steroid in humans with serum concentrations 250-500 times higher than DHEA, 100-500 times higher than testosterone, and 1000-10000 times higher than estradiol. (1,2,3) DHEA-S is produced by sulfation of DHEA by the enzyme DHEA sulfotransferase (SULT2A1), which is most active in the adrenal glands, liver, and intestine. (3,4,5) DHEA and DHEA-S have been thought to serve primarily as precursor molecules that are circulated to peripheral tissues throughout the body. In those locations DHEA-S is desulfated by the enzyme steroid sulfatase (STS) to produce DHEA, which is in turn converted into various estrogenic and androgenic compounds, without significant leakage of these products into the circulation. (6,7,8) STS is found in many tissues throughout the body, but the major tissues where desulfation and conversion of DHEA-S to androgens and estrogens occur include the reproductive tract (endometrium, ovary, prostate, testis, placenta), breast, skin, brain, bone, and blood cells. (9) Because the sulfated and unsulfated forms of DHEA are often interconverted, it is hard to discuss one without the other, and it is common to refer to them together as DHEA(S). Due to the high circulating levels of DHEA-S and the presence of the STS activity in many tissues, it has generally been believed that circulating DHEA-S serves as a reservoir for conversion to DHEA. (5,10) The details of the conversion of DHEA-S in the blood stream appear to require further examination, however, as one recent study was unable to find evidence of significant hepatic conversion of DHEA-S to DHEA in *in vivo* and *in vitro* studies. (5) Humans and some primates are unique in that much of the conversion of DHEA(S) to active sex steroids is carried out locally in specific tissues, thereby avoiding undesirable effects of high circulating levels of these hormones. (6,11)

Circulating levels of DHEA(S) decline after birth until about the age of five, and then begin to rise a few years before sexual maturation begins. The prepubertal onset of adrenal production of DHEA-S, known as the adrenarche, is associated with the development of the zona reticularis layer within the adrenal gland, which shunts steroid biosynthesis away from cortisol and toward DHEA-S. (12) DHEA and DHEA-S have been studied for relationships to child development and behavioral disorders. (13,14,15,16,17,18) DHEA-S levels peak around the age of 20 to 30, and then decline to only 20-30% of peak levels by the age of 70 to 80. (2,3)

DHEA is normally secreted synchronously along with cortisol in response to CRH and ACTH, and DHEA exhibits a diurnal variation similar to cortisol. DHEA-S is also secreted by the adrenal glands in response to ACTH, although secretion is less than that for DHEA. (2,12) DHEA-S levels also change over the course of the day, especially in young adults, but considerable variation has been reported in the timing of the peak levels. (19) It has been suggested that due to its origin by secretion and sulfation, its relatively strong binding to albumin in the blood stream, and a longer half life in serum with lower clearance than DHEA, DHEA-S tends to show less synchronicity with DHEA and cortisol. (20) One study also found that variations in DHEA-S levels in serum are tied to alterations in serum albumin rather than to changes in adrenocortical secretion. (21) Dissociation between cortisol and DHEA(S) levels has been observed



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in connection with stress and various disorders, including depression, psychiatric conditions, and HIV infection. (2,3,22,23,24,25)

In addition to serving as precursors for other steroid hormones, DHEA and DHEA-S are believed to have some physiological properties of their own. DHEA is known to have anti-glucocorticoid effects, and both DHEA and DHEA-S have anti-oxidant, anti-inflammatory, and immunomodulatory effects. (3) Lowered levels of DHEA(S) have been associated with critical illness and a variety of medical conditions, including rheumatic disease, (26) cardiovascular disease, (27) immune system disorders, (28) and osteoporosis. (29) Elevated levels have been observed in connection with obesity, type II diabetes, and female hirsutism. (30,31) DHEA and DHEA-S are being investigated for relationships to mental and physical stress and psychological and behavioral disorders. (32,33,34,35,36)

DHEA and DHEA-S are also synthesized directly in the nervous system, where they appear to serve a protective function, helping to promote nerve growth and survival. (3,37,38) Brain concentrations of both molecules are higher than in plasma, and there is evidence that suggests that DHEA-S found in the brain is most likely due to local synthesis. (3) Alzheimer's patients have been reported to have lower DHEA-S levels, while schizophrenia and psychiatric conditions have been associated with altered levels. (3,12) Studies are currently exploring relationships between DHEA(S) levels and various areas of neurological function, (39,40,41) and at least one paper has suggested that the primary effect of DHEA(S) is in fact neurological, with secondary effects on immune function and growth. (13)

Because of the coincidence between the natural decline of DHEA(S) levels with age and the onset of diseases associated with the aging process, a great deal of research has been directed into an examination of the roles that both hormones play in the body, and to the possibility of supplementing levels to slow or reverse the aging process. Although these studies have reported widespread effects for the hormones, the findings have been inconsistent, and the molecular mechanisms of action for both DHEA and DHEA-S require further study. (3,42,43,44,45,46,47) Recent reviews point out that the lack of understanding about the mode of action of the two hormones, along with differences in design, methodology, and analysis among studies, have led to discrepancies among the findings. (1,3,43)

Entry of DHEA and DHEA-S into saliva.

DHEA is a neutral steroid, and it passes rapidly from blood into saliva by passive diffusion through the neutral lipid membranes of the salivary cells. Salivary concentrations are about 5% of plasma concentrations. (2) DHEA-S, on the other hand, is a charged molecule due to the presence of the sulfate group, and it cannot diffuse through the lipid membranes. The exact mode of entry for DHEA-S into saliva is not clear. Vining and colleagues suggested that it entered only by squeezing through the tight junctions between cells. They noted that the molecule is too large to do this readily, which would explain the relatively small amounts found in saliva—less than 0.1 % of plasma levels in parotid saliva. (48) However, more recent work has identified a large family of organic anion transport polypeptides (OATP) that actively transport molecules such as DHEA-S across membranes. It is likely that a transport polypeptide such as OATP2B1, which is known to transport steroid hormone conjugates in the placenta, brain and skin, may be responsible for the entry of DHEA-S into the saliva glands. (49,50) Because the levels of DHEA-S in blood are so much higher than in saliva, even the presence of minute quantities of blood or gingival fluid in the saliva can cause false



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elevation of DHEA-S levels. For this reason, there has been some concern that salivary measurement of DHEA-S is unreliable. (48) We advise that, if saliva testing for DHEA-S is to be valid, subjects must be properly screened for periodontal disease and advised about proper collection procedures that will minimize the risk of blood or gingival contamination. Saliva may also be screened for blood contamination using the Salimetrics Blood Contamination EIA Kit (Cat. No. 1-1302).

Effect of Flow Rate.

Because the mode of entry appears to limit the rate at which DHEA-S molecules can move through the cell membranes of the salivary glands, it is not surprising that the DHEA-S molecules are not able to keep up with the increased flow as saliva production is stimulated. Concentrations in saliva therefore decrease as flow rates increase. Even though this behavior was clearly documented in a seminal paper on saliva testing, (48) some researchers seem unconcerned by it. Our position at Salimetrics is that measurement of DHEA-S in saliva requires a correction for saliva flow rate. We advise measuring the length of time needed to collect the desired volume of sample, so as to determine the flow rate. The measured concentration can then be combined with the flow rate to express the results as a function of time, i.e. pg/minute.

Which is preferable: DHEA-S or DHEA?

Because of the concern about blood contamination and the need to adjust for flow rate when measuring DHEA-S, and a higher serum/saliva correlation for DHEA, Salimetrics originally chose to develop a kit to measure DHEA in saliva. This kit has functioned well, and it has been successfully used by investigators in published research. (18,34,51,52,53,54) Some researchers prefer to measure DHEA-S rather than DHEA, however, and their work has begun to show some interesting findings. (19,35,55,56,57,58) In response to customer requests, therefore, we have added a kit to measure salivary DHEA-S. We will continue to manufacture the kit for DHEA, as well, and researchers will be able to choose either kit, depending on their requirements.

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