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Plasma dehydroepiandrosterone-sulphate is related to personality and stress response

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Abstract

Dehydroepiandrosterone-sulphate (DHEAS) physiologic relevance remains controversial. However, several central nervous system and behavioural effects of DHEAS have been described. We explored the relation between DHEAS and both pituitary-adrenal axis reactivity and personality in human subjects. We studied 120 consecutive patients assisted at the out patient endocrine department of a public central hospital before medical treatment. Personality was evaluated with the Minnesota Multiphasic Personality Inventory (MMPI) and the pituitary-adrenal axis reactivity was assessed with the CRH test. Baseline DHEAS was inversely related to peak/basal cortisol (parcial r=–0.454, $p<0.05$) response to CRH infusion. DHEAS reactivity in the CRH test was directly related to the Deviant Behaviour triad (BD) (r=0.257, $p<0.05$) and type A personality (AP) (r=0.295, $p<0.05$). Basal ACTH was directly related to baseline DHEAS (r=0.366, $p<0.001$) and together with age and gender explained 34% of DHEAS variability. DHEAS may be a protective factor against an excessive cortisol response when people are under stress situations. Personality may be related to DHEAS reactivity.

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Abbreviations:

AP	- Type A Personality
AUC	- Area Under the Curve
AUC/h	- Area Under the Curve/hour
BD	- Behaviour Deviant Triad
GABA-A	- Gamma-Aminobutyric Acid Type A Receptor
K-S	- Kolmogorov-Smirnov
MMPI	- Minnesota Multiphasic Personality Inventory
NMDA	- N-methyl-D-aspartate receptor
NT	- Neurotic Triad
PD	- Psychotic Dyad
sd	- standard deviation

INTRODUCTION

In humans dehydroepiandrosterone-sulphate (DHEAS) is the most abundant hormone in the peripheral circulation. Its normal levels (2–10 μmol/L) are more than 20 times those of cortisol or thyroxine, more than 100 times those of testosterone, growth hormone and prolactin and more than 10,000 times those of aldosterone, estradiol or insulin. On the other hand, most laboratory animals have only negligible amounts of DHEAS. Even primates have much lower levels than humans (Berr *et al.* 1996).

DHEA is mostly synthesised in the adrenals and gonads, either as the final androgen-like compound or as an intermediate in the synthesis of androgens. However, it is also synthesised in the central nervous system (Paul & Purdy 1992; Berr *et al.* 1996; Baulieu & Robel 1998; Reddy & Kulkarni 1998; Labrie *et al.* 2003; Sicard *et al.* 2007). A sulphotransferase reversibly converts DHEA into DHEAS, and the sulphated form is by far the most abundant in the peripheral circulation. Nevertheless, the nonsulphated form is, however, much more liposoluble and may easily cross biologic membranes presenting a much larger distribution that includes the central nervous system (Berr *et al.* 1996; Sicard *et al.* 2007). DHEA has a short half-life – 1 to 3 hours – as opposed to DHEAS that has a long half-life – 10 to 20 hours (Legrain *et al.* 2000; Muniyappa *et al.* 2006; Komesaroff 2008).

No definitive factors regulating DHEAS synthesis have been so far identified.

DHEAS physiological effects and teleological meaning are unclear and controversial. At the clinical level DHEAS levels are higher in males and dramatically decrease with age – in the seventh decade they are about 20% of those in the third decade (Berr *et al.* 1996; Kimonides *et al.* 1998; Laughlin & Barrett-Connor 2000; Tannenbaum *et al.* 2004; Sicard *et al.* 2007). Furthermore, DHEAS levels relate to morbidity and mortality even after age correction

(Berr *et al.* 1996; Gruenewald *et al.* 2006; Sicard *et al.* 2007). Either specific effects or more generally a cortisol antagonism has been invoked to account for those associations (Akinola & Mendes 2008; Wemm *et al.* 2010).

Regarding DHEAS effects, initial evidence resulted mainly from large observational studies on the elderly and post menopausal women – The Rancho Bernardo Study, Baltimore Longitudinal Study of Aging and Personnes Agées Quid (PAQUID) – studies with DHEAS replacement in the elderly – DHEAge Study – and smaller clinical studies of patients with primary adrenal failure (Barrett-Connor & Edelstein 1994; Berr *et al.* 1996; Wolf *et al.* 1997; Barrett-Connor *et al.* 1999; Baulieu *et al.* 2000; Schlienger *et al.* 2002; Legrain & Girard 2003; Hougaku *et al.* 2006; O'Donnell *et al.* 2006). Nevertheless, during the last years, more and more evidence regarding DHEAS effects in adolescents and adults has been collected.

Similarly to other neurosteroids specific central nervous system effects have been described for DHEAS. DHEAS seems to modulate cognitive function and higher levels of this hormone are related to better results regarding memory, learning and resilience (Barrett-Connor & Edelstein 1994; Morley *et al.* 1997; Compagnone & Mellon 1998; Reddy & Kulkarni 1998; Morrow 2007; Sicard *et al.* 2007; Wemm *et al.* 2010); to higher well being scores and less depression (Moralès *et al.* 1994; Wolf *et al.* 1997; Barrett-Connor *et al.* 1999; Schlienger *et al.* 2002; Dallman *et al.* 2003; Akinola & Mendes 2008) and to higher resistance to the deleterious effects of a stressful situation (Reddy & Kulkarni 1998; Morrow 2007; Morgan *et al.* 2009; Yoon *et al.* 2009).

At the molecular level DHEAS has a general neurostimulatory effect via gabaminergic antagonism [Gamma-Aminobutyric Acid Type A Receptor (GABA-A) antagonism] and glutaminergic agonism [N-methyl-D-aspartate receptor (NMDA) sigma-1 agonism] (Paul & Purdy 1992; Baulieu & Robel 1998; Reddy & Kulkarni 1998; Morrow 2007). Neurotrophic effects have also been described and DHEA and DHEAS may contribute to neocortical organization (Baulieu & Robel 1998; Compagnone & Mellon 1998; Beck & Handa 2004; Suzuki *et al.* 2004). Moreover, DHEA and DHEAS neuroprotective effects after hypoxia have been documented and lower levels of those hormones in older adults could contribute to the enhanced cerebral vulnerability to vascular lesion or other neural insults (Kimonides *et al.* 1998).

The concept of endocrine phenotypes in endocrine research assumes that with regard to hormone levels, intersubject variability is much larger than intrasubject variability throughout the time (Bertagna *et al.* 1994; Coste *et al.*

1994). It is also postulated that these endocrine phenotypes are established at the beginning of one's life. A second related concept is that one of endocrine plasticity, meaning that endocrine responses nonrandomly change throughout the time according to previous experiences (Chrousos *et al.* 1988; Chrousos 1992; Levine 1993). In what concerns behavioural endocrine research personality traits are also individual features established quite early in life. A relation between cortisol and the hypothalamic-pituitary-adrenal axis reactivity and personality has been established (Chrousos *et al.* 1988; Chrousos 1992; Kirshbaum *et al.* 1992; Levine 1993; Bertagna *et al.* 1994; Castanon & Morméde 1994; George *et al.* 2010; Wirtz *et al.* 2010); however, this relation was less studied in what concerns DHEAS (Thomas *et al.* 1994).

The Minnesota Multiphasic Personality Inventory (MMPI) is well validated in the general population and, in addition to its importance in the psychiatric setting, it can also be used to interpret classic personality dimensions (Costa *et al.* 1986). In the corticotropin-releasing hormone (CRH) test, pituitary-adrenal response to CRH administration is classically measured with ACTH and cortisol determinations as an index of the stress response. The CRH test has been extensively used in psychoneuroendocrine research of several psychiatric and psychosomatic disorders (Gold *et al.* 1986; Demitrack *et al.* 1991; Chrousos & Gold 1992) and previous studies from our research team found out significant relations between personality and pituitary-adrenal response to CRH administration in common clinical disorders (Martins *et al.* 2001; Martins *et al.* 2002; Martins *et al.* 2004).

The above evidence suggests the existence of a relation between DHEAS and behaviour, namely with personality and stress response. In the current study we explored the relation between DHEAS and both personality traits and pituitary-adrenal axis reactivity in humans.

PATIENTS AND METHODS

We analysed retrospectively the records of 120 consecutive patients in which CRH test and personality evaluation with the MMPI were included in the clinical workout. Patients belong to several diagnostic groups. Clinical condition was not further taken into account for this study but diagnostic group was retained as a baseline variable in the statistical analysis, so that only significant results after correction for this potential confounding variable are reported. The study protocol was approved by he Hospital Ethical Committee and informed written consent was obtained for every patient. The data used was obtained before beginning medical treatment.

Age, gender, height and weight without shoes or coats were recorded.

The Portuguese translation of the MMPI (Montenegro 1982) was filled by the participants after one of the authors' complete and detailed instructions. The participants remained alone in a quiet room for the entire procedure. Scores were obtained according to MMPI authors' instructions. To avoid the use of multiple comparisons, only conventionally defined type A personality (AP) and superordinate traits were used – neurotic triad (NT): hypochondriasis (Hs) + depression (D) + hysteria (Hy); psychotic dyad (PD): paranoia (Pa) + schizophrenia (Sc) and behaviour-deviant triad (BD): psychopathic deviate (Pd) + masculinity-femininity (Mf) + hypomania (Ma) (Butcher *et al.* 1990; Greene 1991). The original MMPI version was used instead of the revised one (MMPI-2) since the MMPI-2 translation had not been validated yet.

The CRH test was performed the following week, after an overnight fast. In all cases a venous line was obtained in the antecubital region, the participant lying in the supine position; after a 15 to 20 min period of adaptation a venous blood sample was collected – time 0. CRH was then slowly infused in 1 to 2min (human CRH, 100 µg, CRH Ferring GmHb, Kiel, Germany); further blood samples were obtained at 15, 30, 60 and 120 min. All samples were immediately refrigerated at +4 °C and sent to the Endocrine Laboratory after test completion. ACTH and cortisol were measured at 0, 15, 30, 60 and 120 min, DHEAS was measured at 0, 30 and 60 min and prolactin (PRL) was only measured at baseline.

Immunoradiometric assay (IRMA) and enzyme-linked immunoassay (ELISA) methods were used for ACTH (IRMA, Nichols Institute, San Juan Capistrano, CA), PRL (IRMA, Diagnostc Products Corporation, Los Angeles, CA), DHEAS and cortisol (ELISA, Diagnostic Products Corporation, Los Angeles, CA) measurements which were performed in the hospital central laboratory. Intra- and interassay variation coefficients were less than 10% in every case.

Statistical analysis was carried out with the use of the Statistical Package for the Social Sciences Program (SPSS, version 16.0). Results are presented as the mean±standard deviation (sd) or as percentage as appropriate. The area under the curve (AUC) was computed according to the trapezoidal rule (Rowland & Tozer 1995). Mean values per hour were computed. The normal distribution of continuous variables was verified by the Kolmogorov-Smirnov (K-S) goodness of fit test. Non normal distributed variables were log transformed prior to analysis. However, for the sake of simplicity when no differences

were found, results regarding the non-transformed variables are presented. The Chi-Square test was used to compare the distribution of non-continuous variables between selected groups, factorial analysis of variance (ANOVA) to compare continuous variables between selected groups and Multiple linear regression analysis to explore the relation between continuous variables. The limit of statistical significance was selected at 0.05.

RESULTS

All patients results are summarized in Tables 1–3.

Basal DHEAS was different among diagnostic groups – $F(4,119)=3.959$, $p<0.005$ – with hirsute subjects presenting significantly higher basal DHEAS values – 237±113 μg/dL – when compared to all other diagnostic groups. There were no differences in ACTH, cortisol and PRL among diagnostic groups.

Mean baseline DHEAS was 158±99 [20–554] μg/dL and presented a distribution not significantly different from the normal one, K-S test Z=0.862, ns.

DHEAS levels were higher in males when compared to females – 207±87 μg/dL vs 151 ±99 μg/dL, t=2.088, $p<0.05$. DHEAS levels were inversely related to age – r=0.444, $p<0.001$, even after gender correction, the regression equation being DHEAS=272.493–3.736 × age. Together gender and age accounted for 27% of DHEAS variability. DHEAS levels were not significantly related to body mass index (BMI) or body weight.

DHEAS levels were significantly related to ACTH – r=+0.366, $p<0.001$ – and PRL – r=+0.233, $p<0.05$ – but not to cortisol. However, ACTH and PRL were interrelated and when both variables were included in the analysis only ACTH remained as a significant factor. This relation persists even after age, gender and diagnostic group correction. Age, gender and ACTH account for 34% of DHEAS variability.

Baseline ACTH was significantly related to the peak ACTH (r=+0.490, $p<0.001$) and peak cortisol (r=+0.246, $p<0.05$) responses during the CRH test. Baseline cortisol was strongly related to the peak cortisol response (r=+0.782, $p<0.001$). Baseline DHEAS was not related to the peak ACTH or peak cortisol response in the CRH test but baseline DHEAS was inversely related to the peak/baseline cortisol response (parcial r=–0.454, $p<0.05$) after age, gender, baseline ACTH and baseline cortisol correction (multiple linear correlation including peak/baseline cortisol, age, gender, baseline ACTH and baseline

Tab. 1. Clinical characteristics and baseline endocrine values.

	Reference interval	Mean±sd [min-max] or %
Age (years)		33±12 [18–57]
Gender F/M (%)		87/13
BMI (kg/m^2)		27.7±9.0 [14.5–60.1]
DHEAS (μg/dL)	35–430	158±99 [20–554]
ACTH (pg/mL)	0–46	19±14 [1–90]
PRL (ng/mL)	2–29	11±7 [2–33]
Cortisol (μg/dL)	4–23	18±9 [4–51]

Tab. 2. ACTH, cortisol and DHEAS levels in the CRH test.

	ACTH (pg/mL)	Cortisol (μg/dL)	DHEAS (μg/dL)
0'	21±16	19±9	177±106
15'	52±74 [b]	22±8 [c]	–
30'	50±58 [c]	23±8 [c]	177±114
60'	31±31 [a]	24±9 [c]	176±107
120'	16±18 [a]	18±10	–
AUC	32±36 [b]	22±8 [c]	176±107

AUC units are pg/mL.h for ACTH, μg/dL.h for cortisol, and μg/dL.h for DHEAS.
Value different from basal, [a] $p<0.05$, [b] $p<0.01$, [c] $p<0.001$

Tab. 3. Superordinate traits and AP score (MMPI).

	Mean±sd
Neurotic Triad (NT) score	164±30
Psychotic Dyad (PD) score	115±22
Behaviour-Deviant triad (BD) score	158±23
Type A Personality (AP) (%)	38±16

cortisol, total r=0.631, $p<0.005$) (Figure 1). DHEAS was not related to peak/baseline ACTH response.

Baseline DHEAS was inversely related to NT score – r=–0.355, $p<0.001$ – but not to PD or BD triad. However, this relation was no longer significant when age correction was carried out; in fact, age was directly related to NT – r=+0.443, $p<0.001$. Nevertheless, the DHEAS response in the CRH test

(evaluated as the AUC) was significantly and directly related to BD triad and type A personality – simple linear correlation respectively r=+0.257, $p<0.05$ and r=+0.295, $p<0.05$ (Figure 2 and 3) – and that relation remains significant even after age and diagnostic group correction. As noted, DHEAS average levels have not significantly changed after the CRH test. Despite this, DHEAS response was highly variable in what concerns the individual level (–73 µg/dL to +317 µg/dL).

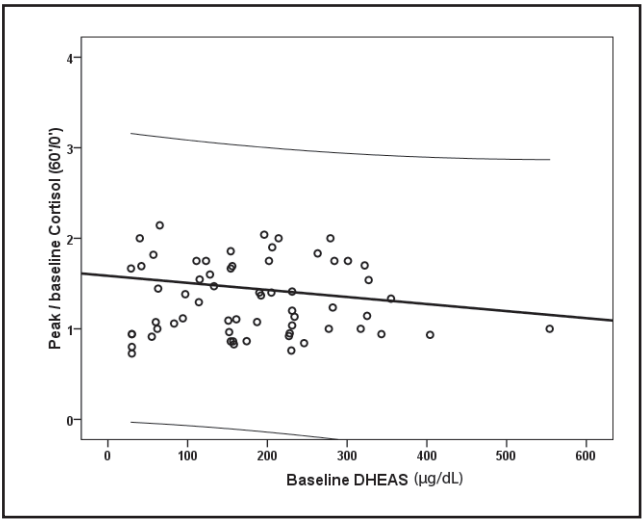

Fig. 1. Relation between baseline DHEAS and peak/baseline cortisol response in CRH test.

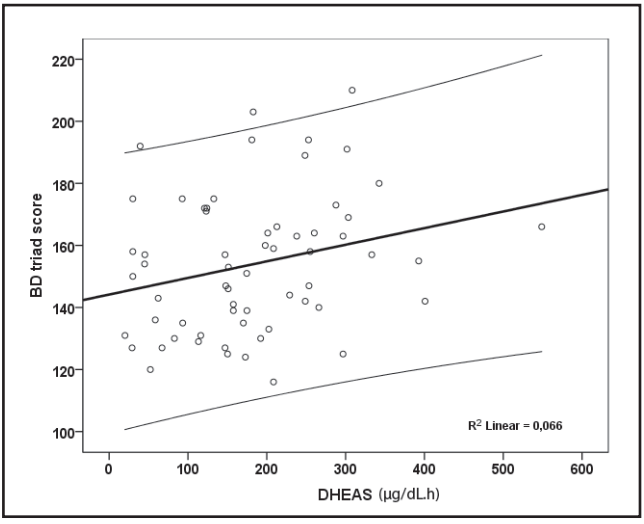

Fig. 2. Relation between DHEAS reactivity and BD triad.

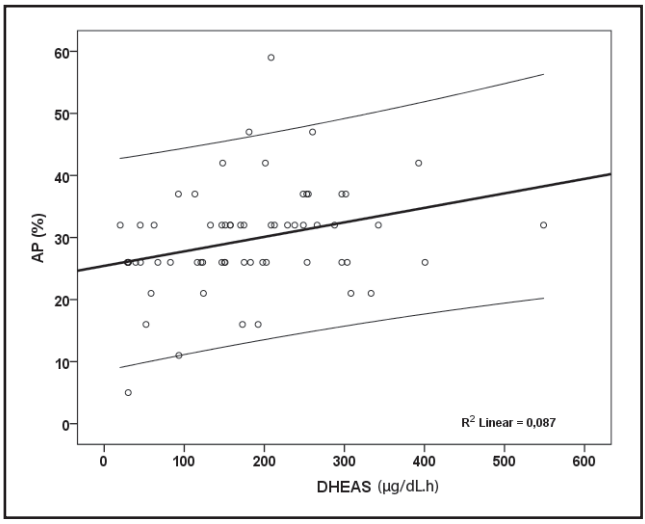

Fig. 3. Relation between DHEAS reactivity and type A Personality.

DISCUSSION

This is an observational retrospective study, whose objective is to explore the relation between DHEAS and both personality and pituitary-adrenal axis reactivity in adult humans.

We used several specific diagnostic groups. As noted before only results remaining significant independently of age and diagnostic group are reported.

Only DHEAS and not DHEA measurements were used. We expected a stronger relation between DHEAS and more stable parameters as age, gender, basal hypothalamic-pituitary-adrenal (HPA) axis activity and personality as that hormone has a longer half-life. On the contrary, acute changes might be more easily detected with DHEA, namely after CRH administration.

The predominance of female participants (87%) reflects the population assisted in the Endocrine outpatient department. Even so, DHEAS levels were significantly higher (37%) in males, as it was expected (Berr *et al.* 1996; Baulieu *et al.* 2000; Laughlin & Barrett-Conner 2000; Tannenbaum *et al.* 2004; Gruenewald *et al.* 2006).

The mean age was 33 years old (the sample was 18 to 57 years old) and DHEAS levels were inversely related to age as it has extensively been described in the

literature (Berr *et al.* 1996; Lane *et al.* 1997; Morley *et al.* 1997; Kimonides *et al.* 1998; Legrain & Girard 2003; Sicard *et al.* 2007). We found a 1.4% mean decline in DHEAS levels per year while other authors had previously described a decline of about 2% per year during adulthood and higher decline rates in post-menopausal women and older men (Laughlin & Barrett-Connor 2000; Tannenbaum *et al.* 2004; Labrie *et al.* 2005).

Age explained 20% of DHEAS variability, gender explained 4% of DHEAS variability and age and gender together explained 27% of DHEAS variability. Both factors have been extensively identified as relevant factors for DHEAS levels.

DHEAS levels were also significantly and directly related to basal ACTH independently of age, gender and diagnostic group; ACTH explains 14% of DHEAS variability. Age, gender and ACTH accounted for 34% of DHEAS variability. This is a relatively new finding since ACTH had not been generally considered as a relevant factor both for DHEAS and adrenal androgen production. In fact, chronic stress is generally associated with increased cortisol levels and decreased DHEAS levels. Moreover, it should be noted that despite the ACTH response, no DHEAS response was found in the CRH test, even if dexamethasone suppression decreases both cortisol and DHEAS. All this points out the complexity of the relation between ACTH and DHEAS until a putative cortical androgen stimulating hormone (CASH) is still to be identified.

As a group, and despite the ACTH response, mean DHEAS levels did not change in the CRH test suggesting no acute effect of ACTH on DHEAS levels. Taking into account the high DHEAS levels and long DHEAS half-life, it may be necessary a longer ACTH rise to increase DHEAS levels (Berr *et al.* 1996). However, individually DHEAS response was highly variable. Baseline ACTH was strongly and directly related to the peak ACTH response and was also directly related to the peak cortisol response and baseline cortisol was strongly related to the peak cortisol response suggesting that baseline HPA axis activity is a strong determinant of the response to CRH. In more detail, baseline ACTH levels seem to be a major determinant of either ACTH or cortisol response. An interesting finding is the fact that baseline ACTH is related to both ACTH or cortisol peak levels but not to ACTH or cortisol peak/baseline ratio suggesting that ACTH does not modulate the intensity of the response, but only that those subjects with higher baseline ACTH and cortisol levels naturally reach higher peak ACTH and cortisol levels. The influence of DHEAS seems much more subtle. Baseline DHEAS was not related to the peak ACTH or peak cor-

tisol response in the CRH test. Similarly, it was not related to peak/baseline ACTH response in CRH test but it was inversely related to the peak/baseline cortisol response (after age, gender, baseline ACTH and baseline cortisol correction). Those results suggest that DHEAS may reduce the magnitude of the cortisol response independently of baseline ACTH or cortisol levels. There is some previous evidence that DHEAS may indeed down-regulate cortisol levels (Kimonides *et al.* 1998; Gruenewald *et al.* 2006; Morrow 2007; Akinola & Mendes 2008).

Lower DHEAS was related to higher NT scores. The relation between DHEAS and NT score persisted after diagnostic group correction. However, that relation was no longer significant after age correction, and in fact, age was directly related to NT score. This is rather surprising not only because personality is generally considered as a stable personal characteristic established at a very early stage of life but also because this is a rather young sample. On the other hand, it seems plausible that aging, bringing about morbidity and mortality of both the patient and their relationships, should be associated with increased hypochondriac and depressive scores, two of the three components of the neurotic triad. Whatever the reason may be, aging is associated with increased NT scores (Zuckerman 1994) and decreased DHEAS baseline levels and that seems to be the reason for the spurious relation between DHEAS and NT. Disappointingly, baseline DHEAS levels were not significantly related to any of the selected psychometric variables and this points out the insensitivity of baseline endocrine levels.

However, DHEAS reactivity in the CRH test is significantly related to BD triad and Type A personality and both relations persist independently from age, gender and diagnostic group. As noted before neuroendocrine reactivity in the CRH test (regarding the ACTH and cortisol response) has been previously shown to be related to other psychometric variables. The apparent paradox is that although there does not seem to be any DHEAS response in the CRH test (evaluated by the mean), the DHEAS response is significantly related to psychometric variables. In fact, although the mean DHEAS does not change in the CRH test, individually considered peak DHEAS – baseline DHEAS changes deeply from –73 to + 317 μg/mL. In short, higher DHEAS responses are associated with Type A behaviour and BD triad (psychopathic deviation + hypomania + masculinity-femininity) and more specifically with Pd score (data not shown).

To conclude we found that DHEAS significantly changes according to gender and age. Moreover, we also noticed that: 1) baseline DHEAS is significantly

modulated by ACTH; 2) baseline DHEAS significantly modulates the intensity of the cortisol response in the CRH test; 3) DHEAS reactivity is a factor for BD triad and Type A behaviour. In short, baseline DHEAS relates to stress response and DHEAS reactivity relates to personality.

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