PTSD and depressive symptoms are linked to DHEAS via personality

Danka Savic\textsuperscript{a,b*}, Goran Knezevic\textsuperscript{b}, Gordana Matic\textsuperscript{c}, Svetozar Damjanovic\textsuperscript{d}

\textsuperscript{a} University of Belgrade, Vinca Institute, Laboratory of Theoretical and Condensed Matter Physics 020/2, Mike Petrovica Alasa 12-14, 11001 Belgrade, Serbia
\textsuperscript{b} University of Belgrade, School of Psychology, Cika Ljubina 18-20, 11000 Belgrade, Serbia
\textsuperscript{c} University of Belgrade, Institute for Biological Research "Sinisa Stankovic", Bulevar despota Stefana 142, 11060 Belgrade, Serbia
\textsuperscript{d} University of Belgrade, Clinic of Endocrinology, Diabetes and Metabolic Diseases, Doktira Subotica 13, 11000 Belgrade, Serbia

\begin{abstract}
Background: Research results on dehydroepiandrosterone sulfate ester (DHEAS) in post-traumatic stress disorder (PTSD) are inconsistent. We hypothesized that personality traits could be the confounders of DHEAS levels and disease symptoms, which could in part explain the discrepancy in findings.

Method: This study was a part of a broader project in which simultaneous psychological and biological investigations were carried out in hospital conditions. 380 male subjects were categorized in four groups: A) current PTSD (n = 132), B) lifetime PTSD (n = 66), C) trauma controls (n = 101), and D) healthy controls (n = 81), matched by age.

Results: The level of DHEAS is significantly lower in the current PTSD group than in trauma controls. All groups significantly differ in personality traits Disintegration and Neuroticism (current PTSD group having the highest scores). DHEAS is related to both PTSD and depressive symptoms; however, Structural Equation Model (SEM) shows that the relations are indirect, realized via their confounder – personality trait Disintegration.

Conclusions: According to our project results, DHEAS is the second putative biomarker for trauma-related disorders that fails to fulfill this expectation. It appears to be more directly related to personality than to the disease symptoms (the first one being basal cortisol). Our data promote personality as a biologically based construct with seemingly important role in understanding the mental health status.

\end{abstract}

1. Introduction

In search of biological markers of stress-induced disorders, as well as of resilience to stress, a lot of research has been done on hypothalamic-pituitary-adrenocortical (HPA) axis and related hormones. One of them is dehydroepiandrosterone (DHEA), the most abundant circulating steroid hormone in humans. DHEA easily converts to its more stable sulfated form – dehydroepiandrosterone sulfate ester (DHEAS) – and back, thus it is common to refer to both forms together as DHEA(S).

Formed mostly in adrenals, but also in the brain and gonads, with the ability to pass through the blood/brain barrier, they serve a multitude of tasks (Maninger et al., 2009). There are suggestions that these neurohormones, which substantially decrease with age (Chahal and Drake, 2010), be considered "a fountain of youth" for they improve physical and psychological wellbeing. Their activities in the brain include modulation of many neurotransmitter systems (for example, Pérez-Neri et al., 2008) and in this capacity, they play an important role in mental health.

Neurosteroids are the key participants in stress response, as well as in the aftermath of stress. DHEA(S) opposes the actions of cortisol (Maninger et al., 2009), antagonizes GABA via GAB\textsubscript{A} receptors, and is an agonist of glutamate (NMDA) receptors (Pérez-Neri et al., 2008). In their review on psychobiological responses to psychological stress, Bonne et al. (2004) conclude that DHEA(S) could be considered a potential anti-stress agent and its levels in PTSD would be expected to be reduced. However, as with all candidate biomarkers, the results for DHEA(S) and PTSD are incongruous.

In different conditions and samples, increased DHEA(S) levels in PTSD were found in several studies (Van Zuiden et al., 2017; Gill and Page, 2008; Pico-Allonso et al., 2004; Spivak et al., 2000; Yehuda et al., 2006), while other studies (Bicanic et al., 2013; Boscariino, 2014; Kanter et al., 2001) found the opposite (lower level). No difference was reported in the third group of studies (Mouthaan et al., 2014; Nijdam et al., 2015; Vythilingam et al., 2010). In depressed patients or those with depressive symptoms, DHEA(S) has also been found to be higher (Heuser et al., 1998; Maayan et al., 2000; Takebayashi et al., 1998), lower (Michael et al., 2000; Morsink et al., 2007; Scott et al., 1999), or without differences (Avgoustinati et al., 2012; Erdincler et al., 2004).

\* Corresponding author.

E-mail addresses: danka.s@sbb.rs (D. Savic), gknezevi@f.bg.ac.rs (G. Knezevic), svetadamjanovic@gmail.com (S. Damjanovic).

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Personality models assume that all human behavior can be mapped onto several basic personality traits – sets of stable behavioral patterns with a strong biological underpinning. Do Vale et al. (2011) emphasize the interrelation between endocrine and personality profile that are both formed early in life. In words of Majewska (1995), neuroendrodelatory activities of DHEA(S) “invite speculation that their profile in plasma and the CNS contributes to the manifestations of different personality traits”.

Personality traits and DHEA(S) are most often discussed together in the context of psychological resilience/vulnerability to stress and recovery from it (Cicchetti, 2010; Haglund et al., 2007; Petros et al., 2013). The majority of studies examined relations of DHEA(S) with a single or a couple of traits (Do Vale et al., 2011; Fava et al., 1987; Grillon et al., 2006; Lieberman et al., 2012). It is interesting that there are studies that assessed both DHEA(S) and personality traits, but did not seek direct relations between them (e.g., Grillon et al., 2006).

Although the prevailing personality model is Big Five (Costa and McCrae, 1992) claiming that there are five basic traits, the evidence in favor of more than five has accumulated recently (Ashton et al., 2004; Saucier, 2008). One of the newly recognized candidates for a basic trait, independent of the Big Five is psychosis proneness (Ashton and Lee, 2012; Knezevic et al., 2017; Watson et al., 2008). We have suggested an empirically based trait Disintegration (Knezevic et al., 2017), covering a wide spectrum of psychotic-like behaviors, roughly indicating mental instability. In other words, high score on Disintegration is actually a risk factor for psychoses. This is in accordance with the dimensional view, by which mental illness can be regarded as the extreme on the trait axis.

1.1. Aims of the study

The goal of this study was to investigate the relations between DHEAS on one side, and PTSD and depressive symptoms on the other, and to test the role of personality in these relations. Based on our previous result (on the same sample) that personality is the confounder of the relations between PTSD and basal cortisol, we hypothesized that it could play the same role here, i.e. it could be the confounder of the relations between disease symptoms and DHEAS (perhaps different personality traits than for cortisol).

This paper is a continuation of a series of reports from the multidisciplinary research project “Psychobiology of post-traumatic stress disorder”, conducted in Serbia in 2005-2008, aimed at correlating the psychology and biology of PTSD. Only the data relevant to the title are presented here.

2. Methods

2.1. Subjects

Initially, 400 male subjects were recruited, but the number was reduced to 380 in this study because of 20 missing values of DHEAS. Subjects were classified in four groups: A) current PTSD (PTSD, n = 132), B) lifetime PTSD (LTPSD, n = 66), C) trauma controls (TC, n = 101) and D) healthy controls (HC, n = 81).

All original groups were matched for age (Table 1) and, incidentally, they all had the same mean body/mass index (BMI). The first three groups had been exposed to war-related traumatic experiences (6-14 years old at the time of the project). Ethical approval was obtained from the Ethical Review Board of the University Medical School, Belgrade, Serbia. With oral explanations being available, all participants signed written informed consent.

2.2. Inclusion/exclusion criteria

The Clinician Administered PTSD Scale CAPS-DX (Blake et al., 1996) was used for diagnosing PTSD. Subjects with satisfied CAPS criteria A-F and a total CAPS score ≥ 50 (a stringent criterion) were assigned to the group with current or lifetime PTSD, depending on whether the PTSD symptoms are still present or not. Those scoring ≤ 30 were classified in the trauma control group that differed from the healthy control group by fulfilling CAPS-DX criterion A; naturally, none of the control groups had the PTSD diagnosis.

Structured Clinical Interview for DSM-IV, SCID-CV (First et al., 2002), was used as a diagnostic tool for comorbidities. Subjects were excluded if they had: any serious medical illness or condition, or Current Psychotic Disorder; endocrinologic, or neurologic illness likely to interfere with HPA axis function; substance (alcohol) dependence/abuse within the last 6 months. The washout period for benzodiazepines and antidepressants was four weeks.

2.3. Procedure and variables

Following a standardized protocol, the participants passed through a series of psychological and biological tests during 2.5 days of hospitalization in the Institute of Endocrinology, Diabetes and Metabolic Disease. All psychological questionnaires were administered and scored by experienced psychologists.

On admission to hospital, the participants underwent a comprehensive medical check-up including a detailed anamnestic interview by a physician. A blood draw was taken at about 0900 h for single analyses (DHEAS among them, as it does not have pronounced circadian variations (Leowattana, 2004)).

Depressive symptoms were assessed by a 21-item multiple-choice self-report instrument Beck Depression Inventory (Beck et al., 1996).

Five basic personality traits (Big Five model) – Neuroticism, Openness, Extraversion, Agreeableness, and Conscientiousness – were assessed by the self-reporting 240-item Revised NEO Personality Inventory (NEO PI-R, Costa and McCrae, 1992).

Disintegration was measured by a self-reporting 282-item questionnaire Delta with a Likert type answering format. This scale was obtained on a sample of almost 3000 senior high school students who were administered (during 3 months) 27 known questionnaires aimed at assessing psychosis proneness and related phenomena. Through a series of factor analyses, nine broad behavioral patterns were extracted forming a strong higher-order factor we named Disintegration. These nine subdimensions were: Perceptual Distortions, General Executive Impairments, Paranoia, Depression, Somatoform Dysregulations, Flattened Affect, Mania, Magical Thinking, and Enhanced Awareness. Delta was validated on about 1500 subjects. Disintegration proved to be the most stable factor in the joint factor analysis with the NEOPI-R even at the item level, and clearly separated from the other five factors (Knezevic et al., 2017).

DHEAS concentrations (μmol/L) were determined by radioimmunoassay (DHEA-S Coated Tube RIA Kit, MP Biomedicals Inc, California, USA), with intra- and inter-assay CV of 3.5 ± 4%, respectively.

2.4. Statistical analyses

Two-tailed ANOVA was used for group comparisons with Tukey’s test for post hoc analyses. To examine the relations between depressive and PTSD symptoms, age, personality, and DHEAS, we applied path analysis. To see which variables to include in this model, i.e., which ones correlate with DHEAS, we applied Pearson’s 2-tailed correlations. Path analysis can be perceived as a set of simultaneous hierarchical multiple regression analyses for each dependent variable which is predicted by all other variables hypothesized to have an effect on it. Being a part of the Structural Equation Modeling (SEM) procedure, path models are evaluated by using standard goodness-of-fit (GoF) criteria for SEM. Several goodness-of-fit (GoF) indices that evaluate misspecification in the hypothesized model (Standardized Root Mean Square Residual, SRMR, Root Mean Square Error of Approximation, RMSEA, and Comparative Fit Index, CFI) were examined (Hu and Bentler, 1999).
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