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RESEARCH ARTICLE

The role of dehydroepiandrosterone on functional innate immune responses to acute stress

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Abstract

The androgen dehydroepiandrosterone (DHEA) responds to stress activation, exhibits anti-glucocorticoid properties, and modulates immunity in diverse ways, yet little is known of its role in acute stress responses. In this study, the effects of DHEA and its sulfate ester DHEA-S on human male immune function during exposure to an acute stressor is explored. Variation in DHEA, DHEA-S, testosterone, and cortisol, along with bacterial killing assays, was measured in response to a modified Trier Social Stress test in 27 young adult males. Cortisol was positively related to salivary innate immunity but only for participants who also exhibited high DHEA responses. Additionally, DHEA positively and DHEA-S negatively predicted salivary immunity, but the opposite was observed for serum-based innate immunity. The DHEA response to acute stress appears to be an important factor in stress-mediated immunological responses, with differential effects on immunity dependent upon the presence of other hormones, primarily cortisol and DHEA-S. These results suggest that DHEA plays an important role, alongside other hormones, in modulating immunological shifts during acute stress.

KEYWORDS

cortisol, dehydroepiandrosterone, immunity, Trier social stress test

1 | INTRODUCTION

Activation of the hypothalamic–pituitary–adrenal (HPA) axis leading to cortisol release is a fundamental component of the stress response in mammals. Cortisol acts to mobilize energy and has numerous effects on multiple aspects of human physiology, growth, and reproduction. Additionally, both acute and chronic cortisol elevations directly modulate immunological parameters (Dhabhar, 2002; Dhabhar & McEwen, 1997; Segerstrom & Miller, 2004). Dehydroepiandrosterone (DHEA) and dehydroepiandrosterone-sulfate (DHEA-S), whose primary physiological role is thought to be as a precursor to other steroids, are also released by the adrenal glands during normal physiological stress in humans. DHEA-S, a sulfated metabolite of DHEA, itself acts as a storage form of DHEA and can be converted to DHEA and downstream steroids in various tissues, and occurs at much higher concentrations due to its low clearance rate. DHEA and DHEA-S increase in response to laboratory stress tests in both adults and children (Izawa et al., 2008; Lennartsson, Kushnir, Bergquist, & Jonsdottir, 2012). An evaluation of the dose-dependent effects of adrenocorticotropin (ACTH) suggests that DHEA is itself more sensitive to HPA stimulation than is cortisol (Arvat et al., 2000). However, these hormones have been characterized as anti-glucocorticoids and have their own potent immunological actions. The role of DHEA in stress responses and the degree to which DHEA responses modulate immunological changes in acute stress are currently unknown.

1.1 | Interactions between DHEA and cortisol in stress physiology

Although part of the HPA axis, DHEA inhibits catecholamine release in the adrenal medulla (Liu & Wang, 2004) and exhibits numerous anti-glucocorticoid properties in various body tissues. Studies of exogenous DHEA supplementation indicate that it can inhibit glucocorticoid-induced weight gain, lipid peroxidation, hypertension, neuronal cytotoxicity, and upregulation of glucocorticoid receptors (Hu, Cardounel, Gursoy, Anderson, & Kalimi, 2000; Kimonides, Spillantini, Sofroniew, Fawcett, & Herbert, 1999; Shafagoj, Opoku, Qureshi, Regelson, & Kalimi, 1992). DHEA supplementation also appears to shield the

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immune system against the negative effects of acute stress, resulting in potential health benefits (Ben-Nathan et al., 1992; Blauer, Poth, Rogers, & Bernton, 1991). However, there is little evidence to suggest that endogenous DHEA has anti-glucocorticoid effects in humans, and much of the research has focused only on the basic DHEA stress response. There are some studies that examine exogenous DHEA in stress responses and outcomes, with mixed results. In elderly participants subjected to a psychosocial stress test, women supplemented with DHEA demonstrate a higher ACTH response to the stressor (Kudielka et al., 1998). Conversely, DHEA supplementation in males neither affects ACTH levels nor influences cortisol production or perceptions of mood or perceived stressfulness of the test (Kudielka et al., 1998). Similar results were found in a study of DHEA supplementation during military training, where supplementation does not affect perceptions of distress during training activities (Taylor et al., 2012). These results suggest that, although DHEA is a characteristic of acute stress responses, exogenous DHEA does not ameliorate endocrine or psychological responses during HPA activation. The particular role that DHEA and DHEA-S play during acute HPA action remains equivocal, and more research is needed to uncover the principal action of these hormones during acute HPA responses. Additionally, much of the anti-glucocorticoid evidence surrounding DHEA was gathered from studies using pharmacological doses in species, like rodents, that do not maintain high circulating concentrations of adrenal androgens in adulthood and have different enzymatic pathways to synthesize these androgens (Maninger, Wolkowitz, Reus, Epel, & Mellon, 2009). It is unclear which, if any, of these anti-glucocorticoid effects translate to human physiology.

1.2 | A role for DHEA in social status and stress?

Variation in stress response is related to multiple psychosocial dimensions, and these relationships may be reflected in endocrine physiology. In a large meta-analysis of psychosocial factors related to acute laboratory stress in humans, Chida and Hamer (2008) find that positive psychological states are related to reductions in HPA reactivity to stress tests. Positive affect is known to moderate stress responses and bolster some immunological parameters (reviewed in Pressman & Cohen, 2005). Under this "stress-buffering" model, positive affect may ameliorate harmful effects of stress, or increase the resilience to stressful events, through alteration of HPA activity (Pressman & Cohen, 2005). Given that DHEA responds to acute stress, acts as a neurosteroid and is known to modulate immune function, it is plausible that variation in DHEA may act mechanistically to direct this relationship.

Additionally, social status may be related to HPA activity through modulation of the effects of acute and chronic stress on health (Pickering, 1999). Social status influences cortisol dynamics and responses to laboratory stressors and is thought to be related to health in a variety of contexts (Adler, Epel, Castellazzo, & Ickovics, 2000; Wright & Steptoe, 2005). Therefore, social status may reflect underlying physiological or psychological vulnerability to the potentially negative aspects of stress activation, via changes in cortisol stimulation. Based on the literature indicating DHEA acts as an anti-glucocorticoid, it is predicted (H1) that individuals with higher perceived social status will have increased DHEA responses to stress.

1.3 | Immunological actions of testosterone, DHEA, and DHEA-S

To date, the role of DHEA and DHEA-S on immune function has not been explored in the context of stress activation in humans. DHEA has well-documented anti-inflammatory activity (Straub et al., 1998). However, DHEA also increases IL-2 concentrations, stimulates T-cells and natural killer cells (reviewed in Hazeldine, Arlt, & Lord, 2010), and is generally characterized as supportive of immunological responses. Additionally, DHEA-S concentrations are inversely related to severity of malaria and *Schistosoma* infections in humans (Kurtis et al., 2006; Leenstra et al., 2003). A positive association is also found between markers of innate immunity and DHEA in wild orangutans, with similar results in humans (Prall & Muehlenbein, 2015; Prall et al., 2015).

Given that DHEA increases with cortisol during acute stress while also exhibiting anti-glucocorticoid properties in some contexts, modulation of immunological parameters by both hormones and the interactions between these hormones is likely. There is currently little understanding of the effects of DHEA on cortisol-mediated immunoredistribution in the context of acute HPA activation. However, based on the stimulatory actions of DHEA on multiple facets of immune function outlined above, in addition to the well-documented responsiveness of DHEA to acute HPA activation, it is predicted (H2) that DHEA responsiveness to acute stress will be associated with increased immunological responses, and that (H3) DHEA will have supportive effects on the role of cortisol in modulating immunological activity during acute HPA activity.

As a downstream product of DHEA, testosterone is physiologically linked to this adrenal androgen and may mediate some of its effects. Testosterone's immunological properties are well studied, and it is generally characterized as immunosuppressive (Muehlenbein & Bribiescas, 2005). Such actions include suppression of T-helper cells, decreased antibody production, and shifts in cytokine synthesis and secretion (Sakiani, Olsen, & Kovacs, 2013). The relative concentrations of DHEA and testosterone during HPA activation may play a role in the determination of immunological responses. The role of testosterone on modulating immunity during acute stress is inchoate, but given these documented immunosuppressive properties in other contexts, it is predicted (H4) that testosterone will play a suppressive role in immunological responses during acute stress.

In addition to cortisol, relative concentrations of DHEA to DHEA-S may mediate immunological responses. DHEA-S itself is not an androgen but is a sulfated metabolite and an inactive form of DHEA. DHEA-S is not known to have direct effects on immunity, but is thought to mediate its activity via conversion of other androgens and estrogens. Previous research indicates that elevated DHEA-S is related to a decrease of some immune parameters (Prall & Muehlenbein, 2015; Prall et al., 2015) and increase in others (Hodges-Simeon, et al., in review). Elevated DHEA-S may signal either increased enzymatic expression of hydroxysteroid sulfotransferase, which converts DHEA to DHEA-S, or reduced expression of steroid sulfatase, reflecting a reduction in available DHEA. Alternately, DHEA-S may exert direct

effects through an unknown mechanism. The role DHEA-S on immunity during acute HPA activation remains unclear, and there is little in the literature to suggest a direct relationship between these variables.

1.4 | Aims and scope

In order to tests the predictions outlined here, male participants were recruited to complete a laboratory stressor, and resulting patterns of immune and endocrine responses were analyzed. Females were not included as part of this study to avoid menstrual cycle effects on physiological outcomes, as well as substantive differences in baseline sex steroid concentrations. Use of a laboratory stressor was preferable to other types of stressors commonly used (e.g., naturalistic stressors such as smoking cessation, or examination stress), in that, it can be more tightly controlled. Our choice of laboratory stressor (uncontrolled public speaking combined with a cognitive task) is among the most effective laboratory stressor in eliciting physiological responses (Dickerson & Kemeny, 2004). Additionally, this study uses novel functional measures of immunity, including bacterial killing assays, which are designed to measure the ability of the body to respond to an immunological challenge, and may be more sensitive at measuring changes in gross immunology rather than quantifying concentrations of single proteins or cell counts (Demas, Zysling, Beechler, Muehlenbein, & French, 2011). Results from this study will elucidate the role of DHEA responses to acute stress on immunological outcomes in association with other hormones.

2 | MATERIALS AND METHODS

2.1 | Participant recruitment

Twenty-seven male participants were recruited to complete the experiment (77.8% Caucasian), with an average age of 21.6 years (SD = 2.7). Participants were recruited via fliers and email listservs from a large mid-western university campus in the United States, and interested participants scheduled an initial appointment to attain informed consent. Inclusion criteria for participation included males age 18 to 30 years who weighed more than 110 lbs. Exclusion criteria included any endocrine, reproductive, metabolic, auto-immune, or immunosuppressive disorders, recent weight gain or loss of 10 lbs over the previous 6 months, current prescription drug usage, and any history of alcohol or drug abuse, depression, or any other psychiatric disorders. After informed consent was obtained, participants were measured for height (to the nearest 0.1 cm) and weight (to the nearest 0.1 kg) and percent body fat via a Tanita InnerScan Body Composition Monitor. Participants were given a survey and asked to schedule a second appointment for testing. This protocol was approved by the Institutional Review Board at Indiana University (#1305011369).

2.2 | Survey instruments

Participants were asked to return the completed survey at the second appointment. The survey included the Perceived Stress Scale (PSS), a validated fourteen-item instrument designed to measure the perception of stressfulness of situations over the past month, with responses ranging from never (0) to very often (4), including reverse coded items (Cohen, Kamarck, & Mermelstein, 1983). Additionally, subjects were asked to assess their comfort with public speaking by responding to the question "On a scale of 1 to 7, where 1 is extremely uncomfortable, and 7 is very comfortable, how comfortable are you with public speaking?" This question was used to assess whether self-perceptions of ability to speak in public may mediate endocrine responses to the stress task, because individuals who feel comfortable speaking in public may find the modified Trier Social Stress Test (mTSST) less stressful and therefor exhibit attenuated endocrine responses to the task as a result. Finally, social status was assessed using the MacArthur "ladder" of subjective social status using a ten-point scale following Operario, Adler, and Williams (2004). This item asks participants to perceive their status in relative to society as a whole, with the highest ranking (10) being people with the highest level of income, most prestigious job, and most education, relative the lowest ranking (1) being individuals with the least money, education, and worst job or unemployed. This ranking is displayed graphically as a ladder, visually representing the hierarchy of social status, where participants are asked to mark which rung on the ladder best represents their status. This measure of social status was used in place more common measures, such as occupation or income, as these items may not accurately reflect status in a student population.

2.3 | Testing procedures

During the second appointment, participants returned to the laboratory to complete an mTSST and to collect four total saliva samples across the testing period. Appointments were scheduled during the afternoon (1:30–5:30 pm, mean = 3:22 pm, SD = 1:08) to limit the confounding effects of diurnal variation in cortisol. Upon arrival to the laboratory, subjects sat for a period of 10 min in order to acclimatize to the exam room, prior to the beginning of procedures. After acclimatization, subjects collected 1–2 mls of saliva (in duplicate) in cryovials. Each saliva collection was timed in order to control for salivary flow rate, and volume was estimated based on the volumetric markings on the cryovials to the nearest 0.1 ml. After saliva collection, subjects were led to another room where a camera was set up in front of the testing area and were introduced to a female research assistant. Following mTSST procedures outlined by Yim, Quas, Cahill, and Hayakawa (2010), subjects completed a 5-minute verbal task (with 3 min of preparatory time) followed by a 4-minute sequential subtraction task. After the final task was complete, participants were led back into the patient exam room, and blood was collected from the forearm using sterile technique. Afterwards, participants collected three saliva samples (in duplicate). The first sample was collected immediately following the blood draw (post-stress sample); the second 10 min after (post-stress +10 sample); and a final collection 20 min after (post-stress + 20 sample). After the final sample was collected, samples were immediately frozen at −80 °C. Only 24 participants yielded adequate volumes of serum for serum bacterial killing assays.

2.4 | Endocrine and immunological assays

Thawed saliva samples were centrifuged and analyzed for hormone content using enzyme immunoassay kits, in duplicate, according to

manufacturer's instructions. Salivary endocrine markers included DHEA, DHEA-S, cortisol, and testosterone (Salimetrics LLC, #1-1202, #1-1252, #1-3002, and #1-2402, respectively). Inter-assay coefficients of variation were calculated by taking the average coefficient of variation of the high and low controls, and intra-assay coefficients of variation were determined by calculating the average coefficient of variation from sample duplicates. Inter-assay and intra-assay coefficients of variation were 7.2% and 6% for DHEA respectively, 9.7% and 9.5% for DHEA-S respectively, 2.4% and 4.9% for cortisol respectively, and 4.9% and 2.4% for testosterone respectively. High and low controls for all assays were within established limits.

Samples were also used to assess innate immunity via a bacterial killing assay (BKA), which measures the functional ability of saliva or serum to lyse a known quantity of *Escherichia coli* bacteria (Demas et al., 2011; Muehlenbein, Prall, & Chester, 2011). A lympholyzed *E. coli* pellet (ATCC #8739, Microbiologistics #0483E7) was diluted in phosphate-buffered saline and then added to saliva diluted 1:2 in CO_2 independent media (Gibco #18045). After a 30-minute incubation, each volume was spread on trypticase soy agar plates in triplicate and incubated overnight. After incubation, mean number of colonies was calculated for each sample, and percent bacterial killing was calculated [(sample mean − positive mean) or positive mean]. The same process was repeated using serum samples diluted at 1:12 in media.

2.5 | Statistics

A repeated-measures ANOVA was used to assess hormone changes across the testing period. Normality was assessed via Shapiro–Wilk tests, and non-normal variables were log transformed when necessary to attain normality. Mauchly's test was used to assess the assumption of sphericity, and a Greenhouse–Geisser correction was applied to variables that were found to be significant. For variables found to statistically differ over the testing period, post-hoc analyses using Bonferonni adjustments were used to explore differences between variables at each testing point.

To capture changes in hormones during the testing period, area under the curve with respect to increase (AUCi) corrected for sampling time was calculated for all hormones and salivary BKA following published formulas (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003). Area under the curve was compared with participant characteristics, endocrine, and immunological variables, using Spearman's correlations. To assess the associations between immune measures and endocrine changes, linear regression was performed on normalized AUCi variables. One subject was unable to complete the post-mTSST saliva sample due to nausea associated with venipuncture, so AUCi calculations by time were calculated for the participant without this sample. Two participants' pre-stress DHEA-S results were excluded due to out-of-range values. Additionally, one influential DHEA AUCi outlier was removed to normalize that variable for use in regression models.

3 | RESULTS

3.1 | Endocrine responses to stress testing

Repeated measures ANOVA revealed statistically significant changes in the predicted directions in DHEA, DHEA-S, and cortisol (see Table 1). Mean DHEA concentrations were highest in the first post-stress sample as compared to baseline, and post-hoc analyses revealed significant increases between baseline and both the post-stress and post-stress +10-minute samples ($p < .05$). However, mean DHEA-S concentrations peaked at the post-stress +10-minute sample relative to the baseline pre-stress sample, and post-hoc tests confirmed that this collection had higher concentrations than the pre-stress and post-stress +20-minute samples ($p < .05$). Similarly with cortisol, post-hoc analyses revealed cortisol concentrations from the post-test +10-minute sample were significantly higher than the pre-test baseline or other post-test samples ($p < .05$). While testosterone concentrations did not yield significant changes over the testing period, testosterone did exhibit a transient decrease from baseline to the post-stress sample.

3.2 | Relationship between endocrine responses and participant characteristics

Based on correlational analyses (see Table 2), age was negatively associated with DHEA ($r_s = -0.60$, $p < .01$), cortisol ($r_s = -0.69$, $p < .01$), and testosterone ($r_s = 0.44$, $p < .05$) responses to the mTSST. Additionally, the ladder scale of social status was significantly related to DHEA ($r_s = 0.41$, $p < .05$), testosterone ($r_s = -0.42$, $p < .05$), and cortisol ($r_s = 0.38$, $p < .05$) responses to mTSST. However, no significant association was found with PSS scores, body fat, the perception of comfort with public speaking, and any endocrines response to stress ($p > .05$).

TABLE 1 Mean (standard deviation) of physiological measurement across the testing period

	DHEA (pg/ml)	DHEA-S (pg/ml)	Cortisol (ug/dl)	Testosterone (pg/ml)	Salivary BKA (% killing)
Pre-stress	166.44 (112.89)	3775.31 (2583.26)	0.17 (0.08)	35.21 (13.25)	65.67 (14.74)
Post-stress	207.63[a] (106.25)	5607.84[ad] (3947.79)	0.26[a] (0.14)	31.27 (13.30)	72.33[c] (13.95)
Post-stress +10	206.54[a] (81.93)	6376.19[a] (5978.84)	0.36[a] (0.23)	31.48 (9.94)	65.60 (13.22)
Post-stress +20	185.36 (66.59)	3927.87 (3886.04)	0.36[a] (0.28)	33.91 (10.65)	67.82 (13.54)

Note. Repeated measures ANOVA reveal statistically significant changes in DHEA [$F(2.13, 49.01) = 8.90$, $p < .01$, partial $\eta^2 = 0.28$], DHEA-S [$F(3, 69) = 11.57$, $p < .01$, partial $\eta^2 = 0.34$], cortisol [$F(1.85, 46.32) = 17.02$, $p < .01$, partial $\eta^2 = 0.41$] and salivary BKA [$F(3, 69) = 3.37$, $p = .02$, partial $\eta 2 = 0.13$] across the sampling period. Notations indicate post-hoc statistical significance ($p < .05$) as follows:

[a]sampling period significantly greater than pre-stress sample.

[b]sampling period significantly greater than post-stress sample.

[c]sampling period significantly greater than post-stress + 10 sample.

[d]sampling period significantly greater than post-stress + 20 sample.

TABLE 2 Descriptive statistics and correlations between hormone changes and participant characteristics

	Physiological responses to the mTSST						Participant characteristics			
	DHEA[a]	DHEA-S[a]	Testosterone[a]	Cortisol[a]	Salivary BKA[a]	Serum BKA (%)	Age	Body fat (%)	PSS[b]	Ladder[c]
DHEA	-									
DHEA-S	0.32	-								
Testosterone	-0.50**	-0.19	-							
Cortisol	0.64***	0.07	-0.48*	-						
Sal BKA	0.29	-0.22	-0.38*	0.40*	-					
Serum BKA	-0.18	0.30	0.03	-0.20	-0.02	-				
Age	-0.60**	-0.25	0.44*	-0.69***	-0.28	0.06	-			
Body fat	0.34[1]	0.32	-0.07	0.12	-0.01	0.42*	-0.14	-		
PSS score	-0.34[1]	0.06	0.19	-0.30	-0.20	0.27	0.35[1]	0.00	-	
Ladder	0.41*	0.04	-0.42*	0.38*	0.11	0.08	-0.40*	0.23	-0.33[1]	-
Mean	1245.62	45609.85	-114.53	5.26	141.55	31.97	21.6	14.1	26.6	5.89
St. Dev.	2854.03	64522.50	239.10	6.00	478.56	31.60	2.7	6.83	6.2	1.6

Note. Hormone responses refer to calculated area under curve with respect to increase, corrected for sample time, for each hormone. DHEA = Dehydroepiandrosterone; DHEA-S = Dehydroepiandrosterone corrected for salivary flow rate; BKA = Bacterial Killing Assay; PSS = Perceived Stress Scale. Ladder: MacArthur ladder scale of subjective social status. Means and standard deviations from untransformed data, and correlations via Spearman's not corrected for outliers or normality. Sample sizes are as follows: DHEA-S AUCi $N = 25$, Serum BKA $N = 24$, all others $N = 27$.

[a]values represent units based on area under the curve calculations.

[b]values represent results of the Perceived Stress Score survey.

[c]values represent self rating on the ladder scale of subjective social status, with possible responses from 1 to 10.

[1]$p < .10$,

*$p < .05$,

**$p < .01$,

***$p < .001$

Given no relationship between age and likert scale scores of comfort with public speaking ($p > .05$), participant age does not appear to skew perceptions of the mTSST.

To further investigate the influence of social status, linear regression was used to predict DHEA AUCi and cortisol AUCi by age and ladder scale. Based on these models, ladder scale predicts DHEA AUCi ($\beta = 0.36$, $p = .05$) in a statistically significant model [$F(3,25) = 5.44$, $p < .01$] with age as a covariate ($\beta = -0.41$, $p = .03$), but not cortisol AUCi ($\beta = 0.16$, $p = .31$) in a statistically significant model [$F(2,26) = 13.17$, $p < .01$] with age as a covariate ($\beta = -0.64$, $p < .01$).

3.3 | Relationships between androgens and immunity

Testosterone is generally described as immunosuppressive, so the roles of baseline testosterone and testosterone AUCi on immune measures were examined. Salivary BKA responses to stress were negatively associated with testosterone AUCi ($r_s = -0.38$, $p < .05$), but baseline testosterone concentrations prior to the stress test were not associated to either salivary BKA at baseline or salivary BKA responses to the mTSST ($p > .05$). Additionally, linear regression to predict salivary BKA AUCi from transformed and normalized age, testosterone, and DHEA AUCi failed to generate a statistically significant model ($p > .05$). Similarly, age, testosterone, and DHEA AUCi failed to generate significant models when predicting serum BKA ($p > .05$).

In response to the mTSST, increases in DHEA and DHEA-S were not correlated in this sample ($p > .05$) and were not significantly related to salivary BKA AUCi or serum BKA. However, using linear regression to predict salivary BKA AUCi from transformed and normalized DHEA-S and DHEA (controlled for age) resulted in a statistically significant model [$F(2,26) = 3.47$, $p < .05$], with DHEA AUCi positively ($\beta = 0.42$, $p < .05$) and DHEA-S AUCi ($\beta = -0.41$, $p < .05$) negatively predicting salivary BKA responses. Additionally, linear regression to predict serum BKA from normalized DHEA and DHEA-S AUCi yielded a statistically significant model [$F(2, 22) = 3.42$] where DHEA negatively ($\beta = -0.42$, $p = .06$) and DHEA-S positively ($\beta = 0.51$, $p < .05$) predicted serum BKA. However, this model lost statistical significance when age-controlled DHEA AUCi was used.

3.4 | Relationship between cortisol and DHEA in associations with immunity

Because it was predicted that DHEA should bolster the effects of cortisol on immunity, a regression was used to predict salivary BKA and serum BKA from cortisol and DHEA AUCi. No models were statistically significant, even when age was added as a covariate ($p > .05$). However, lack of significance may be due to limited statistical power. As an alternate approach, salivary BKA AUCi was compared to cortisol for individuals with high DHEA AUCi ($N = 14$, mean = 2997.96 AUCi) and low DHEA AUCi ($N = 13$, mean = −641.52 AUCi) via a median split. Individuals with high DHEA responses to the mTSST exhibited significant positive associations between cortisol responses and salivary BKA AUCi ($r_s = 0.61$, $p = .02$), although there was no association for those with low DHEA responses ($r_s = -0.04$, $p = .89$; see Figure 1). This relationship lost statistical significance when controlling for the effects of age via partial correlation on transformed normalized variables

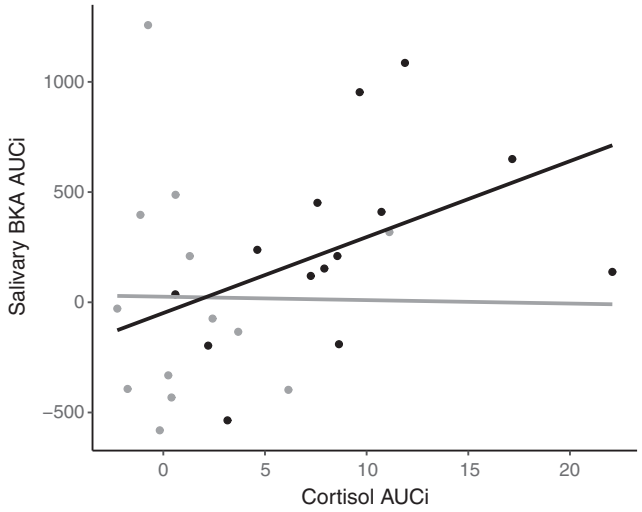

FIGURE 1 Cortisol and salivary bacterial killing responses to the mTSST. Black points and line represent individuals in the high DHEA AUCi category. Gray points and line represent individuals in the low DHEA AUCi category

(participants with high DHEA AUCi: $r = 0.54$, $p = .06$; low DHEA AUCi: $r = 0.29$, $p = .36$).

4 | DISCUSSION

In order to understand the roles that DHEA and DHEA-S play in immunological responses during acute stress, the present study examined the interactions among participant characteristics, hormone responses and hormone interactions to an mTSST, and immunological outcomes to those responses. In accordance with previous studies, significant elevations of adrenal androgens in association with acute stress and significant variation in stress responses in these hormones were identified. Additionally, significant associations between hormone responses and functional immune responses to the stressor were found, implicating the hormone profile and the magnitude of individual hormone responses in moderating immunological reactions to acute stress.

4.1 | Age and social status impact endocrine responses to stress

As with previous studies (Lennartsson et al., 2012), age was negatively associated with DHEA responses to the mTSST despite the fact that participants in this sample had a relatively narrow age range of 18 to 29 years. Such findings suggest that older individuals exhibit attenuated adrenal androgen responses to acute stress or that the stress task may be perceived as less stressful in older individuals. However, DHEA and DHEA-S are known to have significant age-related declines (Orentreich, Brind, Rizer, & Vogelman, 1984), and these senescent processes may extend to acute patterns of adrenal androgen release as well. Other studies have indicated that DHEA and DHEA-S release are mitigated with age, where administration of corticotropin-releasing hormone results in lower concentrations of adrenal androgens in older subjects (Pavlov, Harman, Chrousos, Loriaux, & Blackman, 1986), thereby indicating that reduced DHEA responses to psychological stress tests with age are not only a product of perceptions of stressfulness of the task.

An additional study also indicates that the cortisol/DHEA ratio increases with age in response to acute stress (Lennartsson et al., 2012), further suggesting a decoupling of DHEA and cortisol during stress with increasing age. In the present study, self-perception of comfort in public speaking (which may approximate variation in perceptions of stressfulness of the mTSST) was unrelated to age, implying that reduction in hormone responses with age may be physiologically meaningful, even in this narrow age range.

Unlike previous studies, baseline stress (as evaluated by PSS score) was unrelated to endocrine responses to the stress task. Other studies find that perceived work stress attenuates DHEA-S responses to a laboratory stressor (Lennartsson, Theorell, Kushnir, Bergquist, & Jonsdottir, 2013). The present population of college students may not exhibit enough variation in perceived stress, or it is possible that the PSS tool did not adequately capture perceived stress in this group. The mean PSS score in the present study is higher than both the baseline student sample and the high-stress smoking-cessation sample in the original PSS validation study (Cohen et al., 1983). Other measures of perceived stress, or a more varied (and less stressed) sample may yield different results.

Additionally, the present study evaluated whether social status may mediate acute stress responses. The MacArthur "ladder" scale of subjective social status was used, which accounts for the perceived feeling of status relative to peers. Given the student status of most participants, it was assumed that this measure of social status would be more effective than other measures such as income level or prestige of occupation. Subjective social status is known to have important health correlates, including depression, hypertension, self-rated health, heart rate, sleep latency, and fat distribution (Adler et al., 2000, 2008). Individuals who rate themselves higher on the ladder scale have reduced susceptibility to cold viruses (Cohen et al., 2008). The ladder scale is also negatively related with the cortisol awakening response and positively related with cortisol habituation to a laboratory stressor (Adler et al., 2000; Wright & Steptoe, 2005). In the present study, after controlling for age, individuals with higher ladder ratings had higher DHEA AUCi responses but not higher cortisol responses to acute stress. Although these results should be considered preliminary given the size and characteristics of the sample, these results suggest that DHEA may play an important role in the relationship between stress and social status. The degree of DHEA response to acute stress may act as a proxy for the ability to respond to stress in a healthy manner or the ability to resist negative effects of stress over the long term.

4.2 | Androgen-immune interactions during acute stress

A variety of research supports the contention that testosterone exhibits immunosuppressive properties (Muehlenbein & Bribiescas, 2005), although the role of testosterone and immunity in the context of acute stress is not well understood. Although testosterone did not significantly change in response to acute stress in the present study, AUCi calculations for testosterone (but not baseline pre-stress

concentrations) were negatively correlated with salivary immunity AUCi. Interactions with other hormones and covariates were not statistically significant, but these initial results do suggest some moderating influence of testosterone on stress-mediated changes in immunity. Variation in other hormones may explain some discrepancies found in testosterone-immune relationships in humans (Prall & Muehlenbein, 2014). Future research may yield significant associations between testosterone and adrenal androgens in modulating immunological responses.

Although no specific predictions were made regarding the role of DHEA-S on immunity, it is clear that concentrations of DHEA-S are related to the androgens examined here. DHEA is an androgen with known effects on immunity, but DHEA-S is generally described as an inactive storage form of the active hormone. This framework indicates that increased synthesis of DHEA from DHEA-S should cause alterations in immunity. AUCi calculations for DHEA and DHEA-S were unrelated to salivary innate immune responses to stress; however, after controlling for age, DHEA positively and DHEA-S negatively predicted salivary innate immunity. These results suggest that the effects of DHEA are related to the ability to synthesize DHEA from DHEA-S, with increased concentrations of the storage form of the hormone blocking potentially immunomodulating effects in saliva. Alternately, DHEA-S could be playing a direct role on immunity, although there is no known mechanism for this effect.

Contrary to the results obtained from the salivary measure of innate immunity, results from serum-based bacterial killing assays indicate DHEA-S positively and DHEA negatively predicted serum-based innate immunity during acute stress. This contradiction in results between serum and salivary innate immunity suggests that DHEA plays differential roles on immunity, potentially acting to redistribute facets of immunity to the mucus membranes with actions similar to that of cortisol. Given that (a) androgens are known to modulate mucosal immunity in laboratory rodents (Kaetzel, 2005), (b) DHEA acts on both androgen and estrogen receptors (Chen et al., 2005) and outside steroidogenic receptors (Williams et al., 2004), and (c) and DHEA-S has been previously associated with salivary IgA in other contexts (Hodges-Simeon et al., in review), direct actions on these immunological mechanisms are possible. Additionally, serum and salivary bacterial killing assays may be assessing different immunological parameters (Muehlenbein et al., 2011), so the actions of these hormones may be modulating different immunological attributes independently, in a manner than cannot be assessed using this assay. These results suggest that increased synthesis of DHEA from DHEA-S have important effects on immunological activity, where increased synthesis of DHEA from the storage form acts to enhance some immunological parameters. The complex interactions between DHEA and its sulfated storage form require future study.

4.3 | DHEA and cortisol interactions on immunological responses

Both cortisol and DHEA are known to play diverse roles in immunity. Cortisol increases during acute stress are known to redistribute immunological components (Dhabhar, 2002; Dhabhar & McEwen, 1997). What is unknown is the role that DHEA responses to acute stress play in mediating immunological responses or interacting with cortisol in mediating those responses. As a purported anti-glucocorticoid, one could predict that DHEA may attenuate the effects of cortisol on immune responses. Alternately, DHEA is known to have its own immunological effects, and as such may positively covary in influencing immunological responses. Correlational results from the present study indicate that cortisol, but not DHEA, responses to stress are positively associated with salivary immunity responses. However, comparing cortisol and salivary immunity AUCi by high DHEA and low DHEA categories reveals that only individuals with high DHEA responses to stress exhibit positive associations between cortisol and salivary innate immunity. These results implicate DHEA in healthy immunological responses to acute stress and suggest that (in this immune measure) DHEA is acting in a supportive fashion on cortisol's impacts on immunity.

The mechanism of action for these hormones in modulating salivary innate immunity is unclear. Although cortisol causes increases in secretory component and decreases in salivary IgA (Wira & Rossoll, 1991; Wira, Sandoe, & Steele, 1990), acute stressors are known to be associated with a decrease in salivary lysozyme (Perera, Uddin, & Hayes, 1997) and an increase in salivary IgA secretion (Bosch, Ring, de Geus, Veerman, & Amerongen, 2002). The direct action of DHEA in salivary innate immunity is unknown, but previous studies have found positive correlations between DHEA and salivary innate immunity in males (Prall & Muehlenbein, 2015) and between DHEA-S and salivary IgA in adolescents (Hodges-Simeon et al., in review). Present results further implicate a role for DHEA in salivary innate immunity but provide evidence for interactions with cortisol in mediating immunological responses to stress. Both hormones are known to modulate many different aspects of immunity, and future examination of different immune components may yield different results. Additionally, cortisol's effects during chronic stress are characterized very differently compared to its effects during acute stress, and these effects are not necessarily viewed as adaptive shifts in immunological parameters (McEwen et al., 1997). Under chronic conditions of elevated cortisol, DHEA may play a different role in immunological outcomes.

4.4 | Limitations and future directions

Although interpretations are limited by small sample size, these initial results from the present study implicate the importance of adrenal androgen responses to acute hypothalamic–pituitary–adrenal action as part of a healthy stress response. DHEA is a known potent modulator of various aspects of immunity, but results of the current study also suggest that elevations of DHEA alongside cortisol act to organize immunological changes to acute stress. Cortisol is known to redistribute immunological components in preparation for injury or infection (Dhabhar, 2002), and the results presented here suggest that DHEA either plays a similar role or has a permissive effect on cortisol. Indeed, outside of a pool for hormone synthesis, the interactions with glucocorticoids may be the primary function of elevated DHEA and DHEA-S.

In addition to small sample sizes, several limitations of the current study may restrain interpretation of results. This sample was drawn from a largely white, educated student population, and future studies

should seek to explicate the role of DHEA responses and acute stress using a more diverse sample. Additionally, despite the narrow age range used as part of this sample, some age-related effects were observed. A very narrow age range, or a sample size large enough to explicate the effects of age on DHEA responses to stress is necessary to further elucidate these relationships. The cross-sectional nature of this analysis further limits interpretation of causality. Utilization of other survey instruments may yield additional results. In particular, a different measure of baseline stress prior to the experiment may indicate that baseline perceived stress modulates responses to acute stress, as has been found elsewhere (Lennartsson et al., 2013). Although the mTSST is well demonstrated as an effective laboratory stressor, comfort in public speaking may modulate how participants respond to this task. Here, only a very simple likert-scale question assessed this, but additional measures may be necessary to determine the degree to which comfort with mTSST-like tasks shape endocrine responses to the task. Future research utilizing DHEA supplementation may yield a more nuanced understanding of associations with stress and immunity. Additionally, more diverse immunological measures may be useful in understanding the pleiotropic nature of endocrine effects immunity, and may better explain the actions of DHEA in acute stress.

This study represents the first to examine the role of DHEA on immunity in acute stress in humans, and these results suggest many avenues for future research. DHEA may play some role in modulating immunological responses, but the underlying causative factors for DHEA variation and DHEA variation during acute stress remain unclear. Outside of immunity, the interactions of DHEA and stress in cognition, cardiovascular health, performance, stress resilience, and coping remain largely unexplored.

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CONFLICT OF INTEREST

The authors have declared that they have no conflict of interest.

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