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Original Research Article

Gonadal Steroids and Salivary IgA in Healthy Young Women and Men

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ABSTRACT Empirical evidence from clinical, nonhuman animal, and in vitro studies point to links between immune function and gonadal steroids, including potential androgenic immunosuppression and estrogenic immunoenhancement. This study was designed to test links between steroids and one marker of mucosal humoral immunity—immunoglobulin A (IgA) in healthy individuals, to facilitate comparisons with other species and clinical populations, as there are few existing studies with healthy humans that also allow gender/sex investigations. Participants (86 women, 91 men) provided a saliva sample for measurement of testosterone (T), estradiol (E_2), and IgA. Results showed that E_2 was significantly and positively correlated with IgA in women, and group analyses by E_2 quartile showed that this association was linear. No significant correlations or nonlinear associations were seen between T and IgA in men or women, or E_2 and IgA in men. Evidence from this study indicates that IgA and E_2 are significantly associated in healthy premenopausal women. Am. J. Hum. Biol. 22:348–352, 2010.

Behavioral ecologists have considered why androgens like testosterone (T) are not subject to runaway selection and instead appear to be moderated (e.g. Ketterson et al., 2005; Reed et al., 2006). One possibility is that higher T entails costs like immunosuppression. Accordingly, androgenic immunosuppression is one foundation for the immunocompetence handicap hypothesis (ICHH: Folstad and Karter, 1992; cf. Hamilton and Zuk, 1982), which posits that T is an immunosuppressive mechanism driving energetic trade-offs between male secondary sexual characteristics and health.

Interactions between the endocrine and immune systems have been understood to exist for some time (e.g. Grossman, 1985) and evidence indicates males and females show different though overlapping patterns of immunity and mortality (e.g. Butterworth et al., 1967). Males of many species tend to develop more infections, and also exhibit fewer autoimmune diseases, than females (Klein, 2000b), in part related to sex-specific levels of T and estradiol (E_2) (Klein, 2000a,b; cf. Bilbo and Nelson, 2001). Findings link T and lower immunity in both experimental studies of T administration and correlational studies in males (e.g. Peters, 2000; Duffy and Ball, 2002; Yao et al., 2003; Owen-Ashley et al., 2004; Deviche and Cortez, 2005; Muehlenbein et al., 2006; for a review, see Muehlenbein and Bribiescas, 2005) and females (e.g. Zysling et al., 2006), though evidence is mixed (e.g. Kurtz and Sauer, 1999; Verhulst et al., 1999; Zala et al., 2008; for a review, see Roberts et al., 2004). These associations can be bidirectional, and evidence suggests that immune challenges can suppress T in some mammals (Boonekamp et al., 2008).

In healthy humans, correlational studies have provided weak or conflicting evidence. In one study with healthy men, T was weakly or not at all (depending on statistical method) linked to one measure of immunity and/or immune responses to illness (C-reactive protein), and not linked at all to another (white blood cell count) (Lassek and Gaulin, 2009). Two other studies provide conflicting evidence that healthy men with higher T report either more (Booth et al., 1999) or no difference in number of (Granger et al., 2000) colds. Granger et al. also looked at correlations between T and various measures of immunity in humans, generally finding no associations (B lymphocytes, monocytes, IgA, and IgG), or extremely small positive correlations (in the unexpected direction: T lymphocytes, CD4 cells, CD8 cells, IgM). In contrast to T being linked with immunosuppression (but not exclusively), E_2 is linked with immunoenhancement from correlational and experimental studies (e.g. Ashcroft et al., 1997; Angele and Faist, 2000; Klein, 2000b; Johansson et al., 2001). Evidence also comes from healthy women, by the use of correlational studies over women's menstrual cycles (e.g. with IgG, IgA, interleukin 10 and 1β: Kutteh et al., 1998) and studies of synthetic E_2 administration via hormonal contraceptives. However, most research on immunity and T is conducted with males, and most research on immunity and E_2 is conducted with females. And, there has been little in vivo research into population level associations between immunity and T in healthy humans or other primates (Muehlenbein and Bribiescas, 2005). Muehlenbein and Bribiescas (2005) note that understanding associations between steroids and immunity requires examinations even in healthy individuals, as well as individuals with illnesses.

Despite the mixed evidence on links between T and immunity from human and nonhuman species, some studies draw upon androgenic immunosuppression and the ICHH to explain the value of masculine traits in humans without assaying immunity or androgens directly (e.g. Penton-Voak and Perrett, 2000; Little et al., 2001; Li and Kenrick, 2006; Gangestad et al., 2007; Bressan and Stranieri, 2008; cf. Adamo and Spiteri, 2009), though supportive evidence is ambiguous and sparse (e.g. Swaddle and Reierson, 2002; Rhodes et al., 2003; Boothroyd et al., 2005; Apicella et al., 2007; Apicella and Feinberg, 2009). Understanding how T and immunity are associated in healthy men will help to test the assumptions that the aforementioned studies are based on, i.e. that healthy men's masculinity can be a marker for health.

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Research on population-level associations between any markers of immunity and T or E_2 are limited in healthy humans, and generally conducted within only one gender/sex. Accordingly in this article, I test for correlations between salivary immunoglobulin A (IgA) and steroids (T and E_2) in women and men. IgA is one measure of mucosal immunity, and one of many possible measures of immunity; it is the most abundant immunological constituent of saliva and is involved in early-stage mucosal defense (Brandtzaeg, 2007). For example, higher levels of IgA are associated with lower incidence of subsequent infection/illness (e.g. Gleeson et al., 1999; Neville et al., 2008). And, IgA is the primary defense at the initial stage of exposure to pathogens and is thus relevant to considerations of immune function in healthy individuals (Mestecky and McGhee, 1987). There are serious limitations to using only one measure of immunity, and similarly there are limitations to only using IgA given that there are a host of Ig's and Ig's constitute only one aspect of the complex immune system. Still, epidemiological and behavioral studies have employed single immune measures like IgA successfully to understand how other variables may be related to this one aspect of the immune system (e.g. Libicz et al., 2006; Gallagher et al., 2008; Hasselrot et al., 2009). Helpfully, IgA can be measured in saliva along with gonadal steroids. I expected positive correlations between E_2 and IgA, and negative correlations between T and IgA; given past mixed evidence and few studies in healthy humans, this study was exploratory.

METHODS

Participants

Participants were recruited as part of a larger study designed to address this question of steroid-immunity associations as well as questions unrelated to immunity and this article. Participants were 91 men and 86 women, recruited from the community via advertisements and via the Psychology Subject Pool, and received a small monetary compensation or class credit respectively for participating. Data from participants who reported using hormonal medications or menopause were excluded. Participants were mostly students. Throughout, I use gender/sex despite the article's focus on physiology, because associations cannot knowingly be attributed to biology or gender socialization. Healthy participants were recruited, but some participants volunteered despite use of medications or presence of illness; these participants were excluded from analyses.

Methods and procedure

This study was approved by the Institutional Review Board at Indiana University Bloomington. Participants were tested between 13:00 and 18:00 to control for diurnal rhythms in hormones (Axelsson et al., 2005). Participants completed a questionnaire about health and demographics, including current illness, infections, and medication usage (including past use of hormonal contraceptives). Participants also provided saliva samples (~3–4 ml) by spitting into 17 ml polystyrene tubes. To avoid potential blood contamination from gum abrasion or general contamination from exogenous substances, we asked participants to refrain from eating, smoking, brushing their teeth, or drinking (though water was allowed) for 1 h prior to the session. Tubes were frozen until assay, which were conducted at the Core Biomarkers Lab at Yerkes Primate Research Center at Emory University via radioimmunoassay (salivary T, E_2) and ELISA (salivary IgA). Assays were from commercially prepared kits from Salimetrics, LLC, (E, IgA) (State College, PA) and Diagnostic Systems Laboratories (T) (Webster, TX). For E, the assay range was 1–32 pg/ml; the interassay coefficients of variation were 7.8% at 0.107 μg/dl, 5.48% at 1.071 μg/dl, and 10.21% at 0.20 μg/dl; the intra-assay coefficient of variation was 10.35% at 0.22 μg/dl. For salivary IgA, the assay range was 2.50–600.00 μg/ml; the interassay coefficients of variation were 14.85% at 28.30 pg/ml and 11.68% at 197.06 pg/ml; the intraassay coefficient of variation was 9.96% at 278.10 pg/ml. For T, the assay range was 2–500 pg/ml; the interassay coefficients of variation were 19.16% at 5.03 pg/ml, 15.08% at 170.81 pg/ml, and 16.40% at 25.31 pg/ml; the intraassay coefficient of variation was 3.41% at 26.89 pg/ml. There were participants for whom assay results were unavailable (T, $n = 20$; E_2, $n = 26$; IgA, $n = 16$), generally because of low sample quantity for assays of all three analytes.

Statistics

I conducted Pearson's correlations to test for linear associations between salivary T, E, and IgA in women and men. I conducted independent *t*-tests to examine gender/sex differences in the three analytes. To check for nonlinear associations (i.e. very high and low T or E_2 might be differentially associated with IgA), I divided women and men into gender-/sex-specific steroid quartiles (*n* per quartile = ~14). In women, the quartile ranges for T (pg/ml) were (a) low: 13.5525 and below, (b) moderate-low: 13.55251–19.995, (c) moderate-high: 19.9951–29.3825, (d) high: 29.3825 and up; the quartile ranges for E_2 (pg/ml) were (a) low: 1.735 and below, (b) moderate-low: 1.7351–2.965, (c) moderate-high: 2.9651–4.69, (d) high: 4.691 and above. In men, the quartile ranges for T (pg/ml) were (a) low: 57.515 and below, (b) moderate-low: 57.5151–88.21, (c) moderate-high: 88.211–122.71, (d) high: 122.711 and up; the quartile ranges for E_2 (pg/ml) were (a) low: 2.07 and below, (b) moderate-low: 2.071–3.49, (c) moderate-high: 3.491–5.23, (d) high: 5.231and above. I conducted analyses of variance (ANOVAs), and, when significant, Least Significant Differences post-hoc analyses. I conducted analyses of covariance (ANCOVA) to control for age and time of day. Outliers (over 3 SD from the mean as well as visual) were excluded from analyses (van Anders and Dunn, 2009; for details) to provide a less noisy pattern though their inclusion did not change the pattern of results.

RESULTS

Salivary IgA and steroids

Participants with health conditions or using medications potentially affecting their immune systems were excluded from analyses with salivary IgA.

Correlations. In women, IgA was significantly correlated with E_2 (Fig. 1), $r(37) = 0.37$, $P = 0.019$, but not with T,

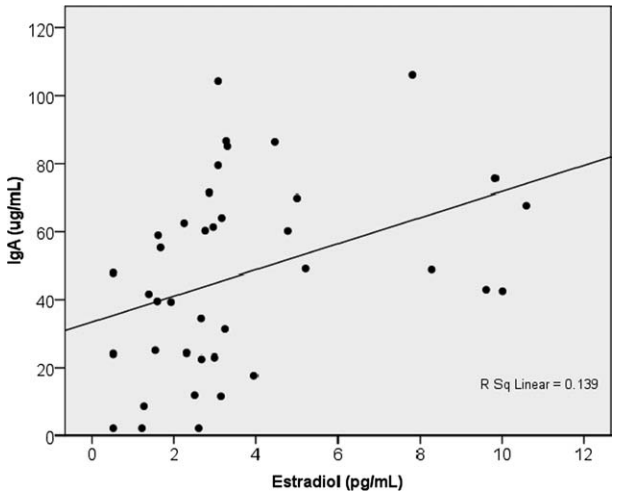

Fig. 1. Scatterplot of correlations between estradiol and immunoglobulin A (IgA) in women.

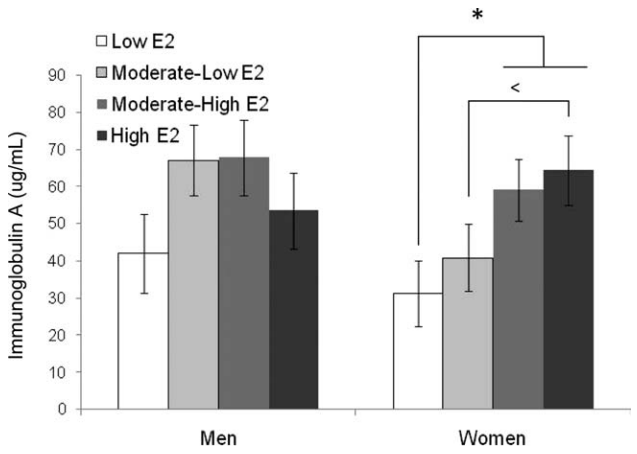

Fig. 2. Means and standard errors of immunoglobulin A (IgA) by low, moderate-low, moderate-high, and high estradiol (E_2) quartiles in men and women. "*" indicates a significant difference at $P < 0.05$, "<" indicates a trend at $P < 0.10$.

$r(39) = 0.03$, $P = 0.849$. T and E_2 in women were not significantly correlated, $r(46) = 0.15$, $P = 0.318$. In men, there were no significant correlations between IgA and E, $r(55) = 0.02$, $P = 0.880$, IgA and T, $r(57) = 0.02$, $P = 0.890$, or between E_2 and T, $r(68) = -0.05$, $P = 0.713$. Partial correlations controlling for age or time of sampling showed the same patterns. A linear regression in women showed that E_2 was significantly associated with IgA, including age and time of sampling, $b = 0.40$, $t(35) = 2.32$, $P = 0.026$.

Quartiles. In women, there was a significant difference in IgA by E_2 quartiles, $F(3,32) = 2.95$, $P = 0.048$ (Fig. 2). Women in the lowest E_2 quartile had significantly lower IgA than the women in the moderate-high E_2 quartile, $P = 0.030$, and the high E_2 quartile, $P = 0.016$. There was a trend for women in the moderate-low E_2 quartile to have lower IgA than women in the high E_2 quartile, $P = 0.081$.

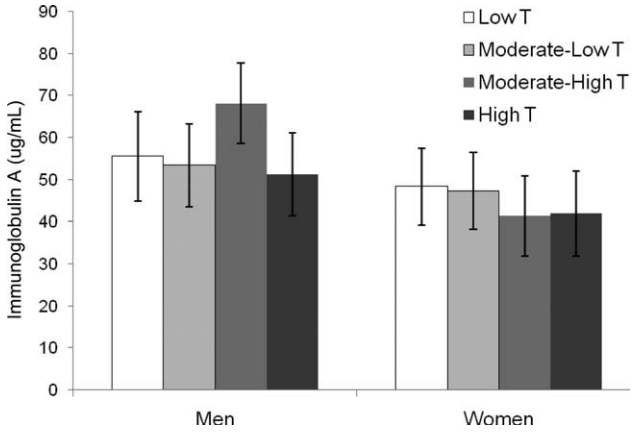

Fig. 3. Means and standard errors of immunoglobulin A (IgA) by low, moderate-low, moderate-high, and high testosterone (T) quartiles in women and men.

In men, there were no significant differences in IgA by E_2 quartiles, $F(3,53) = 1.43$, $P = 0.244$ (Fig. 2).

There were no significant differences in IgA by T quartile for women, $F(3,41) = 0.14$, $P = 0.933$, or men, $F(3,55) = 0.61$, $P = 0.613$ (Fig. 3).

Gender/sex differences in salivary steroids and IgA. As has previously been shown, men had significantly higher concentrations of T than women, $t(81) = 12.36$, $P < 0.001$. There were no significant differences in concentrations of IgA between women and men, $t(119) = 1.34$, $P = 0.182$. Counter to general (but not necessarily empirical) expectations, there were no significant differences between concentrations of E in women and men, $t(104) = 0.34$, $P = 0.738$.

DISCUSSION

In this study, I tested healthy humans for population-level evidence of associations between gonadal steroids and IgA. As such, this is one of the first studies to examine links between IgA and both T and E_2 in healthy men *and* women. Findings indicated significant positive linear associations between E_2 and salivary IgA in women but not men. There was no indication of linear or nonlinear associations between T and salivary IgA in men or women, or between E_2 and IgA in men. This partially accords with Granger et al. (2000) who found no significant correlation between T and IgA in healthy men.

IgA is involved in early-stage mucosal defense in response to pathogens (Brandtzaeg, 2007; Mestecky and McGhee, 1987) and lower IgA levels in healthy individuals are predictive of later illness/infection (e.g. Gleeson et al., 1999; Neville et al., 2008). As such, IgA is a relevant marker to explore in steroid-immune associations in healthy individuals. However, IgA is only one Ig, and Ig's are only one aspect of immunity; as such, other measures of immunity may show evidence of androgenic immunosuppression. In addition, multiple samplings of any analyte will provide a more accurate estimate of individual trait levels, though evidence shows high test-retest reliability for T (Dabbs and de La Rue, 1991). An additional consideration is that IgA, T, and E_2 vary over the menstrual

cycle; given that I did not control for cycle phase in this study, steroid-IgA associations in women may be related to variations in analytes over menstrual cycles.

Although the data from this study do not support assumptions of population-level associations between T and IgA in women or men, there is little extant research on the question in healthy humans and future research is needed to clarify this. Possibilities include studies following endogenous fluctuations of gonadal steroids and immunity, or testing individuals pre-, peri-, and post-illness. Additional and/or broader measures of immunity may show a different pattern. Still, data from this study suggest that the assumptions upon which the theoretical value of masculine traits are built, i.e. population-level negative correlations between T and initial stages of immunity in healthy men (e.g. Penton-Voak and Perrett, 2000; Li and Kenrick, 2006; Gangestad et al., 2007), need to be further tested (Adamo and Spiteri, 2009; Boothroyd et al., 2005; Roberts et al., 2004).

In contrast to what is reported in some species but consistent with evidence in healthy members of other species (e.g. Klein, 2000a) including humans (Butterworth et al., 1967), there were no gender/sex differences in IgA. Although men showed no associations between steroids and IgA, women showed a significant and positive correlation between E_2 and IgA. This corresponds with previous research linking higher estrogens and upregulated immune function (e.g. Angele and Faist, 2000) (which can be beneficial or detrimental, depending on other endogenous circumstances). Evidence from this study points to a linear association, as IgA levels were higher in increasing E_2 quartiles. As such, these data provides some of the first evidence showing a correlation between higher E_2 and IgA at the population level in healthy women.

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