Short Report

Androgens and Energy Allocation: Quasi-Experimental Evidence for Effects of Influenza Vaccination on Men's Testosterone

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ABSTRACT   Androgens are proposed to allocate finite energetic resources away from immune function and toward anabolic processes related to reproductive effort. In situations of pathogen exposure, the significant energetic demands associated with mounting an immune response are expected to produce a decrease in androgen levels and commensurate redistribution of energy. We tested the hypothesis that even the mild immune challenge associated with vaccination may cause a decline in men's testosterone. As predicted, men who received an influenza vaccination exhibited a more negative change in testosterone over a 2-week period than did men in a nonequivalent control group who were not vaccinated. These results suggest that men's androgen concentrations may be finely calibrated to trade-offs between the energetic demands of immune responses and other life history problems. Am. J. Hum. Biol. 21:133–135, 2009.   © 2008 Wiley-Liss, Inc.

Testosterone (T) appears to distribute energy toward processes such as muscle anabolism and away from maintenance functions such as fat storage and immune responses (for reviews, see Bribiescas, 2001; Ellison, 2001; Muehlenbein, 2008; Muehlenbein and Bribiescas, 2005). Evidence suggests that the relationship between T and immune functioning is bi-directional. On the one hand, numerous in vitro studies demonstrate inhibitory effects of T on immune cells (for a review, see Klein, 2004), and T treatment for hypogonadism produces dramatic declines in circulating antibodies and cytokines (Kocar et al., 2000; Yesilova et al., 2000). On the other hand, T has been shown to decline in response to immune challenge (e.g., Derting and Compton, 2003), traumatic injury (Spratt, 2001), and interleukin-6 injection (Tsigos et al., 1999); in addition, men infected with malaria exhibited decreased T relative to uninfected men but had levels return to normal after successful treatment of the infection (Muehlenbein et al., 2005). These patterns suggest a dynamic energy allocation system in which T is downregulated under circumstances in which the fitness benefits of energy investment in immune responses have outweighed the fitness costs of diverting energy away from anabolic processes related to reproductive effort.

Unclear in the human literature is how finely calibrated T responses may be to immune activation, as critical injuries and malaria infections are fairly extreme events. Evidence suggests that even moderate immune responses are associated with large increases in metabolic rate and energy expenditure (Lochmiller and Deerenberg, 2000), and T may therefore also decline in response to more mild events. We sought to test that possibility by examining T responses to influenza vaccination.

We measured salivary T just before and 2 weeks after influenza vaccination in an experimental group and 2-weeks apart without intervening vaccination in a control group. The 2-week time interval was chosen because previous research has shown peak antibody responses to influenza vaccination at that time (e.g., Whitham and Blannin, 2003). We hypothesized an interaction between time of measurement and experimental group such that T change across the 2 weeks would be negative in the vaccine group relative to the control group.

MATERIALS AND METHODS
Participants

Undergraduate men were recruited through advertisements or by approaching men at the university health clinic who were seeking flu shots. Data were excluded from one man whose T was over 3 SD above the mean, and the final sample with complete data ($n = 38$) had mean age = 19.66 years, SD = 2.13. Participants were paid US$20.

Procedure

Two saliva samples were collected at each of two testing sessions spaced ~2-weeks apart. Our original design entailed randomly assigning half the subjects to receive vaccinations immediately after collection of the first session saliva samples and the other half after the second session saliva samples. Because of limited interest in vaccinations, however, all men interested in flu shots were assigned to the experimental condition and a nonequivalent control group was recruited to provide saliva samples on the same schedule without receiving vaccinations. The final design was thus a quasi-experimental, nonequivalent control group pretest post-test design. In addition to providing saliva, participants completed brief demographic surveys. Sessions occurred during November and early December when flu shots were offered at the university clinic. All procedures were approved by the UCSB Institutional Review Board.

Saliva samples were collected via passive drool into polypropylene vials with storage at $-80°$C before shipping on dry ice for assay at the Biomarkers Core Lab at the Yerkes National Primate Research Center, Atlanta, GA. T was assessed via radioimmunoassay, with intra- and interassay coefficients of variation of 8.46 and 7.66, respectively. Further details of the assay procedure are reported in Roney et al. (2007).

RESULTS

The experimental ($n = 20$) and control groups ($n = 18$) did not differ in height, weight, or relationships status, but men in the vaccine group were older (mean = 20.65 years, SD = 2.43) than were men in the control group (mean = 18.56 years, SD = 0.92), t (36) = 3.43, $P < 0.01$; age was therefore controlled in data analyses. Vaccinations were offered more often in the morning than the afternoon; as a result, the time elapsed between waking and collection onset of the first session saliva samples was lower in the vaccine group (mean = 3.50 h, SD = 1.67) than in the control group (mean = 4.94 h, SD = 2.31), t (36) = -2.21, $P = 0.03$ (results were similar for the second session). To control for diurnal variation in T, we constructed a regression equation predicting T from time since waking using data from a separate study on a similar undergraduate population ($n = 57$); this equation was $Y = 164.04$ pg/ml $- 11.68 \times$ (hours since waking), with $\beta = -0.26$, $P = 0.048$. The equation was very similar to that obtained for session 1 in the present study, $Y = 166.22$ pg/ml $- 10.19 \times$ (hours since waking), $\beta = -0.32$, $P = 0.047$, suggesting that the study populations are comparable. We inserted hours since waking in the present study into the regression equation from the previous study to obtain predicted T values and then subtracted those values from the measured T concentrations (using the average of the two samples in each session) to estimate T corrected for time since waking. These residual T values were normally distributed, and first session values did not differ between conditions ($P = 0.42$).

Residual T values were analyzed via a 2 (session: first vs. second) $\times$ 2 (group: vaccine vs. control) mixed model ANOVA, with session a repeated measure and age entered as a covariate. The hypothesized interaction between session and group was confirmed, F (1, 35) = 4.83, $P = 0.035$ (see Fig. 1). The interaction was characterized by a marginally significant decrease in T across sessions in the vaccine group, paired t (19) = 1.57, $P = 0.067$ (one-tailed) and a nonsignificant increase in T across sessions in the control group, paired t (17) = -1.47, $P = 0.159$. Statistical conclusions were unchanged when raw T values were analyzed in lieu of the values corrected for time since waking.

DISCUSSION

Our results provide evidence that even a mild immune challenge may be sufficient to cause a decline in men's T. The findings should be treated with caution, however, given the quasi-experimental nature of the research design. We cannot definitively rule out a selection by maturation interaction, for instance, whereby individuals who self-selected into the vaccine group may have been more likely than other students to show a decline in T across the testing sessions even if they had not received a vaccination. Given the lack of an a priori reason to believe that
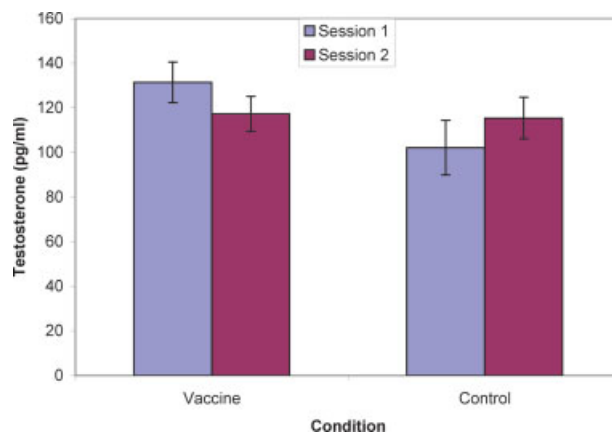

Fig. 1. Mean testosterone concentrations ($\pm$ SEM) depicted by experimental group and test session. Raw values are depicted but statistics were performed on residual values (see text). [Color figure can be viewed in the online issue which is available at www. interscience. wiley.com.]

a selection effect should have produced results that support of our hypothesis, though, the present findings provide at least preliminary evidence for T decline in response to mild immune challenge.

Though caution is warranted in generalizing these results, they may actually underestimate the typical effects of natural pathogen exposure on men's T. Research in animal models demonstrates an attenuated immune response after influenza vaccination compared to actual influenza infection (e.g., Nelson et al., 1998; Webster and Askonas, 1980), such that energy demands are likely to be greater during natural infection. Further, our subject population was well-nourished (mean BMI = 24.58) relative to men in subsistence societies (e.g., Campbell et al., 2003 reported mean BMI = 18.0 among the Ariaal of Kenya) and this surplus energy may have caused a smaller drop in T compared to what might be observed under the more nutritionally stressed conditions that likely characterized most of human evolution.

The demonstration of facultative T adjustment in the face of mild immune challenge complements other research in suggesting that androgens may play an important role in the allocation of energetic resources to life history problems in a manner that reflects the costs and benefits of the present situation. On the assumption that the anabolic and psychological effects of T may have been selected to promote successful mate competition (see Ellison, 2001), one would predict that T should be upregulated when courtship is a salient issue. Consistent with this, men in pursuit of multiple partners exhibit higher T than other men (van Anders et al., 2007) but men in stable relationships (who are presumably less engaged in courtship effort) exhibit lower T than single men (e.g., Gray et al., 2002). The present results, on the other hand, suggest that pathogen exposure can cause a decline in T, presumably as a means of prioritizing energy investment away from mating effort and into immune responses. Future research might address how cues of mating opportunities and cues of pathogen exposure may interact in determining dynamic changes in human androgen concentrations.

ACKNOWLEDGMENTS

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