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Basal salivary cortisol secretion and susceptibility to upper respiratory infection

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ABSTRACT

The immunosuppressive effects of glucocorticoids (GCs) are well-established. However, whether the net effect of GC-elicited alterations in immune function is sufficient to influence a clinically relevant outcome *in healthy adults* has yet to be shown. The aim of the present study was to investigate whether inter-individual differences in basal salivary cortisol production are associated with increased risk and severity of infection and subsequent illness following experimental exposure to a virus that causes the common cold. The present analyses combine archival data from three viral-challenge studies. Participants were 608 healthy adults, aged 18 to 55 years (49.2% female; 65.8% white), who each completed a three-day saliva collection protocol; was subsequently exposed to a virus that causes the common cold; and monitored for 5 days for objective signs of infection (presence of challenge virus in nasal secretions) and clinical illness (mucus weight, mucociliary clearance time). Basal cortisol production (operationalized as the calculated area-under-the-curve averaged across the 3 days) showed a graded association with infection risk, with those producing higher levels of cortisol being at greater risk. Cortisol also showed a continuous association with duration of viral shedding, an indicator of viral replication and continuing infection, such that higher cortisol concentrations predicted more days of shedding. Cortisol was not, however, related to severity of objective illness. These findings are the first to demonstrate in healthy adults an association between basal cortisol production and an objectively measured and clinically relevant infectious disease outcome.

1. Introduction

Chronic dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis has been implicated in the pathogenesis of various forms of immune-related disease. Findings from comparative animal research, as well as from human research conducted *in vitro*, suggest that stress-related elevations in circulating glucocorticoid (GC) hormones may suppress host resistance to infectious disease via downregulatory effects on both innate and adaptive immunity (Bailey et al., 2003; Sheridan et al., 1998). Effects of chronically elevated GCs on natural immunity include inhibition of lymphocyte trafficking during the initial phases of viral infection (e.g., Hermann et al., 1995; Tseng et al., 2005) as well as suppressed synthesis of pro-inflammatory cytokines by macrophages (Brattsand and Linden, 1996). In regard to acquired immunity, GCs have been shown to have modulatory effects on T-helper (Th) activity, simultaneously facilitating a Th2 pattern of cytokine production while inhibiting the production of Th1 cytokines (Elenkov and Chrousos, 1999). One consequence of this shift to a predominantly humoral immune response is attenuation of cell-mediated defense against viral infection (Gern et al., 2000).

The clinical relevance of these *in vitro* and *ex vivo* findings from comparative laboratory research has been demonstrated in populations of patients with pathologically elevated levels of circulating GCs. In these populations, hypercortisolemia—whether induced endogenously (i.e., spontaneous Cushing syndrome) or from exogenous administration of therapeutic corticosteroids—is associated with increased risk for infection by opportunistic pathogens (Lionakis and Kontoyiannis, 2003; Sarlis et al., 2000; Stuck et al., 1989). Furthermore, the severity of established infections has been found to increase in a dose–response manner with the degree of hypercortisolemia (Aucott, 1994; Graham and Tucker, 1984). Even relatively short-term exposure to corticosteroids (days rather than weeks, months, or years) has been found to influence the course of

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upper respiratory virus infection among otherwise healthy adults. Specifically, in a sample of individuals who were experimentally exposed to an upper respiratory virus (rhinovirus), those treated with prophylactic corticosteroids (prednisone) evidenced higher post-challenge viral titers than placebo-treated controls (Gustafson et al., 1996). Paradoxically, however, prophylactic treatment with corticosteroids was unrelated to the overall severity of subsequent upper respiratory *illness* (Farr et al., 1990; Gustafson et al., 1996).

Importantly, the aforementioned effects of circulating GCs on risk for infectious disease *in vivo* have been observed among individuals with conditions characterized by supraphysiologic systemic GC concentrations. Moreover, in the case of exogenous corticosteroid therapy, GCs may be present in circulation, and thus in contact with cells of the immune system, for abnormally long periods of time with the extended duration of contact permitting GCs to have a greater immunomodulatory effect (Spencer et al., 2011).

Whether inter-individual variation in endogenous cortisol *in non-patient samples* likewise affects host resistance to infectious disease has yet to be determined. That changes in circulating cortisol is associated with corresponding alterations in various measures of immunity already has been established. For example, within persons, the number of lymphocytes in the peripheral circulation of healthy adults has been found to vary inversely with normal diurnal fluctuations in plasma cortisol (Eskola et al., 1976; Thomson et al., 1980). *In vitro* assessments of functional immunity show a diurnal profile, as well, with proliferative response of lymphocytes to mitogen stimulation (Eskola et al., 1976; Hiemke et al., 1995) and stimulated cytokine production (Petrovsky et al., 1998) both reaching a peak later in the day when endogenous levels of cortisol are at their lowest. Between persons, higher concentrations of circulating cortisol have been shown to correlate with lower numbers of circulating lymphocytes and a higher neutrophil-to-lymphocyte ratio (Cole, 2008; Cohen et al., 2012).

The present study combines archived data from three large viral-challenge studies to examine whether inter-individual variation in basal cortisol production—i.e., daily levels not produced in response to a physiological (disease) or psychological stressor—is associated with risk for upper respiratory infection following exposure to an experimentally administered virus that causes a common cold-like illness. Given the findings of previous research, we expect that risk of infection will increase with increasing basal cortisol production. We further expect that the duration of the infection, as indicated by the number of days of viral shedding will increase with increasing cortisol. Due to the inconsistent findings regarding the relation of exogenous corticosteroids with clinical disease severity, we make no prediction with respect to the association of basal cortisol levels with objectively measured signs of upper respiratory illness. Given that hallmark physiological indicators of the common cold (e.g., nasal mucus production, mucosal edema) are thought to result largely from the host's pro-inflammatory response to the invading virus (Proud, 2008; Turner, 1997), we also will explore the relation of basal cortisol production with local (nasal) pro-inflammatory cytokine response to infection.

2. Methods

2.1. Participants

The present analyses combine archival data from three viral-challenge studies conducted from 1997 to 2001 (Pittsburgh Cold Study 2 [PCS2]), 2000 to 2004 (Pittsburgh Mind–Body Center Study [PMBC]) and from 2007 to 2011 (Pittsburgh Cold Study 3 [PCS3]), respectively. (These and additional data are available at www.CommonColdProject.com). The studies followed a common set of procedures which included a physical exam; blood and urine screenings; questionnaire assessments of demographics; 3 days of saliva collection for assessment of diurnal cortisol; and subsequent participation in a viral-challenge trial. The total sample included 702 healthy adults, aged 18–55 years who were recruited from the Pittsburgh, PA metropolitan area via newspaper advertisements and community postings. Four participants were excluded from the present analyses due to missing data on relevant covariates; 47 for missing data on saliva cortisol; and 43 for missing data on viral shedding (see below). The remaining sample was comprised of 608 participants, with a mean age of 30.98 ± 10.84 years. Additional characteristics of the sample are reported in Table 1. Excluded participants did not differ from the present sample in terms of average age (mean difference = 0.63 years, $t[700] = 0.53$, $p = .597$), proportions of men and women (44.7% female vs. 49.3% female, $X^2[1] = 0.71$, $p = .400$), and years of educational attainment (mean difference = −0.06 years, $t[700] = -0.30$, $p = .767$). Excluded participants were, however, less likely than those in the present sample to self-identify as white/Caucasian (54.3% vs. 65.8%, $X^2[1] = 4.72$, $p = .030$). All participants provided informed consent and received financial compensation for study participation. Study procedures were approved by the institutional review boards of the University of Pittsburgh and Carnegie Mellon University.

2.2. Procedures

2.2.1. Screening

Volunteers were included for participation if they were in "good general health", as determined by medical history and physical examination. They were excluded from study eligibility if they had diabetes, hepatitis, cardiovascular disease, chronic sinusitis, chronic bronchitis, asthma or any other chronic illness; abnormal clinical profiles discovered via urinalysis, complete blood count,

Table 1
Sample characteristics.

Variable	*N*	%
Sex		
Male	309	50.8
Female	299	49.2
Race		
White	400	65.8
Black	181	29.8
Other	27	4.4
Study		
PCS2	299	49.2
PMBC	119	19.6
PCS3	190	31.3
Virus type		
RV23	101	16.6
RV39	507	83.4
Pre-challenge Ab		
<4	378	62.2
⩾4	230	37.8
Season		
Winter	110	18.1
Spring	267	43.9
Summer	115	18.9
Fall	116	19.1
Education		
High school or less	167	27.5
<2 years college, no degree	185	30.4
⩾2 years college + degree	119	19.6
BA/BS or higher degree	137	22.5