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Chronic stress and regulation of cellular markers of inflammation in rheumatoid arthritis: Implications for fatigue ☆,☆☆

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Abstract

Objectives. This study examined whether chronic interpersonal stress is associated with cellular markers of inflammation and regulation of these responses by *in vitro* doses of glucocorticoids in rheumatoid arthritis (RA) patients. The association between these markers of inflammation and fatigue was also tested.

Methods. Fifty-eight RA patients completed up to 30 daily ratings of the stressfulness of their interpersonal relations. Interleukin-6 (IL-6) production was analyzed in lipopolysaccharide (LPS)-stimulated peripheral blood mononuclear cell cultures with and without varying concentrations of the glucocorticoid hydrocortisone. In addition, plasma levels of IL-6 and C-reactive protein (CRP) were analyzed, and subjective ratings of fatigue and pain were obtained on the day of blood sampling.

Results. Multilevel modeling showed that higher chronic interpersonal stress was associated with greater stimulated IL-6 production ($p < 0.05$) as well as greater resistance to hydrocortisone inhibition of IL-6 production ($p < 0.05$). These relations were not accounted for by demographic factors, body mass index, or steroid medication use. Stimulated production of IL-6, in turn, was associated with greater levels of self-reported fatigue, controlling for pain ($p < 0.05$). Neither chronic stress ratings nor fatigue symptoms were related to plasma levels of IL-6 or CRP ($ps > .05$).

Conclusions. Among RA patients, chronic interpersonal stress is associated with greater stimulated cellular production of IL-6 along with impairments in the capacity of glucocorticoids to inhibit this cellular inflammatory response. Moreover, these findings add to a growing body of data that implicate heightened proinflammatory cytokine activity in those at risk for fatigue symptoms.

Keywords: Stress; Cytokines; Fatigue; Rheumatoid arthritis

1. Introduction

Rheumatoid arthritis (RA) is an autoimmune disease characterized by inflammation of the synovium, with symptoms that include joint pain, stiffness, and fatigue. Fatigue is increasingly recognized as an important factor contributing to quality of life in RA patients, and persistent fatigue is one of the biggest obstacles to optimizing function in these patients (Heller and Shadick, 2007). Progression of RA disease varies considerably from person to person, and is affected by a range of immune, neuroendocrine, and psychosocial factors (Uhlig et al., 2000). Included among the immunological factors implicated as key in RA disease progression is the cellular production of the cytokine interleukin-6 (IL-6; Choy and Panayi, 2001). IL-6 is a sig-

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naling molecule produced primarily by immune cells, and plays an important role in coordinating the acute inflammatory response. By stimulating the production of acute phase proteins, including C-reactive protein (CRP), IL-6 acts to enhance inflammation. Circulating levels of both IL-6 and CRP estimate systemic inflammation (Pearson et al., 2003), and are associated with radiographic evidence of joint destruction in RA patients (Forsblad d'Elia et al., 2003; van Leeuwen MA et al., 1995).

Psychological stress has been identified as a factor that contributes to disease activity in RA patients. In a comprehensive review of 27 independent studies involving over 3000 patients, the stress of minor life events lasting hours to days was associated with increased disease activity among adult RA patients (Herrmann et al., 2000). Although the pathophysiological mechanisms accounting for the association between stress and disease activity in RA are not yet clear, available data point to proinflammatory cytokine activity as a potential mediator. In healthy adults, for example, reports of ongoing stressful circumstances are associated with elevations of *in vivo* markers of systemic inflammation, including increases in circulating levels of IL-6 and CRP (Ranjit et al., 2007). Moreover, brief naturalistic stressors, such as academic examinations, also correlate with increases in stimulated IL-6 production in healthy individuals (Segerstrom and Miller, 2004). Although data in RA patients are limited, they also indicate that exposure to minor naturalistic stressors lasting hours to days is associated with increases in circulating levels of IL-6 (Hirano et al., 2001; Zautra et al., 2004).

The hypothalamic pituitary adrenal axis plays a critical role in the regulation of the inflammatory response, such that the secretion of glucocorticoids in response to stress is thought to counter-regulate increases in inflammatory activity. Cortisol suppresses inflammation, in part, by inhibiting cellular production of pro-inflammatory cytokines, and hence is hypothesized to prevent a prolonged inflammatory response (Raison and Miller, 2003). However, when elevations in cortisol are sustained over time, mononuclear cells may become less responsive to the inhibitory effects of cortisol *in vitro*, which may lead to greater increases in the cellular production of IL-6 and possibly other proinflammatory cytokines (Raison et al., 2006). Indeed, among healthy persons who are exposed to ongoing psychological stress, stimulated IL-6 production shows a greater resistance to the suppressive effects of cortisol *in vitro* (Miller et al., 2002). To our knowledge, no study has examined whether such HPA counter-regulatory cellular mechanisms are associated with changes in IL-6 production among RA patients undergoing chronic psychological stress.

The aim of the current study was to elaborate the role of chronic psychosocial stress in the regulation of cellular markers of inflammation in a community-based sample of RA patients. Consistent with the limited data available, we predicted that chronic daily stress among RA patients would be associated with elevated *in vivo* markers of inflammation, as indexed by circulating levels of IL-6 and CRP. We also hypothesized that chronic stress would be associated with increased stimulated mononuclear cell production of IL-6, and with greater resistance to glucocorticoid inhibition of IL-6 production *in vitro*. Finally, given recent evidence that proinflammatory cytokine activity may play a role in exacerbating symptoms such as fatigue (Dantzer, 2001; Musselman et al., 2001), we explored the associations between *in vivo* and *in vitro* measures of IL-6 production and fatigue symptoms in this sample of RA patients.

2. Methods

2.1. Participants

Participants were 58 adults (35 women and 23 men) with physician-verified RA, recruited from the Phoenix, Arizona metropolitan area via newspaper advertisements, mailings, and physician referrals. The majority of the sample was Caucasian (96%), married/partnered (65%), and unemployed (64%), with a median household income between $30,000 and $39,999.

To be eligible for participation, individuals were required to be at least 18 years of age (mean age = 55, range 23–78 years), could not have a diagnosis of systemic lupus or other inflammatory disorder, and could not be using cyclic hormone replacement therapy. Other health conditions and medication use were not exclusionary. Approximately 55% of the participants indicated that RA was their only chronic health condition, whereas 29% reported having one additional health problem, 11% reported two additional health problems, and 5% reported 3–6 additional health problems. The most common co-morbid conditions reported by participants were lung disease (16%), cardiovascular disease (15%), diabetes (11%), and stroke (7%). The most common medications used by participants were steroids (23%), hormone replacement therapies (23%), antidepressants (18%), and thyroid medications (12%).

2.2. Procedures

After being screened into the study via a phone interview, participants returned an informed consent form by mail along with documents authorizing the research staff to contact their physicians to confirm their RA diagnosis. Once RA diagnosis was confirmed, participants completed (1) self-report measures that included demographic, health, social network, and personality variables; (2) up to 30 consecutive daily diaries that included assessment of interpersonal stress; and (3) a laboratory visit that included measures of inflammatory markers and self-reported pain and fatigue. All procedures were approved by the Institutional Review Boards of Arizona State University and UCLA.

2.2.1. Diary assessment

Participants received a packet of 30 paper diaries and 30 stamped, addressed envelopes, and were trained by study personnel via phone regarding completion of diaries. Each evening prior to retiring, participants completed a diary regarding that day's interpersonal events and the prior night's sleep quality, and placed it in the mail the next morning. Participants received up to $90 for completion of the diaries. The majority of the diary records were returned on time (i.e., 66% post-marked by the next day, 87% by the second day), a compliance rate similar to other mail-based diary studies (e.g., Todd et al., 2003). Over 82% of all participants completed all 30 diaries.

2.2.2. Laboratory visit

Between 1 week and 12 months ($M = 15.72$ weeks, SD = 18.52) following initiation of the diaries, participants attended a laboratory visit that began at 1 p.m. and was conducted at the Phoenix Veterans' Administration Medical Center. Circulating levels of IL-6 and CRP as well as IL-6 regulation were determined from blood samples drawn