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Increases in stimulated secretion of proinflammatory cytokines by blood monocytes following arousal of negative affect: The role of insulin resistance as moderator

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Abstract

We examined the effect of negative affect on changes in stimulated secretion of cytokines by blood monocytes and determined whether insulin resistance (IR), as indexed by the Homeostasis Model Assessment (HOMA), moderated these associations in 58 healthy men (aged 18–65 years). Blood samples and ratings of negative affect were collected at rest and 15 min following subjects' participation in the Anger Recall Interview (ARI). Assessment of lipopolysaccharide (LPS)-stimulated secretion of IL-1β, IL-6, and TNF-α was accomplished by ELISA of supernatant. Regression models controlling for age, body mass index, and race/ethnicity revealed that higher HOMA-IR values were associated with larger stress-induced increases in IL-1β and TNF-α ($p < .05$). Furthermore, arousal of negative affect during the ARI was differentially associated with stress-induced changes in stimulated secretion of TNF-α and IL-6 as a function of HOMA-IR ($p < .05$). Increases in stimulated cytokine secretion were associated with arousal of negative affect, but only among men with higher HOMA-IR values. Among men with lower HOMA-IR values, arousal of negative affect was associated with diminished cytokine secretion. Collectively, these data suggest that the HOMA-IR moderates the impact that arousal of negative affect has on the ability of blood monocytes to secrete inflammatory cytokines in response to LPS. Stress-induced increases in cytokine secretion among high HOMA-IR men are consistent with the role of inflammation in cardiovascular disease, hypertension, type 2 diabetes as well as the metabolic syndrome and underscore the relevance of negative affect in the etiology of these inflammatory conditions.

Keywords: Psychological stress; Negative affect; Insulin resistance; Cytokines; Monocytes; Homeostatic Model Assessment; Men

1. Introduction

Psychological stress and the experience of negative emotions or distress is thought to accentuate a spectrum of disease-promoting mechanisms that are implicated in such chronic conditions as atherosclerotic cardiovascular disease (ACVD) (Smith and Ruiz, 2002), hypertension (Everson-Rose and Lewis, 2005), type 2 diabetes (Wellen and Hotamisligil, 2005), and to some extent, cancer (Kiecolt-Glaser et al., 2002). At this time, however, the mechanism(s) through which stress and negative emotions contribute to disease is not well understood. Although various hypotheses have been proposed, one central hypothesis posits that both psychological stress and negative emotions evoke excessive activation of pathophysiological pathways that, if repeated frequently over time, contribute to disease (Smith and Ruiz, 2002). While most studies testing this general hypothesis have focused primarily on assessing changes in blood pressure, heart rate, and to a lesser extent, neuroendocrine and hemostatic factors, some studies have examined the effects of stress on changes in

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immune parameters (e.g., cell count, protein production or cell function) (Segerstrom and Miller, 2004) and, in a smaller number of studies, the relation of negative emotions to immune changes (Kiecolt-Glaser et al., 2002). In a recent meta-analysis of laboratory studies using acute time-limited stressors (e.g., mental arithmetic, speech stressor), natural immunity appeared to be upregulated while emotional states induced by these same acute stressors had minor effects on immune changes (Segerstrom and Miller, 2004). Results of the meta-analysis also indicated significant heterogeneity among effect sizes suggesting that the relation of stress to changes in immune parameters may be moderated by various factors.

It has been suggested that effects of stress on immune responses may be moderated by numerous vulnerability factors such as physical characteristics (e.g., age, gender, physical fitness/inactivity, disease status, risk factor profile, and smoking status), personality traits (e.g., hostility, anger expression, and optimism), and psychological states (e.g., depression and depressive mood) (Segerstrom and Miller, 2004). For example, greater increases in cellular adhesion molecules on peripheral blood mononuclear cells (PBMC) following a stressful speech task have been reported among hypertensive individuals relative to those who were normotensive (Mills et al., 2003), and among adults who exercise relative to individuals who were more sedentary (Hong et al., 2004). Given these previous observations, we examined whether insulin resistance (IR) moderated the effects of stress on cytokine secretion.

Insulin resistance, the resistance of cells to the effects of insulin to stimulate glucose uptake, is an important risk factor for three related chronic diseases—type 2 diabetes, atherosclerotic cardiovascular disease (ACVD), and hypertension (Reaven, 1988). Moreover, the relation of HOMA-IR to ACVD appears to be linear suggesting that higher values of HOMA-IR are associated with an increased risk of ACVD, even among those individuals not meeting clinical criteria for IR. Insulin resistance is a key component of the metabolic syndrome (MetSyn), a clustering of cardiovascular risk factors that includes central adiposity, hypertension, and dyslipidemia (Grundy et al., 2004). Recent evidence suggests that IR is associated with measures of inflammation even among apparently healthy adults (Chen et al., 2004), suggesting that inflammation is already evident in individuals without clinical disease. Together, these data suggest that IR is a prominent vulnerability factor that is associated not only with clinical disease but also with measures of inflammation. Together, these observations suggest that IR could potentially moderate the relationship between immune changes and stress.

Other lines of evidence provide support for the biological plausibility of the hypothesis that IR moderates the relationship between stress and immune changes. In our laboratory, we have shown that HOMA-IR is positively associated with stress-induced increases in norepinephrine (NE). Others have shown that NE activates the nuclear factor (NF)-κb/Inhibitor (I)-κB complex, which initiates the production of various cytokines (Bierhaus et al., 2003). Recent studies have also indicated that IR has immunoregulatory effects via insulin receptor signaling (Hotamisligil, 2003). IR has also been associated with low production capacity of interleukin-10, an anti-inflammatory cytokine that inhibits the production of proinflammatory cytokines. Given these lines of evidence, we hypothesized that stress-induced cytokine responses would be positively associated with IR and that the magnitude of cytokine responses, among high HOMA-IR men, would be positively associated with the arousal of negative affect.

In testing the above hypotheses, we examined acute stress-induced changes in the secretion of inflammatory cytokines by peripheral blood monocyte after endotoxin stimulation. Peripheral blood monocytes, the precursor to resident macrophages, are an important source for the pro-atherogenic cytokines interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α (Gerrity, 1981). As important, monocytes/macrophages are recognized as key cellular constituents of atherosclerotic plaque (Ross, 1999) and are thought to be an important cellular link between inflammation and metabolism (Wellen and Hotamisligil, 2005). To evoke emotional arousal, and specifically the arousal of negative affect, we administered the Anger Recall Interview (ARI). We, as well as others, have shown that the ARI evokes significant arousal of negative affect in conjunction with increases in blood pressure, heart rate, peripheral vasodilatation, and circulating plasma catecholamines (e.g., Suarez et al., 2004) and left ventricular ejection fraction in cardiac patients (Ironson et al., 1992). Insulin resistance was estimated using the well-established HOMA method as described by Matthews et al. (1985). The outcome variables for all analyses were acute changes (pre vs. post ARI) in secretion of inflammatory cytokines by blood monocytes following in vitro stimulation by endotoxin.

2. Methods

2.1. Participants

Participants were 58 nonsmoking, healthy men between the ages of 18 and 65 years. Subjects were the first 58 men to enroll in a larger study of the relation of inflammatory biomarkers (e.g., C-reactive protein) to psychosocial risk factors of ACVD (Suarez, 2004). Subjects were recruited from the general community via advertisements placed in local newspapers and fliers distributed throughout the community. Interested individuals were screened for entry criteria using a self-report health questionnaire. Participants reported no history or current diagnosis of chronic medical conditions, such as asthma, allergies, arthritis, diabetes, cancer, and cardiovascular disease. Subjects also reported no history of psychiatric conditions and no current or previous use of anti-depressant medication. Also, participants were free of acute infections and recent injuries and had not undergone medical/dental procedures 2 weeks