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Dissociation of inflammatory markers and natural killer cell activity in major depressive disorder

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Abstract

Major depressive disorder is associated with increases in infectious disease risk as well as the incidence of inflammatory disorders. Declines of natural killer (NK) cell activity are reliably found in depression, whereas other studies report evidence of inflammation in depressed patients. The potential association between NK activity and circulating markers of immune activation has not been previously examined in the context of major depression. In this study, we measured levels of NK activity, circulating levels of interleukin-6 (IL-6), soluble interleukin-2 receptor, and acute phase proteins in 25 male patients with current major depressive disorder and 25 age, gender, and body weight comparable controls. As compared to controls, patients with major depressive disorder showed lower NK activity ($p = .05$) and higher circulating levels of IL-6 ($p < .05$). Levels of NK activity were not correlated with IL-6 or with other markers of immune activation. The independent effect of depression on inflammatory markers and natural killer immune responses has implications for understanding individual differences in the adverse health effects of major depressive disorder.

Keywords: Major depressive disorder; Immunity; Natural killer cell activity; Inflammation

1. Introduction

Major depressive disorder, which exceeds a lifetime incidence of 10% (Kessler et al., 2003; Michaud et al., 2001), is a potent risk factor for disease morbidity with depressed persons showing a mortality rate twice that found in nondepressed persons (Penninx et al., 1999; Rudisch and Nemeroff, 2003; Wulsin et al., 1999). Altered functioning of the immune system is implicated as a mechanism that might contribute to medical morbidity of major depressive disorder including risk of infectious disease (Evans et al., 2002) as well as inflammatory disorders (Zautra et al., 2004). For example, depressed persons show reductions of cellular and innate immune responses that are associated with infectious disease susceptibility (Cohen and Miller, 2000; Leserman, 2003), whereas other studies have found that depression is linked to immune activation in patients with inflammatory disorders such as rheumatoid arthritis (Zautra et al., 2004) and cardiovascular disease (Lesperance et al., 2004; Miller et al., 2002a,b). Indeed, several recent meta-analyses have found that major depression is reliably associated with a reduction of natural killer (NK) cell activity and with increases of circulating levels of the proinflammatory cytokine, interleukin-6 (IL-6), and possibly other markers of immune activation such as acute proteins (e.g., haptoglobin) (Herbert and Cohen, 1993; Irwin, 2002; Zorrilla et al., 2001). However, despite the number of studies that have evaluated different aspects of immunity in depression, no study has simultaneously examined the association between NK activity and inflammatory markers in the context of major depression (Raison and Miller, 2003); rather, these immune differences have been generated in separate samples of depressed patients. In this

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study, we evaluate levels of NK activity as well as markers of immune activation including circulating levels of IL-6, soluble interleukin-2 receptor (sIL-2R), and acute phase proteins (haptoglobin, α-1-anti-trypsin, and α-1-acid glycoprotein) in acutely depressed patients as compared to age-, gender, and body weight matched comparison controls.

2. Materials and methods

2.1. Human subjects

Depressed subjects were recruited by flyers and self-referral, fulfilled Diagnostic, and Statistical Manual-IV (DSM-IV) criteria for Major Depressive Disorder, current episode (American Psychiatric Association, 2000), and underwent immunological assessment prior to inclusion in treatment trials. Control subjects were recruited by advertisements, fulfilled DSM-IV criteria for Never Mentally Ill (American Psychiatric Association, 2000), and matched to depressed subjects on the basis of age (± 5 years), gender, and body weight. The total sample was comprised of 25 control subjects and 25 depressed patients; all subjects were male.

Participants were in good health as determined by medical history and laboratory screening blood tests. None fulfilled criteria for current alcohol or substance abuse or dependence, although 10 depressed subjects had lifetime histories of alcohol abuse/dependence in full remission for greater than 6 months. No other major psychiatric co-morbidity was identified in the depressed group. None of the subjects reported recent (<10 days) viral illness, or used immunosuppressive medications such as corticosteroids. Four depressed subjects reported prior treatment with antidepressant and/or anxiolytic medications and reported use of these medication 19–60 days prior to evaluation; the other 21 depressed subjects did not report such psychotropic medication use in the last 6 months. Other medication use was infrequent: one depressed patient and one control reported the daily use of a diuretic medication for hypertension, and one other depressed patient reported use of a β-agonist inhalant for asthma symptoms 7 days prior to evaluation.

2.2. Procedures

Psychiatric diagnoses of depressed and control subjects were made following administration of the Schedule for Clinical Interview and Diagnosis (SCID)—DSM-IIIR or DSM-IV and consensus meeting of psychiatrists, clinical psychologists, research fellows, and nursing staff. Tobacco histories were obtained using a previously validated interview for substance dependence histories (Bucholz et al., 1994). Severity of depressive symptoms was measured using the Hamilton Depression Rating Scale (Williams, 2001).

Blood sampling for assay of NK activity and plasma levels of immune activation was obtained in the morning between 6 a.m. and 9 a.m. After placement of a 21 gauge intravenous catheter, subjects rested in a recliner chair for 30 min and blood samples were obtained.

2.3. Immune assays

As previously described, peripheral blood mononuclear cells were isolated and NK cell activity was assayed using a standard chromium^{51} labeled K562 cytotoxicity assay, with results expressed as percentage specific cytotoxicity across four effector to target (E:T) cell ratios (40:1; 20:1; 10:1; and 5:1) (Jung and Irwin, 1999). Values of NK activity from nine pairs of controls and depressed patients have been previously reported (Irwin et al., 2003), although these previous results were obtained on a different assay day. Serum levels of IL-6 were quantified by means of enzyme-linked immunosorbent assay methods (R&D Systems, Minneapolis, MN) with all samples from matched pairs assayed at the same time, in a single run with a single lot number of reagents and consumables employed by a single operator, with intra-assay coefficients of variation for all variables less than 5%. Serum levels of sIL-2R were measured using Quantikine Immunoassay kits (R&D Systems, Minneapolis, MN). Nephelometry was used to measure serum levels of the acute phase proteins, haptoglobin, α-1-anti-trypsin (AAT), and α-1-acid glycoprotein (AAG) (Dade Behring, Marburg, Germany). For the full set of immune activation markers, values of IL-6, IL-2R, haptoglobin, AAT, and AAG have not been previously reported.

2.4. Statistical analyses

Paired t tests were used to assess differences in age, body weight, severity of depressive symptoms, and serum levels of IL-6, sIL-2R, haptoglobin, AAT, and AAG between the depressed and control subjects. Values of IL-6 and AAG were square root transformed to achieve normality. A 2 (group: controls, depressed subjects) × 4 (E:T ratios) repeated measures ANOVA tested group differences in NK activity. Pearson correlations evaluated associations between the immune measures.

3. Results

3.1. Subject characteristics

The controls and depressed subjects were similar in age (42.7 ± 12.0 vs. 42.5 ± 9.2 years; $t(24) = 0.4$, $p = .97$) and in body weight (181.9 ± 20.0 vs. 175.6 ± 24.8 lbs;