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The pro-inflammatory profile of depressed patients is (partly) related to obesity

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ABSTRACT

Many people with major depressive disorder (MDD) show evidence of systemic inflammation, including elevations in inflammatory factors, but the cause is unclear. The purpose of this analysis was to determine if obesity might contribute to the pro-inflammatory state in MDD patients. Blood was obtained from 135 MDD patients and 50 controls. Serum was extracted and assayed for interleukin (IL) -1β, IL-2, IL-5, IL-6, IL-8, IL-10, IL-12p70, IL-17, interferon-γ (IFNγ), tumor necrosis factor α (TNFα), C-reactive protein (CRP), leptin, and adiponectin using single- or multi-plex human immunoassay kits. The primary analysis contrasted IL-6, TNFα, and CRP between MDD and control groups with body mass index (BMI) as a covariate. The other analytes were compared in an exploratory fashion. IL-6 (but not TNFα or CRP) showed significant differences between MDD and controls even after covarying for BMI. Obese controls and obese MDD groups were significantly higher in IL-6 than both lean groups, but the two obese groups did not differ from each other. In the exploratory analyses, the IL-2 level showed robust and significant differences between MDD and controls even after covarying for BMI. Both lean and obese MDD were higher than lean and obese controls. Adiponectin levels were also lower in the MDD sample than controls. Prior findings of higher IL-6, and CRP in MDD patients may be explained, at least in part, based on obesity. High IL-2, however, was associated with depression and not obesity. The results have significant implications for the understanding of pathophysiology and, potentially treatment of MDD.

1. Introduction

Evidence for systemic inflammation in a subset of depressed patients has been long recognized (Maes et al., 1993, 1995, 1994). Many people with depression are found to have elevations of inflammatory cytokines including interleukin (IL) 6 and tumor necrosis factor α (TNFα) (Dowlati et al., 2010; Raison et al., 2006), acute phase reactants such as C-reactive protein (CRP), chemokines, and cell adhesion molecules (Raison et al., 2006). In spite of decades of research, however, the specific etiologies of systemic inflammation in depressed patients remain elusive. While the mechanistic paths from inflammatory cytokines to depression, such as depressive states induced by interferon (IFN) α treatment, are reasonably well understood (Raison et al., 2006), the reverse is not true. There are many depressed patients who show evidence of a sustained pro-inflammatory state in the absence of known systemic disease.

A number of hypotheses have ventured to explain this phenomenon. For example, psychological stress stimulates the release of cytokines and activates cellular immune mechanisms in both animal and human studies (Bierhaus et al., 2003; Garate et al., 2013; Pace et al., 2006). As well, early life adversity, which is known to increase the risk for depression, is also associated with systemic inflammation (Danese et al., 2009; Pace et al., 2006). In one prospective study, people who experienced early life abuse were more likely to have depression and show increased CRP in adult life (Danese et al., 2009, 2008). However, that study also showed that early life adversity was associated with cardiometabolic risk factors such as hypertension, elevated total cholesterol and reduced HDL cholesterol, and higher glycated hemoglobin, phenomena that are

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associated with obesity, especially increased intra-abdominal adipose tissue (IAAT) (Wajchenberg, 2000). This is consistent with findings that early trauma is also associated with increased risk of general obesity and elevated IAAT in adult life (Thomas et al., 2008).

Both cross-sectional (Papakostas et al., 2005; Simon et al., 2001) and longitudinal (Rotella and Mannucci, 2013) studies have shown increased risk for obesity in depressed patients. What has received considerably less attention, however, is the association between obesity and systemic inflammation in depressed patients. Miller et al. (Miller et al., 2002) assessed the association of depression and cardiometabolic risk factors including systemic inflammation. Depressed participants exhibited higher CRP and IL-6 and meditational analyses indicated that adiposity accounted for a portion of the relationship between depression and increased inflammatory markers. Another recent study assessed IL-2, IL-4, IL-5, IL-10, IL-12, IL-13, granulocyte macrophage colony-stimulating factor (GM-CSF), interferon γ (IFNγ), and TNFα and found higher IL-5, IL-12, IL-13, GM-CSF, IFNγ and TNFα levels in obese depressed participants compared to non-obese depressed and control subjects. (Schmidt et al., 2014)

The primary objective of the current study was to compare the systemic inflammation, particularly IL-6, TNFα, and CRP in a set of obese (body mass index [BMI] $\geq$ 30) versus non-obese depressed patients and both obese and non-obese controls. Secondary exploratory analyses sought to assess a range of inflammatory cytokines, leptin, and adiponectin across obese and non-obese depressed and controls. The primary hypothesis was that obese depressed and controls would show higher inflammatory factors than non-obese groups, but that the obese depressed participants would show the highest levels of systemic inflammation.

2. Material and methods

Samples for this analysis were obtained from two sources. The first set of serum samples were obtained from participants with major depressive disorder (MDD) obtained at baseline in multi-site study of the augmentation of SSRI antidepressants with L-methylfolate previously reported (n = 75) (Papakostas et al., 2012). The second was a set of patients with MDD (n = 53) and normal volunteer controls (n = 50) without history of mental or substance abuse disorder obtained at the University of Alabama Medical Center in Birmingham, AL (UAB). Controls were selected to approximate the proportions of MDD participants with BMI $\geq$ 30. The research was conducted in accordance with the Declaration of Helsinki (6th Revision). The studies were reviewed and approved by local institutional review boards and written informed consent was obtained from all subjects. Participants were males and females ages 19–66 and were physically healthy or had stable medical conditions. None had evidence of systemic inflammatory diseases such as rheumatoid arthritis, lupus, or similar conditions. Diagnosis was confirmed using the Structured Clinical Interview for DSM-IV (First et al., 2002) or the Mini International Neuropsychiatric Interview (Sheehan et al., 1998). The 17-item Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960) was obtained on all participants collected in the L-methylfolate study, and the Montgomery-Åsberg Depression Rating Scale (Montgomery and Asberg, 1979) was obtained on the participants collected at UAB.

Blood samples were obtained from all participants and serum extracted using standard methods and stored at −80 °C until assayed (Tuck et al., 2009). The timing of the blood sample was not controlled in the study and the participants were not fasting. Anthropometrics were collected using National Health and Nutrition Examination Survey (NHANES) methods (NCHS, 2007). BMI was calculated in kg/m^2 from height and weight measures. Obesity was defined as a BMI $\geq$ 30.

2.1. Immunoassays

Plasma samples were analyzed for IL-1β, IL-2, IL-5, IL-6, IL-8, IL-10, IL-12p70, IL-17, IFNγ, and TNFα, using single- or multi-plex human immunoassay kits (Meso Scale Discovery, Gaithersburg, MD). CRP (minimum sensitivity = 0.5 mg/l) was analyzed using immunoassay on a Stanbio Sirrus Analyzer (Stanbio Laboratory, Boeme, TX) using a Pointe Scientific (Canton, MI) turbidimetric CRP reagent. Minimum sensitivity, intra-assay, and inter-assay coefficient of variation (%) were as follows: IL-1β: 0.03 pg/ml, 17.11, 6.36; IL-2: 0.16 pg/ml, 10.62, 10.86; IL-5: 0.11 pg/ml, 13.23, 4.04; IL-6: 0.25 pg/ml, 7.12, 5.77; IL-8: 0.09 pg/ml, 1.21, 1.37; IL-10: 0.07 pg/ml, 6.61, 2.06; IL-12p70: 0.09 pg/ml, 1.96, 12.32; IL-17: 0.91 pg/ml, 3.66, 11.40; IFNγ: 0.56 ng/ml, 4.75, 2.83, TNFα: 0.08 pg/ml, 5.72, 5.61; CRP: 0.5 mg/L, 7.49, 2.13. Leptin (minimum sensitivity = 1.04 ng/ml, intra-assay CV = 1.128%) and adiponectin (minimum sensitivity = 1.24 μg/ml, intra-assay CV = 3.98%) were analyzed using single human radioimmunoassay kits (Millipore, Billerica, MA). All samples were run in duplicate and the mean of the duplicate samples were reported. If the duplicate value was >5% higher or lower than the other value the assay was repeated in duplicate; if the duplicate varied on a second analysis by more than 5%, the sample was excluded.

Study data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at the University of Alabama at Birmingham (Harris et al., 2009). REDCap is a secure, web-based application designed to support data capture for research studies.

2.2. Statistical analysis

Demographic data including age, sex distribution, BMI, weight, and waist and hip circumference, and waist-to-hip ratio were compared between MDD and controls using t-tests for continuous and Chi^2 for categorical data. The primary analysis tested the differences in levels of IL-6, TNFα, and CRP between the MDD and control groups with univariate analysis of variance (ANOVA) with BMI as a covariate and Bonferroni correction. Secondary exploratory analyses also tested the other cytokines, leptin, and adiponectin via ANOVA with BMI as a covariate. A final analysis step assessed a four-group comparison via ANOVA followed by Tamhane's T2 test (Tamhane, 1977) for unequal variances for all analytes: 1. Non-obese controls; 2. Obese controls; 3. Non-obese MDD, and 4. Obese MDD groups. The overall primary hypothesis was that differences between MDD and control groups on the three primary analytes would be accounted for by obesity status.

The associations between BMI, waist and hip circumference (cm), and waist to hip ratio with cytokines, CRP, leptin, and adiponectin were assessed using the Pearson product–moment correlation coefficient. Analyses were conducted using SPSS version 22.

3. Results

A total of 135 patients with MDD and 50 controls were included. Demographic data are included in Table 1. Only age was significantly different between groups (t = −2.454, df = 163, p = 0.015). There were no significant differences between controls and MDD patients in anthropometrics, including weight, waist circumference, hip circumference, or waist-to-hip ratio for the total sample, males, or females. For the MDD participants collected in the L-methylfolate trial (Papakostas et al., 2012) the mean (SD) HRSD score was 21.3 (3.9) and the mean (SD) MADRS scores for the UAB MDD sample was 28.2 (13.4).