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Association of peripheral inflammation with body mass index and depressive relapse in bipolar disorder

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ABSTRACT

Bipolar I disorder (BD) is associated with increased inflammation, which is believed to be central to disease etiology and progression. However, BD patients also have high rates of obesity, itself an inflammatory condition, and the relative contributions of mood illness and obesity to inflammation are unknown. Moreover, the impact of inflammation on clinical illness course has not been well studied. The objectives of this analysis were therefore: (1) to determine if inflammation in BD is mood illness-related or secondary to elevated body mass index (BMI), and (2) to investigate the impact of inflammation on prospectively-ascertained relapse into depression and mania. We measured the serum levels of 7 inflammatory cytokines (TNF-α, γ-interferon, monocyte chemoattractant protein-1 [MCP-1], IL-1α, IL-2, IL-6, and IL-8) and 2 anti-inflammatory cytokines (IL-4 and IL-10) in 52 early-stage BD patients and 22 healthy subjects. In patients, a multivariate multiple regression model that controlled for psychotropic medications found that higher BMI, but not recent (past-6-month) mood episodes, predicted greater inflammatory cytokines ($p = .05$). Healthy subjects also had a BMI-related increase in inflammatory cytokines ($p < .01$), but it was counter-balanced by a compensatory increase in anti-inflammatory cytokines ($p = .02$), reducing their total inflammatory burden from higher BMI. In patients, linear regression showed that two inflammatory cytokines predicted depressive relapse in the 12 months after cytokine measurement: IL-1α ($p < .01$) and MCP-1 ($p < .01$). These results suggest that elevated BMI is a significant contributor to inflammation in BD, more so even than recent mood illness severity. They also point to inflammation as an important predictor of illness course, particularly depressive relapse.

1. Introduction

Mounting evidence implicates inflammation as a key mechanism in the pathophysiology of bipolar I disorder (BD). Compared to healthy individuals, BD patients have increased expression of inflammatory genes in monocytes and elevated serum levels of inflammatory cytokines (Padmos et al., 2008; Modabbernia et al., 2013). Evidence for CNS inflammation includes the presence of neuroinflammatory markers in post-mortem brain samples (Rao et al., 2010), and hippocampal microglial activation in vivo as demonstrated by a recent positron emission tomography study (Haarman et al., 2014). The serum levels of several cytokines are elevated during mood episodes but not euthymia, suggesting that BD itself is at least partly responsible for these inflammatory changes (Modabbernia et al., 2013).

However, other factors may also contribute to inflammation in BD. For example, poor sleep quality and duration (Irwin et al., 2006), psychosocial stress (Rohleder, 2012), and substance abuse (Wang et al., 2010), all more common in people with BD than the general population, generate inflammatory responses. Moreover, BD patients have higher-than-expected rates of psychiatric and medical illnesses with inflammatory components, including anxiety disorders (Hou and Baldwin, 2012), cardiovascular disease (Hansson, 2005), and obesity (Fain, 2010). Nonetheless, aside from mood stabilizing medications such as lithium, which have been shown to decrease inflammatory gene expression and serum cytokine levels (Boufidou et al., 2004; Padmos et al., 2008,), the

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impact of non-mood-illness factors on inflammation in BD has been poorly studied.

Obesity is one of the most common co-occurring conditions in people with BD, who are two-thirds again more likely to be obese than the general population (Goldstein et al., 2011). Data from animal models and non-psychiatric human samples demonstrate that obesity is a pro-inflammatory state (Fain, 2010). Weight gain and fat mass expansion are accompanied by adipocyte hypertrophy, lysis, necrosis, and the release of free fatty acids, which interact with macrophage and adipocyte toll-like receptors, key activators of the innate immune response (Konner and Bruning, 2011). The resulting release of inflammatory mediators leads to the recruitment of macrophages into adipose tissue, and their activation along the M1, or pro-inflammatory, pathway; infiltration of adipose tissue by $T_H1$cells, $CD8^+$ T cells, and B-cells, which produce additional inflammatory cytokines and pathogenic IgG antibodies; and a reduction in anti-inflammatory T_{reg} cells (Sun et al., 2012). The end result is systemic inflammation, as evidenced by increased levels of multiple serum cytokines (Fain, 2010).

Since mood episodes and obesity are both inflammatory conditions, and since obesity rates are elevated in BD, a critical question arises: to what degree is inflammation in BD mood-illness-related, and to what degree is it a result of elevated body mass index (BMI)? Previous serum cytokine studies did not address this question, since they generally measured differences between patients and control subjects without accounting for differences in weight, making the relative contributions of BD and elevated BMI impossible to discern (Tsai et al., 2012). A small number of studies did control for differences in obesity rates, either by using BMI as a covariate or by matching patients and comparators on BMI (Hung et al., 2007; Barbosa et al., 2012). However, while this facilitated the detection of BD-specific inflammation, it artificially minimized the impact of obesity-related inflammation in patients by eliminating differences in obesity between patients and comparators.

The impact of inflammation on psychiatric illness course is also unknown. Short-term studies examining the association of inflammatory markers with the severity of concurrent mood symptoms, or the impact of anti-inflammatory medications on recovery rates from acute mood episodes, have produced mixed results (O'Brien et al., 2006; Kim et al., 2007; Ayorech et al., 2015). However, in the long term, BD has less favourable outcomes when it co-occurs with pro-inflammatory psychiatric or medical conditions, typically including an earlier age of onset, more frequent mood episodes, particularly depressive episodes, and lower medication response rates (McIntyre et al., 2012; Schaffer et al., 2012). This suggests that inflammation may lead to a more severe illness course, but to the best of our knowledge, the impact of directly-measured peripheral inflammation on relapse rates has not been prospectively studied.

The objectives of this analysis were therefore (1) to determine if peripheral inflammation in BD is mood illness-related or due to elevated BMI, and (2) to investigate the impact of inflammation on relapse into depression and mania. We measured the serum levels of 7 inflammatory and 2 anti-inflammatory cytokines in 52 BD patients enrolled in a first-episode mania program, and 22 healthy control subjects. Using multivariate multiple regression models that controlled for the impact of psychiatric medications, we examined the impact of BMI, time in recent (past-6-month) mood episodes, and medication treatment on inflammatory and anti-inflammatory cytokines in patients. For comparison purposes, we also explored the impact of BMI on inflammation in healthy subjects. To determine if inflammation was associated with illness course, we investigated whether inflammatory markers predicted depressive and hypomanic/manic relapses in the 12 months after cytokine measurement. We hypothesized that (1) in patients, time in recent mood episodes and higher BMI would contribute to inflammation, (2) the impact of BMI on inflammation would be greater in patients than healthy subjects, and (3) inflammation in patients would predict depressive relapse over 12 months.

2. Material and methods

2.1. Subjects

Serum samples were obtained from BD patients and healthy subjects enrolled in the Systematic Treatment Optimization Program for Early Mania (STOP-EM), a prospective study of people with BD who recently recovered from their first manic or mixed episode (Yatham et al., 2009). STOP-EM is based at the University of British Columbia (UBC) in Vancouver, Canada, and has been active since July 2004. Patients were recruited from the UBC Mood Disorders Clinical Research Unit and affiliated sites if they were aged 14–35 and experienced their first manic/mixed episode within the previous 3 months. To capture the full spectrum of BD phenotypes, patients with comorbid psychiatric and substance use disorders were included, provided their primary diagnosis was BD. Healthy subjects aged 14–35 were recruited from the greater Vancouver area, through print advertisements and online forums such as Craigslist. The UBC Clinical Research Ethics Board approved STOP-EM, and written informed consent was obtained prior to any study procedures taking place.

2.2. Clinical assessments

At enrolment into STOP-EM, the diagnoses of bipolar I disorder and first manic/mixed episode were made based on a comprehensive assessment by an academic research psychiatrist, and confirmed with the Mini International Neuropsychiatric Interview (MINI). The MINI was also administered to healthy subjects, who were enrolled if they had no personal or family history in first- or second-degree relatives of psychiatric illness. Sociodemographic and clinical data were collected using a standardized protocol. Mood and psychotic symptoms in patients were quantified with the Young Mania Rating Scale (YMRS), Montgomery–Asberg Depression Rating Scale (MADRS), and Brief Psychiatric Rating Scale (BPRS). Participants were weighed in a non-fasting state in light clothing with footwear removed, and their BMI (weight [kg]/height $[m]^2$) was calculated. Normal weight was defined as BMI = 18.50 – 24.99, overweight as BMI = 25.00 – 29.99, and obesity as BMI $\geq$ 30.00.

Patients received treatment for BD according to clinical practice guidelines from the Canadian Network for Mood and Anxiety Treatments (Yatham et al., 2013). Patients and healthy subjects were reassessed every six months. At these visits, their weights were recorded, and, in patients, clinical rating scales were repeated and medication treatments were recorded. Episode recurrence and the number of days ill were determined by clinician assessment, self-report, patient-completed NIMH Life Charts, and additional information from collateral informants and health records as needed.

2.3. Collection and analysis of serum samples

A single non-fasting blood sample was obtained from each participant, either at enrolment into STOP-EM or at a 6-monthly follow-up visit, and typically in the early afternoon. In all participants, the sample was acquired within 4 years of enrolment. Twenty millilitres of blood were collected by venipuncture into two Vacutainer 367820 Serum Tubes (Becton, Dickinson and Company, Rutherford, NJ). The samples were centrifuged at 3000 RPM for 10 min to obtain serum, which was aliquotted into Eppendorf tubes and stored at −80 °C until analyzed. The protein levels of 7