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Bipolar disorder moderates associations between linoleic acid and markers of inflammation

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ABSTRACT

Dietary polyunsaturated fatty acids (PUFA) and inflammatory proteins associate with immune activation and have been implicated in the pathophysiology of mood disorders. We have previously reported that individuals with bipolar disorder (BPD) have decreased PUFA intake, including eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and arachidonic acid (AA); and decreased PUFA concentration of plasma EPA and linoleic acid (LA). We have also reported an association between plasma LA and its metabolites and burden of disease measures in BPD. In the current cross-sectional study we collected blood samples and diet records from both bipolar ($n = 91$) and control subjects ($n = 75$) to quantify plasma cytokine concentrations and dietary LA intake, respectively. Using multiple linear regression techniques, we tested for case control differences in plasma cytokine levels and associations between cytokines and dietary LA intake, adjusting for sex, age, BMI, and total energy intake. We found significantly higher plasma levels of interleukin 18 (IL-18) ($p = 0.036$), IL-18 binding protein (IL-18BP) ($p = 0.001$), soluble tumor necrosis factor receptor (sTNFR) 1 ($p = 0.006$), and sTNFR2 ($p = 0.007$) in BPD compared with controls. Moreover, BPD significantly moderated the associations of dietary LA intake with plasma levels of IL-18, sTNFR1 and sTNFR2, which were inverse associations in bipolar individuals and positive associations in controls (p for dietary LA x BPD diagnosis interaction < 0.05 for all three). These findings suggest potential dysregulation of LA metabolism in BPD, which may extend to a modified influence of dietary LA on specific inflammatory pathways in individuals with BPD compared to healthy controls.

1. Introduction

Bipolar disorder is a medical illness characterized by episodic mood changes, each having potential deleterious effects on overall psychosocial functioning and increased risk of suicide (Rihmer and Kiss, 2002). Despite the high prevalence (Merikangas et al., 2011), little is known of the pathophysiology underlying bipolar disorder. While evidence suggests certain genetic variation enhances risk (Chen et al., 2013), the mechanistic underpinnings of bipolar disorder remain in need of clarification.

A body of evidence identifies mechanistic links between clinical depression and evidence of immune activation (Dantzer et al., 2008). Emerging evidence suggests a potential mechanistic role for inflammasome activation in the underlying pathophysiology of bipolar disorder. Within cells sharing a common dendritic lineage, during the process of activation by various signals, the NLRP3 inflammasome potently induces activation of specific cytokines, most notably, interleukin-1β (IL-1β) and another more potent IL-1 family cytokine, interleukin-18 (IL-18) (Dinarello, 1999a,b; van de Veerdonk et al., 2011). In fact, many of medical illnesses that co-occur with bipolar disorder, such as heart diseases and obesity, have evidence of similar immune activation (Leboyer et al., 2012). For instance, patients with bipolar disorder and their descendants show abnormal inflammatory gene expression in monocytes, which play a critical role in inflammasome activation and subsequent production of various inflammatory cytokines (Padmos et al., 2008). A body of evidence identifies associations between elevated

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plasma concentrations of IL-18 and the presence of major depressive disorders (Al-Hakeim et al., 2015; Merendino et al., 2002; Prossin et al., 2011) and more recent evidence suggests plasma IL-18 concentration is associated with affective state, elevated during sadness and relatively lower during neutral affective states (Prossin et al., 2016). Emerging evidence in individuals with bipolar disorder shows significant elevation of plasma concentrations of certain "pro-inflammatory" cytokines during mood episodes (Fiedorowicz et al., 2015; Goldstein et al., 2009). Given their potential buffering capacity of certain "pro-inflammatory" cytokines, efforts have been taken to investigate the role of "anti-inflammatory proteins" (including specific soluble cytokine receptors) in both Major Depressive Disorder (Myint et al., 2005) and bipolar disorder. As compared to healthy control individuals, plasma concentration of soluble tumor necrosis factor receptor (sTNFR) 1 (Barbosa et al., 2011) and sTNFR2 have been found elevated in Bipolar Disordered patients, even during periods of euthymia (Doganavsargil-Baysal et al., 2013). However, associations between bipolar disorder and other so called "anti-inflammatory" proteins (i.e. interleukin-4 (IL-4), interleukin-10 (IL-10)), lack consistency across studies (Goldstein et al., 2009). These inconsistencies may potentially be explained by lack of control of the various potential confounders related to diet, exercise, medication, and other sociodemographic variances frequently found to confound research studies of bipolar disorder. Studies that attempt to control for these confounds will help to elucidate the nature of the contribution of immune activation to the mechanistic underpinnings of bipolar disorder.

Dietary polyunsaturated fatty acids (PUFA) are important factors that regulate inflammation (Calder, 2002). The n-6, linoleic acid (LA) and the n-3, alpha linolenic acid (LNA), are essential PUFA. Mammals cannot synthesize these *de novo*, but can synthesize all other required PUFA from these two dietary substrates through shared enzymes, Δ6-desaturase, elongases and Δ5 desaturase (Pischon et al., 2003). Eicosanoids derived from n-6 PUFA, including leukotriene B_4 (LTB_4) and prostaglandins E_2 (PGE_2), have potent inflammatory properties when compared with those from n-3 PUFA, including leukotriene B_5 (LTB_5) and prostaglandins E_3 (PGE_3). These opposing inflammatory activities of n-3 and n-6 derived eicosanoids may underlie the importance of the complement of dietary PUFA intake on controlling inflammation. Many studies identified beneficial effects of n-3 PUFA on inflammation, suggesting inverse associations between n-3 PUFA dietary intake and plasma cytokine concentration (Kalogeropoulos et al., 2010; Lopez-Garcia et al., 2004); however, the effects of n-6 PUFA on inflammation are still under debate. Some studies highlight the ratio of n-6 PUFA to n-3 PUFA as important, showing a strong positive association with inflammatory markers, including C-reactive protein, and IL-6, and an inverse association with anti-inflammatory markers, including IL-10 (Ferrucci et al., 2006). However, other studies find inverse associations between both n-3 and n-6 PUFA consumption, and inflammation, suggesting that n-6 PUFA have similar anti-inflammatory roles as n-3 PUFA (Julia et al., 2013). Furthermore, in healthy adult men, diets containing 10.5% energy from LA associated with higher plasma LA concentrations than diets with only 3.8% total energy from LA, but no significant changes on AA concentration were observed. These data suggest that higher LA intake does not cause increased plasma AA, which is the direct precursor to downstream inflammatory eicosanoids (Angela Liou and Innis, 2009). Also, LA supplementation had no effect on either EPA or DHA levels, and the authors concluded the effects of LA on conversion of LNA to EPA or DHA do not reduce anti-inflammatory eicosanoid production (Minihane et al., 2005). Finally, a systematic review of randomized controlled trials concluded that there was not enough evidence to support that dietary LA intake would increase inflammatory cytokines levels (Johnson and Fritsche, 2012). Thus, further studies to understand the relationship between dietary PUFA and inflammation are warranted.

PUFA may also play a key role in mood (Liu et al., 2013). Higher serum n-6 PUFA and lower n-3 PUFA have been found to associate with depressive symptoms (Conklin et al., 2007). Results from plasma and erythrocyte phospholipid in patients with severe depression showed significant and positive correlation between the ratio of AA to EPA, and severity of depression (Adams et al., 1996) and suicidal behavior (Evans et al., 2012b). However, plasma LA inversely associates with burden of disease measures in bipolar patients, including severity of depression and self-reported life functioning (Evans et al., 2015, 2012a, 2014). Other studies of bipolar disorder found higher n-3 and n-6 PUFA levels in the human postmortem superior temporal gyrus, a cortical area related to emotion (McNamara et al., 2014), but no association in the postmortem entorhinal cortex (Hamazaki et al., 2013). Furthermore, Jadoon et al. identified inverse associations between residual depression and levels of the n-6 PUFA, LA, but not levels of n-3 PUFA, in both erythrocyte and plasma. In this study, the inverse association between LA and depression may have been due to inefficient conversion of LA to AA, with decreased production of AA by inhibition of Δ6-desaturase activity (Jadoon et al., 2012). Although several studies have evaluated the effect of PUFA on mood function (Sublette et al., 2007), the results are still inconsistent. Moreover, few have studied the association between PUFA and inflammation in bipolar disorder.

Our previous studies found decreased dietary PUFA intake and PUFA plasma concentrations in bipolar individuals compared to healthy controls (Evans et al., 2014). Furthermore, we found several LA-derived metabolites associated with bipolar disorder. Results from our studies indicate that LA metabolism may be dysregulated in bipolar disorder. Based on these data, the aim of the current study was to identify whether dietary LA intake would predict plasma cytokine levels differently in bipolar individuals compared to controls.

To accomplish this aim, we quantified concentrations of specific inflammatory cytokines from plasma of individuals with a confirmed diagnosis of bipolar disorder for comparison against plasma concentrations in healthy control individuals, following prospective collection of 7-day diet records. Inflammatory cytokines were selected based on evidence from the extant literature and included IL-1β, interleukin-6 (IL-6), IL-10, IL-18, IL-18 binding protein (IL-18BP), IL-1 receptor antagonist (IL-1RA), IL-6 receptor alpha (IL-6RA), sTNFR1, sTNFR2, and C-reactive protein (CRP). Results from these assays were coalesced with dietary intake data, and plasma n-3 and n-6 PUFA concentrations from the same individuals.

2. Materials and methods

2.1. Participants

Individuals were recruited from the Heinz C. Prechter Longitudinal Study of Bipolar Disorder at the University of Michigan Depression Center previously described (Langenecker et al., 2010). Briefly, all individuals were diagnosed using the Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994), and were recruited carrying a diagnosis of bipolar I disorder (BP I) with history of treated BP I mania, or schizoaffective manic type or BP II disorder with history of treated major depression, or were non-psychiatric controls. Individuals with current and active substance abuse or suffer from a medical illness specifically associated with depression (including terminal cancers, Cushing's disease, or