Neurology, Psychiatry and Brain Research 30 (2018) 39–46

Contents lists available at ScienceDirect

Neurology, Psychiatry and Brain Research

journal homepage: www.elsevier.com/locate/npbr

Associations of plasma interleukin-6 with plasma and cerebrospinal fluid monoamine biosynthetic pathway metabolites in treatment-resistant depression

Manivel Rengasamy[a,*], Lora McClain[a], Pranali Gandhi[b], Anna Maria Segreti[a], David Brent[a], David Peters[c], Lisa Pan[a]

[a] Department of Psychiatry, University of Pittsburgh, Pittsburgh, USA
[b] University of Pittsburgh, Pittsburgh, USA
[c] Department of Obstetrics, Gynecology, & Reproductive Science, University of Pittsburgh, Pittsburgh, USA

ARTICLE INFO

Keywords:
Interleukin 6
Depression
Treatment-resistant
Serotonin
Cerebrospinal fluid
Immune

ABSTRACT

Background: Current research suggests that depression is associated with several changes in the immune system, including alterations in inflammatory cytokines, the hypothalamic-pituitary-adrenal axis, and downstream effects on neurotransmitters. Specifically, plasma interleukin-6 (IL-6) is elevated in depressed individuals compared to non-depressed controls, and these same inflammatory processes may be implicated in treatment resistant depression (TR-MDD). IL-6 has also been theorized to affect central monoamine pathway metabolites. Few studies have assessed the relationship of IL-6 and plasma/CSF monoamine biosynthetic pathway metabolites and symptomatic correlates of depression.

Methods: We analyzed plasma IL-6 levels in an outpatient treatment-resistant depressed cohort (n = 67) and healthy control cohort (n = 40). We also assessed relationship of plasma IL-6 with plasma/CSF monoamine pathway metabolites and symptomatic correlates of depression.

Results: Higher levels of plasma IL-6 were found in the TR-MDD cohort compared to the control cohort. Plasma IL-6 correlated with plasma serotonin levels among all participants, although there was no association of plasma IL-6 and plasma serotonin in the TR-MDD cohort on subgroup analysis. No correlations were found between plasma IL-6 and plasma/CSF monoamine breakdown products, depressive symptomatology, or suicidality.

Limitations: Our analysis was a post-hoc analysis and we were not able to exhaustively control for confounds of IL-6 levels, such as sleep or stress.

Conclusion: The findings of the current study extend current evidence that plasma IL-6 levels are elevated in TR-MDD, after adjusting for body mass index. Additionally, plasma IL-6 and serotonin regulation may vary between healthy and TR-MDD populations. Lastly, our study finds no association between plasma IL-6 and CSF monoamine pathway metabolites, suggesting that further research is needed to elucidate the association of IL-6 and depression.

1. Introduction

Major depressive disorder (MDD) is characterized as a mental disorder where affected individuals experience at least two weeks of constant low mood, loss of interest, and low energy, hopelessness, or disrupted sleep (Insel & Charney, 2003). Individuals diagnosed with MDD are more likely to also be diagnosed with other comorbid psychiatric diseases (Kessler, Zhao, Blazer, & Swartz, 1997). Furthermore, MDD has been associated with up to a 1–3% risk for suicide (Brown, Beck, Steer, & Grisham, 2000; Fawcett et al., 1990; Guzzetta, Tondo, Centorrino, & Baldessarini, 2007). Treatment with antidepressants helps mood symptoms in some patients, but up to 10–30% of individuals do not respond to current treatments (Nemeroff, 2007; Souery et al., 1999). Thus, treatment resistant major depressive disorder (TR-MDD) continues to remain a dilemma for clinicians, with difficulties in early identification of these patients (Mrazek, Hornberger, Altar, & Degtiar, 2014). Numerous unique metabolic and immunologic characteristics of these patients may play a role in their treatment resistant status and aid in both their diagnosis and treatment (Martins-de-Souza, 2014; Miller, Maletic, & Raison, 2009; Moaddel et al., 2015).

* Corresponding author: 3811 O'Hara Street, Pittsburgh, PA, 15213, USA.
E-mail address: rengasamym@upmc.edu (M. Rengasamy).

https://doi.org/10.1016/j.npbr.2018.05.001
Received 28 December 2017; Received in revised form 30 April 2018; Accepted 4 May 2018

Immune system activation in the context of depression has been well described in recent years (Raison, Capuron, & Miller, 2006). Cytokine activation (secondary to infection and exogenous cytokine administration such as TNFα, IL-1β, IL-6, and IFNα) has been associated with clinical depression and "sickness behavior", with symptomatology similar to depression in its psychobiological characteristics (Lotrich, Rabinovitz, Gironda, & Pollock, 2007; Maes et al., 2012; Sukoff Rizzo et al., 2012). Furthermore, anti-inflammatory treatments have shown promising anti-depressant effects in depressed populations (Akhondzadeh et al., 2009).

Of all the cytokines, Interleukin-6 (IL-6) has the strongest and most consistent association with depressive symptomatology, through a variety of mechanisms. IL-6 is associated with hypothalamic-pituitary-adrenal (HPA) axis activation per proxy measures such as elevated corticotropin-releasing hormone (CRH), elevated cortisol, elevated adrenocortopic hormone, and glucocorticoid receptor insensitivity, consistent with endocrine alterations in depression (Blume, Douglas, & Evans, 2011; Girotti, Donegan, & Morilak, 2013; Mastorakos, Chrousos, & Weber, 1993; Raison et al., 2006; Steensberg, Fischer, Keller, Møller, & Pedersen, 2003). Similarly, IL-6 directly regulates NMDA glutamate (Qiu, Sweeney, Netzeband, & Gruol, 1998) and serotonin activity (Donegan et al., 2015; Kong et al., 2015; Zalcman et al., 1994), both of which are associated with depression. Peripheral IL-6 has been associated with changes in metabolism of both dopamine and serotonin in the CNS (Song, Merali, & Anisman, 1999; Wang & Dunn, 1998; Zalcman et al., 1994; J.-j. Zhang, Terreni, De Simoni, & Dunn, 2001). IL-6 may contribute to depressive symptoms via increasing oxidative stress, activating the kynurenine pathway, or adjusting levels of brain-derived neurotrophic factor (Mondelli et al., 2011; Schulte-Herbrüggen et al., 2005). Genetic studies also find associations between expression variations in IL-6 genes and MDD (Iacob et al., 2013; Jansen et al., 2015; Zhang, Wu, Zhao, Wang, & Fang, 2016).

Furthermore, alterations in peripheral IL-6 are associated with changes in depression-relevant brain regions, including the hippocampus and prefrontal cortex (Frodl et al., 2012; Marsland, Gianaros, Abramowitch, Manuck, & Hariri, 2008; Pandey et al., 2012; Yang et al., 2013). Examining suicide attempters, Lindqvist et al. found increased levels of IL-6 in the cerebrospinal fluid (CSF) of individuals and positive correlation of CSF IL-6 levels with depressive indices (Lindqvist et al., 2009); however these findings were not found in depressed individuals (Carpenter, Heninger, Malison, Tyrka, & Price, 2004). To our knowledge, no prior studies have examined the association of peripheral IL-6 and both peripheral and central metabolites involved in monoamine biosynthesis in the TR-MDD population.

Despite known elevations of plasma IL-6 in populations of depressed patients, limited research has been done in treatment-resistant depressed populations (Dowlati et al., 2010).

Select studies have examined peripheral IL-6 after failure of *one* trial of antidepressants, with some but not all reporting elevations of IL-6 in treatment non-responders (Lanquillon, Krieg, Bening-Abu-Shach, & Vedder, 2000; O'Brien, Scully, Fitzgerald, Scott, & Dinan, 2007). However, to our knowledge, only Carvahlo et al. and Kiraly et al. examined peripheral IL-6 in patients using more typical definition of TR-MDD of failure of at least *two* trials of antidepressants, finding elevations of IL-6 in studies of less than 40 TR-MDD participants (Carvalho et al., 2013; Kiraly et al., 2017). However, those studies respectively did not control for SNRI medication usage (which has been associated with elevation in IL-6 levels) or excluded participants with nicotine use, limiting generalizability of their findings (Fornaro, Martino, Battaglia, Colicchio, & Perugi, 2011).

Thus, the literature is unclear if the initial inflammatory marker elevation in acute-onset depression continues after multiple failed trials of anti-depressants or therapy interventions as in chronic treatment-resistant depression. Notably, depressed patients characterized as nonresponders also have elevated post-treatment IL-6 serum levels when compared with either formerly depressed or healthy cohorts (Maes et al., 1997; O'Brien et al., 2007; Sluzewska et al., 1995). From an immunological standpoint, the acute inflammatory phase response from IL-6 appears to be associated with onset and initial continuation of depressive symptoms, although it appears unclear if the initial sustained inflammatory activation continues several months after continuation of severe and nonremitting depressive symptoms. Similarly, no prior studies have examined the role of the relationship of plasma IL-6 and other related plasma monoamine or cerebrospinal monoamines, which would elucidate the role of potential chronic inflammatory changes in individuals with refractory depression.

In our post hoc analysis comparing a cohorts of TR-MDD participants to non-depressed healthy controls, we sought to identify (i) associations of IL-6 with presence of TR-MDD and other correlates of depression (ii) associations of IL-6 with plasma and CSF monoamine biosynthetic pathway metabolites. We expect that IL-6 will be elevated in TR-MDD participants and correlated with depressive symptomatology, while plasma/CSF monoamine biosynthetic pathway metabolites will be associated with IL-6 levels.

2. Materials and methods

Our manuscript reflects data obtained as part of an ongoing research trial, of which initial findings and methodology are described in another manuscript (Pan et al., 2016).

2.1. Participants

Participants consisted of 103 TR-MDD adults and adolescents aged 15 to 52 years with clinical treatment-refractory depression, defined by failure of response to three maximum dose medication trials. Failure of three medication trials was chosen given that we sought to assess those patients with severe TR-MDD. Controls consisted of 43 healthy adults, without personal or first-degree relative history of diagnosed psychiatric disorder or suicidal behavior. Recruitment of participants was done through advertisement or clinical referral. Informed assent/consent was obtained from all adult participants. Informed assent was obtained from adolescent participants with consent obtained from parents. Given the risk of lumbar puncture, adolescent healthy controls were excluded from recruitment in the study. The Institutional Review Board of the University of Pittsburgh approved this study.

In order to reduce interparticipant time variability (which can affect IL6) our sample consists of those participants in this study in whom IL6 was obtained between times of 1030–1330, namely, 68 TR-MDD participants and 41 controls (see Fig. 3 for participant flowchart). We also excluded IL-6 levels in one control participant due to sample compromise due to laboratory error and one depressed participant due to active hepatitis. There were no significant differences in ratings on Beck Depression Inventory (BDI) or Suicidal Ideation Questionnaire (SIQ), between included and excluded participants.

Of eligible participants, 68 TR-MDD and 41 control participants presented for initial evaluation, with 49 TR-MDD and 25 control participants completing all components of follow-up visit. Some participants did not complete all components of the follow-up visit (n = 49), due to participant decision to opt out of lumbar puncture and other clinical rationales, as described in Section 2.3. Participants were referred for clinical treatment.

2.2. Participant evaluation

On initial evaluation, participants completed a structured psychiatric interview to assess demographic variables, individual depression history and other variables, including age of onset of depression, history of trauma, history of suicide attempt, and baseline clinical variables, along with blood draw for various plasma metabolites. Participants completed the Beck Depression Inventory (BDI) and Suicidal Ideation Questionnaire (SIQ) at initial visit (Beck, Ward, Mendelson, Mock, &