Journal of Psychiatric Research 84 (2017) 113–118

Contents lists available at ScienceDirect

Journal of Psychiatric Research

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

Change in cytokine levels is not associated with rapid antidepressant response to ketamine in treatment-resistant depression

Minkyung Park, Laura E. Newman, Philip W. Gold, David A. Luckenbaugh, Peixiong Yuan, Rodrigo Machado-Vieira*, Carlos A. Zarate Jr.

Experimental Therapeutics & Pathophysiology Branch, National Institute of Mental Health, NIH, 10 Center Drive, Room 7-5432, Bethesda, MD 20892, USA

ARTICLE INFO

Article history:
Received 1 July 2016
Received in revised form
9 September 2016
Accepted 28 September 2016

Keywords:
Major depressive disorder
Bipolar disorder
Cytokine
Ketamine
Interleukin-6 (IL-6)
Soluble tumor necrosis factor receptor 1 (sTNFR1)

ABSTRACT

Several pro-inflammatory cytokines have been implicated in depression and in antidepressant response. This exploratory analysis assessed: 1) the extent to which baseline cytokine levels predicted positive antidepressant response to ketamine; 2) whether ketamine responders experienced acute changes in cytokine levels not observed in non-responders; and 3) whether ketamine lowered levels of pro-inflammatory cytokines, analogous to the impact of other antidepressants. Data from double-blind, placebo-controlled studies of patients with major depressive disorder (MDD) or bipolar disorder (BD) who received a single infusion of sub-anesthetic dose ketamine were used (N = 80). Plasma levels of the eight cytokines were measured at baseline and at 230 min, 1 day, and 3 days post-ketamine. A significant positive correlation was observed between sTNFR1 and severity of depression at baseline. Cytokine changes did not correlate with changes in mood nor predict mood changes associated with ketamine administration. Ketamine significantly increased IL-6 levels and significantly decreased sTNFR1 levels. IL-6 and TNF-α levels were also significantly higher—and sTNFR1 levels were significantly lower—in BD compared to MDD subjects. The functional significance of this difference is unknown. Changes in cytokine levels post-ketamine were not related to antidepressant response, suggesting they are not a primary mechanism involved in ketamine's acute antidepressant effects. Taken together, the results suggest that further study of cytokine levels is warranted to assess their potential role as a surrogate outcome in the rapid antidepressant response paradigm.

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1. Introduction

Chronic mild inflammation has long been linked to depressive symptoms, and inflammatory cytokines are known to precipitate or contribute to depressive states (Dantzer et al., 2008; Maes, 2011; Maes et al., 1990). Such cytokines include tumor necrosis factor alpha (TNF-α), soluble tumor necrosis factor receptor 1 (sTNFR1), interferon gamma (IFN-γ), interleukin 2 (IL-2), IL-5, IL-6, IL-8, and IL-10. Previous studies found that selected plasma cytokine levels were elevated in patients with mood disorders—both major depressive disorder (MDD) and bipolar disorder (BD)—and that these elevations were associated with increased inflammation (Dowlati et al., 2010; Munkholm et al., 2013). Furthermore, antidepressant-induced remission of depressive symptoms has also been associated with significant decreases in pro-inflammatory cytokine levels (Leo et al., 2006; Pizzi et al., 2009).

Currently available antidepressants have typically low treatment response rates. Indeed, only one-third of patients diagnosed with MDD respond to their first antidepressant, and only approximately two-thirds will respond even after receiving several classes of antidepressants (Trivedi et al., 2006). Furthermore, even when effective, these agents are associated with a significant latency period of several weeks before antidepressant effects manifest, which significantly increases risk of suicide and self-harm and represents a key public health issue in psychiatric practice (Machado-Vieira et al., 2009). Therefore, identifying novel antidepressants that may act faster and more effectively for a larger number of individuals with mood disorders is a key need in this field. New agents targeting alternative neurobiological systems—most notably the glutamatergic system—have shown promising results. In this context, identifying clinically useful predictors and moderators may shed light on the pathophysiology and

* Corresponding author.
E-mail address: machadovieirar@mail.nih.gov (R. Machado-Vieira).

http://dx.doi.org/10.1016/j.jpsychires.2016.09.025
0022-3956/Published by Elsevier Ltd.

mechanisms of action of specific drugs, and may also provide useful information regarding which patients will respond best to specific pharmacological interventions; however, few studies have sought to identify genetic markers of potential clinical utility for pharmacogenetic tests.

The N-methyl-D-aspartate (NMDA) receptor antagonist ketamine, which has significant antidepressant effects in MDD and BD (reviewed in (Machado-Vieira et al., 2015)), also affects a wide range of biological targets beyond NMDA antagonism (Sleigh et al., 2014). Interestingly, a recent study from our laboratory found that adipokines may predict response to ketamine and may also play a role in its possible therapeutic effects (Machado-Vieira et al., 2016). Because of the potential integrated regulation between adipokines and cytokines, this study sought to investigate the short-term impact of ketamine on plasma cytokine levels in order to assess whether these play a role in ketamine's antidepressant effects. Specifically, we measured: 1) the extent to which baseline levels of these cytokines predicted positive antidepressant response to ketamine; 2) whether ketamine responders experienced acute changes in cytokine levels not observed in non-responders; and 3) whether ketamine lowered levels of pro-inflammatory cytokines, analogous to the impact of other antidepressants.

2. Material and methods

2.1. Patients

This exploratory analysis used data collected from three clinical trials (clinical trials identifier: NCT0008699) that explored the antidepressant efficacy of ketamine in individuals with treatment-resistant depression (MDD or BD-I/BD-II) (Ibrahim et al., 2012; Zarate et al., 2012). Treatment-resistance was defined as a lack of response to two adequate antidepressant medication trials as determined by the Antidepressant Treatment History Form. Briefly, participants (ages 18–65) were admitted to the Experimental Therapeutics and Pathophysiology Branch of the NIMH as inpatients. Plasma samples from 80 randomized study participants were included; 49 had a diagnosis of MDD (21F/28M; mean age: 43.1 ± 12.8 years) and 31 had a diagnosis of BD-I or BD-II (11 M/20 F; mean age: 44.3 ± 12.1 years). Written informed consent was obtained from all patients in accordance with the NIH Combined Neuroscience (CNS) Institutional Review Board. All participants were evaluated by a psychiatrist and by the Structured Clinical Interview for Axis I Diagnostic and Statistical Manual (DSM)-IV-TR Disorders.

Patients were included if they scored 20 or higher on the Montgomery Åsberg Depression Rating Scale (MADRS) at the time of screening and before each ketamine infusion. Exclusion criteria included the presence of psychotic symptoms during the current major depressive episode, an Axis I diagnosis of primary psychotic disorder, or a diagnosis of substance use within the three months prior to consent (with the exception of nicotine or caffeine). All participants were required to be medication-free for at least two weeks before ketamine infusion (five weeks for fluoxetine and aripiprazole) with the exception of BD patients, who were maintained on a therapeutic dose of mood stabilizer (lithium 0.6–1.2 mEq/L, valproic acid 50–125 mg/mL) for at least four weeks prior to the first infusion. A single dose of ketamine hydrochloride (0.5 mg/kg) or saline placebo was administered intravenously over 40 min. Psychiatric rating scales were administered 60 min before ketamine infusion and 40 min, 80 min, 120 min, 230 min, 1 day, 2 days, and 3 days post-infusion. At each time point, participants were asked to report their symptoms since the last assessment. The MADRS was the primary clinical outcome measure.

2.2. Measurement of cytokine levels

Whole blood samples were obtained using the vacutainer system at 60 min before ketamine infusion and at 230 min, one day, and three days post-infusion. Samples were centrifuged at 3000 rpm at 4 °C for 10 min and stored at −80 °C until assay. Circulating levels of TNF-α, sTNFR1, IFN-γ, IL-2, IL-5, IL-6, IL-8, and IL-10 were measured in plasma using the high sensitivity multiplex Luminex immunoassay (xMAP technology) and the fluorescently color-coded magnetic microsphere beads from R&D Systems (Minneapolis, MN) according to the manufacturer's instructions. All samples were diluted 1:2 and measured in duplicate blind to clinical information. The standard cocktail was diluted at a four-fold dilution series as instructed. After the addition of biotinylated antibody cocktail and streptavidin-PE, levels of all analytes were determined by reading with a Bio-Plex Magpix Multiplex Reader (Bio-Rad, CA). Concentration values were calculated automatically with Bio-Plex Manager MP Software by generating a five parameter logistic (5-PL) curve-fit standard curve for each analyte.

2.3. Statistics

Cytokine levels below the detectable limit were included as half of the detectable limit. Raw cytokine levels were transformed using a natural log. Linear mixed models with restricted maximum likelihood estimation and a compound symmetry covariance structure were used to examine the course of cytokine levels over time before and after a ketamine infusion, where each of eight cytokines were examined in separate models. Secondary models included age, body mass index (BMI), or sex as a covariate to ensure findings were not due to these factors. Only one covariate was included at a time. Another set of models included diagnosis as an additional factor. These were re-run with baseline as a covariate to understand whether group differences were baseline differences only.

To understand whether initial cytokine levels might predict antidepressant response, Pearson correlations were used to examine the relationship between baseline cytokine levels and percent change in depressive symptoms (as assessed via the MADRS), as well as the relationship between changes in cytokine levels and changes in mood. Additional correlations used raw change in MADRS score from baseline as well as response (50% or greater improvement on the MADRS) as the outcome measure. Significance was evaluated at $p < 0.05$, two-tailed. Corrections for multiple comparisons were made using Hochberg's (1988) adjusted Bonferroni correction where there was one correction per cytokine. Significance levels are shown prior to correction. Significance levels after covariates were interpreted without multiplicity corrections.

With a total of 80 participants, we had at least 80% power to detect a correlation with $r = 0.31$, a moderate relationship, or a pre-post difference with Cohen's $d = 0.32$, a small-to-moderate difference.

3. Results

All participants were diagnosed with treatment-resistant MDD ($N = 49$) or BD ($N = 31$). Mean baseline MADRS score was 33.2 ± 4.7. The sample was 51.2% female. Patient demographic details are presented in Table 1.

Linear mixed models were run for each of the eight cytokines.s After correcting for multiple comparisons, levels of IL-6 ($F_{3,209} = 25.51$, $p < 0.001$) and sTNFR1 ($F_{3,206} = 4.27$, $p = 0.006$) were altered in response to ketamine infusion; IL-6 levels significantly increased, and sTNFR1 levels significantly decreased at 230 min post-ketamine (Fig. 1). Levels changed significantly for IL-5