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Change in Cytokine Levels is Not Associated with Rapid Antidepressant Response to Ketamine in Treatment-Resistant Depression

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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 minutes, 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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Author Contributions

Drs. Park and Gold wrote and edited the manuscript. Ms. Newman and Mr. Luckenbaugh ran the data analysis, created the figures, and edited the manuscript. Dr. Yuan analyzed the samples and edited the manuscript. Drs. Machado-Vieira and Zarate developed the project and edited the manuscript. All authors saw and approved the final version of the manuscript.

Keywords

major depressive disorder; bipolar disorder; cytokine; ketamine; interleukin-6 (IL-6); soluble tumor necrosis factor receptor 1 (sTNFR1)

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 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.

Material and Methods

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 50-125mg/mL) for at least four weeks prior to the first infusion. A single dose of ketamine hydrochloride (0.5mg/kg) or saline placebo was administered intravenously over 40 minutes. Psychiatric rating scales were administered 60 minutes before ketamine infusion and 40 minutes, 80 minutes, 120 minutes, 230 minutes, 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.

Measurement of cytokine levels

Whole blood samples were obtained using the vacutainer system at 60 minutes before ketamine infusion and at 230 minutes, one day, and three days post-infusion. Samples were centrifuged at 3,000 rpm at 4°C for 10 minutes 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.

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 $p < .05$, 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 $r = .31$, a moderate relationship, or a pre-post difference with Cohen's $d = .32$, a small-to-moderate difference.

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. After correcting for multiple comparisons, levels of IL-6 ($F_{3,209} = 25.51$, $p < .001$) and sTNFR1 ($F_{3,206} = 4.27$, $p = .006$) were altered in response to ketamine infusion; IL-6 levels significantly increased, and sTNFR1 levels significantly decreased at 230 minutes post-ketamine (Figure 1). Levels changed significantly for IL-5 ($F_{3,197} = 5.65$, $p = .001$) and TNF- α ($F_{3,205} = 4.18$, $p = .007$), but no significant changes were observed from baseline to the later time points. No differences were noted for INF- γ ($F_{3,205} = 3.41$, $p = .018$), IL-10 ($F_{3,205} = 3.00$, $p = .03$), IL-2 ($F_{3,206} = 1.52$, $p = .21$), or IL-8 ($F_{3,208} = 0.79$, $p = .50$). The changes in IL-6 and sTNFR1 (from baseline to

230 minutes) levels remained significant when separately co-varying for age, body mass index (BMI), and sex (Table 2).

BD patients had significantly higher overall IL-6 ($p=0.002$) and TNF- α ($p<.001$) levels, and lower sTNFR1 ($p=.001$) levels, than MDD patients (Figure 2). After co-varying for baseline, IL-6 ($p=.028$) and TNF- α ($p=.039$) levels remained higher overall in BD patients. Levels of sTNFR1 ($p=.016$ for interaction) remained lower in BD patients but only at day 1. IL-8 levels were also higher in BD patients ($p=.007$).

Baseline sTNFR1 levels were significantly correlated with baseline MADRS score ($r=.33$, $p=.003$) even after multiplicity correction, with higher sTNFR1 levels associated with higher depression rating scale scores; these correlations remained significant after controlling for multiple covariates. All other baseline levels of cytokines were not significantly related to baseline depression rating scale scores.

Finally, baseline cytokine levels and change in cytokine levels at 230 minutes post-ketamine infusion were not related to changes in depression rating scale scores at 230 minutes, regardless of whether this measure was assessed as percent change in MADRS score, raw change in MADRS score, or antidepressant response (50% or greater improvement on the MADRS) (Table 2). All correlations had r values at the absolute value of .22 or below.

Discussion

This exploratory study of cytokine levels in treatment-resistant individuals with MDD or BD who received a single infusion of the NMDA antagonist ketamine had several salient findings. First, we found that baseline levels of the cytokine sTNFR1 correlated with severity of depression, but that change in sTNFR1 levels did not correlate with symptom improvement. Second, we found that in the overall group of MDD and BD patients combined, plasma levels of IL-6 were significantly higher, and levels of sTNFR1 were significantly lower, at 230 minutes post-ketamine infusion. These changes were not correlated with the magnitude of clinical improvement in the patient group. Finally, we found that compared to individuals with MDD, BD subjects had significantly higher levels of IL-6 and TNF- α , and lower levels of sTNFR1, from baseline through day 3 post-ketamine infusion.

Ketamine exerts anti-inflammatory effects in both humans and animals, and this has been suggested as a possible mechanism underlying its rapid antidepressant effects (Dale et al., 2012, Yang et al., 2013, Zunszain et al., 2013). However, the present study found no consistent association between these changes and rapid antidepressant effects despite observing changes over time in specific cytokines. Interestingly, a previous study from our laboratory found that low baseline plasma adiponectin levels predicted clinical response to ketamine, and that ketamine significantly decreased plasma resistin levels (Machado-Vieira, Gold, 2016). The ketamine-induced reduction of pro-inflammatory compounds such as resistin suggested that resistin could potentially transduce some of the putative anti-inflammatory properties of ketamine. Previous studies had found that sTNFR1 correlated with baseline severity of depression (Brunoni et al., 2015, Grassi-Oliveira et al., 2009), but

this finding was not always consistent (Diniz et al., 2010). Other reports showed that sTNFR1 levels correlated significantly with clinical response (Himmerich et al., 2006) but, again, the findings were not consistent (Brunoni, Machado-Vieira, 2015, Teixeira et al., 2015). However, the fact that a previous study reported that baseline sTNFR1 levels correlated positively with depression rating scale scores suggested that this compound might play a significant role in the pathophysiology of depressive illness. sTNFR1 levels falling systematically in the context of ketamine-induced antidepressant response would support this hypothesis. However, although we showed that baseline depression levels correlated positively with baseline sTNFR1 levels, changes in cytokine levels post-ketamine administration were inconsistent in terms of what the results might mean with respect to ketamine's effects on the pro-inflammatory state in patients with mood disorders.

Our study observed increased IL-6 levels at 230 minutes post-ketamine infusion. This is likely a non-specific stress response, given that IL-6 levels increased in response to both ketamine (0.5mg/kg) and saline placebo infusion in patients who were undergoing coronary artery bypass surgery (Cho et al., 2009). It is difficult to draw any conclusions from our finding that TNF- α levels decreased significantly at 230 minutes post-infusion, especially because this reduction did not correlate with clinical improvement.

A recent study suggested that BD patients might have more severe or refractory inflammatory dysregulation than MDD patients (Bai et al., 2015). Consistent with this finding, BD subjects in the present study had higher IL-6 and TNF- α levels, but lower sTNFR1 levels, than MDD subjects. Hypothetically, when TNF- α levels are high, sTNFR1 may work as a decoy receptor, with sTNFR1 binding to TNF- α and inactivating it (Aderka et al., 1992). This compensatory binding of sTNFR1 with excess TNF- α may result in lower concentrations of (unbound) sTNFR1. While this cytokine profile difference between BD and MDD patients is interesting, it should be noted that such differences did not correlate with baseline severity of mood or with clinical response to ketamine; in other words, BD patients did not have higher MADRS scores at baseline than MDD patients, nor did BD patients display less clinical improvement in response to ketamine than MDD patients. The results do suggest, however, that cytokine differences between BD and MDD subjects warrant further scientific investigation in the context of clinical response.

This study is associated with several strengths. First, the study was performed in a controlled environment in an inpatient setting, thus controlling for some of the variables associated with outpatient studies such as non-adherence, use of prohibited medications or substances, or acute medical illnesses. Second, the use of a placebo control in this study addressed natural fluctuations in cytokine levels over time. Third, we were able to measure baseline cytokine levels in medication-free MDD subjects (as well as in BD patients receiving mood stabilizers exclusively) and change in cytokine levels within minutes after ketamine infusion; this avoided potential confounding factors such as the effects of: 1) psychotropic medications on cytokines; 2) time; and 3) other psychosocial stressors that may emerge with time.

As noted above, this was an ongoing, exploratory study; we are currently recruiting control subjects. When such data are available, we will be able to compare cytokine levels in both

patients and healthy controls at baseline and after ketamine infusion. Without data from healthy controls, the study remains preliminary, as we cannot conclude whether the observed changes in cytokine levels are specific to patients with mood disorders. Additional limitations include that: 1) this was a post-hoc analysis; 2) the true association between cytokine levels in the periphery and central inflammation have consistently been questioned; 3) there was a short period of time between ketamine infusion and the measurement of cytokine levels, which may not have sufficed to induce activation of this pathway; and 4) the use of add-on mood stabilizers in a subsample of BD subjects may have confounded the results.

Taken together, results of this study suggest that cytokine levels may not be effective biomarkers of depression severity or antidepressant treatment response. However, the differences we observed in cytokine levels between MDD and BD subjects are well worth further exploration to understand the similarities and differences between these disorders.

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Figure 1. Significant but transient changes in cytokine levels in patients with major depressive disorder (MDD) or bipolar disorder (BD) over time. (a) sTNFR1 and (b) IL-6 levels at -60 minutes (pre-treatment), 230 minutes, 1 day, and 3 days post-infusion. * $p < .001$, ** $p < .01$

Figure 2. Differential cytokine profiles by diagnosis, co-varying for baseline level. (a) IL-6 and (b) TNF- α were overall significantly higher in patients with bipolar disorder (BD) versus those with major depressive disorder (MDD). (c) sTNFR1 was significantly lower in BD patients compared to MDD patients at day 1.

Table 1

Demographics

	Total (N=80)		BD (n=31)		MDD (n=49)	
	Mean	SD	Mean	SD	Mean	SD
Age, years	44.3	12.1	46.1	11.0	43.1	12.8
Age of Onset (Years)	18.5	10.2	17.2	7.3	19.4	11.6
Duration of Current Episode (Months)	44.9	90.5	18.4	21.0	61.8	111.9
Duration of Illness (Years)	25.8	12.4	28.9	10.6	23.9	13.2
BMI, kg/m ²	29.2	5.8	30.1	6.3	28.7	5.4
HDRS17 (Baseline)	21.2	4.0	21.1	3.9	21.3	4.1
MADRS (Baseline)	33.2	4.7077	32.8	4.4	33.5	4.9
	n	%	n	%	n	%
Gender (Female)	41	51.2	20	64.5	21	42.9
Ethnicity (Caucasian)	72	90	27	87.1	45	91.8
Education (Completed College)	45	56.2	13.0	41.9	32.0	65.3

BMI: body mass index; HDRS17: Hamilton Depression Rating Scale, 17-item; MADRS: Montgomery-Asberg Depression Rating Scale; MDD: major depressive disorder; BD: bipolar disorder

Table 2

Correlation between Cytokines and Clinical Characteristics

Time	F	df	Age		BMI		Sex		Diagnosis		MADRS		% Change at 230 Minutes		(With Change in Cytokine at 230 Min.) % Change at 230 Minutes	
			r	p	r	p	r	p	r	p	r	p	r	p	r	p
INFα	3.41	3, 205	0.018	0.018	0.22	0.052	0.23	0.04	-0.08	0.49	-0.18	0.12	0.03	0.81	0.17	0.14
IL2	1.52	3, 206	0.210	0.001 *	-0.01	0.93	-0.10	0.38	-0.16	0.16	-0.20	0.07	-0.09	0.42	-0.03	0.77
IL5	5.65	3, 197	0.001 *	0.001 *	0.31	0.005 *	0.36	0.001 *	-0.34	0.003 *	0.37	<0.001 *	-0.04	0.73	-0.12	0.29
IL6	25.51	3, 209	<0.001 *	0.10	0.37	0.45	<0.001 *	0.11	-0.01	0.03	0.24	0.03	-0.12	0.28	-0.04	0.73
IL8	0.79	3, 208	0.503	0.007 *	0.20	0.07	0.18	0.85	-0.25	0.934	0.09	0.45	0.19	0.10	-0.10	0.36
IL10	3.00	3, 205	0.032	0.007 *	0.00	0.97	0.02	0.85	-0.25	0.02	-0.20	0.08	0.05	0.70	0.19	0.10
TNFα	4.18	3, 205	0.007 *	0.008	0.46	0.46	0.11	0.33	-0.30	0.008	0.53	<0.001 *	0.06	0.63	0.09	0.45
TNFR1	4.27	3, 206	0.006 *	0.16	0.15	0.22	0.22	0.049	0.01	0.92	-0.27	0.02	0.33	0.003 *	0.01	0.91
															-0.21	0.06

* Indicates p<.05, two-tailed, after multiple comparisons correction

MADRS: Montgomery-Asberg Depression Rating Scale; BMI: body-mass index

* p<.05, two-tailed, after multiple comparisons correction.