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Rapid inflammation modulation and antidepressant efficacy of a low-dose ketamine infusion in treatment-resistant depression: A randomized, double-blind control study

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ABSTRACT

Increasing evidence supports the rapid antidepressant effect of a low-dose ketamine infusion in treatment-resistant depression (TRD). Proinflammatory cytokines play a crucial role in the pathophysiology of TRD. However, it is unknown whether the rapid antidepressant effect of ketamine is related to the rapid suppression of proinflammatory cytokines. Seventy-one patients with TRD were randomized into three groups according to the treatment received: 0.5 mg/kg ketamine, 0.2 mg/kg ketamine, and normal saline infusion. Proinflammatory markers, including C-reactive protein (CRP), interleukin (IL)-6, and tumor necrosis factor (TNF)-α were examined at baseline and at 40 min, 240 min, Day 3, and Day 7 postinfusion. Montgomery–Åsberg Depression Rating Scale (MADRS) was assessed for depressive symptoms across time. Log-transformed IL-6 and TNF-α levels differed significantly over time. The decrease in TNF-α between baseline and 40 min postinfusion was positively correlated with a decrease in MADRS scores across time in the 0.5 mg/kg ketamine group. This is the first clinical study to support a positive correlation between changes in cytokine levels after ketamine infusion and improvements in depressive symptoms with TRD. The rapid suppression of proinflammatory cytokines may contribute to the rapid antidepressant effect of the ketamine infusion.

1. Introduction

Major depressive disorder (MDD) is a severe chronic mental illness, and will become the leading cause of disability worldwide by the year 2030 (Mathers et al., 2006). The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study reported no symptomatic remission in up to 40% of MDD patients after at least two trials of antidepressants. Such patients were then defined as having treatment-resistant depression (TRD), and 33% were found to continue to suffer from depression after four trials of different antidepressant treatments, including combination therapy and augmentation therapy (Howland et al., 2008). In this respect, the discovery and replication of the rapid and robust antidepressant effects of ketamine may constitute an important treatment advance for TRD that addresses some of the limitations relating to current antidepressant treatment (Berman et al., 2000; Krystal et al., 2013; Kishimoto et al., 2016). For example, our previous study indicated that approximately 50% of patients with TRD rapidly responded to a single dose of ketamine infusion within hours (Su et al., 2017).

Increasing evidence suggests that proinflammatory markers, such as C-reactive protein (CRP), interleukin (IL)−6, and tumor necrosis factor (TNF)-α, play a crucial role in the pathophysiology of MDD and TRD. Reports have shown that optimal modulation of these cytokines could relieve the depressive symptoms of TRD (Dowlati et al., 2010; Liu et al., 2012, Bhattacharya et al., 2017). Two meta-analysis studies demonstrated that levels of TNF-α and IL-6 were significantly higher in chronically ill patients with MDD than in controls, and suggested that MDD was associated with immunological dysregulation and activation of an inflammatory response system (Dowlati et al., 2010; Liu et al., 2012). Chamberlain et al. reported that CRP was elevated in patients

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with major depression, and more so in treatment-resistant patients, and suggested that elevated CRP was associated with childhood adversity and vegetative depressive and anxious symptoms (Chamberlain et al., 2018). In addition, Raison et al. assessed whether inhibition of TNF-α through the TNF-α antagonist infliximab would reduce depressive symptoms in patients with TRD, and found that infliximab was effective for TRD patients with relatively high CRP and TNF-α levels at baseline (Raison et al., 2013).

Previous studies have reported that a rapid increase in the brain-derived neurotrophic factor (BDNF) level and increased synaptogenesis contribute to the rapid antidepressant effect of ketamine (Andrade et al., 2017). However, it has not yet been clarified whether ketamine possesses an anti-inflammatory effect that can modulate proinflammatory cytokines in TRD (Yang et al., 2015; Kiraly et al., 2017; Park et al., 2017; Tan et al., 2017). Park et al. explored the levels of baseline cytokines, including IL-6 and TNF-α, and changes in cytokine levels relating to a positive antidepressant response to ketamine, but revealed that baseline cytokine levels and changes in the cytokine levels at 230 min after ketamine infusion were not related to changes in depression rating scale scores at 230 min (Park et al., 2017); they concluded that modulation of proinflammatory cytokines was not a primary mechanism involved in the rapid antidepressant effects of ketamine in TRD. In addition, Kiraly et al. reported that for 33 patients with TRD, examination of cytokine levels 240 min posttreatment showed a modest, but statistically significant, decrease in the levels of IL-6 and IL-1α from baseline values. However, they also found that changes in cytokine levels were not associated with a response to ketamine treatment at either time point (Kiraly et al., 2017). Their findings suggested that although ketamine rapidly modulated the proinflammatory cytokines, especially IL-6, this modulation did not appear to be crucial in the response to ketamine treatment.

However, in chronic restraint stress (CRS) mice models, Tan et al. found that CRS-induced depressive behavior was associated with activation of the hippocampal inflammatory response, whereas down-regulation of proinflammatory cytokines, including IL-6 and TNF-α, contributed to the antidepressant effect of ketamine (Tan et al., 2017). Furthermore, Yang et al. investigated the antidepressant effects of ketamine and the expression of IL-1β and IL-6 in the prefrontal cortex and hippocampus of a Wistar rat model, and demonstrated that compared with the saline group, ketamine administration significantly decreased the immobility time of rats during a forced swimming test, and significantly reduced the expression of IL-1β and IL-6 in the rat prefrontal cortex and hippocampus (Yang et al., 2013). Walker et al. explored the association between the rapid antidepressant-like effects of ketamine and peripheral proinflammatory profile in a Wistar rat model of antidepressant-resistance, and found that ketamine non-responders had lower TNF-α and CRP levels than ketamine responsive rats; however these trends did not reach significance (Walker et al., 2015). They suggested that antidepressant-resistant rats with elevated CRP responded to ketamine, while others with lower levels did not (Walker et al., 2015). These animal studies may support the hypothesis that ketamine possesses an anti-inflammatory effect that promotes its rapid antidepressant effect.

Our previous study provided evidence for the efficacy of ketamine for TRD, and also found that the BDNF had no role in the treatment response of ketamine in Taiwanese patients with TRD (Su et al., 2017). In our current study, we further investigate the changes in cytokines after ketamine infusion with respect to the antidepressant effects and treatment response of ketamine. We hypothesize that changes in cytokines will be associated with improvements in the depressive symptoms of TRD.

2. Methods

2.1. Inclusion criteria for case

Details of candidates enrolled in the study and the experimental procedure involved are reported in our previous article (Su et al., 2017). A total of 71 patients were recruited at the outpatient clinic of Taipei Veterans General Hospital between 2012 and 2015. These patients met Diagnostic and Statistical Manual of Mental Disorders-IV-Text Revision (DSM-IV-TR) criteria for recurrent MDD without psychotic features (determined using a Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998), and had failed to respond to more than two adequate antidepressant trials. Patients with mild symptoms (MADRS score < 18) were excluded in our study. Patients were excluded if they had a history of bipolar disorder, psychotic symptoms, substance dependence other than nicotine, and major medical illness (i.e., epilepsy, stroke, autoimmune diseases, chronic infectious diseases, acute infectious state). This study was approved by the Institutional Review Board of TPEVGH and the Department of Health of Taiwan. Informed consent was provided by all participants.

2.2. Study design and procedure

Patients were randomized into three groups (0.5 mg/kg vs. 0.2 mg/kg R/S-ketamine hydrochloride [Ketalar, Pfizer Pharmaceuticals] vs. normal saline placebo) and completed a single dose of 40-min intravenous ketamine or placebo infusion on the test day (Day 1). Patients were assessed using the Montgomery–Åsberg Depression Rating Scale (MADRS) prior to initiation of test infusions and at 40, 80, 120, and 240 min postinfusion. Telephone (Day 2, Day 4, Day 5, Day 6) or face-to-face ratings (Day 3, Day 7, Day 14) were subsequently conducted after ketamine infusion. Responder status was identified by response (> = 50% reduction of mood ratings) at any two daily MADRS measurements during the period 24–96 h (Days 2–5) postinfusion. Levels of proinflammatory markers, including CRP, IL-6, and TNF-α, were examined prior to initiation of test infusions, 40 min postinfusion, 240 min postinfusion, and on Day 3 and Day 7. In addition, MADRS was used in current study because MADRS is a more specific scale for depressive core symptoms in relative to Hamilton Rating Scale for Depression (Montgomery et al., 1979).

2.3. Measurement of proinflammatory markers

Proinflammatory markers in all subjects were assayed using enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems, Minneapolis, MN, USA). Fasting serum samples were collected in serum separator tubes (SSTs) and clotted for 30 min. All samples were then stored at −80 °C until use. All assays were performed according to the manufacturer's instructions. Final absorbance of the mixture was measured and analyzed at 450 nm using an ELISA plate reader with Bio-Tek Power Wave Xs and Bio-Tek's KC junior software (Winooski, VT, USA). The standard range depended on the manufacturer's instructions, and a linear regression, R^2 value, of ≥0.95 represented a reliable standard curve.

2.4. Statistical methods

The one-way analysis of variance (ANOVA) for continuous variables and Fisher's chi-square tests for nominal variables were used to assess differences between demographic and clinical data in the three subgroups (0.5 or 0.2 mg/kg ketamine and placebo). Kolmogorov–Smirnov tests indicated that proinflammatory markers were not normally distributed; they were then transformed using a log. Linear mixed models were used to examine changes in proinflammatory markers. Time was a fixed factor with maximum likelihood estimates and a compound symmetry covariance structure. Correlation analysis with an adjustment of demographic data was performed to investigate the association between percentage changes in proinflammatory markers and percentage changes in MADRS scores at each time point. In addition, logistical regression analysis was used to assess baseline levels (high vs. low) of proinflammatory cytokines that were likely to respond to treatment