Journal of Affective Disorders 225 (2018) 709–714

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Research paper

Persistent antidepressant effect of low-dose ketamine and activation in the supplementary motor area and anterior cingulate cortex in treatment-resistant depression: A randomized control study

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ARTICLE INFO

Keywords:
Ketamine
Treatment-resistant depression
PET
Supplementary motor area
Dorsal anterior cingulate cortex

ABSTRACT

Background: A single low-dose ketamine infusion exhibited a rapid antidepressant effect within 1 h. Despite its short biological half-life (approximately 3 h), the antidepressant effect of ketamine has been demonstrated to persist for several days. However, changes in brain function responsible for the persistent antidepressant effect of a single low-dose ketamine infusion remain unclear

Methods: Twenty-four patients with treatment-resistant depression (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. Standardized uptake values (SUVs) of glucose metabolism measured through ^{18}F-FDG positron-emission-tomography before infusion and 1 day after a 40-min ketamine or normal saline infusion were used for subsequent whole-brain voxel-wise analysis and were correlated with depressive symptoms, as defined using the Hamilton Depression Rating Scale-17 (HDRS-17) score

Results: The voxel-wise analysis revealed that patients with TRD receiving the 0.5 mg/kg ketamine infusion had significantly higher SUVs (corrected for family-wise errors, $P = 0.014$) in the supplementary motor area (SMA) and dorsal anterior cingulate cortex (dACC) than did those receiving the 0.2 mg/kg ketamine infusion. The increase in the SUV in the dACC was negatively correlated with depressive symptoms at 1 day after ketamine infusion

Discussion: The persistent antidepressant effect of a 0.5 mg/kg ketamine infusion may be mediated by increased activation in the SMA and dACC. The higher increase in dACC activation was related to the reduction in depressive symptoms after ketamine infusion. A 0.5 mg/kg ketamine infusion facilitated the glutamatergic neurotransmission in the SMA and dACC, which may be responsible for the persistent antidepressant effect of ketamine much beyond its half-life.

1. Introduction

Major depressive disorder (MDD) has been increasingly recognized as a chronic and deteriorating mental illness over recent decades (Krishnan, 2003). Without adequate and optimal treatment, the residual symptoms of major depression can lead to worsening clinical outcomes such as high relapse rates, suicidality, and diminished quality of life and psychosocial functioning (Roose et al., 2001; KrishnanKrishnan, 2003; Kennedy and PaykelPaykel, 2004; Kennard et al., 2006). In fact, up to 50% of patients with major depression exhibited poor or partial responses to traditional antidepressant medication treatments (Trivedi et al., 2006; MollerMoller, 2008), and those who were resistant to antidepressant treatment accounted for most of the overall disease burden caused by depression (Roose et al., 2001; KrishnanKrishnan, 2003; Kennedy and PaykelPaykel, 2004; Kennard et al., 2006). Antidepressant-resistant depression has been associated with poor clinical and psychosocial outcomes (DignamDignam, 2009; Fekadu et al., 2009; LittleLittle, 2009).

Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, has been approved to be an anesthetic agent by the U.S. Food and Drug

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http://dx.doi.org/10.1016/j.jad.2017.09.008
Received 18 August 2017; Received in revised form 7 September 2017; Accepted 7 September 2017
Available online 09 September 2017
0165-0327/

Administration in 1970 and is widely used in anesthesia, particularly in pediatric surgery. The half-life values of ketamine and its active metabolites, norketamine and dehydronorketamine, are approximately 3, 5, and 7 h, respectively (Hijazi et al., 2003). A growing body of evidence suggests that a 0.5 mg/kg ketamine infusion has a rapid antidepressant effect for treatment-resistant patients (i.e., onset of the antidepressant effect occurs within hours following injection), which may be related to the rapid synaptogenesis and brain-derived neurotrophic factor release (Zunszain et al., 2013; Abdallah et al., 2016; Lener et al., 2016). The results from several recent ^{18}F-FDG positron-emission-tomography (PET) studies investigating changes in brain function before and immediately after a 0.5 mg/kg ketamine infusion in patients with treatment-resistant depression (TRD) may explain the mechanisms underlying the rapid improvement in the clinical symptomatology of depression (Carlson et al., 2013; Lally et al., 2015; Li et al., 2016). For example, Carlson et al. conducted an open-labeled study and measured glucose metabolism through ^{18}F-FDG PET at the baseline and 2 h post-ketamine infusion. They reported that improvement in depression symptoms was correlated directly with changes in metabolism in the right superior and middle temporal gyri (Carlson et al., 2013). In another open-labeled study, Lally et al. reported that reduced anhedonia, a core symptom of depression, was significantly correlated with increased glucose metabolism in the hippocampus and dorsal anterior cingulate cortex (dACC), as measured through PET at the baseline and 2 h post-ketamine infusion (Lally et al., 2015).

Our previous study assessed changes in brain function measured through ^{18}F-FDG PET at the baseline and immediately after a 40-min infusion of low-dose ketamine (0.5 or 0.2 mg/kg) or normal saline (control); we found that the standardized uptake values (SUVs) of the prefrontal cortex (PFC), supplementary motor area (SMA), and dACC in patients with TRD provided with the low-dose ketamine infusion were higher than those in the control group (Li et al., 2016). We also demonstrated that increased glucose metabolism in the PFC was significantly associated with improved depressive symptoms (Li et al., 2016). Furthermore, recent clinical studies have revealed that the rapid antidepressant effect of ketamine not only occurred within hours after a single-dose infusion but may also persist for days and even up to 2 weeks, which is a considerably longer period than the half-life of ketamine and its metabolites (Zunszain et al., 2013; Lener et al., 2016). The persistent antidepressant effect of ketamine and related changes in brain function remain unclear, despite our knowing that activations in specific brain regions, such as the PFC, hippocampus, SMA, and dACC, contribute to the rapid antidepressant effect of ketamine. The question as to whether the aforementioned brain regions or other potential regions that are involved in the brain circuit of depression are responsible for the persistent antidepressant effect of ketamine requires further study.

In the current study, we followed the same protocol as in our previous study (Li et al., 2016) and enrolled a new group of 24 patients with TRD, who were divided randomly into three treatment groups: 0.5 mg/kg ketamine, 0.2 mg/kg ketamine, and normal saline infusion. Moreover, ^{18}F-FDG PET was performed at the baseline and 1 day after a 40-min low-dose ketamine or normal saline infusion. On the basis of the results of our previous study, we hypothesized that a persistent increase in the SUVs of glucose metabolism in the PFC, SMA, and dACC may contribute to the persistent antidepressant effect of ketamine in TRD.

1.1. Experimental procedures

1.1.1. Inclusion criteria of subjects

We followed the same study inclusion criteria and the study procedures of our previous study (Li et al., 2016). In all, 24 adult patients aged between 21 and 65 years with a Diagnostic and Statistical Manual of Mental Disorders-IV-Text Revision (DSM-IV-TR) diagnosis of major depressive disorder who had failed to respond to at least three different antidepressants with adequate dosage and treatment duration were enrolled in our current study. The enrolled TRD patients did not have major medical or neurological illnesses or a history of alcohol or substance abuse. This study was performed in accordance with the Declaration of Helsinki and was approved by the Taipei Veterans General Hospital Institutional Review Board. Informed consent was provided by all of the participants.

1.1.2. Study procedures

Each enrolled patient underwent a detailed psychiatric and medical history-taking, a diagnostic interview. Following at least 2-week concomitant stable antidepressant treatment, patients received an add-on intravenous ketamine infusion using a randomized, double-blind, placebo-controlled design. Each patient received a single dose of ketamine infusion with A: 0.5 mg/kg, B: 0.2 mg/kg, or C: normal saline (placebo), which was administered over 40 min. First ^{18}F-FDG-PET scan was performed immediately before a single dose of ketamine infusion. Depressive symptoms were rated using the 17-item Hamilton Depression Rating Scale (HDRS-17) at baseline (immediately before the first ^{18}F-FDG-PET scan) and at 40, 80, 120, 240 min, and 1 day (second day) post-ketamine administration. To investigate the persistent antidepressant effect of a single dose of ketamine infusion, the second ^{18}F-FDG-PET scan was performed at 1 day later after ketamine infusion. The current study primarily focused on the persistent antidepressant effects of the low-dose ketamine infusion and neuroimaging findings between the baseline and one day later after ketamine infusion. Primary outcomes, such as 24-h HDRS-17 scores, were correlated with imaging results. Responders were defined as having at least a 50% decrease in their HDRS-17 score from baseline.

1.1.3. Imaging procedures

MR images were acquired with a 3.0 GE Discovery 750 whole-body high-speed imaging device. High-resolution structural T1-weighted images were acquired, for improving co-registration of the PET images, in the sagittal plane using a high resolution sequence (repetition time (TR), 2530 ms; echo spacing, 7.25 ms; echo time (TE), 3 ms; flip angle 7°) with isotropic 1 mm voxels and FOV = 256 × 256 mm. Two volumes of ^{18}F-FDG PET scans (i.e., before and 1 day after ketamine injections; the brain acquisition time for each PET volume is 15 min) of at rest glucose utilizations were acquired on a PET/CT scanner (Discovery VCT; GE Healthcare, USA) with the 3D brain mode. All PET scans were done in the morning (9.00–12.00 h); all subjects fasted for at least 8 h before the 1st PET examination. The 1st 15-min PET scan was acquired while staying awake in a deem-light room 45 min after an intravenous injection of about 222 MBq of ^{18}F-FDG. Around 1 day after the 1st PET imaging, another 15-min PET scan was acquired under the same condition (i.e., fasting condition for at least 8 h and 45 min' rest after iv bolus of about 222 MBq of ^{18}F-FDG while staying awake in a dim-light room). The system produces 47 consecutive slices over an axial length of 15.7 cm, with a slice thickness of 3.75 mm and a transaxial FOV of 70 cm. PET images will be then reconstructed, and corrected for attenuation with the ordered-subset expectation maximization iterative reconstruction algorithm (6 iterations and 14 subsets). Then the axial images will be realigned to yield sagittal and coronal images.

1.1.4. Voxel-wise analysis of PET data

PET data were analyzed using Statistical Parametric Mapping version 8 software (SPM8; Wellcome Department of Cognitive Neurology, Institute of Neurology, University College London, London, England) implemented in Matlab 7.1 (The Mathworks Inc., Sherborn, MA, USA). A group-specific MRI-aided ^{18}F-FDG template was created (Signorini et al., 1999; Gispert et al., 2003; Li et al., 2016) and used to normalize each subject's PET images, followed by smoothing with a 3D Gaussian kernel (FWHM = 8 mm). The smoothed and normalized PET images in the standardized brain space were created and then submitted for further analysis. Since relative changes of the brain metabolic activity within one hour were our primary interests, we used the standardized