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Serum level of vascular endothelial growth factor decreased in chronic ketamine abusers

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ABSTRACT

Aims: To evaluate the serum level of vascular endothelial growth factor (VEGF) in a group of chronic ketamine abusers in comparison to healthy controls.
Methods: Eighty-one ketamine abusers who were hospitalized for the treatment of ketamine dependence and 39 healthy controls were recruited. Serum VEGF level was measured by enzyme linked immunosorbent assay (ELISA). Psychopathological symptoms were assessed using Positive and Negative Syndrome Scale (PANSS), Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI).
Results: Serum level of VEGF was significantly lower in chronic ketamine abusers compared to healthy controls (64.6 ± 42.1 vs. 92.4 ± 59.4 pg/ml, $F = 7.243$, $p = 0.008$).
Conclusions: Serum level of VEGF decreased in chronic ketamine abusers compared to healthy controls.

1. Introduction

Ketamine, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist was used widely in medicine, pain management and anesthesia. Its use as a recreational drug of abuse has become widespread after its hallucinogenic effects were discovered in 1970s. Ketamine provokes distinctive pathopsychological symptoms similar to schizophrenia, as well as cognitive impairments in humans and rodents (Becker et al., 2003; Aalto et al., 2005). A single intravenous dose of ketamine given to healthy volunteers produced acute psychotic symptoms, as well as impairment of memory (Krystal et al., 1994; Morgan et al., 2004). Recreational ketamine use has also been reported to produce psychotic symptoms and memory deficits (Morgan et al., 2004). Intriguingly, an acute, single intravenous, subanesthetic dose of ketamine has a rapid-acting antidepressant effect in depressed patients (Berman et al., 2000).

Vascular endothelial growth factor (VEGF), a potent growth factor secreted by endothelial cells, brain cells and other cells, is involved in the regulation of vasculogenesis and vascular function (Takahashi and Shibuya, 2005). Importantly, VEGF was also acknowledged as a key signaling protein in the central nervous system functioning in neuroprotection, neuronal survival, axonal outgrowth, long-term potentiation, and learning (Ruiz de Almodovar et al., 2009). VEGF exerts its effects mainly via binding to specific tyrosine kinase receptors VEGF1 and VEGF2 (Brockington et al., 2004). The alterations of VEGF in multiple mental disorders were identified. It was reported that the VEGF mRNA expression was decreased in the dorsolateral prefrontal cortex of schizophrenia patients (Fulzele and Pillai, 2009). Also serum level of VEGF and its receptor was altered in patients with severe autism (Emanuele et al., 2010).

Even though studies about ketamine are burgeoning, little is known about the alteration of serum level of VEGF in ketamine abusers. Previously, we reported the decrease of another neurotrophic factor, brain derived neurotrophic factor (BDNF) and nerve growth factor (NGF) in chronic ketamine abusers (Ke et al., 2014). Considering the role of VEGF in the central nervous system and the reported effects related to ketamine use, as well as the possibly entwined regulation of BDNF and VEGF expression (Lin et al., 2014), we investigated the serum level of VEGF in a group of chronic ketamine abusers to test the hypothesis that the chronic ketamine abuse will alter the serum level of VEGF. The associations between the serum VEGF level and ketamine use characteristics were also analyzed.

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Table 1
Clinical and demographic characteristics of ketamine abusers and healthy controls.

	Ketamine users ($N = 81$)	Healthy subjects ($N = 39$)	t/x^2
Age (years)	25.7 ± 5.16	25.1 ± 4.8	$t = 0.626$
Gender (male/female)	77/4	34/5	$x^2 = 2.358$
Years of education*	10.6 ± 2.72	11.7 ± 1.7	$t = -2.205$
Age of first ketamine use (years)	19.8 ± 5.12		
Duration of ketamine use (months)[a]	71.3 ± 36.88		
Duration of dependence (months)[b]	34.9 ± 24.54		
Current frequency of ketamine use (days per week)[c]	6.28 ± 1.45		
Current average daily ketamine use (g)	3.25 ± 3.09		
PANSS			
Positive symptom subscale	7.95 ± 1.87		
Negative symptom subscale	12.91 ± 4.13		
General psychopathology subscale	24.28 ± 5.56		
Total	45.14 ± 9.54		
BDI	12.13 ± 6.07		
BAI	14.75 ± 8.79		
Use of other psychoactive compounds[d]			
Never use	16 (19.8.0%)		
Methamphetamine	26 (32.1%)		
MDMA	60 (74.07%)		
Codeine hydrochloride	11 (13.6%)		
Heroin	2 (2.5%)		
Cannabis	23 (28.4%)		
Cocaine	1 (1.2%)		
Triazolam	1 (1.2%)		
Alcohol			
Drink frequently[e]	21 (25.9%)	5 (12.8%)	$x^2 = 2.664$
Not drink frequently[f]	60 (74.1%)	34 (87.2%)	
Smoking**			
Smoke frequently[g]	74 (91.4%)	19 (48.7%)	$x^2 = 27.449$
Not smoke frequently[h]	7 (8.6%)	20 (51.3%)	

Data are the mean ± SD.
Data about use of other psychoactive compounds, alcohol consumption and tobacco smoking are the number of cases (%). MDMA: 3,4-methylenedioxymethamphetamine.
[a] Total months of ketamine use from the first time till now.
[b] Total months of ketamine use from dependent till now.
[c] Frequency of ketamine use in recent 1 month.
[d] Use of other psychoactive compounds in one's life span, alcohol and tobacco excluded.
[e] Drink no less than once a week.
[f] Including abstinence, drinking less than once a week and never drinking.
[g] Smoke no less than 3 days per week.
[h] Including cessation, smoking less than 3 days per week and never smoking.
* $p < 0.05$.
** $p < 0.01$.

2. Methods

2.1. Subjects

The recruitment of ketamine abusers and healthy controls was as described previously (Ke et al., 2014). Briefly, ketamine abusers were recruited from two hospitals in Guangzhou, China. Healthy controls were recruited through local advertisements. Subjects' socio-demographic characteristics, psychopathological status, and substance use characteristics were documented during a semi-structured interview. Among ketamine users, the average interval between the interview and last ketamine use was 8.22 ± 4.88 days. The inclusion criteria for ketamine abusers were: (1) subjects met the criteria of substance dependence according to DSM-IV-TR; (2) no other substance dependence other than tobacco; (3) no other substance use other than alcohol and tobacco for at least 6 months; and (4) age between 16 and 45 years old. Inclusion criteria for healthy subjects included: (1) no axis I diagnosis according to DSM-IV-TR criteria; (2) no familial history (including first- or second-degree relatives) of psychiatric disorders; and (3) age range match with the ketamine group (16–45 years old). Participants were excluded if they had: (1) any known organic diseases or (2) history of head trauma with loss of consciousness, or (3) any unstable physical illnesses, or (4) impairments of color vision or hearing. The study was approved by the Institutional Ethics Committee and signed informed consent was obtained from each participant after giving information about the study.

2.2. Assessment of psychotic symptoms

Clinical symptoms among ketamine users were evaluated with the Positive and Negative Syndrome Scale (Kay et al., 1987), administered by two trained psychiatrists with 3 or more years of clinical experience. The intraclass correlation coefficient (ICC) between raters on the PANSS was 0.954. In addition, ketamine users were asked to complete Beck Depression Inventory (BDI; Beck and Beamesderfer, 1974) and the Beck Anxiety Inventory (BAI; Beck et al., 1988), which assessed their depressive and anxiety symptoms during the two weeks before they were hospitalized.

2.3. Blood sampling

A venous blood sample was drawn from each subject using standard venipuncture technique. The average days of blood drawing since last ketamine use were 8.22 days ± 4.88 days. Serum was obtained by centrifuge at 4000 rpm for 15 min, then aliquoted and stored at −80 °C until assay.

2.4. Measurement of serum VEGF level

Serum VEGF level was measured by enzyme linked immunosorbent (ELISA) kit (VEGF Emax Immunoassay System, Boster, Wuhan, Hubei, China) according to the manufacturer's instructions. The minimal detection limits was 31.2 pg/ml for VEGF. No cross-reactivity was observed. All samples were assayed in duplicate. VEGF levels were determined by absorbance at 450 nm wave length (BIO-RAD iMark™) using optical density values against standard curves calibrated with known amounts of proteins.

2.5. Statistical analysis

All statistical analyses were performed using SPSS version 13.0 for windows. A Chi-square test was used to examine the difference of sex, alcohol consumption and tobacco smoking variables between ketamine users and healthy controls. Spearman's rank order correlation was applied for non-normally distributed data to investigate the correlations between serum VEGF level and ketamine use characteristics. A covariance analysis, with smoking as covariate in univariate general linear model, was implemented to compare the serum VEGF levels across the two groups. Differences at $p < 0.05$ level (two tailed) were considered significant.