Drug and Alcohol Dependence 142 (2014) 290–294

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

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

Serum brain-derived neurotrophic factor and nerve growth factor decreased in chronic ketamine abusers

Xiaoyin Ke[a,b], Yi Ding[a], Ke Xu[c], Hongbo He[a], Minling Zhang[a], Daping Wang[a], Xuefeng Deng[d], Xifan Zhang[d], Chao Zhou[a], Yuping Liu[a], Yuping Ning[a,*], Ni Fan[a,**]

[a] Guangzhou Brain Hospital, The Affiliated Hospital of Guangzhou Medical University, 36 Mingxin Road, Liwan District, Guangzhou, Guangdong 510370, China
[b] Shenzhen Mental Health Center, 1080 Cuizhu Road, Luohu District, Shenzhen, Guangdong 518020, China
[c] Department of Psychiatry, Yale School of Medicine, 300 George street, New Haven, CT 06510, USA
[d] Guangzhou Baiyun Voluntary Drug Rehabilitation Hospital, 586 North of Baiyun Road, Baiyun District, Guangzhou, Guangdong 510440, China

ARTICLE INFO

Article history:
Received 17 February 2014
Received in revised form 23 May 2014
Accepted 28 June 2014
Available online 11 July 2014

Keywords:
Ketamine
Brain-derived neurotrophic factor
Nerve growth factor

ABSTRACT

Aims: This study investigated the serum levels of brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) in a group of chronic ketamine abusers in comparison to healthy controls. The correlations between the serum BDNF, NGF level with the subjects' demographic, pattern of ketamine use were also examined.
Methods: 93 subjects who met the criteria of ketamine dependence and 39 healthy subjects were recruited. Serum BDNF and NGF levels were assayed 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: Both serum levels of BDNF and NGF were significant lower in the ketamine users compared to the healthy control subjects (9.50 ± 6.68 versus 14.37 ± 6.07 ng/ml, $p = 0.019$ for BDNF; 1.93 ± 0.80 versus 2.60 ± 1.07 ng/ml, $p = 0.011$ for NGF). BDNF level was negatively associated with current frequency of ketamine use ($r = -0.209$, $p = 0.045$).
Conclusions: Both BDNF and NGF serum concentrations were significantly lower among chronic ketamine users than among health controls.

1. Introduction

Ketamine, a derivative of phencyclidine (PCP), was first successfully synthesized by the American chemist Calvin Stevens in 1962. Recreational use of ketamine became popular in Europe and the United States and other countries after its hallucinogenic effects were discovered in 1970. The main pharmacologically action of ketamine is as a non-competitive antagonist of the N-methyl-D-aspartate (NMDA) receptor. Ketamine has central excitatory and inhibitory effects, as well as anti-anxiety, narcotic, hallucinogenic and generally psychotomimetic effects. A low dose of ketamine produces sedative and analgesic effects, while a high dose leads to dissociative anesthesia. The hallucinogenic effect is thought to underlie the ketamine abuse (Wolff and Winstock, 2006). Ketamine is known as "k powder" in China where several epidemiological surveys carried out in urban areas have reported that the percentage of ketamine abusers among all drug addicts had increased from 21.5% in 2001 to 40% in 2009 (Chen et al., 2009; Lian et al., 2005; Liu et al., 2003; Wang et al., 2008). In 2004, ketamine was classified as a psychotropic substance in Schedule I in China (F.D.A., 2004).

Both animal and human studies have shown that ketamine can impair cognitive function, such as episodic memory, semantic memory, working memory, executive function and procedural learning (Curran and Monaghan, 2001; Morgan et al., 2004a, 2004b, 2006, 2010). Brain-derived neurotrophic factor (BDNF) is an important neurotrophic factor associated with cognitive function, learning and memory as well as synaptic plasticity (Bekinschtein et al., 2008; Binder and Scharfman, 2004). BDNF is mainly synthesized in brain tissues, primarily distributed in the hippocampus, cerebral cortex, striatum, basal forebrain, hypothalamus, brainstem and cerebellum (Aid et al., 2007). In recent years, BDNF has also been found in the peripheral nervous system, as well as in other organs, such as the ovaries, lung, heart, platelet and skeletal muscle

* Corresponding author.
** Corresponding author. Tel.: +86 2081682912.
E-mail addresses: fanni2005@126.com, nfan007@gmail.com (N. Fan).

http://dx.doi.org/10.1016/j.drugalcdep.2014.06.043
0376-8716/

(Balkowiec and Katz, 2000). Nerve growth factor (NGF) is another kind of neurotrophic factor, which is widely distributed in vivo. NGF may play an important role in promoting the development of the nervous system; maintaining neuronal growth, survival and differentiation; and influencing synaptic plasticity (Yuen et al., 1996).

Human and animal studies have implied that ketamine use is associated with changes in serum BDNF and NGF levels, although results differ across studies. Studies related to human ketamine users are limited. Ricci et al. (2011) reported an elevation of serum BDNF in 17 chronic ketamine abusers. However, the sample size was small and it is difficult to draw a conclusion. In this study we explored the level of serum BDNF and NGF concentrations in a group of chronic, treatment-seeking ketamine abuse inpatients as compared to health controls. The correlations between the serum BDNF, NGF level with the demographic, drug use characteristics were also examined.

2. Methods

2.1. Participants

Ketamine abusers were recruited from Guangzhou Brain hospital and Guangzhou Baiyun voluntary drug rehabilitation hospital. Healthy controls were recruited through advertisements. All the participants underwent a semi-structured interview to assess sociodemographic characteristics psychopathological status, and substance use. Among ketamine users, the average interval between the interview and last ketamine use was 8.16 ± 4.51 days. Urine was collected to confirm self-report psychoactive drug use. The inclusion criteria for ketamine abusers were: (1) subjects met the criteria of substance dependence according to DSM-IV-TR; (2) no other substances dependence other than tobacco; (3) no other substances 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 | 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 written informed consents were signed by participants themselves or their guardians. A total of 93 ketamine users and 39 healthy subjects were recruited in the present study.

Clinical symptoms among ketamine users were evaluated with the Positive and Negative Syndrome Scale (PANSS; He and Zhang, 2000; 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, 13-item; 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.

2.2. Blood sampling

Venous blood sample was drawn from each subject using standard venipuncture technique. The average days of blood drawing since last ketamine use was 9.34 days ± 5.97 days. Serum was obtained by centrifuged at 4000 rpm for 15 min, then aliquoted was stored at −80 °C until assay.

2.3. Measurement of serum BDNF and NGF levels

Serum BDNF and NGF levels were measured by ELISA using commercially available kits respectively (BDNF E_{max} Immunoassay System, Promega, USA; NGF E_{max} Immunoassay System, Promega, USA) according to the manufacturer's instructions. The minimal detection limits were 15.6 pg/ml for BDNF and 7.8 pg/ml for NGF respectively. The BDNF E_{max} Immunoassay System and NGF E_{max} Immunoassay System typically offered less than 3% cross-reactivity with other related neurotrophic factors (NT-3 and NT-4) at 100 ng/ml and 10 ng/ml respectively. All samples were assayed in duplicate. BDNF and NGF levels were determined by absorbance at 450 nm wave length using optical density values against standard curves calibrated with known amounts of proteins.

2.4. Statistical analysis

All the data input were double entry, with verification using EpiData software, version 3.1 (a free software released by the non-profit organization "The EpiData Association" Odense, Denmark). All statistical analyses were performed using SPSS version 21.0 for windows. 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 neurotrophin levels, levels of ketamine use among users. A covariance analysis, with alcohol consumption and cigarettes smoking as covariate in univariate general linear model, was implemented to compare the serum neurotrophic factors levels across the two groups. For all statistical tests, a two-tailed $p < 0.05$ was considered to be significant.

Table 1
Clinical and demographic characteristics of ketamine users and healthy subjects.

	Ketamine users ($N = 93$)	Healthy subjects ($N = 39$)
Age (years)	25.56 ± 4.61	24.77 ± 4.75
Gender (male/female)	87/6	34/5
Years of education	10.91 ± 2.56	11.54 ± 1.70
Age of first ketamine use (year)	19.75 ± 5.02	
Duration of ketamine use (month)[a]	70.78 ± 34.52	
Duration of dependence (month)[b]	31.57 ± 18.77	
Current frequency of ketamine use (days per week)[c]	6.12 ± 1.58	
Current average doses of ketamine consumption (gram per day)	3.16 ± 3.02	
Use of other psychoactive compounds[d]		
Never use	20 (21.51%)	
Methamphetamine	27 (29.03%)	
MDMA	66 (70.97%)	
Codeine hydrochloride	13 (13.98%)	
Cannabis	22 (23.66%)	
Cocaine	1 (1.08%)	
Heroin	2 (2.15%)	
PANSS		
Positive symptom subscale	8.01 ± 1.82	
Negative symptom subscale	13.10 ± 3.74	
General psychopathology subscale	24.23 ± 5.09	
Total score	45.34 ± 8.70	
BDI	12.69 ± 6.08	
BAI	15.10 ± 8.37	
Alcohol		
Drink frequently[e]	27 (29%)**	5 (12.8%)
Not drink frequently[f]	66 (71%)**	34 (87.2%)
Tobacco		
Smoke frequently[g]	88 (94.6%)**	19 (48.7%)
Not smoke frequently[h]	5 (5.4%)**	20 (51.3%)

Data are the mean ± standard deviation.
Data about use of other psychoactive compounds, alcohol consumption and tobacco smoking are the amount of cases (percentage).
N, number of subjects included in the study; M, male; F, female; 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 one 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 value < 0.01.

3. Results

3.1. Demographic characteristics of ketamine users and healthy controls

A total of 93 ketamine abusers and 39 healthy subjects were recruited. The demographic characteristics of the two groups are summarized in Table 1. There were no significant differences in age, gender, or years of education between the two groups although alcohol consumption and cigarette smoking were higher among ketamine users (p value < 0.01).

In the ketamine group, the positive symptom, negative symptom and general psychopathology scores of PANSS were 8.01 ± 1.82, 13.10 ± 3.74 and 24.23 ± 5.09 respectively. The BDI score was 12.69 ± 6.08, which indicated mild to severe depressive symptoms (Beck and Beamesderfer, 1974). The BAI score was