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ORIGINAL INVESTIGATION

Chronic ketamine use increases serum levels of brain-derived neurotrophic factor

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Abstract
Rationale Ketamine is a non-competitive *N*-methyl-D-aspartate (NMDA) receptor antagonist which interferes with the action of excitatory amino acids (EAAs) including glutamate and aspartate. The use of ketamine at subanaesthetic doses has increased because of its psychotomimetic properties. However, long-term ketamine abuse may interfere with memory processes and inhibit the induction of long-term potentiation (LTP) in the hippocampus, an effect probably mediated by its NMDA antagonist action. Neurotrophins such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) serve as survival factors for selected populations of central nervous system neurons, including cholinergic and dopaminergic neurons. In addition, neurotrophins, particularly BDNF, may regulate LTP in the hippocampus and influence synaptic plasticity.
Objectives The purpose of this study was to test the hypothesis that ketamine use in humans is associated with altered serum levels of neurotrophins.
Methods We measured by enzyme-linked immunosorbent assay the NGF and BDNF serum levels in two groups of subjects: frequent ketamine users and healthy subjects.
Results Our data show that BDNF serum levels were increased in chronic ketamine users as compared to healthy subjects, while NGF levels were not affected by ketamine use.
Conclusion These findings suggest that chronic ketamine intake is associated with increases in BDNF serum levels in humans. Other studies are needed to explore the pharmacological and molecular mechanism by which ketamine, and/or other NMDA antagonists, may induce modification in the production and utilization of BDNF and alter normal brain function.

Keywords Ketamine · BDNF · Drug abuse · NGF · Serum levels · NMDA receptors · Neurotrophin · Neurotoxicity

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Introduction

Ketamine is a non-competitive *N*-methyl-D-aspartate (NMDA) receptor antagonist which interferes with the action of excitatory amino acids (EAAs) including glutamate and aspartate (Anis et al. 1983). Initially used as a dissociative anaesthetic, the non-medical use of ketamine has increased because of its psychotomimetic properties. The diverse subjective experiences of ketamine include the sensation of light through the body; novel experiences concerning 'body consistency' (e.g. being made of wood or rubber); grotesque distortion of shape or size of body parts; visions, hallucinations; sensations of melting together with people or things in the environment; and 'out of body' experiences (Hansen et al. 1988; Curran and Morgan 2000a, b). Other studies have shown that ketamine, at subanaesthetic doses, disrupts attentional function and explicit memory (Ghoneim et al. 1985; Krystal et al.

1994; Harborne et al. 1996; Malhotra et al. 1996; Adler et al. 1998; Newcomer et al. 1999). Moreover, ketamine inhibits the induction of long-term potentiation (LTP) in the hippocampus (Harris et al. 1984), an effect probably mediated by its NMDA antagonist action (Muller et al. 1988; Zhang and Levy 1992).

Neurotrophins such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) serve as survival factors for selected populations of central nervous system (CNS) neurons, including cholinergic and dopaminergic neurons (Lad et al. 2003; Hyman et al. 1991; Ha et al. 1999). In addition, neurotrophins, particularly BDNF, may regulate LTP in the hippocampus (Minichiello 2009) and influence synaptic plasticity (Verpelli et al. 2010). Thus, deficits in the production and utilization of these proteins can lead to a variety of CNS dysfunctions (Connor and Dragunow 1998), including those elicited by psychoactive compounds (Meredith et al. 2002; Angelucci et al. 2007a). Supporting this idea in human studies, we found that chronic use of drugs, such as heroin and cocaine and cannabis, is associated with decreased serum concentrations of both NGF and BDNF (Angelucci et al. 2007b, 2008, 2009).

Studies performed in rats showed that prolonged exposure to ketamine may increase neurodegeneration and BDNF levels in developing brains (Ibla et al. 2009), while expression of messenger RNA of neurotrophins and their receptors were found to be altered after subchronic ketamine treatment used as a model of schizophrenia (Becker et al. 2008). These findings suggest that ketamine use in humans may be associated with altered serum levels of neurotrophins. To test this hypothesis, in this study, we measured by enzyme-linked immunosorbent assay (ELISA) the NGF and BDNF serum levels in two groups of subjects: frequent ketamine users and healthy subjects.

Materials and methods

Subjects

This study was performed at the Department of Clinical and Behavioural Neurology, IRCCS Santa Lucia Foundation and at the Psychiatry Division of the Catholic University (Policlinico Gemelli), Rome, Italy. The characteristics of the experimental groups are summarized in Table 1. Participants were recruited using a 'snowball' sampling technique (Solowij et al. 1992) and only frequent ketamine users (defined as subjects taking ketamine at least four times/week) were included in the study (Curran and Morgan 2000a, b). Urine samples were also analysed (Medscreen, London, UK) to confirm the inclusion criteria in the group of ketamine users. Drug screening tests were also

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

	Ketamine users (N=17)	Healthy subjects (N=11)
Age (years)	24.47±4.47	24.18±2.89
Sex (male/female)	9 M/8 F	6 M/5 F
Years of education	13.41±3.33	14.81±1.83
Age at first ketamine use	16.88±2.89	–
Years of ketamine use	4.70±1.68	–
Years of regular use (at least 4 times/week)	3.23±1.09	–
Days since last use	1.52±0.87	–
Frequency of ketamine use (tablets per week)	4.94±0.89	–
Use of other psychoactive compounds (times/week)		
Cannabis (n=10)	2/week	
Ecstasy (MDMA) (n=3)	1/week	
Amphetamine (n=1)	1/week	
Cocaine (n=4)	2/week	
HDRS	5.23±3.40	1.14±0.89
HARS	6.94±4.13	1.28±1.11
MMSE	29.11±1.21	30±0
Cigarette/day	16.17±4.01	6.70±5.69
Alcohol intake	Low/moderate use	Low/moderate use

Data are the mean ± standard deviation

N number of subjects included in the study, *n* number of subjects within the ketamine user group, *M* male, *F* female, *MDMA* 3,4-methylenedioxymethamphetamine, *HDRS* Hamilton Depression Rating Scale, *HARS* Hamilton Anxiety Rating Scale, *MMSE* Mini Mental State Examination

performed to ascertain the use of other psychoactive compounds: among ketamine users, ten subjects assumed at irregular intervals cannabis and three subjects other psychostimulants such as cocaine and amphetamine (see Table 1).

Ketamine users fulfilled DSM-IV criteria for ketamine dependence at the time of the study. The diagnosis was determined in a consensus procedure using clinical material and the Mini International Neuropsychiatric Interview for psychiatric disorders (First et al. 1997). The psychopathological status of the ketamine and control groups was assessed by a trained physician using the 21-item Hamilton Depression Rating Scale (Hamilton 1960) for depression and the Hamilton Anxiety Rating Scale (Hamilton 1959) for anxiety. Cognitive status was evaluated with the Mini Mental State Examination (Folstein et al. 1975). Drug users were required to abstain from psychotropic drug use for at least 15 h prior to testing, to have no history of head injury or organic brain damage. Control subjects had neither self-reported personal or familial psychiatric history nor medication history. The study was approved by the institutional ethics committee and all subjects gave written informed consent.

Blood sampling

Venous blood was collected into sampling tubes that were centrifuged within 20 min after sampling at 2,000×*g* for 20 min. Serum was then aliquoted and stored at −80°C until analysis.

Determination of NGF and BDNF content in serum

BDNF and NGF were detected in sandwich ELISAs according to the manufacturer's instructions (R & D Systems, Minneapolis, MN, USA). These sandwich ELISAs are set in order to measure natural and recombinant human mature BDNF and NGF in cell culture medium and serum. All assays were performed on F-bottom 96-well plates (Nunc, Wiesbaden, Germany).

Tertiary antibodies were conjugated to horseradish peroxidase. Wells were developed with tetramethylbenzidine and measured at 450/570 nm. Neurotrophin content was quantified against a standard curve calibrated with known amounts of protein. The detection limits were 15 pg/ml for BDNF and 8 pg/ml for NGF. Measurements were performed in duplicate and are expressed as nanogram per millilitre (BDNF) or picogram per millilitre (NGF). Cross-reactivity to related neurotrophins (NT-3, NT-4) was less than 3%.

Statistical analysis

Student's *t* test was used with experimental groups (ketamine users and healthy subjects) as variables. The statistical significance level was set at $P<0.05$.

Results

Demographic characteristics of ketamine users and control subjects

The demographic characteristics of the two groups are shown in Table 1. No differences in age, sex or years of education were found. Also, no evidence for age and gender differences in circulating neurotrophin levels was found. Therefore, data were pooled for subsequent analysis.

BDNF serum levels in ketamine users and controls

Figure 1 shows the levels of circulating BDNF in ketamine users and healthy subjects. Student's *t* test showed that circulating BDNF levels were significantly higher (DF=1, 26; *F* value=12.6; *P* value=0.0015) in ketamine users than in healthy subjects (12.70±1.33 ng/ml ketamine; 6.159±0.97 ng/ml control).

NGF serum levels in ketamine users and controls

NGF serum levels in ketamine users and controls are also shown in Fig. 1. As assessed by Student's *t* test, NGF levels in ketamine users were comparable to those of healthy subjects (DF=1, 26; *F* value=0.022; *P* value=0.884) (100±46.1 pg/ml ketamine; 110.7±55.4 pg/ml control).

Discussion

This study was performed in order to elucidate the effect of chronic ketamine intake on serum levels of neurotrophins in human subjects. The results demonstrated that BDNF serum levels were increased in chronic ketamine users as

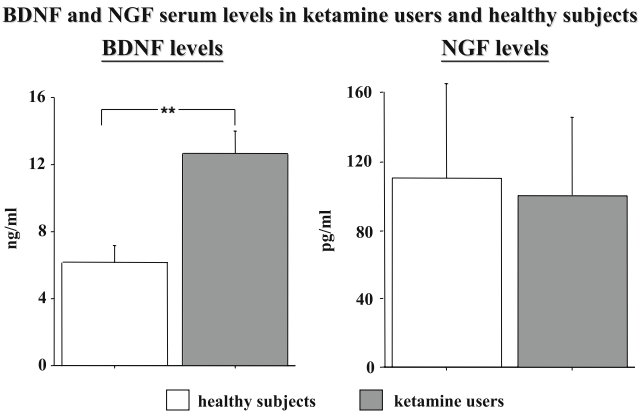

Fig. 1 BDNF and NGF serum levels in ketamine users and healthy subjects. Data are the mean ± SEM. Values are expressed in nanogram per millilitre (BDNF) and picogram per millilitre (NGF). $^{**}P<0.01$ indicates a significant difference between groups

compared to healthy subjects, while NGF levels were not affected by ketamine use.

This is the first study showing a significant increase in serum BDNF concentrations in subjects with a history of frequent ketamine use. Ketamine is an antagonist of NMDA receptor, while BDNF is a trophic factor and involved in the maintenance of midbrain dopaminergic neurons (Hyman et al. 1991) and in the regulation of synaptic plasticity (Thoenen 1995). Noteworthy, BDNF has been shown to influence, or be influenced by, glutamate signalling. It was demonstrated that elevated glutamate extracellular levels stimulate the production of BDNF in neurons (Marini et al. 1998; Lee et al. 2002). On the other hand, ketamine is able to elevate glutamate levels in the extracellular compartment of the mediofrontal cortex, as shown by an in vivo microdialysis study (Moghaddam et al. 1997). Thus, one possibility is that BDNF levels are increased because of NMDA antagonist action of ketamine. Another option is that increased BDNF levels are the result of adaptive mechanisms to ketamine withdrawal. In fact, drug users were required to abstain from psychotropic drug use for at least 24 h prior to testing. Nonetheless, because of the short time of drug withdrawal and the fact that subjects with withdrawal symptoms were excluded from the study, it is reasonable to believe that altered BDNF levels are a consequence of chronic adaptation to ketamine use, rather than an effect of withdrawal syndrome.

Other studies have shown that non-competitive NMDA receptor antagonists are also able to elevate the concentration of extracellular dopamine (Adams and Moghaddam 1998; Bristow et al. 1993; Carboni et al. 1989; Imperato et al. 1990), and low-dose ketamine may increase dopamine turnover in the nucleus accumbens (Irifune et al. 1991, 1997). A possible link between the effect of dopamine stimulation and BDNF has already been evidenced. In rats, both increased (Meredith et al. 2002) and reduced (Angelucci et al. 2007a) BDNF expression in brain areas after exposure to amphetamine has been reported, while methamphetamine (Kim et al. 2005) and ecstasy (Angelucci et al. 2010) abusers are characterized by increased plasma or serum BDNF levels. Since BDNF supports the function of dopaminergic neurons, these findings may also support the idea that a ketamine-induced BDNF increase could be part of an adaptive response to changes in dopamine turnover.

Interestingly, an antidepressant action of ketamine has been recently described in humans and animal models. More intriguing, other evidences suggest that BDNF is involved in depression, namely the expression of BDNF is decreased in depressed patients (De Oliveira et al. 2009). In addition, chronic, but not acute, antidepressant treatment induces increasing of BDNF expression and BDNF immunoreactive fibres in the hippocampus of rodents (Nibuya et al. 1996; De Foubert et al. 2004). Therefore, the general consensus is that an increase in BDNF is necessary for antidepressant drugs to exert their action (Drzyzga et al. 2009). Clinical studies have shown that acute administration of ketamine (as well as other NMDA antagonists) ameliorates depressive symptoms in major depressed patients (Zarate et al. 2006; Berman et al. 2000). In line with these findings, ketamine induces anxiolytic- and antidepressant-like effects in rodent models of anxiety and depression (Kos et al. 2006; Yilmaz et al. 2002; Silvestre et al. 1997), an effect also associated with an increase in BDNF in the hippocampus (Garcia et al. 2008). Thus, it is possible that the described antidepressant action of ketamine in humans can be mediated by BDNF. Nevertheless, it is important to note that the majority of the above cited studies focused on the acute effect of ketamine, whereas little is known about the effects of long-term ketamine abuse.

A limitation to the interpretation of our data is that we measured the BDNF levels in serum and a direct correlation between central and peripheral neurotrophin levels has not yet been demonstrated. However, some studies reported that neurotrophins are able to cross the blood–brain barrier via a high-capacity saturable transport system (Kastin et al. 1999; Pan et al. 1998). Another limitation of this study is that the majority of ketamine users were also polydrug users. Unfortunately, ‘pure’ ketamine users are very rare and confounding factors caused by the concomitant use of other substances cannot be totally excluded. Nevertheless, our findings may be of interest since we enrolled subjects with prevalent use of ketamine in their lifetime.

In conclusion, this study has shown that chronic ketamine intake increases BDNF serum levels in humans. Whether this effect is a consequence of a direct neurotoxic insult of ketamine is still matter of debate, as well as the possible association with ketamine antidepressant action. Other studies are needed to elucidate the pharmacological and molecular mechanism by which ketamine, and/or other NMDA antagonists, may induce modification in the production and utilization of BDNF and alter normal brain function.

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Conflict of interest The authors declare no conflicting financial or other competing interests.

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