ORIGINAL ARTICLE

Relationship of ketamine's antidepressant and psychotomimetic effects in unipolar depression

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Abstract

OBJECTIVES: Ketamine and other NMDA (N-methyl-D-aspartate) antagonists produce fast-acting antidepressant-like effects, although the underlying mechanism is unclear. Furthermore, high affinity NMDA antagonists such as ketamine are associated with psychotomimetic effects. To date the link between the antidepressant and psychotomimetic effects of ketamine has not been explored. We examined the relationship between the antidepressant and psychotomimetic effects of a single ketamine infusion in subjects diagnosed with major depressive disorder.

METHODS: In a double-blind, cross-over, placebo-controlled, two weeks clinical trial we studied the effects of ketamine (0.54 mg/kg within 30 min) in a group of 27 hospitalized depressive patients.

RESULTS: Higher intensity of psychotomimetic symptoms, measured using BPRS, during ketamine administration correlated with alleviation in mood ratings during the following week with maximum on day seven. Ketamine was superior to placebo in all visits (day 1, 4, and 7) assessed by MADRS with effect size (Cohen´s d) of 0.62, 0.57, and 0.44 respectively. There was no significant correlation between ketamine and nor-ketamine plasma levels and MADRS score change at any study time point.

CONCLUSION: The substantial relationship between ketamine's antidepressant and psychotomimetic effects was found. This relationship could be mediated by the initial steps of ketamine's action, trough NMDA receptors, shared by both ketamine's clinical effects.

Abbreviations:
Brief Psychiatric Rating Scale (BPRS); Gas Chromatography–Mass Spectrometry (GC-MS); Hamilton Depression Rating Scale (HDRS); intent-to-treat (ITT); lower limit of quantification (LLOQ); limit of detection (LOD); Montgomery-Åsberg Depression Rating Scale (MADRS); Mini-International Neuropsychiatric Interview (M.I.N.I.); N-methyl-D-aspartate (NMDA)

Introduction

The antidepressant effect of the dissociative anesthetic ketamine has been increasingly studied over the last ten years (Berman *et al* 2000; Zarate Jr. *et al* 2006; Diaz-Granados *et al* 2010a). Ketamine and other NMDA (N-methyl-D-aspartate) antagonists produce fast-acting antidepressant-like effects, although the underlying mechanism is unclear (Autry *et al* 2011). Furthermore, high affinity NMDA antagonists such as ketamine, are associated with psychotomimetic effects (Skolnick 1999; Domino 1992). To date, the link between the antidepressant and psychotomimetic effects of ketamine has not been examined.

Depending on the individuals, their expectations, the setting and the dose, ketamine produces a wide range of psychotomimetic states (Dalgarno & Shewan 1996). Dissociative anesthetics mimic the positive and the negative symptoms (social withdrawal and apathy) of schizophrenia through antagonism at NMDA glutamate receptors (Krystal *et al* 1994; Anis *et al* 1983). These effects are usually mild to moderate at subanesthetic doses, although they can be more pronounced in a minority of cases (Murrough 2012). The intensity of these alterations of consciousness and perception is dose-dependent (Vollenweider & Kometer 2010). It is often claimed that the psychotomimetic effects of ketamine may limit clinical use, despite its reported efficacy (Skolnick *et al* 2009).

The improvement associated with ketamine infusion reflects a lessening of core symptoms of depression and is disconnected from ketamine-induced psychotomimetic symptoms (Berman *et al* 2000). Zarate Jr. *et al* reported that the higher change in positive BPRS (Brief Psychiatric Rating Scale) symptoms during ketamine infusion have trended to predict a greater decrease in Hamilton Depression Rating Scale (HDRS) scores the next day (Zarate Jr. *et al* 2006). The pharmaceutical industry has tried to develop new NMDA antagonists with antidepressant, without provoking psychotomimetic symptoms, and the relationship between these two factors has yet to be examined.

The purpose of our study was the evaluation of ketamine's antidepressant properties, and to determine the link between the antidepressant and psychotomimetic effects. We also examined the role of plasma levels of ketamine and its metabolite nor-ketamine. A priori we hypothesized that the single infusion of ketamine in subanesthetic dose induces a higher decrease in depression scale score than placebo infusion. We also hypothesized greater antidepressant effect in subjects with more psychotomimetic effects during the infusion.

Material and methods

Subjects

Right-handed ketamine-naive inpatients aged between 18 and 65 years old with major depressive disorder (recurrent or single episode) diagnosed according to DSM-IV criteria (APA 2006), established by means of the Mini-International Neuropsychiatric Interview (M.I.N.I.) (Sheehan *et al* 1998), Czech version 5.0.0 were assessed for study eligibility. Subjects were included who reached at least the total score of 20 on the Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery & Åsberg 1979). All patients were hospitalized at the Department of Affective Disorders of Prague Psychiatric Centre between December 2009 and December 2011. All subjects were on a stable dose of antidepressant medication for a minimum of three weeks prior to admission and remained on the same medications and dosages throughout the duration of the study (Table 1). Exclusion criteria were: any suicidal risk assessed by clinical examination, current psychiatric comorbidity on Axis I and II, serious unstable medical illness or neurological disorder (e.g. epilepsy, head trauma with loss of consciousness), lifetime history of psychotic symptoms and psychotic disorder in first- or second-degree relatives and electroconvulsive therapy within 3 months before the start of the study. The study was approved by the Prague Psychiatric Centre Institutional Review Board and was performed in accordance with the ethical standards laid down in the Declaration of Helsinki 1975, revised Hong Kong 1989. Written informed consent was obtained from all subjects before inclusion in the study. The study was registered with the European Clinical Trials Database (EudraCT number 2009-010625-39).

Study design and procedures

In this two week, double-blind, placebo controlled, crossover study each participant attended one ketamine and one placebo session in a randomized order in one week intervals. Both sessions were performed at the same time from 8 a.m. to 10 a.m. A unilateral intravenous catheter was inserted into the subjects' forearm for ketamine infusion. Racemic ketamine hydrochloride (Calypsol, Gedeon Richter Plc., Czech Republic) or a placebo (0.9% saline solution) was administered into the right cubital vein using an infusion pump (ID 20/50, Polymed medical CZ Ltd). Ketamine was administered in a loading dose of 0.27 mg/kg for the first 10 min, followed by a maintenance infusion of 0.27 mg/kg within 20 min. These infusion rates were calculated with respect to the pharmacokinetics of ketamine (Hetem *et al* 2000; Horacek *et al* 2010) in order to: (a) produce stable ketamine blood levels, (b) apply a total dose very close to clinical studies in depression (Berman *et al* 2000; Zarate Jr. *et al* 2006), and (c) maximize safety by using a loading dose over 10 min. Ketamine has an elimination half-life of 2 to 2.5 hours with a distribution half-life of 10 to 15 min when given parenterally. To measure ketamine and nor-ketamine serum levels, 2 ml of vein blood was sampled from the left arm 5 min before and 10 and 30 min after the beginning of the infusion.

The possibility of occurrence of side effects such as vivid dreaming, floating sensations, dizziness and blurred vision were explained before treatment and subjects were assured that if the occurred, they would be temporary. Each participant was interviewed and evaluated with the Brief Psychiatric Rating Scale (BPRS) (Overall & Donald 1962) before and 30 minutes after the ketamine/placebo infusion. During and three hours after the session each subject was monitored for any adverse effects.

The subjects were assessed by MADRS, at baseline and subsequently one, four and seven days after each session. Ratings were made by two independent experienced clinical psychiatrists who were trained to the criterion of the intra-class correlation >0.80 for each clinician prior to conducting the ratings.

The primary outcome measures for the study were MADRS score change at day 1, 4 and 7 between ketamine and placebo. The secondary outcomes included response rates (defined as equal to or more than a 50% reduction of the MADRS score) and plasma levels of ketamine and its metabolite nor-ketamine during ketamine infusion (baseline, 10 minutes, 30minutes of the infusion) between ketamine and placebo at the same time points.

Gas Chromatography–Mass Spectrometry (GC-MS)

The GC-MS toxicological method was developed and validated according to international standards (Penders & Verstraete, 2006) for determination of ketamine and nor-ketamine serum levels. The analytical standards nor-ketamine, ketamine and deuterated ketamine (ketamine-D4), supplied as hydrochlorides from Cerilliant, USA, were used for toxicological analyses. For quantitation, the internal standard method was applied using ketamine-D4. Isolation of analytes from blood serum samples was performed using SPEC-DAU discs and analyses were performed with acetyl derivatives using an HP 6890–5973 instrument (Agilent, Germany) operating in electron impact single ion monitoring (SIM) mode. The lower limit of quantification (LLOQ) for ketamine was 50 ng/ml and for nor-ketamine 8 ng/ml. The limit of detection (LOD) for ketamine was 20 ng/ml and for nor-ketamine 1 ng/ml (Horacek *et al* 2010).

Statistical analyses

Data are expressed as means (standard deviation) or in the case of non-Gaussian distributed measures as medians (inter-quartile range). The baseline clinical data of the groups according to the treatment sequence were compared using the Mann-Whitney test or unpaired t-test, and by Fisher's exact test. The primary efficacy analyses were based on a modified intent-to-treat (ITT) data set, which was defined as the subset of patients who completed a baseline and at least one post-baseline visit after the cross-over. A general linear model for a two-period crossover design with BPRS change during ketamine infusion as a covariate, sequence (placebo-ketamine, ketamine-placebo) as a between-subjects factor, and period (week 1, week 2), treatment (ketamine, placebo) and time (baseline, day 1, day 4, day 7) as the within-subjects factors followed by Bonferroni post-hoc tests was used to compare the changes in MADRS between ketamine and placebo over the study period All repeated measures effects are reported with the original degrees of freedom and Greenhouse-Geisser corrected p-values. The differences between treatments were expressed as both the mean score change treatment difference with 95% confidence intervals and Cohen's d. Prescott's test for cross-over trials with binary outcomes was used to test for a treatment difference in response rate (≥50% reduction in MADRS) at day 1, 4 and 7. These associations were analysed by Pearson's correlation coefficient: a) between BPRS score change during ketamine administration and MADRS score change at day 1, 4 and 7; b) between ketamine and/or nor-ketamine plasma levels and change in psychometric scales. The statistical analyses were performed using Statistica 9.0 (StatSoft, Inc.).

Results

Demographics

Thirty-eight subjects were screened, of whom 30 depressive subjects who met the inclusion criteria and agreed to participate, were randomized by a flip of a coin (Armitage 1982). Eight subjects were not included, four of them had comorbidity on Axis I, one of them had a MADRS score under twenty points, three of them decided not to participate. Eleven subjects received ketamine and nineteen received the placebo in Week 1. Two subjects discontinued the study due to a worsening of their depression after the placebo infusion and one subject did not receive ketamine after the placebo infusion (Week 2) because of a maintained placebo response for the week (Figure 1). Thus, twenty-seven patients received the intended treatment and were included in all analyses (intention-to-treat analysis; ITT), 9 of whom were randomized into the K-P group and 18 into the P-K group. In five patients who did not complete all of the visits after crossover analyses were performed using the last observation analysis (LOAN) (Figure 1). The K-P and P-K groups differed in MADRS scores at baseline (t=2.23, df=25, p=0.03). Otherwise, both groups were comparable under the relevant demographic and clinical characteristics (Table 1).

Adverse effects

Ketamine was well-tolerated and no serious adverse or side-effects (other than the expected acute psychotomimetic effect) occurred during the study. Typical effects occurring at subanesthetic doses of ketamine were dissociation/perceptual disturbances, confusion, mild increases in blood pressure, emotional blunting and euphoria. The majority of these effects ceased within 30 minutes after the ketamine infusion. In no case did emotional blunting, euphoria or dissociation persist beyond 60 minutes.

Tab. 1. Demographic and outcome data according to the treatment sequence.

	ketamine first (K-P) (n=11) mean ± SD	placebo first (P-K) (n=19) mean ± SD	Statistical significance level
Age (years)	42.2±15.1	44.6±10.9	NS [a]
Gender (M : F)	5:6	10:9	NS [b]
Duration of depressive disorder (years)	10.2±9.4	10.4±8.3	NS [c]
Duration of current episode (months)	11.2±9.9	11.6±11.5	NS [c]
Number of previous psychiatric hospitalizations	2.2±1.2	3.6±2.4	NS [c]
Baseline MADRS score	20.4±4.7	24.6±4.8	p=0.04 [c]
Treatment before enrolment	SSRI (n=2) NaSSA (n=1) SNRI (n=1) AD comb. (n=5) AD augm. (n=2) BZD (n=6)	SSRI (n=2) NaSSA (n=2) SNRI (n=3) AD comb. (n=7) AD augm. (n=5) BZD (n=7)	NA

[a] Student's t-test; [b] Fisher Exact Test; [c] Mann-Whitney U Test; NA – not applicable; NS – not significant; AD – antidepressant; NaSSA – Noradrenergic and Specific Serotonergic AD; SNRI – Serotonin–Norepinephrine Reuptake Inhibitor; AD comb. – various combinations of AD; AD augm. – augmentation of AD with atypical antipsychotics; BZD – benzodiazepines

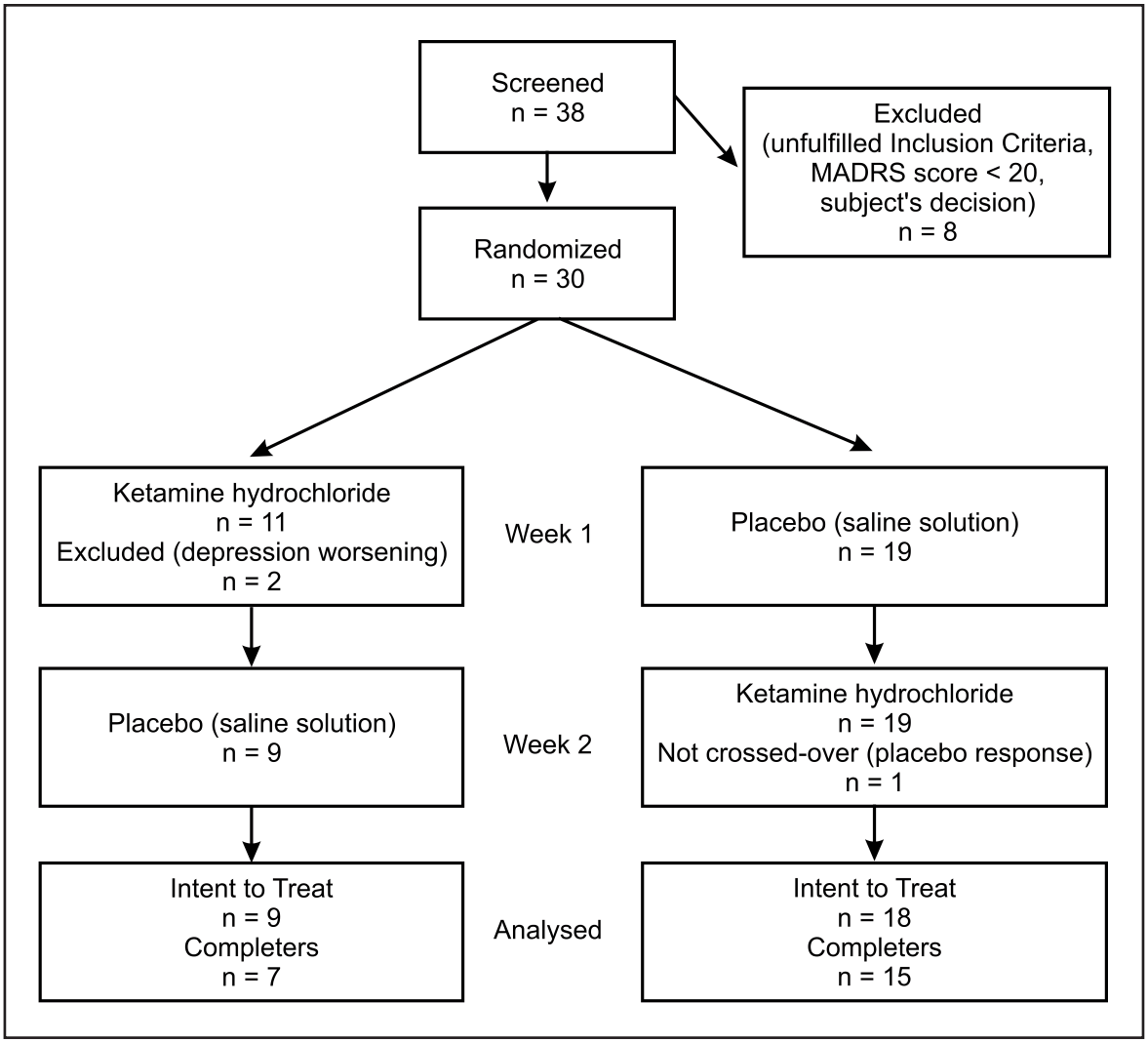

Fig. 1. Patient flow chart.

Efficacy

General linear model revealed a treatment effect ($F(1,24)=5.87$, $p=0.03$), time effect ($F(3,72)=5.58$, $p=0.002$) and treatment to time interaction ($F(3,72)=4.11$, $p=0.01$) irrespectively to effect of sequence ($F(1,24)=2.05$, $p=0.17$) and period ($F(1,24)=3.49$, $p=0.07$), i.e. there were no significant carry-over effects. BPRS score change as a covariate did not achieve statistical significance ($p=0.10$). In post hoc analysis superiority of ketamine over placebo at all post-infusion visits was found (day 1: $p<0.001$ day 4: $p=0.002$; day 7: $p=0.02$). The mean MADRS total score change differences were 5.7 (95%CI 3.4–7.9) at day 1, 4.7 (95%CI 2.5–7.0) day 4 and 4.0 (95% CI 1.8–6.2) at day 7 (Figure 2). Effect sizes (Cohen's d) were 0.62 at day 1, 0.57 at day 4, and 0.44 at day 7.

Comparison of categorial responses to the placebo vs. ketamine showed a significantly higher number of responders to ketamine compared to the placebo at day 1 (ketamine n=10 (37.0%), placebo n=1 (3.7%); Prescott's test, $p=0.008$) at day 4 (ketamine n=11 (40.7%), placebo n=1 (3.7%); Prescott's test, $p=0.003$) and at day 7 (ketamine n=10 (37.0%), placebo n=3 (11.1%); Prescott's test $p=0.02$, respectively). Additionally, 10 patients were classified as responders to ketamine on at least two visits and 5 of them remained responders from day 1 to day 7 in comparison with none such responder to placebo.

When we analysed association between the BPRS total score and the MADRS score changes there was a significant correlation at day 7 ($r=-0.40$, $p=0.04$) and trend toward to significance at day 1 ($r=-0.37$, $p=0.06$) and day 4 ($r=-0.36$, $p<0.07$) were found (Figure 3). No significant correlations were demonstrated when the same analyses were applied to the BPRS subscales.

Ketamine and nor-ketamine serum levels

Neither ketamine nor its metabolite nor-ketamine was detectable in the placebo or in the active ketamine session at baseline. In the case of ketamine infusion, the serum levels increased after 10 min and 30 min for ketamine (306±136 ng/ml, resp. 237±95 ng/ml) and its metabolite nor-ketamine (11±7 ng/ml, resp. 50±21 ng/ml). There were no differences found between responders and non-responders in ketamine and/or nor-ketamine serum levels.

Further, no correlations were found between change in total BPRS score and ketamine or nor-ketamine plasma levels. Significant correlation was found only between BPRS Anergia Factor (emotional withdrawal, motor retardation, blunted affect and disorientation) and nor-ketamine plasma level after 10 min of infusion ($r=-0.47$, $p<0.05$).

Discussion

To our knowledge, this study is the first *a priori* to examine the relationship between psychotomimetic symptoms and antidepressant efficacy of a single ketamine infusion in patients with major depressive disorder.

We found a significant correlation between, the two temporally distinct ketamine's effects, the intensity of transient altered mental function (as measured by the BPRS score) during ketamine administration and lessening of core symptoms of depression (as measured by the MADRS score) during the following week with maximum on day seven. The extent of psychotomimetic symptoms was similar to that reported in other ketamine studies of major depressive disorder and bipolar depression (Diazgranados *et al* 2010b). As

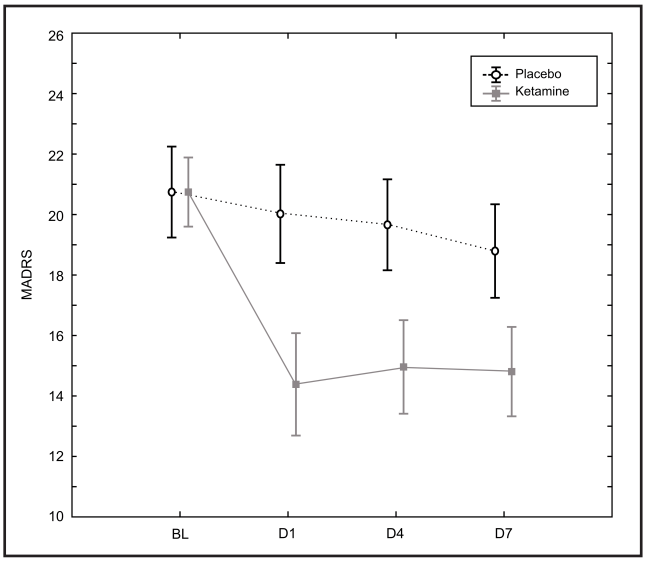

Fig. 2. Superiority of ketamine over placebo at all post-infusion visits was found (day 1: $p<0.001$ day 4: $p=0.002$; day 7: $p=0.02$).

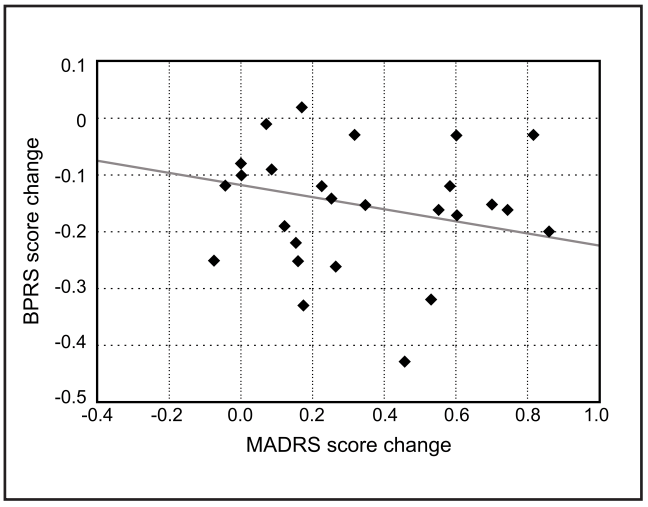

Fig. 3. Association between BPRS score change during acute administration of ketamine and MADRS score change at day seven, analysed by Pearson's correlation coefficient ($r=-0.40$, $p=0.04$).

noted by others, (Zarate Jr. *et al* 2006), there was a trend, but not significance, for an inverse relationship between HDRS (Hamilton Depression Rating Scale) scores at day 1 and peak change in BPRS positive symptoms subscale scores.

This study supports previous findings of robust, rapid (hours), and relatively prolonged (1 week) antidepressant action with single dose of ketamine (summarized in Bunney & Bunney 2012). In our study, the strongest effect size was found at the first day after infusion during a one week period. When comparing our results with the study by Zarate Jr. *et al* (2006), we found smaller effect-size for the drug difference (0.44 vs. 0.68), but similar magnitude of response rate (37% vs. 35%) one week after the ketamine infusion.

Both, the intensity of transient altered mental function (Passie *et al* 2003), and improvement in mood ratings, are dose-dependent and occur with low to medium doses (Horacek *et al* 2010). In our study, a moderate correlation was found between BPRS Anergia Factor (emotional withdrawal, motor retardation, blunted affect and disorientation) and nor-ketamine plasma level after 10 mins of infusion ($r=-0.47$, $p<0.05$). This can be supported by evidence that ketamine may primarily induce negative symptoms through its direct inhibition of the NMDA receptor (Stone *et al* 2008). No correlations were found between psychotomimetic (positive BPRS) symptoms or depressive symptoms (MADRS score) change and ketamine or nor-ketamine plasma levels. This fact supports our hypothesis that the early ketamine effects initiate subsequent downstream signalling processes, which are not directly related to ketamine and nor-ketamine blood levels (Horacek *et al* 2010).

The leading neurobiological theory for the antidepressant effects of ketamine is that its antagonistic activity at NMDA receptors leads to diversion of glutamate signalling to AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionate) receptors. Increased extracellular glutamate or serotonin in the prefrontal cortex could contribute to the psychotropic effects of ketamine (Chan *et al* 2012). Furthermore, the incidence of psychotomimetic effects after administration of NMDA receptor antagonists appears to correlate with the following factors: 1) the affinity of the drug for the PCP binding site of the NMDA receptor complex (Kornhuber & Weller 1997); 2) individuals expectations; 3) the setting; and 4) the dose of the drug (Dalgarno & Shewan 1996). In addition, it can be speculated that the sensitivity of NMDA receptors to ketamine predicts the acute subjective effects and the outcome of antidepressant treatment.

Several factors limit interpretations of our data. Despite our sample size was relatively small, in comparison with previous randomized, placebo controlled studies with ketamine (summarized in Bunney & Bunney 2012), it ranks among the most populated studies and the effect sizes were relatively large. Consistent with previous studies, we also used inactive placebo without psychotomimetic properties, which could have affected the study blind. Rather than the flip of a coin a block randomization design with equal sizes of the sample groups would have been preferable.

Conclusion

The results of our study show the substantial relationship between ketamine's antidepressant and psychotomimetic effects. This relationship could be mediated by the initial steps of ketamine's action, trough NMDA receptors, shared by both ketamine's clinical effects. These effects are not directly related to ketamine and nor-ketamine blood levels. Further studies should address the question if the sensitivity of NMDA receptors to ketamine predicts the acute subjective effects and the outcome of antidepressant treatment.

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Conflict of Interest Statement

The Authors declare that there is no conflict of interest.

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