Journal of Affective Disorders 186 (2015) 306–311

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Research report

Serum BDNF as a peripheral biomarker of treatment-resistant depression and the rapid antidepressant response: A comparison of ketamine and ECT

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ARTICLE INFO

Article history:
Received 24 April 2015
Received in revised form
19 June 2015
Accepted 20 June 2015
Available online 29 July 2015

Keywords:
Treatment-resistant depression
Ketamine
ECT
Brain-derived neurotrophic factor
Biomarker

ABSTRACT

Background: Ketamine is associated with rapid antidepressant efficacy but the biological mechanisms underpinning this effect are unclear. Serum brain-derived neurotrophic factor (sBDNF) is a potential circulating biomarker of treatment-resistant depression (TRD) and ketamine response but it is unclear if this is a common target of both ketamine and electroconvulsive therapy (ECT), the current gold standard for TRD. Moreover, the impact of multiple ketamine infusions on sBDNF has not yet been established.
Methods: Thirty five TRD patients with a current DSM-IV diagnosis of recurrent depressive disorder received up to 12 ECT sessions ($N=17$) or up to three intravenous infusions of low-dose (0.5 mg/kg) ketamine ($N=18$). Blood samples were taken over the course of the study for assessment of sBDNF. Symptom severity and response were monitored using the 17-item Hamilton Depression Rating Scale (HDRS). sBDNF was assessed in 20 healthy controls to allow comparison with TRD patients.
Results: As expected, sBDNF was lower in TRD patients at baseline compared to healthy controls. Ketamine and ECT treatment were both associated with significant reductions in depressive symptoms. However, sBDNF was significantly elevated only at one week following the first ketamine infusion in those classified as responders one week later. sBDNF was not elevated following subsequent infusions. ECT reduced depressive symptoms, as expected, but was not associated with an enhancement in BDNF.
Limitations: Patients continued with their psychotropic medications throughout this trial.
Conclusions: SBDNF normalisation does not appear to be a prerequisite for symptomatic improvement in TRD following ketamine or ECT treatment.

1. Introduction

The consequences of major depression are devastating (Ferrari et al., 2013). Treatment-resistant depression (TRD), a lack of symptomatic response to adequate first-line pharmacological therapy is common (Trivedi et al., 2006). The current gold standard for TRD is electroconvulsive therapy (ECT; UK ECT Review Group, 2003), but there is still an urgent need for novel rapidly acting treatment strategies with superior response and remission rates (O'Leary et al., 2015). Sub-anaesthetic doses of the NMDA receptor antagonist ketamine produce rapid antidepressant effects in TRD research studies (Berman et al., 2000; Zarate et al., 2006). The mechanisms underpinning the response to ketamine and ECT are not well defined, although preclinical studies suggest the biological effects of both treatments may modulate common neurobiological pathways (O'Connor et al., 2013).

The neurotrophic hypothesis of depression (Duman et al., 1997) is supported by robust evidence of reduced serum brain-derived neurotrophic factor (sBDNF) in patients with depression (Molendijk et al., 2011, 2014), higher levels of peripheral BDNF in remission following conventional treatment (Polyakova et al., 2015),

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http://dx.doi.org/10.1016/j.jad.2015.06.033
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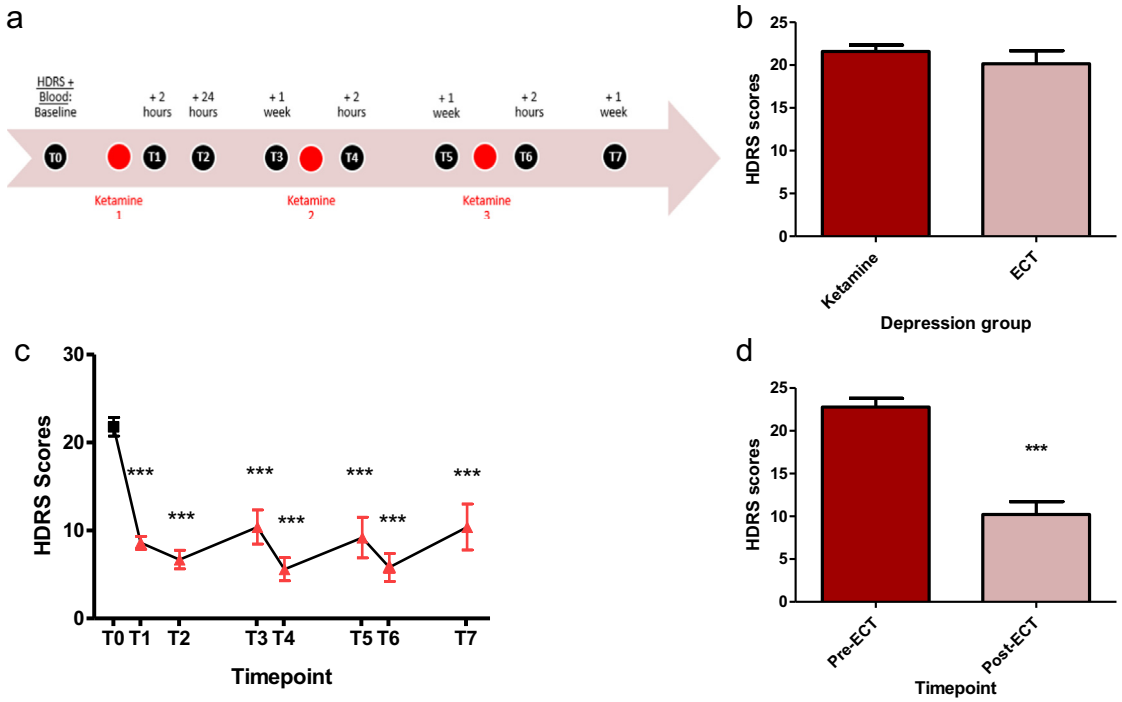

Fig. 1. (a) Sampling time points for ketamine cohort. (b) Baseline symptom severity in ketamine and ECT cohort. HDRS scores were not significantly different in the ketamine and ECT cohorts at baseline, $t(33)=0.83$, $p>0.05$, Cohen's $d=0.28$. (c) Depressive severity in TRD patients at baseline (T0) and following ketamine infusions. HDRS scores were reduced following ketamine infusion, $F(2.3, 20.7)=22.56$, $p<0.001$, partial eta squared=0.72 (Greenhouse-Geisser adjusted). Post-hoc comparisons indicated that, compared to baseline, HDRS scores were significantly lower at all post-infusion time points (in all cases, $p<0.001$), and HDRS scores were lower at T4 compared to T3 ($p=0.01$) and at T6 compared to T5 ($p=0.02$). Error bars represent standard error of the mean. *** represents $p<0.001$, compared to baseline. (d) Depressive severity in TRD patients pre- and post-ECT treatment. ECT significantly reduced HDRS compared to pre-ECT baseline, $t(17)=4.15$, $p=0.001$, Cohen's $d=0.98$. Error bars represent standard error of the mean. *** represents $p=0.001$.

and heightened hippocampal BDNF expression in depressed patients receiving antidepressant treatment compared to untreated patients (Chen et al., 2001). By enhancing glutamatergic transmission, ketamine triggers a chain of neurobiological events (see review: Naughton et al., 2014), including a rapid BDNF increase which appears to be critical for the beneficial effects of ketamine (Lepack et al., 2015). In humans, the rapid antidepressant impact of single ketamine infusions may be tracked by peripheral BDNF alterations (Duncan et al., 2013; Haile et al., 2014). It is unclear whether this is maintained following repeated ketamine infusions. Ketamine may need to be given repeatedly in the clinic, as its effects often do not last longer than one week (Berman et al., 2000; Zarate et al., 2006), and evidence for the feasibility of repeated-dose ketamine to maintain antidepressant effects is lacking (aan het Rot et al., 2010; Sisti et al., 2014). Consequently, more research is required to examine the effects of multiple ketamine infusions.

ECT has been shown to be effective in ameliorating TRD (Folkerts et al., 1997; Kornhuber and Weller, 1995; UK ECT Review Group, 2003). There is evidence that ECT can enhance BDNF (Bocchio-Chiavetto et al., 2006; Brunoni et al., 2014; Bumb et al., 2014; Taylor, 2008). Unlike ketamine, this effect appears to be delayed, and there is some contradictory evidence concerning the effects of ECT on BDNF (Fernandes et al., 2009; Rapinesi et al., 2015). ECT and repeated ketamine infusions may have comparable effects upon depressive symptoms (Ghasemi et al., 2014). However, the ECT arm of this study involved 3 ECT sessions. More typical courses involve 6–12 ECT sessions (Campion, 2015). It is thus of interest if there is similar BDNF enhancement following repeated ketamine infusions compared to standard ECT treatment.

In the present study, patients with TRD were either administered up to three ketamine infusions or up to 12 ECT sessions. We hypothesised that sBDNF would be lower in patients with TRD compared to healthy controls and that ketamine and ECT-induced amelioration of TRD would be associated with increased levels of sBDNF.

2. Materials and methods

Ethical approval for the ketamine component of the study was obtained from the Clinical Research Ethics Committee of the Cork Teaching Hospitals and the Irish Medicines Board (now the Health Products Regulatory Authority). The ECT component of the study was approved by the Research Ethics Committee of St. Patrick's Mental Health Services.

2.1. Study design

The effects of ketamine and ECT were studied through repeated-measures designs by comparing sBDNF and depression severity at baseline and post-treatment. To assess associations between BDNF and treatment response, changes from baseline at each time point were assessed in those patients who responded symptomatically to treatment at that time point. We defined treatment response as a 50% or more reduction in Hamilton Depression Rating Scale (HDRS) score relative to baseline. The impact of TRD was assessed by between-participants comparisons of TRD patients (pre-treatment) and healthy controls, who provided a single blood sample.

2.2. Study participants and recruitment

Patients with unipolar TRD were recruited from a mental health service in Cork, Ireland, and low-dose intravenous ketamine was administered in Cork University Hospital. ECT was administered in St. Patrick's University Hospital.

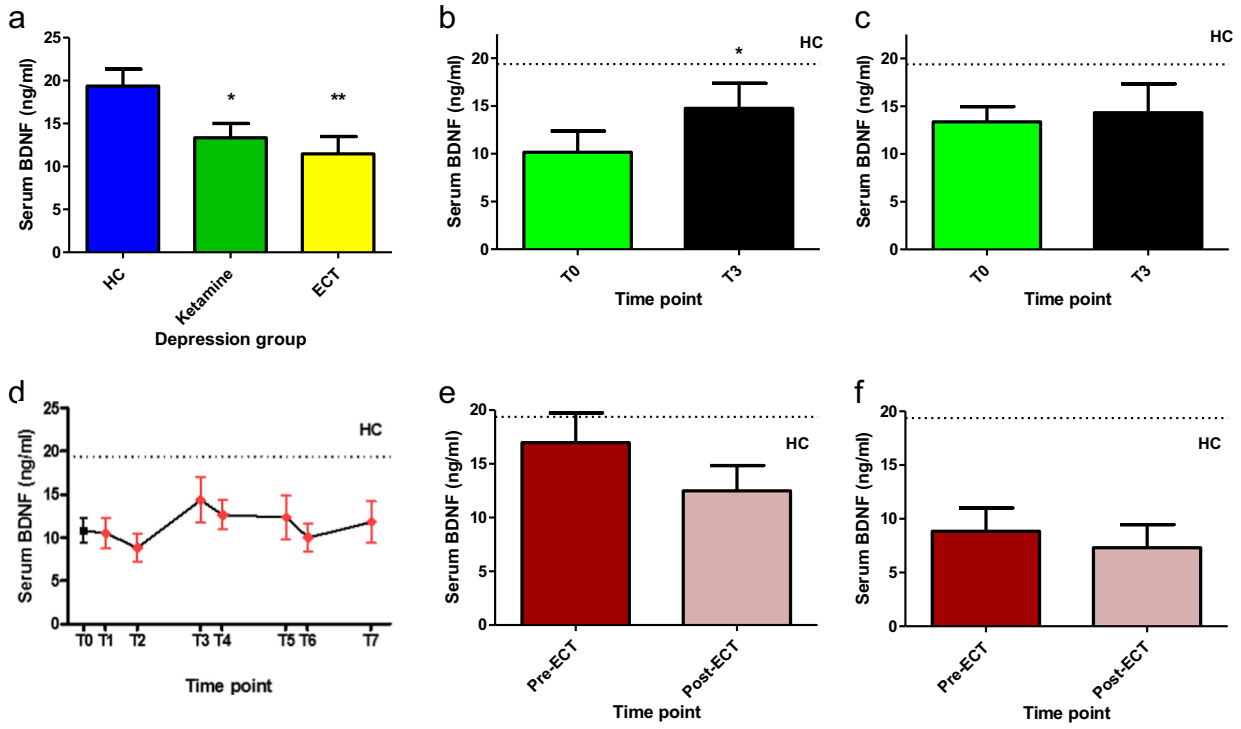

Fig. 2. (a) Baseline sBDNF in healthy controls versus treatment-resistant depression. Baseline sBDNF differed significantly between groups, $F(2, 49)=4.88$, $p=0.01$, partial eta squared=0.17. Post-hoc analyses indicated that the ketamine cohort had lower BDNF compared to healthy controls ($p=0.03$), as did the ECT cohort ($p=0.005$). However, the ketamine and ECT cohorts did not differ significantly from one another ($p>0.05$). Error bars represent standard error of the mean. * represents $p<0.05$. ** represents $p<0.01$. (b). sBDNF in ketamine responders at baseline (T0) and at 1 week post-infusion 1 (T3). Those who responded symptomatically to ketamine at 1 week post-first infusion (50% reduction in HDRS at this time point compared to baseline) had increased sBDNF at this time, $t(6)=-2.85$, $p=0.03$, Cohen's $d=1.08$. Dotted lines represent sBDNF levels for healthy controls. Error bars represent standard error of the mean. * represents $p<0.05$. (c). sBDNF in ketamine non-responders at baseline (T0) and at 1 week post-infusion 1 (T3). Those who did not respond symptomatically at T3 did not show an increase in serum BDNF at this time. Dotted lines represent sBDNF levels for healthy controls. Error bars represent standard error of the mean. (d). sBDNF following ketamine infusion for patients completing all three ketamine infusions (including non-responders). Dotted lines represent sBDNF levels for healthy controls. Error bars represent standard error of the mean. (e). sBDNF in ECT responders pre- and post-treatment. BDNF levels were lower post-ECT in those who responded to ECT, but this was not significant. Dotted lines represent sBDNF levels for healthy controls. Error bars represent standard error of the mean. (f). sBDNF in ECT non-responders pre- and post-treatment. ECT did not affect BDNF in non-responders. Dotted lines represent sBDNF levels for healthy controls. Error bars represent standard error of the mean.

All participants were interviewed using the Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998). All patients had a diagnosis of major depressive disorder and had failed to respond to at least two adequate trials of antidepressant medication, as assessed with a modified version of the Antidepressant Treatment History Form (Prudic et al., 1996, 1990; Sackeim et al., 2001, 1990). All healthy control participants were recruited from Cork University Hospital staff. Informed consent was obtained from all participants. (See Supplementary materials for detailed inclusion/exclusion criteria).

2.3. Procedure

Participants received either twice-weekly brief-pulse bi-temporal ECT or up to three sub-anaesthetic (0.5 mg/kg) intravenous infusions of ketamine once a week (see Supplementary materials for detailed procedure).

For all participants, a baseline (or healthy control) blood sample was collected in serum clot activated container between 8 a.m. and 11 a.m. on the morning of the first visit, prior to treatment. For the ketamine cohort, further samples were taken post-infusions (see Fig. 1a). For those receiving ECT, post-treatment serum was taken 4–7 days after the final session. In patients, the HDRS was administered at the same time points as blood samples.

2.4. Biochemical analysis

Serum was stored at −80 °C until analysis. sBDNF levels were assessed using MesoScale Discovery custom assays according to manufacturer's instructions (lower limit of detection=0.035 pg/ml).

2.5. Statistical analysis

Statistics were calculated using SPSS-18. A p-value of 0.05 was selected as the threshold of statistical significance. Data were parametric and were analysed by either Student's t-test or repeated measures ANOVA as appropriate.

3. Results

3.1. Participant characteristics

Patients did not differ significantly from healthy controls in terms of age (patients: mean age=49.1, SD=15.4, controls: mean age=42.85, SD=9.9, $p>0.05$) or gender profile (patients: 15 males, 20 females, controls: 10 males, 10 females, $p>0.05$). Of the 17 patients recruited for ketamine infusions, 17 had one infusion, 12 had two infusions and 10 had three infusions. The ketamine and ECT cohorts were similar in baseline depression severity (see Fig. 1b). For ECT treatment, patients received 5–12 sessions (median number of sessions=8). See Supplementary Table 1 for a clinical comparison of the ketamine and ECT cohorts.

3.2. Clinical effects of ketamine and ECT

Depression severity was reduced following ketamine infusion. Compared to baseline, HDRS scores were lower 2 h after all three infusions (see Fig. 1c). ECT also significantly reduced HDRS compared to pre-ECT baseline (see Fig. 1d). A majority of patients indicated a 50% or more reduction in HDRS at 2 h following the first infusion (see Supplementary Table 1).

3.3. Treatment-resistant depression and sBDNF

Baseline sBDNF differed significantly between TRD and HC groups. The ketamine and ECT cohorts had lower sBDNF compared to healthy controls. However, the ketamine and ECT cohorts did not differ from one another (see Fig. 2a).

3.4. Treatment response and sBDNF

Those classified as responders to ketamine at 1 week post-first infusion had increased sBDNF at this time (see Fig. 2b). However, sBDNF was only partially normalised compared to the healthy control group. Ketamine infusion did not increase sBDNF in non-responders at any time point, and ketamine infusion did not increase sBDNF in the ketamine cohort as a whole at any time post-treatment (see Fig. 2c and d). ECT did not normalise BDNF levels in those who responded to ECT, nor did it affect BDNF in non-responders (see Fig. 2e and f).

4. Discussion

The present results build on previous demonstrations of a rapid antidepressant effect of ketamine (Berman et al., 2000; Zarate et al., 2006), that is comparable to ECT (UK ECT Review Group, 2003). Our study design took account of the current literature on facilitating a sustained response by including multiple infusions. However, not all patients completed the three infusions. sBDNF levels were lower in TRD compared with healthy controls, consistent with evidence for reduced BDNF in MDD (Brunoni et al., 2008; Sen et al., 2008) and TRD specifically (e.g. Salehi et al., 2014). sBDNF levels were only enhanced one week post-infusion in those patients who met the criteria for response to ketamine at this time, suggesting a delayed effect incongruent with rapid symptomatic improvement. However, ketamine did not increase sBDNF in the ketamine cohort as a whole at any time post-treatment, nor was sBDNF enhanced at subsequent time points in those who responded at those time points. Unlike previous findings (Duncan et al., 2013; Haile et al., 2014), there was not a rapid effect of ketamine on BDNF. This may be because blood was sampled at two rather than four hours post-infusion. If this is the case, the order of these effects would challenge whether BDNF mediates antidepressant ketamine effects, as one would expect changes in BDNF to precede symptom improvement in this case. Neither of the recent studies which indicated a response at 4 h post-infusion examined blood at one week post-infusion, so further research on the timeframe of ketamine effects on symptoms and biomarker levels is required. Thus, although multiple infusions of ketamine may be required to maintain a clinical response, subsequent infusions did not increase sBDNF.

4.1. Limitations and strengths

A possible limitation is that patients were allowed to continue with other antidepressant treatments. However, the fact that sBDNF was lower at baseline compared to healthy controls suggests that reduced BDNF is resistant to first-line pharmacological therapies. There is controversy over the use of peripheral measures of BDNF and what they represent, as tissues other than the brain may act as a source of peripheral BDNF (Lommatzsch et al., 2005; Nockher and Renz, 2005). However, peripheral BDNF can rapidly cross the blood–brain barrier (Pan et al., 1998) and peripheral and CSF BDNF are highly correlated (Pillai et al., 2010). Hippocampal BDNF is reduced in patients with depression, and restored by antidepressant treatment (Chen et al., 2001; Karege et al., 2005), and serum BDNF and symptom severity are correlated (Teixeira et al., 2010).

The sample size in this study was small, but was sufficient to demonstrate expected differences between patients and healthy controls in BDNF levels and to pick up subtle time-dependent alterations following ketamine treatment. The sample size is also similar to that of previous studies which have demonstrated alterations in similar biomarkers (e.g. Bocchio-Chiavetto et al., 2006; Haile et al., 2014). Our results suggest the need for the evaluation of other mechanistically-oriented candidate biomarkers. In this regard, vascular endothelial growth factor (VEGF) may be an interesting option and, although variably altered in major depression (Clark-Raymond and Halaris, 2013), it does appear to be responsive to ECT (Minelli et al., 2011).

4.2. Summary

Our study confirms the comparable efficacy of ECT and ketamine in TRD. Ketamine transiently increased sBDNF in symptomatic responders at one week following a first infusion, but was not altered following subsequent infusions or in a manner that was consistent with symptomatic improvement. Similarly, symptomatic improvement post-ECT was not associated with normalisation of BDNF. This suggests a complex interplay between depression, neurotrophins and antidepressant responses that is difficult to accurately track using peripheral BDNF.

Contributors

Andrew P. Allen: Analysis of serum samples, statistical analysis.

Marie Naughton: Coordination of ketamine arm of project, submission of application to the local ethics committee and the Irish Medicines Board, participant recruitment, collation of questionnaire data, collection and preparation of blood samples.

John Dowling: Clinical evaluation of participants and administration of the ketamine infusion, including monitoring respiratory and cardiac function.

Abigail Walsh: Clinical evaluation of participants and administration of the ketamine infusion, including monitoring respiratory and cardiac function.

Fahmi Ismail: Monitoring of participants post-ketamine infusion alongside the senior registrars in anaesthetics.

George Shorten: Supervised and oversaw the project from an anaesthetic perspective.

Lucinda Scott: Participant recruitment.

Declan M. McLoughlin: Coordination of ECT arm of project.

John F. Cryan: Study design, management of project.

Timothy G. Dinan: Study design, management of project.

Gerard Clarke: Management of sample analysis, statistical analysis.

All authors contributed to and approved the submitted manuscript.

Conflict of interest

None.

Disclosure

None.

Role of funding source

The sources of funding were not involved in the study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

Acknowledgements

The Alimentary Pharmabiotic Centre is funded by Science Foundation Ireland (SFI), through the Irish Government's National Development Plan. The authors and their work were supported by SFI (Grant nos. SFI/12/RC/2273, 02/CE/B124 and 07/CE/B1368) and by the Health Research Board (HRB) through Health Research Awards (Grant nos. HRA_POR/2011/23; TGD, JFC and GC, and HRA_POR/2012/32; JFC, TGD). The Centre has conducted studies in collaboration with several companies including GSK, Pfizer, Wyeth and Mead Johnson. JFC is also funded by the European Community's Seventh Framework Programme (Grant no. FP7/2007–2013, Grant agreement 201714). GC is supported by a NARSAD Young Investigator Grant from the Brain and Behavior Research Foundation (Grant no. 20771).

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jad.2015.06.033.

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