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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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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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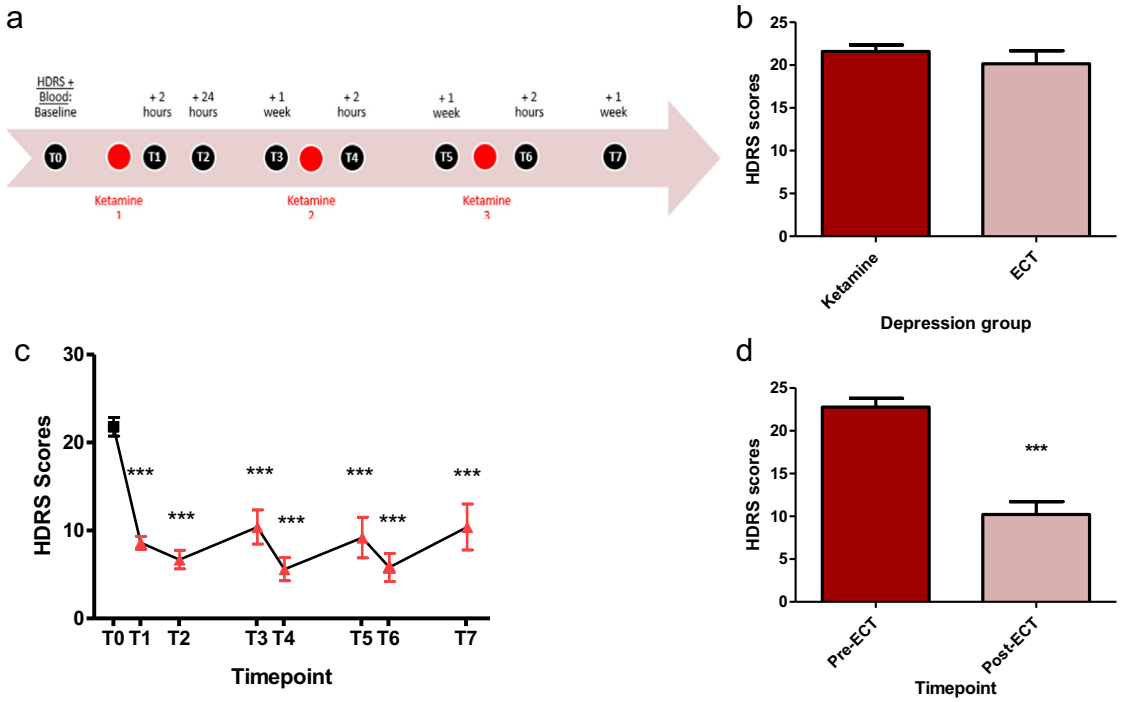

Fig. 1. (a) Sampling time points for ketamine cohort. (b) Baseline symptom severity in ketamine and ECT cohort. HDRS scores were not significantly different in the ketamine and ECT cohorts at baseline, $t(33)=0.83$, $p>0.05$, Cohen's $d=0.28$. (c) Depressive severity in TRD patients at baseline (T0) 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.