Are serum brain-derived neurotrophic factor levels related to symptom improvement following ketamine in treatment-resistant depression?

University College Cork, Ireland
Coláiste na hOllscoile Corcaigh

EMAIL: andrewallen@ucc.ie

Poster CG14P-0967 Allen, A.P.[1,2], Naughton, M.[1], Clarke, G.[1,2], Dowling, J.[3], Walsh, A.[3], Ismail, F.[1], Shorten, G.[3], Scott, L.[1], Cryan, J.F.[2,4], Dinan, T.G.[1,2]

1. Department of Psychiatry, University College Cork; 2. Alimentary Pharmabiotic Centre, University College Cork, Ireland; 3. Department of Anaesthesia and Intensive Care Medicine, University College Cork,; 4. Department of Anatomy & Neuroscience, University College Cork

Alimentary Pharmabiotic Centre

1. Introduction

Ketamine is associated with rapid antidepressant efficacy [**1**], but research is required to unearth the biological mechanisms underpinning this effect [**2**; see **Figure 1**]. Brain derived neurotrophic factor (BDNF), a neurotrophin associated with hippocampal neurogenesis, is reduced in depression and can be normalised following successful treatment. BDNF has thus emerged as a potential circulating biomarker of the ketamine response. Previous research has shown that ketamine enhancement of plasma BDNF four hours post-infusion in patients with treatment-resistant depression (TRD) was associated with symptomatic response to ketamine treatment [**3**]. However, although the clinical response to ketamine can persist for up to one week or longer, it is unknown if increases in BDNF are stable over this time period. Furthermore, although ketamine can occasionally be given repeatedly in off-licence protocols to patients with TRD, it is unknown if multiple infusions are additive or lead to sustained effects on BDNF levels.

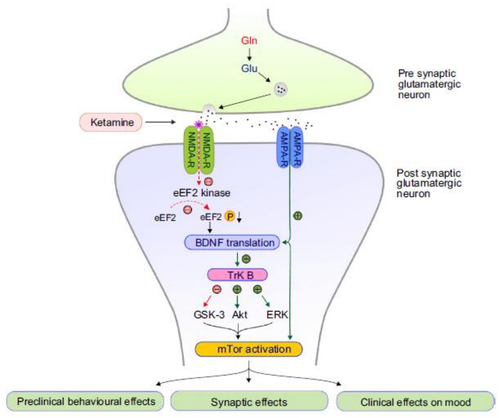

Figure 1 [Adapted from **2**]: Blockade of the NMDA receptor by the glutamatergic drug ketamine reduces activation of eukaryotic elongation factor 2 (eEF2), which results in the reversal of BDNF gene transcription silencing [**4**]. This in turn impacts upon mood via TrK B and mTor activation.

2. Aims & Hypothesis

Aim: Examine the effect of multiple ketamine infusions on the relationship between serum BDNF and severity of depressive symptoms. Hypothesis: Ketamine treatment has a rapid effect upon CNS BDNF, which is evident in an increase in serum BDNF that accompanies symptom improvement in treatment-resistant depression.

3. Methods

Participants

Age- and gender-matched patients with TRD (N = 17) and healthy controls (N = 20) were recruited. Exclusion criteria: >10% above ideal body weight, endocrine, immune or metabolic disorder. Severity of depression was assessed using the Hamilton Depression Rating Scale (HDRS). 76% of the TRD cohort had a diagnosis of major depressive episode- recurrent with melancholia and 6% had a diagnosis of major depressive episode with melancholia using the MINI-Neuropsychiatric interview. Patients who showed a 50% or greater HDRS reduction were classified as responders.

Table 1: Participant characteristics

	Healthy Controls	TRD
Males:Females	10:10	9:8
Mean age	42.85 (SD = 9.9)	41.9 (SD = 12.7)
Baseline HDRS	-	20.9 (SD = 5.1)

Procedure

1-3 infusions of ketamine (0.5mg/kg) were administered to TRD patients at visits one week apart. Blood samples were collected at baseline in all participants, and within the TRD cohort at 24 hours following the first infusion and at 2 hours and 1 week following each infusion (see **Figure 2**).

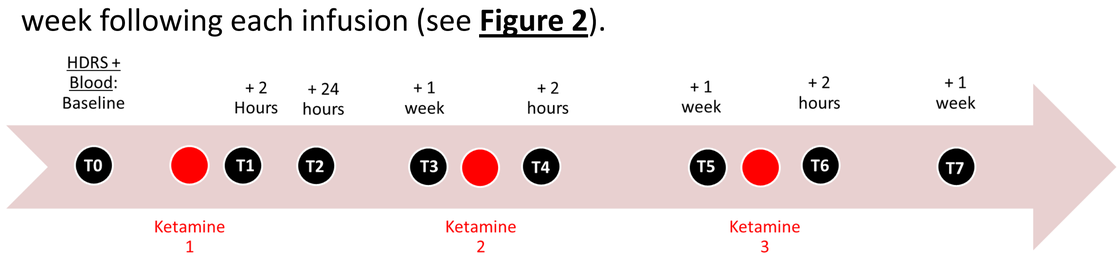

Figure 2: Study timeline

BDNF levels were assessed in serum using MesoScale Discovery custom assays according to manufacturer's instructions. Lower limit of detection = 0.035 pg/ml. For each sampling time, to assess the effect of ketamine treatment on BDNF, post-ketamine BDNF data were compared to corresponding baseline data for patients who responded symptomatically.

4. Results

Clinical effects of ketamine

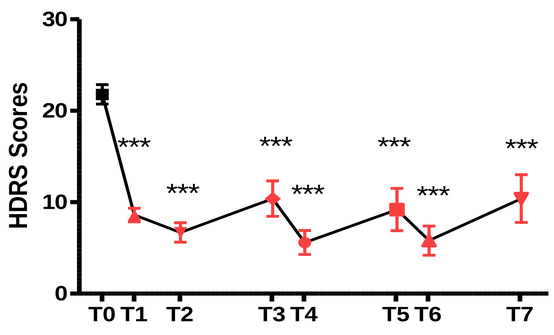

Figure 3: Clinical response to ketamine infusions

Ketamine was associated with a significant reduction in depressive symptoms, $F(2.3, 20.7) = 22.56$, $p < .001$, partial eta squared = .72.

Depression and serum BDNF

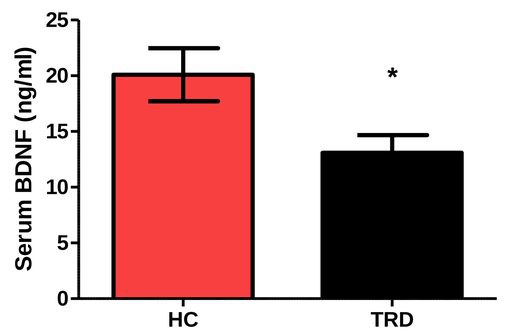

Figure 4: Baseline differences in serum BDNF

At baseline, the treatment-resistant depression group had significantly lower serum BDNF compared to the healthy controls, $t(34) = -2.26$, $p = 0.03$, Cohen's $d = 0.77$.

Ketamine effects on serum BDNF

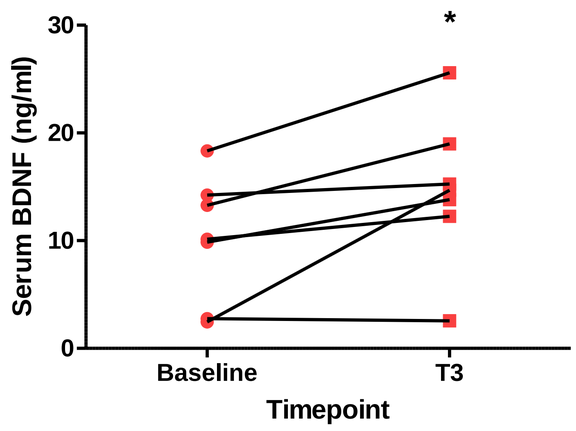

Figure 5: Effect of ketamine on BDNF in responders at T3

Patients who exhibited a sustained clinical response to ketamine at T3 showed enhanced BDNF at this time compared to baseline, $t(6) = -2.85$, $p = .03$, Cohen's $d = 1.08$.

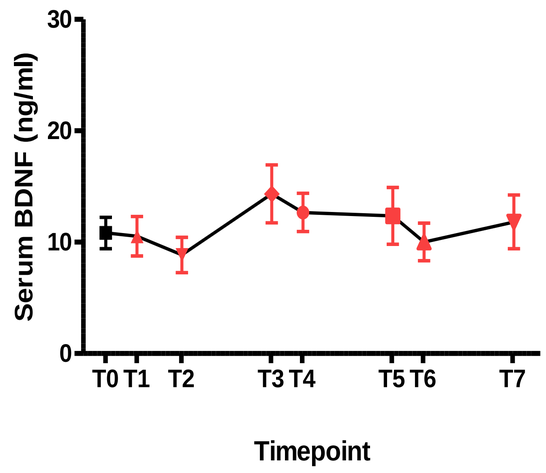

Figure 6: Effect of ketamine on serum BDNF

Ketamine was not associated with a significant change in serum BDNF overall, nor was it associated with clinical response at any time other than T3.

5. Discussion & conclusions

- Ketamine was associated with a significant reduction in depressive symptoms in a majority of patients.
- Treatment-resistant depression was associated with lower serum BDNF at baseline compared to healthy controls.
- At one week after the first infusion, those patients who responded to ketamine also had heightened serum BDNF.
- Future research is required to further clarify the potential importance of the delayed BDNF response to the initial ketamine infusion.

6. Acknowledgements & Disclosure

The Alimentary Pharmabiotic Centre is a research centre funded by Science Foundation Ireland (SFI), through the Irish Government's National Development Plan. The authors and their work were supported by SFI (grant numbers SFI/12/RC/2273, 02/CE/B124 and 07/CE/B1368) and by the Health Research Board (HRB) through Health Research Awards (grants no 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 201 714). GC is supported by a NARSAD Young Investigator Grant from the Brain and Behavior Research Foundation (Grant Number 20771). Thanks to Berniece Riedewald for assistance with image preparation. The first author gratefully acknowledgements funds received through the ECNP 2014 Travel Award.
The authors declare no conflict of interest.

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