The cortisol awakening response in treatment-resistant depression is not a biomarker of the clinical response to ketamine

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Alimentary Pharmabiotic Centre

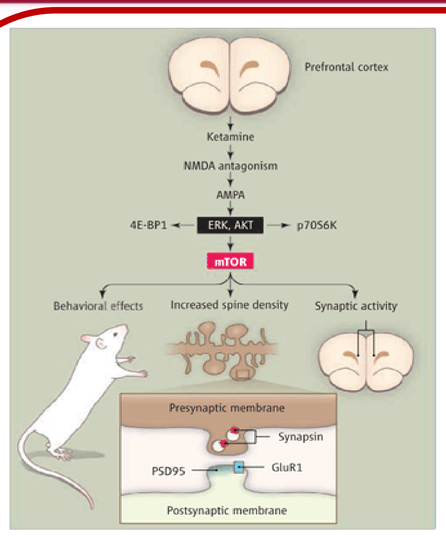


Figure 1: Rapid action of ketamine
Ketamine, an NMDA receptor agonist, produces rapid antidepressant effects, although the underlying mechanism is currently unknown [4].

1. Introduction

Many patients suffering from depression do not respond to antidepressant therapy [**1**]; novel therapeutic strategies are therefore required. Ketamine is associated with rapid antidepressant efficacy [**2**]. However, as it is also associated with psychotomimetic effects [**3**] research is urgently required to unearth the biological mechanisms underpinning ketamine's antidepressant efficacy [**4**; see **Figure 1**]. The hypothalamic-pituitary-adrenal axis [HPA axis; see **Figure 2**] responds to stress and is altered in depression, as evidenced by an altered cortisol awakening response (CAR). However, it has not yet been investigated if ketamine can impact upon the CAR in treatment-resistant depression. Furthermore, it is unknown if the clinical response to ketamine may moderate any effects on the CAR.

2. Aims & Hypothesis

Aim: Examine the effect of multiple ketamine infusions on the relationship between the cortisol awakening response and severity of depressive symptoms. Hypothesis: Ketamine treatment has a normalising effect upon the HPA axis, which is evident in normalised cortisol awakening response.

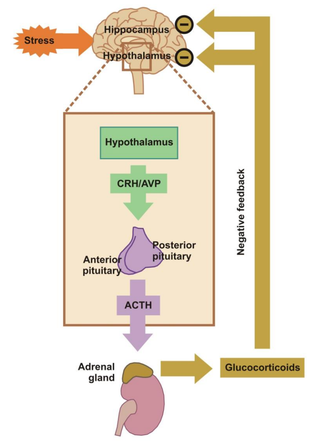


Figure 2: The HPA axis
In response to a stressor, the hypothalamus triggers a chain of CNS events leading to glucocorticoid release by the adrenal cortex [5].

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. Saliva was collected at awakening, 30 and 150 minutes after awakening for assessment of CAR; at baseline in all participants, and within the TRD cohort at one week following each infusion (see **Figure 2**). HDRS was taken 2 hours post-infusion and 24 hours post infusion 1 to assess rapid clinical response.

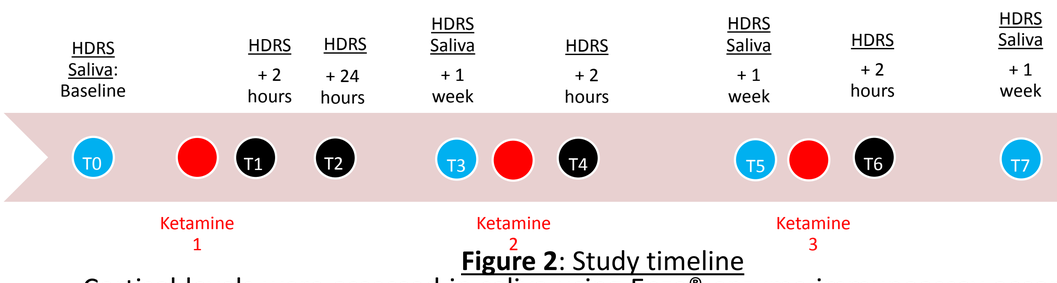


Figure 2: Study timeline

Cortisol levels were assessed in saliva using Enzo® enzyme immunoassay according to manufacturer's instructions. Assay detection limit was 0.16 nmol/L. Inter and intra-assay % C.Vs were 11.24% and 8.2% respectively. The overall impact of ketamine on CAR was assessed using ANOVA and t-tests as appropriate. To assess the effect of clinical response to ketamine on CAR, post-ketamine CAR data were compared to corresponding baseline data for patients who responded symptomatically.

4. Results

Clinical effects of ketamine

Figure 3: Mean clinical response to ketamine

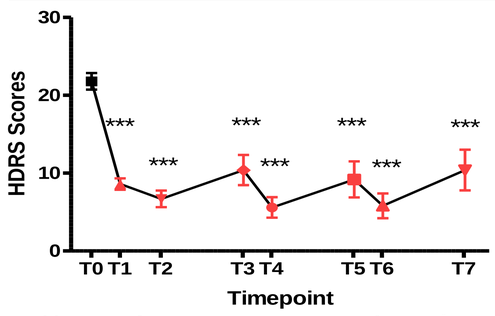


Table 2: Ketamine response rates

	T1	T2	T3	T4	T5	T6	T7
Ketamine Response Rate	13/17 (76%)	13/16 (81.5%)	7/15 (47%)	11/11 (100%)	8/11 (72%)	9/9 (100%)	6/9 (67%)

Ketamine was associated with a significant reduction in depressive symptoms, $F(2.3, 20.7) = 22.56$, $p < .001$, partial eta squared = .72 (see **Figure 3**). At all timepoints, a majority of patients responded symptomatically to ketamine infusion (see **Table 2**).

Depression and CAR

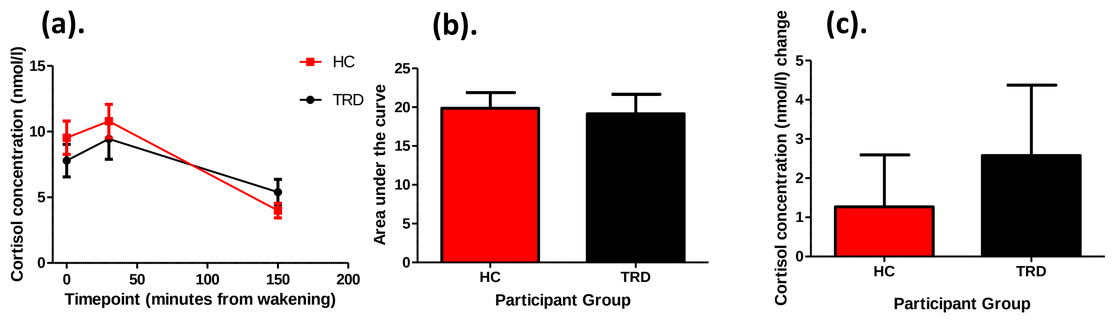
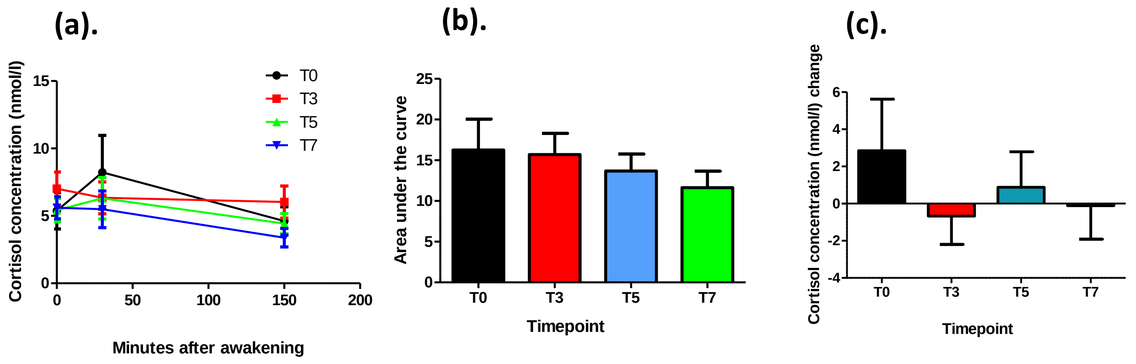


Figure 4: Baseline differences in (a). cortisol awakening response, (b). AUCg (c). delta

At baseline, the treatment-resistant depression group did not differ significantly from healthy controls in terms of (a). cortisol awakening response, (b). AUCg or (c). delta.

Ketamine effects on CAR



Ketamine treatment was not associated with a significant change in (a). CAR, (b). AUCg or (c). delta, and clinical response was not associated with a change in any of these parameters.

5. Discussion & conclusions

- Ketamine was associated with a significant reduction in depressive symptoms in a majority of patients.
- Treatment-resistant depression was not associated with an altered cortisol awakening response.
- Neither ketamine treatment nor clinical response to ketamine were associated a change in the cortisol awakening response.
- Further research is required to better describe the biological underpinnings of the clinical effect of ketamine.

6. Acknowledgements & Disclosure

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The authors declare no conflict of interest.

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