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.

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). 70% 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

<table>
<thead>
<tr>
<th>Health Control</th>
<th>TRD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males/Females</td>
<td>10:10</td>
</tr>
<tr>
<td>Mean age</td>
<td>42.85 (SD = 9.9)</td>
</tr>
<tr>
<td>Baseline HDRS</td>
<td>41.9 (SD = 12.7)</td>
</tr>
</tbody>
</table>

Procedure

1-3 infusions of ketamine (0.5mg/kg) were administered to TRD patients at visits each 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

4. Results

Clinical effects of ketamine

Ketamine was associated with a significant reduction in depressive symptoms, F(7, 20.7) = 22.56, p < 0.001, 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

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 with 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

The Alimentary Pharmacological 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 11/L2/2273, 02/CE/2124 and 07/CE/1836). and by the Health Research Board (HRB) through Health Research Awards (grants no. HRG/2010/29; TIG, JFC and GC; and HRG/2012/22; JFC; TIG). The Centre has also received funding from several companies including GSK, Pfizer, Wyeth and Meda Johnson. JFC is also funded by the European Community’s Seventh Framework Programme (grant no: FP7/2007-2013, grant agreement 201371). GC is supported by a NARSAD Young Investigator Grant from the Brain and Behavior Research Foundation (Grant Number 207713). Thanks to Dr Marcela Julia for assistance with image preparation. The first author gratefully acknowledges funding received through the ECPN 2014 Travel Award.

The authors declare no conflict of interest.

7. References


Figure 1: Rapid action of ketamine

Ketamine, an NMDA receptor agonist, produces rapid antidepressant effects, although the underlying mechanism is currently unknown [4].

Figure 2: The HPA axis

Ketamine, an NMDA receptor agonist, produces rapid antidepressant effects, although the underlying mechanism is currently unknown [4].