Rapid Antidepressant Response to Ketamine in Treatment-resistant Depression is Not Dependent on Normalising Kynurenine Pathway Metabolism

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1. Introduction

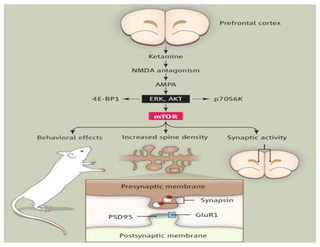

Figure 1: Rapid Action of Ketamine
Ketamine, an NMDA receptor antagonist, produces rapid antidepressant effect via an as yet unknown mechanism [1].

The delay in onset of action and the fact that a substantial proportion of patients fail to achieve remission after antidepressant therapy are serious limitations of current standard of care treatments for major depression. Recently, the NMDA receptor antagonist ketamine has emerged as a fast acting antidepressant with therapeutic potential for treatment-resistant depression (TRD) cohorts but its clinical use is hampered by its psychotomimetic properties [2]. Biological markers of the rapid antidepressant response associated with ketamine are urgently required to understand its mechanism of action and to facilitate the rational design of rapidly acting antidepressants without the deleterious side effect profile and abuse potential. The kynurenine pathway has been suggested as a putative target for ketamine [3].

2. Hypothesis & Aims

Hypothesis: Ketamine treatment rapidly reverses abnormal kynurenine pathway metabolism and that this effect mediates the clinical improvement in TRD Aim: To monitor the production of kynurenine from tryptophan at multiple time points following ketamine infusion.

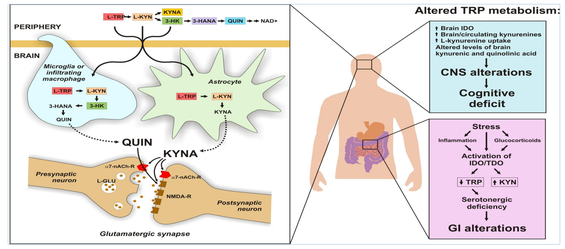

Figure 2: The Kynurenine Pathway
Tryptophan metabolism along the kynurenine pathway produces neuroactive metabolites which may modulate glutamatergic neurotransmission [4].

3. Methods

Age- and gender-matched patients with TRD (N = 17) and healthy controls (N = 20) were recruited. 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. 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 2 hours, 24 hours and 1 week following the first infusion and at 2 hours and 1 week following each subsequent infusion as per timeline below.

Procedure

Table 1: Study Participants

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

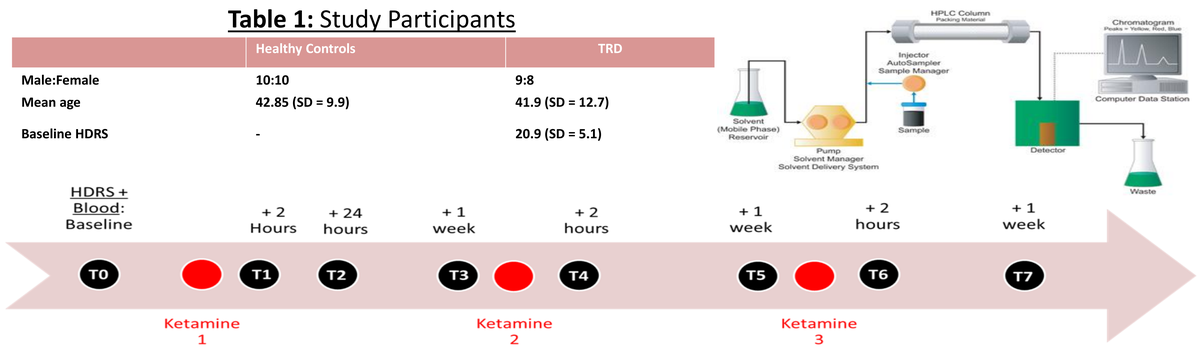

Figure 3: Study Protocol Tryptophan and kynurenine pathway metabolites were measured in plasma by HPLC. Samples were collected at baseline (T0) and at multiple time points following repeated ketamine infusion (T1-T7).

4. Results

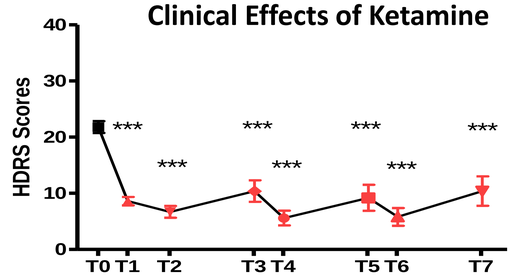

Figure 4: Clinical response to ketamine infusions
Ketamine was associated with a significant reduction in depressive symptoms (p <0 .001)

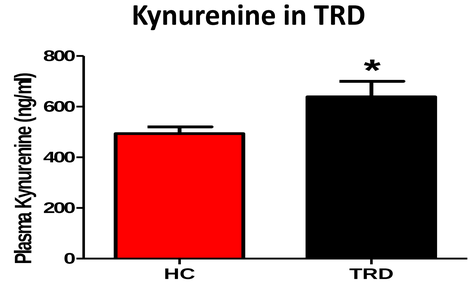

Figure 5: Baseline elevation in kynurenine
Significantly elevated kynurenine in TRD compared to the healthy controls (P<0.05)

Treatment has no effect on altered kynurenine pathway metabolism in TRD

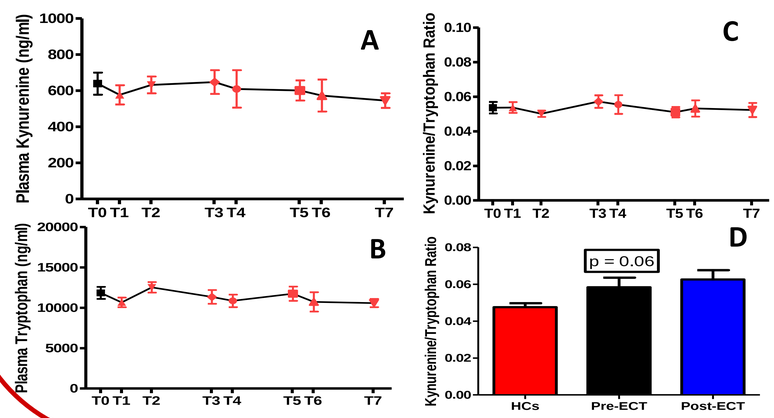

Figure 6: Effect of treatment on tryptophan and kynurenine

Ketamine treatment did not reduce the elevated kynurenine concentrations in the TRD cohort at any time point following the first or subsequent ketamine infusions (p > 0.05). Moreover, there was no effect of repeated ketamine infusion on tryptophan concentrations or the kynurenine:tryptophan ratio at any time point evaluated (A-C). In a separate TRD cohort, ECT treatment also improved symptoms but did not normalise kynurenine pathway metabolism as indicated by the kynurenine:tryptophan ratio (D).

5. Discussion & Conclusions

- Ketamine was associated with a significant and rapid reduction in depressive symptoms in a majority of patients.
- Increased tryptophan metabolism along the kynurenine pathway may be a hallmark of TRD
- A positive treatment outcome in TRD is not dependent on normalising kynurenine pathway abnormalities
- Future studies should assess whether kynurenine pathway abnormalites can be used to optimise treatment selection strategies for particular patient subgroups

6. Acknowledgements & Disclosure

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7. References

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