

## **The Kynurenine Pathway and Bipolar Disorder: The Intersection of the Monoaminergic, Glutamatergic Systems and Immune Response**

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**Methodological Question Being Addressed:** Alterations in glutamate metabolism have been implicated in pathophysiology of depression and treatment resistance. Multiple lines of evidence indicate that abnormal activation of kynurenine (KYN) pathway may trigger production of microglial byproducts that alter glutamate release/reuptake and ultimately leading to decreased neurotrophic support and excitotoxicity. This study aimed on assessing the impact of ketamine on kynurenine pathway in patient with treatment-resistant bipolar disorder, as well as assessing its interrelation with behavioral and peripheral inflammatory markers related to depression.

**Background:** Growing evidence from both animal and human clinical studies supports the hypothesis that the underlying pathophysiology of depression implicates dysfunction in wide array of systems, including immune, monoaminergic and glutamatergic system. One potential intersection point for these three systems is the kynurenine (KYN) pathway of tryptophan metabolism. We explored the potential impact of ketamine on attenuating the pro-inflammatory effects of KYN pathway activation in subjects with bipolar disorders (BD).

**Methods:** Thirty-nine BD patients with treatment-resistant depression (23F, 18-65-years-old). Subjects received a single infusion of ketamine (0.5 mg/kg) over 40 minutes. Using specific ELISA kits, KYN pathway analytes—including plasma concentration of indoleamine-2,3-dioxygenase (IDO), kynurenine, kynurenic acid (KA), and quinolinic acid (QA)—were studied at 60 minutes prior to infusion (baseline), and 230 minutes, Day 1, and Day 3 post-infusion. General linear models with restricted maximum likelihood estimation and robust sandwich variance estimators were implemented. A repeated effect of time was used to model the covariance of the residuals with an unstructured matrix.

**Results:** After controlling for age, sex and BMI, post-ketamine IDO levels were significantly reduced from baseline at all three time points. Inversely, ketamine administration both KYN and KA were significantly elevated at Days 1 and 3 relative to baseline. No change in QA levels was observed post-ketamine. Interestingly, a post-ketamine reduction in the QA/KYN ratio was observed at Day 1. We observed that at baseline pro-inflammatory cytokines and behavioral measures predicted change in the KYN pathway in response to ketamine.

**Conclusions:** Overall, this result suggests that ketamine, in addition to its rapid and sustained antidepressant effect in patients with bipolar depression, also impacts key components of the kynurenine pathway. This pathway is positioned at the interaction where immune, monoaminergic and glutamatergic system interrelate. In the future, we aim on adding findings from the placebo arm.