Activation of inflammation and stress conditions within the brain contribute to treatment-resistant bipolar depression. 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.

STUDY AIMS

- We sought to examine whether a single infusion (0.5 mg/kg over 40 minutes) of the glutamatergic modulator ketamine could alter the potential proinflammatory and excitotoxic effects associated with downstream activation of KYN metabolites.
- Examined the impact of baseline proinflammatory cytokines (TNF-α, sTNFR1, IFN-γ, IL-1, IL-6, IL-8) and anti-inflammatory markers (Il-2, IL-8 (negative loading), and IL-10) on kynurenine pathway
- Assessed whether baseline kynurenine pathway analytes predicted changes in depressive symptoms post-ketamine infusion.

METHODS

STUDY DESIGN AND KYNURENINE PATHWAY MEASURES IN BIPOLAR DEPRESSION

RESULTS

BASELINE INFLAMMATORY MARKERS AS MODERATORS OF CHANGE IN KYNURENINE PATHWAY (PANEL A) AND BASELINE KYNURENINE PATHWAY AS MODERATORS OF CHANGE IN DEPRESSION SYMPTOM RATINGS (PANEL B)

CONCLUSIONS

- We found that single ketamine infusion induced significant decrease in brain IDO of patient with bipolar disorder, while increased the levels of Kyn and KynA.
- Ketamine-induced increase in hepatic kynurenine production is expected to counter the substantial peripheral - pro-inflammatory state of depressive illness. On the other hand, increased hepatic kynurenine production presents a greater kynurenine load to the brain.
- While this might ordinarily increase the rise of the production of toxic metabolites, ketamine-induced suppression of IDO would protect against this potential eventuality.
- This work highlights the significant salutary effect of ketamine not only in core components of depressive symptoms but also in the interplay of inflammatory, monoaminergic and glutamatergic pathways in patients with bipolar depression.
- Only studies of larger scales that aim on addressing neuroinflammatory pathway both centrally and peripherally are needed to confirm these preliminary findings.

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REFERENCES