Where did the tryptophan go? A meta-analytic journey through the kynurenine system in major depression, schizophrenia, and bipolar disorder

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List of Abbreviations: Bipolar Disorder (**BD**); Cerebrospinal Fluid (**CSF**); Indoleamine 2,3-dioxygenase (**IDO**); Kynurenine 3-monooxygenase (**KMO**); Kynurenic Acid (**KYNA**); Major Depressive Disorder (**MDD**); Non-Steroidal Anti-inflammatory Drugs (**NSAIDs**); Quinolinic Acid (**QUINA**); Tryptophan 2,3-dioxygenase (**TDO**).

Introduction

What it the Kynurenine Pathway?

Tryptophan is an essential amino acid that is absorbed in varying levels in the gut depending on a homeostatic microbiome. Among other elements, tryptophan can be converted into bioactive compounds like serotonin and melatonin. However, up to 95% of the tryptophan degradation in humans is performed by the kynurenine pathway (Wolf, 1974), which yields NAD^+ and other tryptophan catabolites (TRYCATs) as its core end products.

Altered levels of TRYCATs have been implicated in tumor progression, type 2 diabetes, and the modulation of immune and inflammatory responses, most notably regulated by proinflammatory cytokines such as TNF-α and IL-1β, and toll-like receptor agonists such as LPS, which enhances IDO expression.

Recent studies identified conflicting associations between altered levels of TRYCATs and genetic polymorphisms in MDD, schizophrenia, and BD. Despite clear evidence suggesting that neuro-inflammatory pathways might influence the pathogenesis of schizoaffective spectrum disorders and biological evidence that cytokine levels directly influence levels of TRYCATs, no firm conclusions have been drawn about specific directions in which levels of TRYCATs change, and its clinical significance remains largely unknown.

Methods

We screened original studies on MEDLINE, EMBASE, Cochrane, and PsycINFO that collected levels of TRYCATs from blood or CSF of healthy adults and compared against adult participants diagnosed with type 1 BD, schizophrenia, or MDD without comorbid psychiatric diagnoses. We used comprehensive meta-analysis version 3.0 to analyze the data in a random-effects model (Hedge's g for effect size; p<0.05 for statistical significance).

Results

A total of 1,343 entries were screened, and 36 studies were included in the overall analysis. When compared with healthy controls, participants diagnosed with MDD had moderately decreased levels of tryptophan associated with a moderate increase of Kynurenine/Tryptophan ratios (**Figure 1).** In addition, levels of KYNA and the ratio KYNA/QUINA were also moderately decreased. No significant differences were found in schizophrenia during the overall analysis. Only three studies met inclusion criteria for the overall model of bipolar depression. These participants had a mild decrease of 3-HK, moderate decrease of kynurenine, and a significant reduction of KYNA levels.

Participants diagnosed with schizophrenia had no differences in any of the TRYCATs. However, KYNA studies found opposing directions of effect sizes depending on sample source, with higher KYNA when collected from the CSF and lower levels in the periphery.

Few studies evaluated TRYCATs in BD. Depressed participants had a significant decrease of KYNA and mild decreases in kynurenine and 3-Hydroxy-Kynurenine. Although a trend for lower tryptophan was also observed, it did not reach statistical significance.

Figure 1 - Cross-diagnostic Amazonia plot

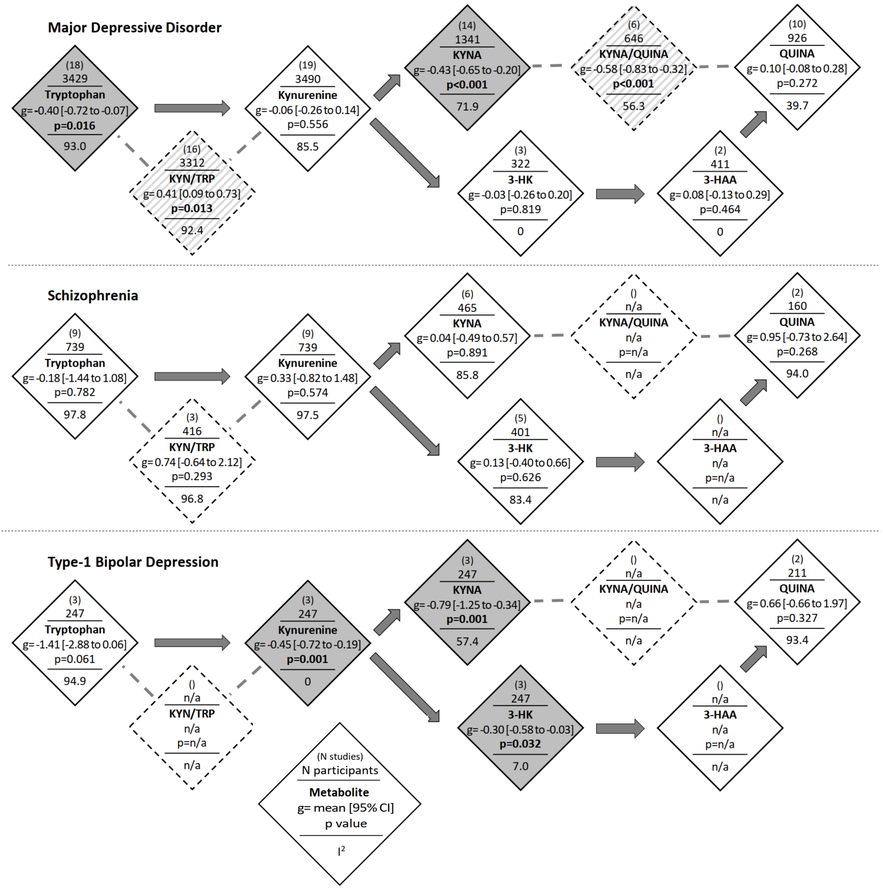

Figure 1: Levels of tryptophan and kynurenines of healthy controls were compared against participants diagnosed with major depressive disorder (MDD), schizophrenia, and bipolar disorder. Each diamond shape represents the overall results for metabolites (solid lines) or their ratios (dashed lines), as well as data about the number of studies, sample size, and heterogeneity (I^2).

Discussion

What influences levels of TRYCATs?

Levels of TRYCATs are influenced by the activity of enzymes related to the kynurenine system (**Figure 2**), which is in turn determined by genetic polymorphisms, levels of cytokines, and other inflammatory factors.

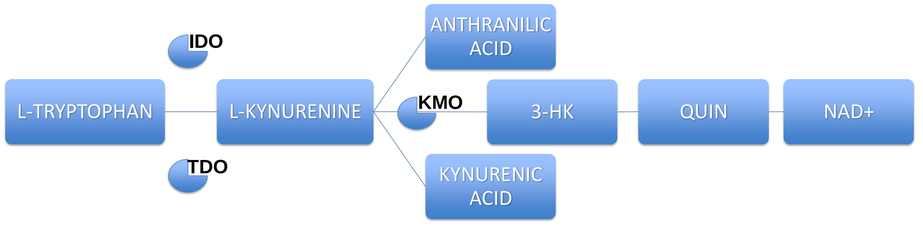

Figure 2: Elements of the kynurenine pathway are metabolized by distinct enzymes at different ratios depending on the anatomic site. Only negligible levels of KYNA and QUINA crosses the blood-brain barrier, and about 60% of kynurenine comes from the periphery. Therefore, most of the CNS KYNA is locally produced by astrocytes, whereas the microglia generate QUINA. This process is fine-tuned by type 1 and 2 cytokines, which stimulate the activity of IDO mainly under the influence of TNF-α and IFN-γ levels to use more or less L-Kynurenine.

Why is there significant heterogeneity in these results?

MDD, schizophrenia, and bipolar disorders appear to be polygenic in nature. Hence, the effect sizes of individual genes to manifest unique psychopathologic traits is rather small when compared with canonical Mendelian disorders (e.g. Cystic fibrosis). **Increased genetic and epigenetic heterogeneity may also lead to clinically diverse phenotypes**, not to mention the possibility of endophenotypes (subgroups with similarly manifested traits) and phenocopies (environmental factors leading to a clinically similar phenotype). Of note, the first Genome-Wide Association Study (GWAS) that investigated TRYCATs was published in 2016, by Sellgren *el al*, who found that **elevated cerebrospinal fluid levels of kynurenic acid were associated with positive psychotic symptoms and executive function deficits in bipolar disorder** with a common variant within 1p21.3, which was linked with reduced SNX7 expression. Similarly, our results indicate that CSF levels of KYNA were increased in participants diagnosed with schizophrenia, an association that warrants further investigation. Also, both bipolar and unipolar depression shared the reduction in levels of KYNA, although its clinical significance remains unclear.

Are TRYCATs, inflammation, and monoamines connected?

Both quinolinic and kynurenic acid impact glutamatergic neurotransmission through NMDA and α-7 nicotine receptors, while cytokines and other immune/inflammatory elements modulate the transcription and activity of enzymes related to the kynurenine system. This framework suggests crosstalk between neurotransmitter and neuroinflammatory pathways to regulate complex neurophysiologic functions (e.g. neuroplasticity), which may lastly influence psychiatric presentations. In addition, levels of TRYCATs may be modulated by dietary changes, the use of probiotics, exercise, and management of inflammation with NSAIDs, which may open additional venues to individualized psychiatric treatment.

Conclusions

- ✓ Both **inflammatory** and **genetic factors** can shift the balance between the serotonin and kynurenine poles of tryptophan metabolism;
- ✓ Neurotransmitter systems are influenced by levels of TRYCATs (especially glutamate). **This suggests that TRYCATs might be involved in neuroplastic** changes that occur in the MDD, schizophrenia, and BD;
- ✓ Increased CSF levels of KYNA were found in individuals diagnosed with schizophrenia, and preliminary data suggest that this might be shared during a psychotic episode of bipolar disorder;
- ✓ Future studies are necessary to control for potential confounding factors that interfere with enzymes of the kynurenine system, so that we can understand its influence in the pathogenesis of clinical endophenotypes.

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Abstract

Aims: To understand how tryptophan catabolic pathways are altered in major depressive disorder (**MDD**), schizophrenia, and bipolar disorder (**BD**), as well as how these changes may connect with clinical endophenotypes and unique treatment strategies. **Background:** Tryptophan is a large essential amino acid that is absorbed in varying levels by the gut depending on a homoeostatic microbiome. Up to 95% of unbound tryptophan is converted into Tryptophan Catabolites (**TRYCATs**) through the kynurenine system, which has been implicated in tumor progression, type 2 diabetes, and the modulation of immune and inflammatory responses. Recent studies identified conflicting associations between altered levels of TRYCATs and genetic polymorphisms in MDD, schizophrenia, and BD. However, its clinical significance remains unknown. **Methods:** We screened original studies that collected levels of TRYCATs from blood or CSF of healthy adults and compared against adult participants diagnosed with type 1 BD, schizophrenia, or MDD without comorbid psychiatric diagnoses. We used comprehensive meta-analysis version 3.0 to analyze the data in a random-effects model (Hedge's g for effect size; p<0.05 for statistical significance). **Results:** A total of 1,343 entries were screened, and 36 studies were included in the overall analysis. When compared to healthy controls, participants diagnosed with MDD had moderately lower levels of tryptophan associated with a moderate increase of kynurenine/tryptophan ratios with no difference in kynurenine. Patients diagnosed with MDD also had moderately lower levels of Kynurenic Acid (**KYNA**) and KYNA/**QUINA** (Quinolinic Acid) ratios with unaltered levels of QUINA. Participants diagnosed with schizophrenia had no differences in any of the TRYCATs. However, KYNA studies found opposing directions of effect sizes depending on sample source, with higher KYNA when collected from the CSF and lower levels in the periphery. Few studies evaluated TRYCATs in BD. Depressed participants had a significant decrease of KYNA and mild decreases in kynurenine and 3-Hydroxy-Kynurenine. Although a trend for lower tryptophan was also observed, it did not reach statistical significance. **Conclusions:** Both quinolinic and kynurenic acid impact glutamatergic neurotransmission through NMDA and α-7 nicotine receptors, while cytokines and other immune/inflammatory elements modulate the transcription and activity of enzymes related to the kynurenine system. This framework suggests crosstalk between neurotransmitter and neuroinflammatory pathways to regulate complex neurophysiologic functions (e.g. neuroplasticity), which lastly influences psychiatric presentations. Levels of TRYCATs may be changed by dietary changes, the use of probiotics, exercise, and management of inflammation with NSAIDs. Future studies are necessary to control for potential confounding factors that interfere with enzymes of the kynurenine system so that we can understand its influence on clinical endophenotypes.