Tryptophan Challenge in People with Schizophrenia and Healthy Controls: Acute Effects on Circulating Kynurenine and Kynurenic Acid, Cognition and Cerebral Blood Flow

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INTRODUCTION

- Cognitive impairments may be causally related to increased levels of kynurenic acid (KYNA), a major metabolic product of tryptophan (TRYP).
- In the brain, KYNA acts as an antagonist of the of α7-nicotinic acetylcholine and glutamatergic NMDA receptors, both of which are involved in cognitive processes.
- We examined whether KYNA plays a role in the pathophysiology of schizophrenia, comparing the acute effects of a single oral dose of TRYP (6 g) in 32 healthy controls (HC) and 37 people with a schizophrenia-related disorder (PSz).
- **Study Aims**: To evaluate whether an acute TRYP challenge, relative to placebo, would (1) significantly elevate plasma kynurenine and KYNA levels; (2) impair performance of cognitive tasks hypothesized to be impaired by KYNA antagonism on α7 nicotinic and NMDA receptor function; and (3) impact resting brain cerebral blood flow (CBF).

Table 1. Demographic and Clinical Information

	HC (n=32)	PSz (n=37)	t or χ^2 statistic	p-value
Age (years)	35.9±11.4	34.8±9.9	-0.43	0.67
Sex (M/F)	16/16	26/11	0.09	0.14
Race (%)	47% Black, 38% White, 6% Asian, 9% Mixed	51% Black, 41% White, 5% Asian, 3% Mixed	1.45	0.69
BPRS score	n/a	32.6±8.7		
BACSS	49.1±11.2	36.4±14.0	-4.1	<0.001
HVLT-R	52.0±8.7	38.9±10.0	-5.7	<0.001
WMSIISS	50.5±10.6	41.0±11.4	-3.6	0.001
LNS	50.0±11.1	40.0±11.2	-3.7	<0.001
BVMT-R	47.5±11.5	36.6±12.6	-3.7	<0.001
CPTIP	48.3±10.8	39.7±11.8	-3.2	0.002

BACSS: BACS Symbol Coding; BPRS: Brief Psychiatric Rating Scale; BVMT-R: Brief Visuospatial Memory Test Revised; CPTIP: Continuous Performance Test Identical Pairs; HVLT-R: Hopkins Verbal Learning Test Revised; LNS: Letter-Number Sequencing; WMSIISS: Working Memory III Spatial Span; HC: healthy controls; PSz: participants with a schizophrenia-related disorder

METHODS

- Design: Randomized, double-blind, placebo-controlled, crossover study (e.g all participants completed both challenge days of TRYP treatment and placebo; randomized to the order that they received TRYP or placebo).
- PSz were treated with antipsychotic medication(s) for at least 60 days and were taking a stable dose of antipsychotic medication for the last 30 days.
- For the active-treatment arm of the study, TRYP slurry was prepared by mixing 6 g of TRYP with 7.8 g of Domino 10X Confectioner's Sugar (Yonkers, NY, USA) and 6 g of Nestlé's Cocoa mix (Glendale, CA, USA). Placebo slurry was prepared using lactose monohydrate powder in place of TRYP .
- On each challenge day, participants…

(a) had blood drawn 105 min before (baseline fasting levels) and 30, 60, 90 and 240 min after the ingestion of TRYP or placebo to examine plasma levels of kynurenine and KYNA

(b) completed 6 cognitive assessments from the MATRICS battery at baseline and ~240 min after the administration of TRYP/placebo (post-treatment).

(c) completed an MRI scan approximately 2 hr following TRYP or placebo, which included a pseudo-continuous arterial spin labeling (ASL) scan.

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METHODS

- Following preprocessing of the ASL data (following the guidelines of Alsop et al. 2015), partial volume corrected CBF maps were used to extract the whole-brain CBF (in ml/100 g/min) averaged across all voxels in the gray matter mask. The average CBF signals (in ml/100 g/min) for 48 bilateral cortical regions of interest (ROIs) were extracted using the Harvard-Oxford cortical maximum probability maps template, and for two subcortical ROIs (bilateral hippocampus, bilateral dorsal striatum) from the Brainnetome atlas.
- Partway through the trial, the MR scanner was upgraded from a Siemens Trio 3T MR system to a Siemens PRISMA^{fit} MR system, resulting in different scales of measured CBF intensity for values obtained from the Trio scanner vs. the PRISMA scanner. To harmonize these values, we applied the NeuroCombat harmonization procedure (https://github.com/Jfortin1/neuroCombat).
- Statistical Analysis: Using R software, linear mixed effect models estimated the main effect of TRYP (relative to placebo), the main effect of diagnosis (PSz vs. HC), and potential TRYP*diagnosis interaction effects on the major outcome measures described in the Study Aims. Conservative Bonferroni correction was applied to correct for multiple statistical tests.

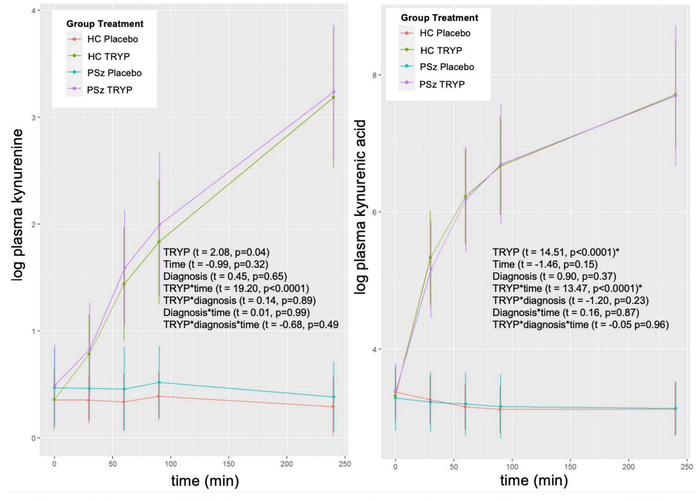

Figure 1. Effects of TRYP Administration on Plasma Levels of Kynurenine and KYNA. Compared to placebo (HC in red; PSz in blue), the plasma levels of both kynurenine and kynurenic acid showed robust responses to TRYP treatment in both healthy controls (HC; green; N=32) and participants with a schizophrenia-related disorder (PSz; purple; N=37). Responses to TRYP treatment were not significantly different across PSz and HC groups, such that the TRYP*diagnosis and TRYP*diagnosis*time interaction effects were not significant. Error bars represent standard error of the mean.

RESULTS

- For both plasma kynurenine and KYNA, there were significant main effects of TRYP and significant TRYP*time effects (**Fig 1**). Responses to TRYP were similar in both groups, such that the TRYP*diagnosis interaction effects were non-significant.

Use this QR code to check out our study recently published online (28 Apr 2023) at *Neuropsychopharmacology!*

Use this QR code to connect with Dr. Hare on LinkedIn!

RESULTS

- Eight participants' ASL data did not pass quality control assessment (n = 61; 31 HC and 30 PSz), which included visual examination of the CBF maps and excluding those with abnormally high or low intensities and insufficient coverage of the whole brain.
- There was a significant TRYP effect on the average whole brain gray matter CBF (b = 5.55, t = 3.09, p=0.003), i.e., administration of TRYP was associated with elevated CBF (**Fig 2**). There was a significant TRYP*diagnosis interaction effect on average whole brain gray matter CBF (b = -5.34, t = -2.16, p=0.04), such that HC exhibited higher CBF with TRYP compared to placebo. The main effect of diagnosis was non-significant (b = -6.64, t = -1.67, P=0.10), but showed a trend for CBF to be decreased in PSz relative to HC (**Fig 2**).
- Regarding cognitive task performance, no significant results survived Bonferroni correction for six statistical tests (P<0.008). At an uncorrected P<0.05 threshold, we observed effects of TRYP (b= -4.24, t = -2.12, p=0.04) and diagnosis (b = -4.20, t = -2.07, p=0.04) on the change in brief visuospatial memory performance (BVMT-R).

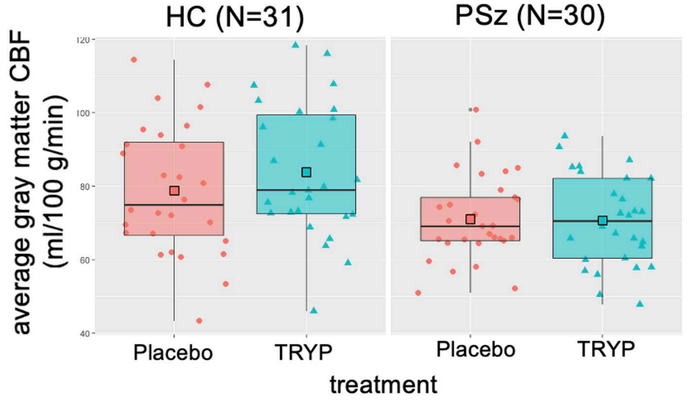

Figure 2. Effect of TRYP administration on CBF in Healthy Controls (HC) and Participants with a Schizophrenia-related disorder (PSz). The average whole brain gray matter CBF was elevated 2 hours after TRYP compared to placebo (t=3.09, p=0.003). This effect was strongest in the healthy controls (HC) (significant TRYP*diagnosis interaction effect on CBF: t = -2.16, p=0.04). Lines in boxplots: median values; small square in boxplot: mean values; large box: interquartile range (IQR; 25th percentile to 75th percentile); whiskers: range of minimum (Q1 – 1.5*IQR) to maximum (Q3 + 1.5*IQR) values.

CONCLUSIONS

Oral TRYP administration significantly elevated plasma levels of kynurenine and KYNA in both HC and PSz; TRYP (vs. placebo) was associated with greater CBF in HC, but not PSz. Large-scale, longitudinal studies are required to examine the impact of kynurenine pathway fluctuations on brain function and behavior in both HC and PSz. We are also currently performing follow-up analyses to examine effects of diagnosis (PSz vs. HC) on CBF across cortical and subcortical brain regions, controlling for confounding effects of age and sex.

Competing Interests: RS is co-founder of KyNexis AB. RWB performs consultation for Boehringer-Ingelheim and serves on the Data Safety and Monitoring Boards of Roche, Merck and Newron; and on the Advisory Boards of Merck, Acadia, and Neurocrine. DLK is a consultant for Janssen, Alkermes and Sunovion. All other authors declare no competing interests.