International Journal of Neuropsychopharmacology (2011), **14**, 756–767. © CINP 2011
doi:10.1017/S1461145710001689

ARTICLE

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3-Hydroxykynurenine and clinical symptoms in first-episode neuroleptic-naive patients with schizophrenia

Ruth Condray[1,2], George G. Dougherty Jr.[1,2], Matcheri S. Keshavan[2,3], Ravinder D. Reddy[1,2], Gretchen L. Haas[1,2], Debra M. Montrose[2], Wayne R. Matson[4], Joseph McEvoy[5,6], Rima Kaddurah-Daouk[6] and Jeffrey K. Yao[1,2,7]

[1] *VA Pittsburgh Healthcare System, Medical Research Service, Pittsburgh, PA, USA*
[2] *University of Pittsburgh Medical Center, Department of Psychiatry, Pittsburgh, PA, USA*
[3] *Beth Israel Deaconess Medical Center and Harvard University, Department of Psychiatry, Boston, MA, USA*
[4] *Bedford VA Medical Center, Medical Research Service, Bedford, MA, USA*
[5] *John Umstead Hospital, Department of Psychiatry, Butner, NC, USA*
[6] *Department of Psychiatry and Behavioral Sciences, Duke University, Durham, NC, USA*
[7] *University of Pittsburgh School of Pharmacy, Department of Pharmaceutical Sciences, Pittsburgh, PA, USA*

Abstract

One branch of the tryptophan catabolic cascade is the kynurenine pathway, which produces neurotoxic [3-hydroxykynurenine (3-OHKY), quinolinic acid] and neuroinhibitory (kynurenic acid) compounds. Kynurenic acid acts as a competitive antagonist at the glycine site of *N*-methyl-D-asparate receptors at high concentrations and as a non-competitive antagonist on the α_7-nicotinic acetylcholine receptor at low concentrations. Kynurenine compounds also influence cognitive functions known to be disrupted in schizophrenia. Alterations in tryptophan metabolism are therefore of potential significance for the pathophysiology of this disorder. In this paper, tryptophan metabolites were measured from plasma using high-pressure liquid chromatography coupled with electrochemical coulometric array detection, and relationships were tested between these metabolic signatures and clinical symptoms for 25 first-episode neuroleptic-naive schizophrenia patients. Blood samples were collected and clinical and neurological symptoms were rated at baseline and again at 4 wk following initiation of treatment. Level of 3-OHKY and total clinical symptom scores were correlated when patients were unmedicated and neuroleptic-naive, and this relationship differed significantly from the correlation observed for patients 4 wk after beginning treatment. Baseline psychosis symptoms were predicted only by neurological symptoms. Moreover, baseline 3-OHKY predicted clinical change at 4 wk, with the lowest concentrations of 3-OHKY being associated with the greatest improvement in symptoms. Taken together, our findings suggest a neurotoxic product of tryptophan metabolism, 3-OHKY, predicts severity of clinical symptoms during the early phase of illness and before exposure to antipsychotic drugs. Baseline level of 3-OHKY may also predict the degree of clinical improvement following brief treatment with antipsychotics.

Received 21 September 2010; Reviewed 10 November 2010; Revised 1 December 2010; Accepted 21 December 2010; First published online 28 January 2011

Key words: Cognition, first-episode psychosis, 3-hydroxykynurenine, neuroleptic-naive, neurological symptoms, schizophrenia, tryptophan.

Introduction

Schizophrenia is associated with a wide range of biological and behavioural perturbations and compromises to social and life functioning. The pathophysiology underlying these diverse disturbances has not been confirmed as either a single, fundamental pathology or, conversely, multiple abnormalities involving independent biological processes. It is also not known which of the candidate biological processes are linked to symptom formation and clinical course, or whether treatment may modify such relationships. Hypotheses have included altered neurotransmission and signal transduction, and abnormalities in neuropeptides and autoimmune

Address for correspondence: J. K. Yao, Ph.D., Neurochemistry and Psychopharmacology Laboratory (Bldg 13), VA Pittsburgh Healthcare System 151U-H, 7180 Highland Drive, Pittsburgh, PA 15206, USA.
Tel.: +1-412-954-5787 *Fax*: +1-412954-5786
Email: jkyao@pitt.edu

dysfunction (as reviewed by Javitt & Laruelle 2006; Lieberman & Koreen 1993; Tandon *et al*. 2008). Evidence from studies of neurotransmitter (dopaminergic, serontonergic, glutamatergic, noradrenergic) systems implicates a number of alterations, but how to interpret these findings has been uncertain due to the important fact that neurotransmitter systems are linked with one another, as well as with signal transduction systems and a diverse range of membrane-bound and cellular systems. Viewing biological processes as integrated systems of genetic, protein, metabolic, cellular, and pathway cascades provides a new paradigm (Clish *et al*. 2004) that has the potential to transform knowledge about the major psychiatric disorders, including schizophrenia and mood disorders (Kaddurah-Daouk *et al*. 2007, 2008, 2009; Yao & Reddy, 2005). This new perspective can increase understanding about how psychiatric disorders are shaped by biological systems that behave in dynamic and interdependent ways. Comprehensive study of one such system, the metabolome, concerns the repertoire of biochemicals present in cells, tissue, and body fluids. Identification of metabolic signatures for pathways of interest can provide enhanced understanding about complex disorders at the molecular level, which is now technically possible through novel high-resolution multidimensional separation and characterization methods.

While the dopamine hypothesis of schizophrenia has retained prominence for over four decades (Carlsson & Lindqvist, 1963; Howes & Kapur, 2009), progress in the field has stimulated alternate views that recognize complex relationships among multiple neurotransmitter systems and include a renewed interest in the importance of serotonin for schizophrenia (Geyer & Vollenweider, 2008). Results from early studies showed that both hyperserotonaemia (Garelis *et al*. 1975; Muck-Seler *et al*. 1988; Stahl *et al*. 1983) and serotonin deficiency (Aschcroft *et al*. 1966; Manowitz *et al*. 1973; Reddy *et al*. 2007) were associated with schizophrenia, suggesting a disturbance in central serotonin function. Because serotonin is produced during tryptophan metabolism, these collective findings implicate a dysregulation of tryptophan metabolism for schizophrenia. Tryptophan is catabolized primarily through the kynurenine pathway (Stone, 1993), which is functionally related to the glutamatergic system and neurodegenerative disease. In view of the accumulating evidence that supports an important role for glutamatergic dysfunction in the pathophysiology of schizophrenia (Javitt, 2007; Olney *et al*. 1999; Tamminga, 1998), determining how metabolism within the kynurenine pathway may influence its clinical profile could advance knowledge about the molecular underpinnings of this severe psychiatric disorder.

Tryptophan is either transaminated to kynurenate, which acts as an endogenous glutamate receptor antagonist, or hydroxylated to 3-hydroxykynurenine (3-OHKY), which is then further degraded to the excitotoxic *N*-methyl-D-aspartate (NMDA) agonist, quinolinate. Kynurenic acid appears to be neuroprotective, while 3-OHKY and quinolinic acid are neurotoxic (Foster *et al*. 1983; Guidetti & Schwarcz, 1999; Stone, 1993). The nature of the influence of kynurenic acid on glutamatergic neurotransmission is generally believed dependent on level or concentration, although the parameters are continuing to be defined. Kynurenic acid at high concentrations acts as a competitive antagonist of the glycine site of NMDA receptors (Stone, 1993), and at low concentrations functions as a non-competitive antagonist of α_7-nicotinic acetylcholine receptors (Alkondon *et al*. 2004; Hilmas *et al*. 2001). However, even low concentrations of endogenous kynurenic acid have been shown to influence physiological responding reflected in the amplitude of evoked responses in CA1 pyramidal cells (Scharfman *et al*. 2000).

Converging lines of evidence provide support for the recent proposal of kynurenine pathway metabolism as a unique and novel target for the treatment of schizophrenia (Wonodi & Schwarcz, 2010). Increased degradation of tryptophan through the kynurenine pathway has been observed in patients diagnosed with psychotic disorder (Barry *et al*. 2009), and elevated levels of kynurenic acid have been found in cerebrospinal fluid (CSF) of schizophrenia patients at first episode and prior to treatment with antipsychotics (Erhardt *et al*. 2001). Increased levels of kynurenine have also been identified in the post-mortem tissue of schizophrenia patients within Brodmann areas 9 and 19 (Schwarcz *et al*. 2001), brain regions that have been implicated in schizophrenia. Importantly, linkages have been demonstrated between the products of kynurenine pathway and clinical status and cognitive dysfunction. CSF levels of 3-OHKY in unmedicated chronic schizophrenia patients predicted their clinical improvement following 6 wk of treatment with antipsychotic medication (Issa *et al*. 1994). Moreover, findings from animal studies show that kynurenine compounds influence cognitive functions that are known to be disrupted in schizophrenia: 7-chlorokynurenic acid, an NMDA receptor antagonist, reduced acquisition of spatial memory in rats and inhibited induction of long-term potentiation (LTP) in rat hippocampal slices (Watanabe *et al*. 1992); while

elevated level of kynurenic acid in rats reduced spatial working memory performance (Chess *et al*. 2007), and altered sensory processing (Erhardt *et al*. 2004; Shepard *et al*. 2003) and conditioned learning (Chess & Bucci, 2006). As candidate influences for the pathophysiology underlying schizophrenia, the products of tryptophan metabolism may therefore play an important role in the hallmark symptoms of schizophrenia.

Understanding of these molecular processes can be increased using the novel powerful and rapid multidimensional separation and characterization method of high-pressure liquid chromatography coupled with electrochemical coulometric array detection (LCECA) (Kristal *et al*. 2007; Mannelli *et al*. 2009; Patkar *et al*. 2009; Rozen *et al*. 2005; Shi *et al*. 2002; Yao & Cheng, 2004), which provides resolving power that is superior to one-dimensional approaches. In an earlier report, our group documented altered interactions of tryptophan metabolites, measured with LCECA, for first-episode neuroleptic-naive schizophrenia patients at baseline (FENNS-BL) and at 4 wk (FENNS-4w) after initiating treatment with antipsychotic drugs (Yao *et al*. 2010*a*). Healthy controls and both patient groups (FENNS-BL, FENNS-4w) showed correlations between tryptophan and its metabolites melatonin, kynurenine, 3-OHKY, and tryptamine. However, certain interactions of tryptophan metabolites appeared only in healthy controls. In healthy controls, but in neither of the FENNS groups, serontonin was highly correlated with tryptophan, melatonin, kynurenine, and tryptamine. Also in healthy controls, but in neither of the FENNS groups, 5-hydroxyindoleacetic acid (5-HIAA) was highly correlated with tryptophan, melatonin, kynurenine, and 3-OHKY. In the present report, relationships are detailed between these metabolic signatures of tryptophan-degraded products and clinical symptoms in the same sample of FENNS. The main research questions concerned whether tryptophan metabolites are associated with clinical symptoms in FENNS at baseline when neuroleptic-naive and drug-free and/or at 4 wk after beginning pharmacological treatment, and, if present, whether these relationships differ significantly between the two time periods. The primary hypothesis concerned the potential influence of kynurenine pathway metabolism on clinical symptomatology. Based on recent empirical and conceptual advances that suggest a coupling of kynurenine metabolism and glutamatergic neurotransmission, kynurenine and its metabolite 3-OHKY were expected to be associated with the cardinal symptoms of schizophrenia, including positive and negative symptoms.

The secondary hypothesis concerned the role of antipsychotic treatment regimen on glutamatergic neurotransmission. Classes of drugs known to reverse NMDA antagonism, and presumably glutamatergic hypofunction, include $GABA_A$ agonists, muscarinic antagonists, non-NMDA glutamate antagonists, and atypical antipsychotics such as clozapine and olanzapine (Olney *et al*. 1999). The predicted influence of kynurenine pathway on symptom severity and profile was therefore expected to manifest primarily at baseline when patients were unmedicated; treatment with antipsychotics was expected to reduce or eliminate the relationship between kynurenine pathway metabolites and clinical symptoms. As a final consideration, the relative importance of tryptophan metabolism and neurological function for the clinical profile of schizophrenia is unknown. The latter has a demonstrated relationship to psychiatric symptoms and cognition in schizophrenia (Sanders *et al*. 2000, 2004) and to neuroanatomical regions (Keshavan *et al*. 2003) relevant for some of the cognitive deficits associated with this disorder. Tryptophan metabolites and neurological function were expected to exert independent effects on clinical symptoms.

Methods and materials

Clinical design

Twenty-five patients were recruited during their first episode of psychosis after they provisionally met DSM-IV criteria for schizophrenia, schizophreniform, or schizoaffective disorder based on the Structured Clinical Interview for DSM Disorders (SCID). Diagnostic assessments and ratings of clinical and neurological symptoms were performed by experienced research clinicians. Initial and follow-up diagnoses were confirmed at diagnostic conferences attended by research faculty and staff, and chaired by an experienced psychiatrist (M.S.K.). Sample characteristics (mean $\pm$ S.D.) included: age = 22.6 $\pm$ 7.2 yr; education = 12 $\pm$ 3.3 yr; parental socioeconomic status = 36.1 $\pm$ 14.3 (Hollingshead, 1975); weight = 146.4 $\pm$ 38.4 lb; height = 67.3 $\pm$ 3.4 in.; body mass index = 22.4 $\pm$ 4.8. The ethnicity composition of the sample comprised 15 Caucasian, eight African-American, one Asian Pacific, and one other/unknown. Plasma and clinical data were available at both baseline and 4-wk follow-up for 24 patients. Blood samples were collected and clinical symptoms were evaluated prior to initiation of clinicians' choice of antipsychotic agents. A second set of blood samples and clinical ratings were obtained for the same patients $\sim$4 wk after treatment was initiated

Table 1. Clinical symptom ratings for first-episode schizophrenia patients at baseline and 4 wk

Clinical symptom	Baseline (neuroleptic naive), mean ± S.D.	4 wk (medicated), mean ± S.D.	t[a]	d.f.[a]	p value[b]
BPRS total score	52.58 ± 8.9	42.91 ± 7.5	4.13	23	< 0.001[b]
BPRS symptom clusters					
Psychosis	24.46 ± 4.6	19.00 ± 4.5	7.06	23	< 0.001[b]
Thought disturbance	18.87 ± 3.7	14.04 ± 3.5	5.80	23	< 0.001[b]
Paranoia	9.71 ± 3.2	7.54 ± 2.9	4.28	23	< 0.001[b]
Mood (anxiety-depression)	18.50 ± 6.2	14.71 ± 3.9	2.56	23	0.017
Positive symptoms (SAPS)	24.29 ± 11.0	14.21 ± 12.1	4.91	23	< 0.001[b]
Negative symptoms (SANS)	45.46 ± 10.3	42.17 ± 8.2	1.48	23	0.156
Neurological symptoms – Total[c]	6.95 ± 3.5	5.35 ± 2.9	2.31	19	0.032

BPRS, Brief Psychiatric Rating Scale; SAPS, Schedule for the Assessment of Positive Symptoms; SANS, Schedule for the Assessment of Negative Symptoms.

[a] t test, paired samples; two-tailed; d.f., degrees of freedom.

[b] Bonferroni correction of standard $\alpha \leqslant 0.05 \leqslant 0.00625$; $p \leqslant 0.10 \leqslant 0.0125$.

[c] NES Total Subscale (Sanders *et al*. 2000) from Neurological Evaluation Scale (NES; Buchanan & Heinrichs, 1989).

with one or more of the following antipsychotic drugs: risperidone ($n = 17$), olanzapine ($n = 5$), quetiapine ($n = 2$), aripiprazole ($n = 1$), haloperidol ($n = 1$). The number equals more than 24 due to polypharmacy. One patient was unmedicated. The mean and S.D. dosage of antipsychotics (chlorpromazine equivalents) (Woods, 2003) was 221.4 ± 171.1 mg/d (median 150, range 100–900). Clinical and neurological symptoms were rated by experienced research clinicians at both time-points using standard rating scales: Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962), Scale for Assessment of Negative Symptoms (SANS) and Scale for Assessment of Positive Symptoms (SAPS; Andreasen, 1983; 1984), Global Assessment Scale (GAS; Endicott *et al*. 1976), Clinical Global Impression (CGI; Guy, 1976), Neurological Evaluation Scale (NES; Buchanan & Heinrichs, 1989). Following a complete description of the study to each individual, written informed consent was obtained in accordance to the study protocol that was approved by the Institutional Review Board at the University of Pittsburgh and the VA Pittsburgh Healthcare System.

Laboratory assays

All blood samples were collected in the morning after overnight fasting. Samples were prepared for analysis by extraction in acidified acetonitrile and analysed by LCECA. Complete details of this methodology are provided in Yao *et al.* (2010*a*, *b*).

Data analyses

Clinical symptom ratings and concentrations of tryptophan metabolites measured from plasma were examined for the first-episode neuroleptic-naive patients with schizophrenia. The focus of analyses concerned those metabolites that previously showed altered interactions within the tryptophan pathway in this sample of schizophrenia patients, including tryptophan, serotonin, 5-HIAA, melatonin, kynurenine, 3-OHKY, and tryptamine (Yao *et al*. 2010*a*). All analytes are expressed as ng/ml of plasma. Two groups of clinical ratings and metabolite variables were analysed: 25 FENNS at baseline and 24 of those same patients 4 wk after beginning treatment with antipsychotic drugs ($n = 24$ at 4 wk due to one patient missing some clinical ratings). Descriptive statistics were computed for the 24 patients for whom clinical symptom ratings were available at both time-points (Table 1). For these analyses, individual items from the BPRS were combined to form symptom clusters as follows: Total score (items 1–18); Psychosis (items 4, 7, 8, 10, 11, 12, 14, 15); Mood (items 1, 2, 5, 6, 9, 13). Additional BPRS clusters enabled a more fine-grained examination of psychosis-related symptomatology, including Thought Disturbance (items 4, 8, 11, 12, 15, 18) and Paranoia (items 10, 11, 14). Control of type I error was achieved for these multiple comparisons using Bonferroni correction. Table 2 presents descriptive statistics for the set of tryptophan metabolites included in this report, as well

Table 2. Descriptive statistics for metabolites in tryptophan pathway

Metabolites	HC ($n=30$)	FENNS-BL ($n=25$)	FENNS-4w ($n=25$)	p values		
				HC *vs.* BL	HC *vs.* 4w	BL *vs.* 4w
TRP	7628±3043[a]	6426±3493	5469±2977	0.069	0.007[b]	0.133
5-HT	200±145	238±152	182±147	0.301	0.562	0.020
5-HIAA	18±11	19±16	17±21	0.496	0.014	0.263
MEL	1.03±0.44	0.80±0.39	0.70±0.34	0.073	0.003[b]	0.156
KYN	161±86	125±79	111±75	0.077	0.013	0.287
3-OHKY	10±8	8.17±8.10	7.73±8.75	0.176	0.071	0.751
TRPA	19±7	17±9	16±6	0.144	0.175	0.791

HC, Healthy controls; FENNS, first-episode neuroleptic-naive patients with schizophrenia; BL, baseline; 4w, 4-wk treatment with antipsychotic drugs; TRP, tryptophan; 5-HT, serotonin; 5-HIAA, 5-hydroxyindoleacetic acid; MEL, melatonin; KYN, kynurenine; 3-OHKY, 3-hydroxykynurenine; TRPA, tryptamine.

[a] Each value (ng/ml) represents mean and standard deviation. All data were adapted from Yao *et al*. (2010*a*).

[b] Because the parametric assumptions for the Student's t test are not met, a non-parametric test, the Wilcoxon Rank Sum test was used to compare the locations of samples from disparate groups, and the Wilcoxon Signed Rank test was done to compare paired samples (i.e. BL *vs.* 4w). Significant difference after Bonferroni correction of an α of 0.05–0.0038, or 0.10–0.0077.

as p values from the tests of differences between baseline and 4 wk for patients, and between the age-matched healthy volunteers and patients at each time-point (data adapted from Yao *et al*. 2010*a*).

The relationship between analytes within the tryptophan pathway and clinical symptom ratings was examined for both time-points. Most of the analytes within the tryptophan pathway and the clinical symptom ratings either were, or were able to be transformed to, approximate univariate and multivariate normality using natural log (ln), square root (sqrt), quartic root, negative inverse, negative inverse square root, and/or negative inverse quartic root transformations.

A correlation test (Johnson & Wichern, 1998) and Henze & Zirkler's test (1990) were used to assess approximate univariate and multivariate normality, respectively, requiring $p<0.10$ for rejection of normality. Following normality determination and, if necessary, transformations, both groupings of data had the hypothesis of complete independence of all metabolite and clinical symptom variables tested, and each hypothesis was rejected with $p<10^{-8}$.

Simultaneous tests of the hypotheses that multiple correlation coefficients were equal to zero were computed separately for the data at baseline and for the data at 4 wk (Drton & Perlman, 2004). Simultaneous tests of the hypotheses that correlations at baseline and at 4 wk were equal were additionally computed using the Larntz & Perlman (1988) procedure to screen for any baseline to 4-wk between-group correlation differences. Both methods use Šidák simultaneous confidence intervals (or p values) to correct for multiple tests.

p value results obtained from the Drton & Perlman (2004) and the Larntz & Perlman (1988) procedures were additionally verified by Monte Carlo simulation using 10 000 randomly generated datasets. The test statistics and Monte Carlo p values did not differ greatly, but the Monte Carlo p values were considered to be more accurate. Significant effects were confirmed using a repeated-measures model to estimate clinical symptom(s) under different levels of metabolite at each time-point.

Finally, any significant relationship obtained between metabolite and clinical symptom based on the above procedures was examined further using linear regression analysis. Included in this approach was an evaluation of the relative contributions of metabolite(s) showing a significant relation to clinical symptoms and of neurological symptoms that have a demonstrated relationship to clinical symptoms, cognitive performance, and neuroanatomical regions of interest for schizophrenia. The model included metabolite and neurological symptoms [total score for the modified 13-item version of the NES (Buchanan & Heinrichs, 1989) from Sanders *et al*. (2000)] as independent or predictor factors using a forward selection procedure. The joint (or interaction) effects of these two variable classes were also examined, as well as the effects of control variables (age, education, body mass index). Collinearity was evaluated using correlation coefficients for the predictor or independent variables and tests of tolerance, variance inflation factor, and condition indices (Pedhazur, 1997). Unstandardized betas are reported. Bonferroni correction was used to control type I error.

Table 3. Within-group correlation coefficients for tryptophan metabolites and clinical symptoms for first-episode schizophrenia patients (tests for zero correlation, two-sided)

	Tryptophan metabolites						
Clinical symptoms	TRP	5-HT	5-HIAA	MEL	KYN	3-OHKY	TRPA
Baseline (neuroleptic-naive)							
BPRS							
Total	−0.234	−0.090	−0.306	−0.186	−0.384	**−0.618**[a]	−0.369
Psychosis	−0.195	0.049	−0.107	−0.233	−0.283	−0.339	−0.221
Thought disturbance	−0.136	0.184	−0.165	−0.291	−0.308	−0.387	−0.261
Paranoia	−0.094	−0.129	−0.006	0.027	−0.042	−0.088	−0.096
Anxious depression	0.082	−0.204	−0.279	0.136	−0.016	−0.331	−0.076
SAPS – Total	−0.229	−0.143	−0.317	−0.235	−0.276	−0.387	−0.111
SANS – Total	−0.035	−0.019	−0.342	−0.121	−0.163	−0.129	−0.072
4 wk (medicated)							
BPRS							
Total	0.022	0.164	−0.020	0.044	0.259	0.413	0.163
Psychosis	−0.120	0.070	−0.075	0.052	0.165	0.302	0.100
Thought disturbance	−0.022	0.166	−0.019	0.119	0.220	0.409	0.207
Paranoia	−0.003	0.120	−0.062	0.171	0.245	0.278	0.093
Anxious depression	0.019	−0.086	0.070	−0.079	0.271	0.403	0.189
SAPS – Total	−0.098	0.129	−0.020	−0.063	0.056	0.235	0.110
SANS – Total	0.063	0.175	−0.207	0.118	−0.011	0.060	0.204

TRP, Tryptophan; 5-HT, serotonin; 5-HIAA, 5-hydroxyindoleacetic acid; MEL, melatonin; KYN, kynurenine; 3-OHKY, 3-hydroxykynurenine; TRPA, tryptamine; BPRS, Brief Psychiatric Rating Scale; SAPS, Schedule for the Assessment of Positive Symptoms; SANS, Schedule for the Assessment of Negative Symptoms.

[a] Drton–Perlman simultaneous p values, significant at $p<0.05$ and trend significant at $p<0.10$.

Results

Most clinical symptom scores improved significantly from baseline levels after following initiation of treatment with antipsychotic drugs (Table 1). Exceptions were the mood and negative symptom scores, and the total neurological symptoms score. Within-group correlations for tryptophan pathway metabolites and clinical symptoms for FENNS at baseline and 4-wk follow-up are provided in Table 3. Figure 1 presents the correlation obtained between 3-OHKY and overall clinical symptoms (BPRS total score) for patients ($n=25$) at baseline ($r=-0.62$, $p=0.086$), when they were neuroleptic-naive and drug-free during their first psychotic episode, and the correlation obtained for these two factors at 4 wk after patients ($n=24$) began treatment ($r=0.41$, $p=0.98$). The difference between these correlations obtained at baseline and at 4 wk was highly significant statistically ($p=0.009$, Larntz–Perlman procedure). The direction of the relationship observed at baseline indicates that higher plasma levels of 3-OHKY at baseline were associated with lower total clinical symptom scores at baseline. This result is supported by the repeated-measures model for BPRS at different levels of 3-OHKY and time-point [Hotelling's trace: $F_{1,46}=7.57$, $p=0.008$; mean z score difference between baseline and 4 wk: −1.06, 95% CI (Šidák adjustment) −1.836 to −0.285].

The relationship between baseline 3-OHKY and baseline clinical symptoms was examined further using linear regression analysis. The model included 3-OHKY and neurological symptoms as independent or predictor variables, and clinical symptoms as the dependent factors. The two predictor variables were not significantly correlated (Pearson's $r=-0.37$, $p=0.091$), and results of collinearity tests were within acceptable limits for each regression equation (see Methods section). Table 4*a* shows the results for this model for the dependent measures of total, psychosis, and mood symptoms. The model accounted for 38% of the variance (adjusted R^2) associated with patients' score for total symptoms, 44% of the variance associated with their score for psychosis symptoms, and 53% of the variance associated with their score for mood symptoms. The only significant predictor of total symptom score was 3-OHKY, which showed that

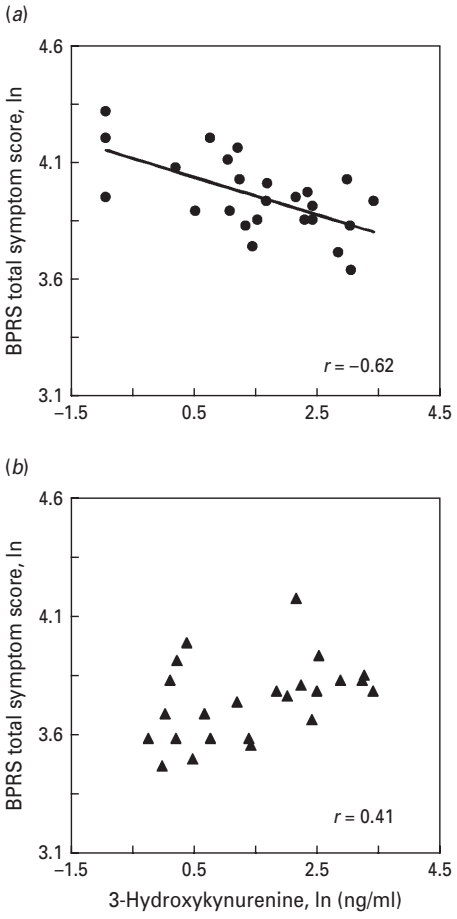

Fig. 1. Association between 3-hydroxykynurenine (ln) and clinical symptoms (ln) in first-episode neuroleptic-naive schizophrenia (FENNS) patients. (*a*) FENNS patients at baseline; (*b*) FENNS patients after 4-wk antipsychotic treatment. The between-group correlation difference was significant at $p = 0.009$ (Monte Carlo simulation 10 000 randomly generated datasets). The correlation coefficients (r) and simultaneous p values were calculated according to the Larntz–Perlman procedure (Larntz & Perlman 1988). ln, natural log.

higher plasma levels of this metabolite were associated with lower total clinical symptom scores. Interestingly, the only significant predictor of psychosis symptoms was the neurological symptoms factor, and the direction of this relationship indicated increases in patients' neurological symptoms to be associated with increases in their psychosis symptoms. In contrast, both 3-OHKY and neurological symptoms were significant predictors of patients' mood symptom score. The directions of these relationships show that increases in metabolite concentration and neurological symptoms were associated with decreases in symptoms of anxiety and depression.

The same set of predictors measured at baseline was tested for prediction of clinical improvement at 4 wk. Baseline 3-OHKY and neurological symptoms were entered as the independent or predictor variables. Table 4*b* shows the results for clinical outcome reflected in the change in total, psychosis, and mood symptoms at 4 wk (e.g. change score for total symptoms = total symptoms at baseline *minus* total symptoms at 4 wk). The model was successful in accounting for 41% of the variance associated with the change in total symptoms, 35% of the variance associated with change in psychosis symptoms, and 38% of the variance associated with change in mood symptoms. In contrast to the results for baseline predictors of baseline clinical symptoms, 3-OHKY at baseline was the only significant predictor of clinical improvement at 4 wk. As shown in Fig. 2, the direction of these relationships indicates that lower plasma levels of 3-OHKY at baseline predicted greater improvement in total, psychosis, and mood symptoms at 4 wk.

In addition to the main-effects model of baseline 3-OHKY and neurological symptoms as independent or predictor factors of clinical symptomatology, the joint effects of these two variables (3-OHKY × neurological symptoms interaction) were also examined. This interaction term was not a significant predictor of total, psychosis, or mood symptoms at baseline or of clinical improvement at 4 wk (all p values = n.s.). Moreover, none of the control variables (age, education, body mass index) were significant predictors of clinical symptomatology, either at baseline or for clinical change at 4 wk, and inclusion of these factors did not alter any of the results based on the primary model (all p values = n.s.).

Discussion

Level of 3-OHKY, a neurotoxic byproduct of tryptophan degradation, was associated with overall level of clinical symptoms when first-episode schizophrenia patients were unmedicated and neuroleptic-naive. The source of this relationship appears to have been patients' symptoms of mood; baseline psychotic symptoms were predicted only by neurological symptoms. Importantly, baseline level of 3-OHKY predicted clinical improvement at 4 wk after beginning treatment, with the lowest concentrations of 3-OHKY associated with the greatest degrees of symptom improvement. Again, this effect appeared strongest for change in mood symptoms.

It is important to view the relationship between 3-OHKY and clinical symptoms for these first-episode patients within the larger context of their clinical

Table 4. 3-Hydroxykynurenine (3-OHKY) and neurological symptoms predict clinical symptoms for first-episode schizophrenia patients

	R	Adj. R^2	F ratio	d.f.	$p \leqslant$	β	S.E. β	t test	$p \leqslant$	95% CI
(*a*) Baseline metabolite and neurological factors predict baseline clinical symptoms[a]										
(1) BPRS Total symptoms	0.64	0.38	14.17	1, 20	0.001[b]					
3-OHKY						−4.418	1.174	−3.76	0.001[b]	−6.866 to −1.97
(2) BPRS Psychosis symptoms	0.68	0.44	17.66	1, 20	0.001[b]					
Neurological symptoms, Total						5.849	1.392	4.20	0.001[b]	2.946 to 8.753
(3) BPRS Mood symptoms	0.76	0.53	12.78	2, 19	0.001[b]					
3-OHKY						−3.319	0.746	−4.45	0.001[b]	−4.880 to −1.758
Neurological symptoms, Total						−7.318	2.191	−3.34	0.003[b]	−11.904 to −2.733
(*b*) Baseline metabolite predicts clinical change at 4 wk										
(1) BPRS Total symptom change	0.66	0.41	15.68	1, 20	0.001[b]					
3-OHKY						−0.733	0.185	−3.96	0.001[b]	−1.120 to −0.347
(2) BPRS Psychosis symptom change	0.62	0.35	12.58	1, 20	0.002[b]					
3-OHKY						−0.252	0.071	−3.55	0.002[b]	−0.401 to −0.104
(3) BPRS Mood symptom change	0.64	0.38	14.15	1, 20	0.001[b]					
3-OHKY						−0.502	0.134	−3.76	0.001[b]	−0.781 to −0.224

R, Multiple correlation coefficient; F ratio, test of significance of R; d.f., degrees of freedom; β, regression coefficient or slope; S.E., standard error; CI, confidence interval for regression coefficient; BPRS, Brief Psychiatric Rating Scale.

[a] Predictors: 3-hydroxykynurenine and neurological symptoms – Total.

[b] Bonferroni correction of standard $\alpha \leqslant 0.05 \leqslant 0.0083$; $p \leqslant 0.10 \leqslant 0.016$.

status and tryptophan metabolism at the baseline and 1-month time-points. First, these patients showed significant clinical improvement after 4 wk of treatment with antipsychotic drugs. Improvement occurred primarily in the domain of positive symptoms, including symptoms of psychosis, thought disturbance, and paranoia. Changes in mood, negative, and neurological symptoms did not reach statistical significance. Regarding the latter, however, it is possible that the conservative nature of our correction against type I error may be concealing real improvement in these clinical domains. In contrast, their absolute levels of tryptophan metabolites in plasma did not differ significantly between the assessments at baseline and 4 wk, nor did the levels of kynurenine and its metabolic compounds differ between healthy volunteers and patients at either time-point (reported in Yao *et al.* 2010*a*). Second, both patients and healthy controls showed highly significant correlations between tryptophan and kynurenine, 3-OHKY, and tryptamine, which is suggestive of tight control over relative metabolite ratios along the tryptophan pathways (Yao *et al*. 2010*a*). The findings for 3-OHKY revealed in the present report may therefore be due to effects outside the stream of metabolic linkages within the kynurenine pathway, with a strong candidate being the known influence of kynurenine compounds on the glutamatergic system (for details see Introduction). An additional, potentially important implication of the present data is that 3-OHKY and its downstream effects may influence the degree of clinical improvement that can be achieved through brief treatment with pharmacological agents.

Alterations in cortical kynurenic acid have been reported for schizophrenia, and, although plasma kynurenic acid was not examined in the present study, the relationship observed between 3-OHKY and clinical symptoms is generally consistent with those previously reported alterations. Importantly, the directions of the relationships obtained between metabolite and psychological disturbance suggest this relationship is not straightforward. Baseline concentration of metabolite was inversely related to baseline clinical symptoms, with lower concentrations of 3-OHKY associated with greater psychological disturbance when patients were unmedicated and neuroleptic-naive. In contrast, baseline level of metabolite showed the opposite relationship to clinical improvement at 4 wk, with lower baseline concentrations of 3-OHKY predicting greater improvement in patients' clinical symptoms 1 month after beginning treatment with antipsychotics. As noted, patients did not differ from controls for absolute levels of tryptophan, kynurenine, or 3-OHKY at either time-point, and all groups were characterized by a tight coupling between tryptophan and kynurenine and between tryptophan

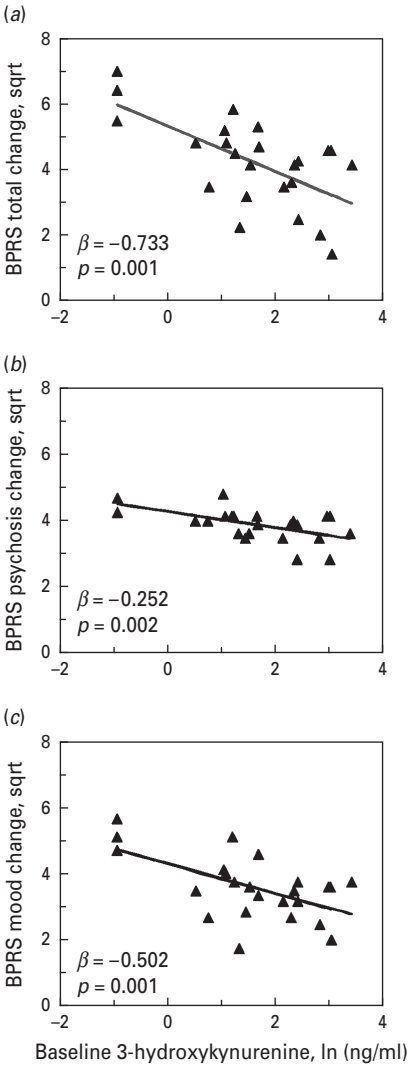

Fig. 2. Baseline 3-hydroxykynurenine (3-OHKY) (ln) predicts clinical change at 4 wk for (*a*) total symptoms (sqrt); (*b*) psychosis symptoms (sqrt); (*c*) mood symptoms (sqrt). The regression coefficient or slope (β) and p values were calculated by multiple regression analyses. ln, natural log; sqrt, square root.

and 3-OHKY (Yao *et al.* 2010*a*). Thus, the pattern in the present data cannot be accounted for by elevated levels of kynurenine metabolites, or by alterations in metabolic linkages along this pathway.

One mechanism that may account for the pattern of associations that was observed in the present study concerns the relationship between tryptophan catabolism and transmitter dynamics, including the previously mentioned modulatory action of kynurenic acid on glutamatergic transmission. Moreover, the indication in the present data that antipsychotic agents modify these dynamics receives support from recent work. First, Issa *et al*. (1994) found an association between the amount of change in CSF 3-OHKY and change in clinical symptoms following 6 wk of treatment with haloperidol in unmedicated chronic schizophrenia patients who were judged to be treatment resistant. Second, Schwieler *et al*. (2008) administered clozapine to rodents, which increased activation of dopamine neurons in the ventral tegmental area (VTA). However, pretreatment with agents that either produced elevated or decreased brain levels of kynurenic acid resulted in inhibition or potentiation, respectively, of the excitatory effect of clozapine on dopamine neurons in VTA. The kynurenine pathway may therefore influence dopaminergic as well as glutamatergic transmission.

The relationship between tryptophan metabolism and clinical symptoms appeared strongest for mood symptoms in this sample of first-episode patients. Due to the growing understanding that symptoms of depression are present even in the prodrome as well as during the first episode of schizophrenia (Häfner *et al*. 2005; Iyer *et al*. 2008; Owens *et al*. 2005; Romm *et al*. 2010), this metabolite–clinical symptom linkage has implications for early identification and intervention strategies. In contrast, symptoms of psychosis in these patients showed a different pattern at baseline and 4 wk; baseline neurological symptoms predicted baseline psychosis symptoms, while baseline metabolites predicted change in psychosis symptoms at 4 wk. This former relationship, which showed increases in neurological symptoms to be associated with increases in psychotic symptoms, is generally consistent with earlier findings for unmedicated chronic patients (Mittal *et al*. 2007; Sanders *et al*. 2000).

In summary, biochemical–clinical relationships were examined for first-episode schizophrenia patients at baseline when they were unmedicated and neuroleptic-naïve, and again at 1 month after beginning treatment. Key biochemical variables within the tryptophan metabolic pathway and clinical symptoms relevant to schizophrenia were targeted. Results suggest this metabolic pathway may play a role in clinical presentation and outcome during the early course of schizophrenia illness.

Acknowledgements

This material is based on work supported by grants from the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Biomedical Laboratory R & D [Merit Reviews (J.K.Y.) and Senior Research Career Scientist Award (J.K.Y.)], VA Pittsburgh Healthcare System

(J.K.Y., G.G.D., R.D.R.), National Institute of Mental Health [MH58141 (J.K.Y.), MH64118 (R.D.R.), MH45203 (M.S.K), and MH84941 (R.K.D.)], National Institute of General Medical Sciences [R24 GM078233 (R.K.D.)]. The authors are grateful to Dr Nina Schooler and Dr Cameron Carter, and the clinical core staff of the Center for the Neuroscience of Mental Disorders (MH45156, David Lewis, M.D., Director) for their assistance in diagnostic and psychopathological assessments, and to P. Cheng, C. Korbanic and J. Haflett for their technical assistance. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The contents of this article do not represent the views of the Department of Veterans Affairs or the United States Government.

Statement of Interest

Dr McEvoy received honoraria from Lilly, and grant support from GlaxoSmithKline, Pfizer and Dainippon Sumitomo Pharmaceuticals America. Dr Kaddurah-Daouk is an equity holder in Metabolon Inc., a biotechnology company in the metabolomics domain, and also holds patent in this field.

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