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Kynurenic Acid in Schizophrenia: A Systematic Review and Meta-analysis

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Kynurenic acid (KYNA) is an endogenous antagonist of *N*-methyl-D-aspartate and α7 nicotinic acetylcholine receptors that is derived from astrocytes as part of the kynurenine pathway of tryptophan degradation. Evidence suggests that abnormal KYNA levels are involved in the pathophysiology of schizophrenia. However, this has never been assessed through a meta-analysis. A literature search was conducted through Ovid using Embase, Medline, and PsycINFO databases (last search: December 2016) with the search terms: (kynuren* or KYNA) and (schizophreni* or psychosis). English language studies measuring KYNA levels using any method in patients with schizophrenia and healthy controls (HCs) were identified. Standardized mean differences (SMDs) were calculated to determine differences in KYNA levels between groups. Subgroup analyses were separately performed for nonoverlapping participant samples, KYNA measurement techniques, and KYNA sample source. The influences of patients' age, antipsychotic status (%medicated), and sex (%male) on study SMDs were assessed through a meta-regression. Thirteen studies were deemed eligible for inclusion in the meta-analysis. In the main analysis, KYNA levels were elevated in the patient group. Subgroup analyses demonstrated that KYNA levels were increased in nonoverlapping participant samples, and centrally (cerebrospinal fluid and brain tissue) but not peripherally. Patients' age, %medicated, and %male were each positively associated with study SMDs. Overall, KYNA levels are increased in patients with schizophrenia, specifically within the central nervous system. An improved understanding of KYNA in patients with schizophrenia may contribute to the development of novel diagnostic approaches and therapeutic strategies.

Key words: kynurenine/tryptophan/psychosis/neuroinflammation

Introduction

Schizophrenia

While schizophrenia is characterized by positive, negative, and cognitive symptoms, neurometabolic abnormalities have also been identified as key features of the illness.[1,2] The longstanding dopamine hypothesis of schizophrenia suggests that dysregulated functioning of the dopaminergic system underlies its pathophysiology.[3–7] However, the dopamine hypothesis does not readily explain negative and cognitive symptoms.[8,9] Moreover, a subset of patients (20%–35%) show partial or no response to standard antipsychotic treatments, which exert their effect primarily through dopamine receptor antagonism.[10,11]

Another widely purported pathophysiological mechanism is the glutamatergic hypothesis of schizophrenia. Evidence for this hypothesis arises from pharmacological studies in which *N*-methyl-D-aspartate receptor (NMDAR) antagonist administration leads to the emergence of positive, negative, and cognitive symptoms in human volunteers.[12–17] These agents also elicit symptom exacerbation in patients with schizophrenia.[16,18,19] Olney and Farber proposed that hypofunctioning NMDARs on gamma-aminobutyric acid (GABA)-ergic inhibitory interneurons result in the disinhibition of downstream pyramidal neurons, increasing presynaptic glutamate release within various brain regions.[20] In support, disturbed glutamatergic signaling has been observed in healthy volunteers following acute exposure to an

NMDAR antagonist[21,22] and in patients with schizophrenia.[23–28] The known effects of exogenous NMDAR antagonists on glutamatergic dysregulation and schizophrenia-like symptomatology have resulted in increased attention towards kynurenic acid (KYNA), the only currently known endogenous NMDAR antagonist.

Kynurenine Pathway

KYNA is produced through the kynurenine (KYN) pathway of tryptophan (TRP) degradation, accounting for over 90% of the metabolism of this essential amino acid.[29] TRP is oxidized to *N*-formylkynurenine by 1 of 3 enzymes: indoleamine 2,3-dioxygenase 1 (IDO1), IDO2, or tryptophan 2,3-dioxygenase (TDO2). Next, deformylation of *N*-formylkynurenine by formamidase produces KYN. KYN is thereafter metabolized through 3 distinct branches of the KYN pathway. KYN can be irreversibly transaminated to KYNA by 4 kynurenine aminotransferases (KATs). KYN can also be oxidized by kynurenine 3-monooxygenase (KMO) to produce 3-hydroxykynurenine (3-HK). Lastly, KYN can undergo oxidative cleavage by kynureninase to form anthranilic acid (for additional details on this pathway, see reviews by Dounay et al,[30] Schwarcz et al,[31] and Vécsei et al[32]).

The KYN pathway of TRP degradation is initiated by IDO and TDO2.[30] These enzymes are known to exist at higher levels in the periphery compared to the central nervous system (CNS).[31] Downstream, KYN readily crosses the blood-brain barrier through the large neutral amino acid transporter[33]; approximately 60% of brain KYN is believed to be contributed from the periphery.[34] In contrast, due to its polar structure, KYNA does not cross the blood-brain barrier.[33] Thus, brain KYNA is predominantly derived from brain KYN.[31] The conversion of KYN to KYNA takes place primarily within astrocytes, as these cells contain KATs but not KMO and therefore cannot degrade KYN to 3-HK and its metabolites.[35] Of the 4 existing KATs, KAT II is thought to be the main enzyme of KYNA production.[36]

KYNA acts as an antagonist of all 3 ionotropic glutamate receptors, including NMDARs, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors, and kainate receptors.[37] However, of these, KYNA preferentially and competitively inhibits the glycine site of the NMDAR.[38,39] KYNA is also an antagonist of α7 nicotinic acetylcholine receptors (α7nAChR)[40]; its inhibitory effect on these receptors is achieved noncompetitively through its interaction with an allosteric potentiating site, which is oppositely stimulated by galantamine, an α7nAChR positive allosteric modulator.[41] KYNA also activates the G-protein-coupled receptor GPR 35 and the aryl hydrocarbon receptor.[42,43] Additionally, KYNA functions as a free radical scavenger and an antioxidant.[44] Given its capacity to block neuronal excitation and scavenge free radicals, KYNA is widely considered to have neuroprotective and anticonvulsant properties.[45]

KYNA Hypothesis of Schizophrenia

The KYNA hypothesis of schizophrenia posits that disrupted KYNA levels are implicated in the pathophysiology of the illness.[46] This hypothesis is supported by the notion that KYNA, as an endogenous glutamate receptor antagonist, may mimic schizophrenia-like phenomena induced by exogenous glutamate receptor antagonists, along with evidence from both preclinical and clinical literature.[41,47,48] Preclinical studies manipulating levels of KYNA have demonstrated its influence on both behavior (eg, cognitive functioning) and neurotransmission (eg, glutamatergic, dopaminergic) observed to be aberrant in patients with schizophrenia.[41,48] Furthermore, KYNA levels have also been measured in schizophrenia patient populations and deviations from healthy controls (HCs) have often been reported.[41]

Study Aims

Although individual studies have reported KYNA disruptions in patients with schizophrenia, their findings have not been assessed through a meta-analysis. The primary aim of this systematic review and meta-analysis was to evaluate the difference in KYNA levels between patients with schizophrenia and HCs. As secondary aims, subgroup analyses examined nonoverlapping participant samples, KYNA measurement techniques, and KYNA sample source. Also, the influences of patients' age, antipsychotic status, and sex were explored through a meta-regression.

Methods

Literature Search

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analysis group.[49] Two authors (E.P., J.K.) independently performed the search (last search: December 2016) and assessed eligibility, and 2 authors (E.P., J.K.C.) independently extracted data. English language human published articles were searched for using Embase, Medline, and PsycINFO. The Ovid search was conducted using the following terms: (kynuren* or KYNA) and (schizophreni* or psychosis). The reference sections of major review articles[30–32,41,46–48,50–54] were also searched.

Inclusion Criteria

Full-length English language articles were included if: (1) they included patients with schizophrenia or related disorders, (2) they included a HC group, (3) KYNA levels were measured in both groups using any method, and (4) data were sufficient to calculate standardized mean differences (SMDs).

Exclusion Criteria

When studies reported upon a sample completely overlapping with another study, as described within their texts, the study with the largest sample size was used and the other excluded. Where publications reported partially overlapping samples, both were included in the primary analysis. Studies missing baseline KYNA levels or examining KYNA production were excluded.

Outcome Measures

The main outcome measure was KYNA levels. We aimed to investigate group differences in KYNA between patients with schizophrenia and HCs.

Recorded Variables

The variables recorded from each included study were KYNA levels, diagnoses, age, sex, antipsychotic status, method of KYNA measurement, and participant sample overlap with other studies.

Data Analysis

Meta-analysis. The primary meta-analysis, subgroup analyses, and sensitivity analyses were conducted using Review Manager Version 5.2 (http://tech.cochrane.org/revman). The meta-regression was carried out using Comprehensive Meta Analysis (www.meta-analysis.com). Differences in KYNA levels between patients with schizophrenia and HCs were determined by calculating SMDs.[55] If the total number of study participants exceeded the number that underwent KYNA measurement, only subjects in whom KYNA was measured were included. When studies separately reported KYNA levels from multiple brain areas, average SMDs were calculated and utilized. Where mean values were not stated, authors were contacted for additional data or, if reported, median values were utilized. Where SD values were not reported, values were obtained through calculations from available data according to the Cochrane Handbook for Systematic Reviews of Interventions (http://www.handbook.cochrane.org). Effects were interpreted as small (SMD = 0.2), moderate (SMD = 0.5) or large (SMD = 0.8),[55] with positive values indicating elevated KYNA levels in the schizophrenia group. To adjust for study heterogeneity, the inverse variance statistical method and random effects model were employed.[56] Significance was assessed using 2-sided 95% confidence intervals (CIs).

The I^2 statistic was utilized to assess study heterogeneity for the primary analysis; $I^2 \geq 50\%$ represented significant heterogeneity. If heterogeneity was found, one-leave-out sensitivity analyses were performed to examine influences of any single study on the pooled SMD and associated P values. The possibility of publication bias was assessed using funnel plots and Egger's regression test[57]; if identified, the trim-and-fill procedure[58] was utilized.

Moderator Analyses. Moderator analyses were conducted to investigate the influence of study and patient characteristics on KYNA levels. Subgroup analyses were separately examined for: (1) nonoverlapping participant samples using the study with the largest sample size, (2) KYNA measurement technique (ie, cerebrospinal fluid (CSF), brain tissue, plasma/serum, saliva), and (3) KYNA sample source (ie, central, peripheral). Meta-regression analyses were conducted for patients' age, the proportion of antipsychotic-medicated patients (%medicated), and the proportion of male patients (%male). When participant information was presented only for the full sample, this data was used for meta-regression analyses.

Risk of Bias. The Risk of Bias Assessment tool for Nonrandomized Studies[59] was employed, using the following factors: participant selection, confounding variables, measurement of exposure, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting.

Significance for all tests was set at $P < .05$ (2-tailed). Continuous variables are reported as mean ± SD.

Results

Included Individual Studies

Thirteen studies were deemed eligible for inclusion in the meta-analysis (total number of subjects, $n = 961$).[60–72] The PRISMA flow diagram is presented in supplementary figure 1 and characteristics of included studies are summarized in table 1. The average number of subjects was 73.9 ± 47.1 (range: 26 to 174). Average age and %male of the patient group were 37.7 ± 7.0 years and 68.0% ± 17.5%, respectively. Average age and %male of the control group were 34.2 ± 9.7 years and 64.0% ± 18.6%, respectively. Average %medicated was 69.0% ± 35.3%. Four studies measured KYNA in CSF,[64,65,68,72] 3 in brain tissue,[66,70,71] 5 in plasma/serum,[60,62,63,67,69] and 1 in saliva.[61] Of the 13 included studies, 10 had completely nonoverlapping samples.[60–63,66–71]

Risk of Bias

Six (46.2%) of 13 studies showed a "low" risk of bias for all items. The detailed assessment is displayed in supplementary figure 2.

Meta-analyses

KYNA levels were moderately higher in patients with schizophrenia in comparison to HCs (SMD = 0.66, CI = 0.25 to 1.06, $P = .001$) (figure 1).

Moderator Analyses

Subgroup Analyses. Nonoverlapping Samples Excluding 2 studies[64,65] with smaller, partially overlapping samples with another study,[72] KYNA levels were still moderately elevated in

Table 1. Summary of Included Studies (n = 13)

Authors (Year)	n	Mean Age (SD)	Sex (%Male)	Antipsychotic Status (%Medicated)	KYNA Measurement Technique	SCZ KYNA Mean (SD) [Units], HC KYNA Mean (SD) [Units], P value[a]	Key Findings[b]
Fazio et al (2015)	90 SCZ; 84 HC	SCZ: 33.4 (11.7); HC: 32.8 (10.4)	SCZ: 68.9%; HC: 44.0%	66.7%; 30 patients unmedicated	Serum	SCZ: 3.79 (2.03) [ng/ml]; HC: 3.28 (1.84) [ng/ml]	KYNA levels higher in SCZ group
Schwieler et al (2015)[c]	23 SCZ[d]; 37 HC	Median (IQR), SCZ: 35.0 (32.0–41.0); HC: 23.0 (22.0–25.5)	SCZ: 65.2%; HC: 62.2%	100.0%	CSF	Median (IQR), SCZ: 1.87 (1.63–2.29) [nM]; HC: 1.50 (1.14–1.92) [nM]; P = .006	KYNA levels higher in SCZ group
Chiappelli et al (2014)	64 SCZ[d]; 64 HC	SCZ: 37.7 (12.4); HC: 38.9 (12.9)	SCZ: 65.6%; HC: 54.7%	82.8%; 11 patients unmedicated for at least 1 mo	Saliva	SCZ: 7.40 (1.05) [nM]; HC: 6.02 (0.74) [nM]	Mean KYNA level higher in SCZ group
Fukushima et al (2014)	25 SCZ; 27 HC	SCZ: 28.2 (4.4); HC: 26.5 (5.6)	SCZ: 44.0%; HC: 44.4%	100.0%	Serum	SCZ: 26.5 (11.95) [nmol/L]; HC: 28.7 (11.17) [nmol/L]	No difference in KYNA levels between groups
Kegel et al (2014)[c]	19 SCZ[d,e]; 26 HC	SCZ: 37.5 (7.5); HC: 24.9 (5.8)	SCZ: 57.1%; HC: 69.2%	100.0%	CSF	SCZ: 2.1 (0.87) [nM]; HC: 1.6 (0.51) [nM]	KYNA levels elevated in SCZ group
Linderholm et al (2012)[c]	16 SCZ; 29 HC	SCZ: 36.8 (7.9); HC: 25.4 (7.3)	SCZ: 100.0%; HC: 100.0%	100.0%	CSF	SCZ: 2.03 (0.92) [nM]; HC: 1.36 (0.43) [nM]	KYNA levels elevated in SCZ group
Myint et al (2011)	53 SCZ; 48 HC	SCZ: 33.3 (12.2); HC: 32.6 (10.3)	SCZ: 43.4%; HC: 43.8%	0.0%; all patients unmedicated for at least 4 mo	Plasma	SCZ: 26.90 (16.38) [nmol/L]; HC: 35.95 (9.49) [nmol/L]	KYNA levels lower in SCZ group
Sathyasaikumar et al (2011)	15 SCZ; 15 HC	SCZ: 50.0 (17.0); HC: 46.7 (16.3)	SCZ: 73.3%; HC: 66.7%	80.0%; 3 patients unmedicated	Brain tissue	BA 10, SCZ: 4.03 [pmol/mg protein]; HC: 2.2 (0.77) [pmol/mg protein]; P = .011	KYNA levels elevated within BA 10 in SCZ group
						BA 9, SCZ: 2.50 [pmol/mg protein]; HC: 1.7 (0.77) [pmol/mg protein]; P = .058	KYNA level elevation within BA 9 in SCZ group approached significance
Barry et al (2009)	34 SCZ[f]; 36 HC	SCZ: 37.3 (8.9); HC: 33.7 (6.6)	SCZ: 76.5%; HC: 72.2%	85.3%; 5 patients unmedicated	Plasma	SCZ: 6.433 (2.93) [ng/mL]; HC: 6.785 (2.80) [ng/mL]	No difference in KYNA levels between groups
Miller et al (2006)	12 SCZ; 14 HC	SCZ: 43.8 (12.8); HC: 48.6 (10.9)	SCZ: 66.7%; HC: 57.1%	75.0%; 3 patients unmedicated	Brain tissue	SCZ: 1.719 (1.45) [pmol/10mg tissue]; HC: 1.034 (0.32) [pmol/10mg tissue]	Mean KYNA level higher in SCZ group

Table 1. *Continued*

Authors (Year)	*n*	Mean Age (SD)	Sex (%Male)	Antipsychotic Status (%Medicated)	KYNA Measurement Technique	SCZ KYNA Mean (SD) [Units], HC KYNA Mean (SD) [Units], *P* value[a]	Key Findings[b]
Nilsson et al (2005)	90 SCZ; 49 HC	SCZ: 29.9 (8.5); HC: 27.0 (5.6)	SCZ: 100.0%; HC: 100.0%	37.8%; 56 patients unmedicated for at least 21 d	CSF	SCZ: 1.45 (0.95) [nM]; HC: 1.06 (0.42) [nM]	KYNA levels elevated in SCZ group
Schwarcz et al (2001)	30 SCZ; 31 HC	SCZ: 49.8 (15.1); HC: 49.8 (15.9)	SCZ: 70.0%; HC: 64.5%	70.0%; 9 patients unmedicated for at least 6 mo	Brain tissue	BA 9[e]: SCZ: 2.9 (2.2) [pmol/mg protein]; HC: 1.9 (1.3) [pmol/mg protein]	KYNA levels increased within BA 9 in SCZ group
						BA 10: SCZ: 2.7 (2.2) [pmol/mg protein]; HC: 2.0 (1.3) [pmol/mg protein]	Trend towards increased KYNA levels within BA 10 and 19 in SCZ group
						BA 19: SCZ: 1.1 (0.6) [pmol/mg protein]; HC: 0.9 (0.4) [pmol/mg protein]	
Ravikumar et al (2000)	15 SCZ; 15 HC	Range, SCZ: 20–35	SCZ: 53.3%; HC: 53.3%	0.0%	Plasma	SCZ: 271.21 (22.44) [ng/ml]; HC: 172.60 (16.46) [ng/ml]	KYNA levels elevated in SCZ group

Note: BA, Brodmann area; HC, healthy controls; KYNA, kynurenic acid; SCZ, schizophrenia.
[a]Where *P* values were utilized to calculate SD, corresponding *P* values are presented in this table.
[b]For ease of presentation, only findings concerning group differences in KYNA levels are included in this table.
[c]Consist of partially overlapping samples.
[d]Included patients with schizoaffective disorder.
[e]Sample size presented here does not reflect total sample size, from which variables for meta-regression analyses were utilized.
[f]Included patients with schizoaffective disorder and psychosis not otherwise specified.

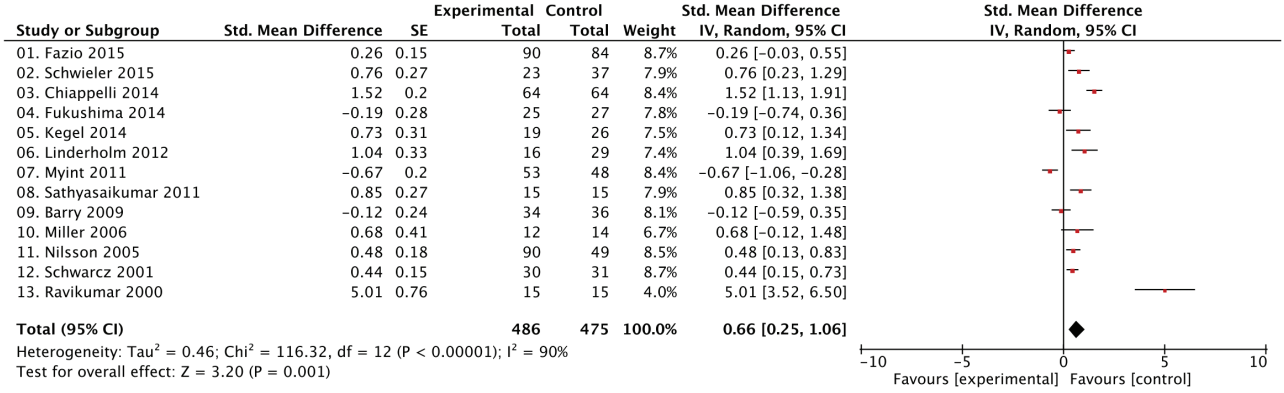

Fig. 1. Group differences in KYNA levels between patients with schizophrenia and healthy controls. CI, confidence interval; IV, inverse variance; Std, standardized.

patients with schizophrenia compared to HCs (SMD = 0.62, CI = 0.17 to 1.07, $P = .007$) (supplementary figure 3).

KYNA Measurement Technique KYNA levels were moderately increased in patients with schizophrenia compared to HCs in studies using CSF (SMD = 0.66, CI = 0.42 to 0.91, $P < .00001$) and brain tissue samples (SMD = 0.55, CI = 0.31 to 0.79, $P < .0001$). KYNA levels did not differ between groups in studies using plasma/serum measurement techniques (SMD = 0.51, CI = −0.32 to 1.33, $P = .23$) (supplementary figure 4). There were insufficient studies using saliva to permit an analysis in this subgroup.

KYNA Sample Source In the 7 studies measuring KYNA centrally, KYNA levels were moderately higher in patients with schizophrenia in comparison to HCs (SMD = 0.61, CI = 0.43 to 0.78, $P < .00001$). In contrast, in the 6 studies measuring KYNA peripherally, KYNA levels did not differ between groups (SMD = 0.74, CI = −0.12 to 1.59, $P = .09$) (supplementary figure 5).

Meta-regression Analyses. Meta-regression analyses showed that the higher the patients' age, the higher (ie, more positive) the study SMD (12 studies, $n = 931$, slope = 0.022, 95% CI: 0.005 to 0.039, $P = .012$). Also, the higher the %medicated, the higher the study SMD (13 studies, $n = 961$, slope = 0.008, 95% CI: 0.004 to 0.013, $P < .001$). Lastly, the higher the patients' %male, the higher the study SMD (13 studies, $n = 961$, slope = 0.012, 95% CI: 0.004 to 0.020, $P = .002$) (supplementary figure 6). Notably, excluding the study with the lowest SMD[67] led to the loss of significance for the meta-regression analyses mentioned above (all P values > .17). In contrast, excluding the study with the highest SMD[61,69] did not alter findings (all P values < .012).

Sensitivity Analysis

Significant study heterogeneity existed in the main analysis ($I^2 = 90\%$). Sensitivity analyses indicated that no single study significantly contributed to heterogeneity.

Publication Bias

Egger's test showed no publication bias in the analysis. The funnel plot is displayed in supplementary figure 7.

Discussion

Main Findings

This is the first meta-analysis to compare KYNA levels between patients with schizophrenia and HCs. The main analysis found elevated KYNA in patients with schizophrenia. Subgroup analyses demonstrated that: (1) this group difference remained when studies with partially overlapping samples were removed, (2) KYNA was increased in patients with schizophrenia when measured in CSF and brain tissue samples, and (3) KYNA was increased in patients with schizophrenia when measured in the CNS but not in the periphery. Lastly, meta-regression analyses revealed that the higher patients' age, %medicated, and %male, the more positive the SMDs comparing KYNA between groups. Upon removing the study with the lowest SMD, significance for these relationships was lost.

Analysis of Included Studies

Four included studies measured KYNA in CSF. Nilsson et al[68] found elevated KYNA levels in a mostly unmedicated sample of patients with schizophrenia compared to HCs. The other 3 studies measuring KYNA in CSF used partially overlapping participant samples, each investigating a unique primary objective. In their samples of olanzapine-treated patients with schizophrenia or schizoaffective disorder (SA), each of the 3 studies found increased KYNA levels in the patient group compared to HCs.[64,65,72]

Three included studies measured KYNA in brain tissue samples. In a seminal study, Schwarcz et al[71] found increased KYNA in a sample of mostly medicated patients with schizophrenia within Brodmann area (BA) 9 but not 10 or 19, although a trend towards an increase was seen in the latter 2 areas. Sathyasaikumar

et al[70] found increased KYNA within BA 10 but not 9 in a mostly medicated sample of patients with schizophrenia; the elevation in BA 9 approached significance. Miller et al[66] noted an increase in KYNA in samples of the anterior cingulate gyrus from mostly medicated patients with schizophrenia as compared to HCs, but the study was only powered to assess significance for a greater degree of change than that seen.

Five included studies measured KYNA in the plasma or serum. Fazio et al[62] reported increased KYNA levels in a mostly medicated sample of patients with schizophrenia. Ravikumar et al[69] found elevated plasma KYNA levels in unmedicated patients with schizophrenia. Contrastingly, Myint et al[67] reported decreased plasma KYNA in antipsychotic-naïve or antipsychotic-free patients with schizophrenia. Also, Fukushima et al[63] reported no difference in serum KYNA between medicated patients with schizophrenia and HCs, and Barry et al[60] found no difference in plasma KYNA between mostly medicated patients with schizophrenia, SA, or psychosis not otherwise specified (NOS) and HCs.

Lastly, 1 included study measured KYNA in saliva. Chiappelli et al[61] reported higher mean saliva KYNA in a mostly medicated sample of patients with schizophrenia or SA compared to HCs.

Analysis of Meta-regression Findings

The findings from meta-regression analyses suggest that patients' age, %medicated, and %male are positively related to study SMDs. First, with respect to age, the current meta-regression results are in line with previous studies that report a positive correlation between age and KYNA in patients with schizophrenia.[68,73] This supports the notion that increasing KYNA levels may explain cognitive deterioration with age.[50,54] Also, given that α7nAChRs may be the preferred target of endogenous KYNA,[40] and have been linked to cognitive impairment, increases in KYNA with age may also explain why cognitive symptoms arise early in the course of schizophrenia.[74] However, it should be noted that not all studies find an association between age and KYNA levels.[65,71] Second, in terms of antipsychotic status, these findings contrast those of previous studies suggesting that antipsychotic medication reduces brain KYNA levels.[71,75] One included study showed a trend towards decreased KYNA within brain tissue samples of treated vs untreated patients,[66] although other studies have found no relationship between antipsychotic status and KYNA levels.[61,65] Finally, with respect to sex, results from the present meta-analysis contrast those of a previous study that found higher KYNA levels in female HCs than male HCs.[76]

However, the removal of Myint et al[67] from the meta-regression analysis led to the loss of significance in each of the aforementioned relationships. Thus, the meta-regression results may in fact hold greater implications for interpreting the findings from Myint et al[67] than those of the entire meta-analysis. It is proposed that the results of Myint et al,[67] which was the only study to report decreased KYNA in the patient group, were influenced by their comparatively young, unmedicated, and mostly female patient sample.

Putative Mechanisms of KYNA Elevation in Schizophrenia

One explanation for elevated KYNA in schizophrenia might be a greater availability of KYN to be metabolized by KAT II to KYNA. In keeping with the notion that schizophrenia has an inflammatory component,[77–79] evidence suggests that inflammatory processes activate KYN pathway enzymes in the periphery, leading to increases in peripheral KYN.[31,47,53,80,81] As KYN readily crosses the blood-brain barrier, elevated peripheral KYN may contribute to elevated brain KYNA. Accordingly, elevated KYN has been detected centrally and peripherally in patients with schizophrenia[63–66,71,72] and has been shown to correlate with brain KYNA.[65,71]

Further, studies examining KYN pathway enzyme expression and activity within brain areas highly implicated in schizophrenia pathophysiology have reported increased TDO2 and decreased KMO, with no change in IDO or KAT II.[66,70,82,83] An increase in TDO2 would contribute to elevated brain KYN. This would be increasingly directed towards KYNA production in the presence of KMO disturbances, as supported by genetic studies that report KMO gene alterations to be related to increased KYNA.[84,85] Likewise, preclinical studies administering a KMO blocker or genetically disrupting KMO have observed KYNA elevations.[86–89]

In addition, astrocytic activation may have an important role in explaining elevated KYNA. As previously described, KAT II, the enzyme primarily responsible for converting KYN to KYNA in the brain, has been found to exist preferentially in astrocytes. Thus, astrocytic activation may increase KYNA production. In support, increases in S100B, a marker for astrocyte function, have been found in patients with schizophrenia, reflecting increased astrocytic activity.[90] Moreover, administration of interleukin 6 to cultured human astrocytes has been shown to increase KYNA, consistent with the aforementioned inflammation and astrocyte mechanisms.[72]

Overall, peripheral inflammation, altered brain TDO2 and KMO, and astrocytic activation may provide a framework through which to understand elevated KYNA in schizophrenia.

Implications of KYNA Dysregulation

KYNA and Behavior. KYNA has a demonstrated capacity to affect behavior and has been posited to be especially influential in cognitive dysfunction.[31,52] In the present review, 4 included studies reported upon relationships

between KYNA and behavior. Fazio et al[62] found negative correlations between KYNA levels and Positive and Negative Syndrome Scale (PANSS) positive symptom scores, and between KYNA levels and speed of processing, in subgroups of patients with multi-episode schizophrenia and first-episode schizophrenia, respectively; the authors identified no other relationships between KYNA levels and measures of symptomatology and functioning. Chiappelli et al[61] noted that patients who experienced distress intolerance had higher KYNA levels both at baseline and following a stressor paradigm than patients who tolerated the psychological stressor and HCs. Also, in patients with distress intolerance, the change in KYNA was positively related to Brief Psychiatric Rating Scale (BPRS) total scores; however, baseline KYNA levels were not related to BPRS total scores. In addition, neither baseline KYNA nor change in KYNA levels were correlated with processing speed or working memory in patients or HCs.[61] Linderholm et al[65] noted no relationship between KYNA levels and BPRS and the Global Assessment of Functioning scores. Finally, Myint et al[67] found that initial plasma KYNA levels were associated with a greater reduction in PANSS positive symptom scores as well as Korean Version of the Calgary Depression Scale for Schizophrenia depressive symptom scores after 6 weeks of antipsychotic treatment, though no cross-sectional relationships existed.

Beyond the included studies, other investigations in humans have provided evidence for associations between KYNA and behavior in patients with schizophrenia. Wonodi et al[83] found that a single-nucleotide polymorphism in the KMO gene (the rate-limiting enzyme of KYN breakdown) was related to impaired smooth pursuit eye movement and visuospatial working memory in a clinical sample. Similarly, Wonodi et al[91] found an association between variations in the KMO gene and deficits in cognitive function, an effect that was more marked in patients with schizophrenia than in HCs.

While human studies provide some evidence for the role of KYNA in modulating schizophrenia-like behavior, stronger support arises from preclinical work. In animal studies, KYNA levels can be raised through focal application of KYNA, administration of KYN, genomic KMO elimination, or KMO blockade.[41,52] These manipulations cause cognitive impairments similar to those observed in patients with schizophrenia, including deficits in prepulse inhibition,[92,93] auditory sensory-gating,[94] stimulus processing and conditioned responding,[95] spatial working memory,[96] contextual fear conditioning and context discrimination,[97] spatial learning and memory,[98–100] and cognitive flexibility.[101–103] In addition, KYNA increases have been shown to enhance spontaneous and amphetamine-induced locomotor activity.[104]

Conversely, experimentally induced reductions in KYNA by genetic deletion or acute inhibition of KAT II have led to improved cognitive functioning. Improvements have been noted in contextual memory and spatial discrimination,[105] spatial learning and memory,[100] sustained attention, amphetamine- and ketamine-induced disruptions in auditory gating, and ketamine-induced deficits in working memory and spatial memory.[106]

In summary, while human literature on the topic is emergent, preclinical studies provide evidence to suggest that increased KYNA levels may account for certain schizophrenia-like behaviors, specifically those observed within cognitive and social domains.

KYNA and Neurotransmission. Of the studies included in the current review, only one measured indices of neurotransmission. Among other neurometabolites, Fukushima et al[63] found decreased plasma serotonin and increased glutamate in the schizophrenia group, although relationships with KYNA were not reported. Moreover, another human study reported positive correlations between CSF KYNA and CSF homovanillic acid and 5-hydroxy-indoleacetic acid, indicative of dopamine and serotonin turnover, respectively.[107]

Unlike currently available human studies, preclinical literature has provided ample evidence to suggest that KYNA has inverse bi-directional relationships with several neurotransmitters, including glutamate, dopamine, acetylcholine, and GABA. Studies have demonstrated that increasing KYNA results in decreased glutamate[99,100,102,108–112]; notably galantamine administration normalizes this effect.[102,110,112] Accordingly, decreasing KYNA leads to increased glutamate.[100,105,108,110,112]

Similarly, studies investigating dopaminergic neurotransmission have found that increasing KYNA results in decreased dopamine levels[87,113,114]—an effect that can also be attenuated by galantamine[113,114]—whereas decreasing KYNA increases dopamine levels.[114,115] Furthermore, KYNA's influence on midbrain dopamine neurons has been thoroughly studied; reliably, increased KYNA leads to increased firing rate and burst firing activity,[93,116–119] whereas decreased KYNA has an opposite effect.[119,120] These effects are believed to result from KYNA's blockade of glutamate receptors.[116,118,119] Moreover, the influence of KYNA on the dopamine system has been explored through the assessment of its effect on amphetamine-induced responses. Akin to NMDAR antagonists, KYNA has an amplifying effect on amphetamine-induced dopamine release through a mechanism involving reduced inhibition by amphetamine on firing rate and burst activity of ventral tegmental area dopamine neurons.[121,122] Finally, it deserves mention that KYNA modulates the effects of clozapine—an atypical antipsychotic with particular efficacy in patients with treatment-resistant schizophrenia—and nicotine on midbrain dopamine neurons.[46,120,123]

Further, an inverse relationship between KYNA and acetylcholine is observed, with a decrease in KYNA leading to increased acetylcholine levels.[124] Lastly, a

bi-directional relationship between KYNA and GABA has been noted. An increase in KYNA results in decreased GABA—an effect prevented by galantamine—while a decrease in KYNA increases GABA.[108,125]

In summary, preclinical literature supports KYNA's inverse effects on glutamate, dopamine, acetylcholine, and GABA, through its antagonism of α7nAChRs. In contrast, KYNA's influence on midbrain dopamine neurons' firing rate and burst firing activity, and amphetamine-induced responses, is likely related to its antagonism of glutamate receptors. These inverse associations remain unclear in schizophrenia, as hallmark neurotransmitter disruptions such as elevated striatal dopamine synthesis and release,[4,6] and increased subcortical glutamate,[2] seem incongruent with observed elevations in KYNA levels; heterogeneous brain KYNA distribution might explain this discrepancy.

KYNA and Drugs. Several pharmacological agents can be utilized to manipulate KYNA levels. As per the above evidence, treatments that are intended to benefit patients with schizophrenia might aim to reduce KYNA levels. Given that there are no known KYNA degradation enzymes or specific targetable reuptake sites, the optimal method to lower KYNA appears to be via KAT II inhibition.[41] KAT II has been shown to be highly substrate-specific, further making it an attractive target.[41] Preclinical studies have shown that agents inhibiting KAT II lower KYNA levels by approximately 30% to 40%.[52,100,106,112,124,126–128] Additionally, preclinical work suggests that these agents are procognitive[100,106,128] and increase neurotransmitter levels described to be influenced by KYNA above.[100,108,110,112,115,124,125]

Pharmacological treatments might also attempt to counter KYNA's mechanism of action. Preclinical findings presented above suggest that agonism of α7nAChRs or NMDARs might mitigate schizophrenia-like behavior and/or neurotransmission derangements. However, studies examining such agents in patients with schizophrenia have shown minimal efficacy to-date.[55,129–131]

Other possible targets to reduce KYNA are peripheral IDO and TDO2. Decreasing their activity might attenuate overproduction of peripheral KYN, thereby preventing increases in brain KYN and ultimately, brain KYNA. While IDO and TDO2 inhibitors have been studied as possible cancer treatments, their use in psychiatric diseases has been limited.[31] IDO and TDO2 have important physiological functions, including immunomodulation and NAD production, respectively, and their inhibition can cause significant adverse effects.[132–135]

Nonselective inhibitors of cyclooxygenase (COX)-1 and COX-2 have also been found to influence KYNA levels: the former elevating KYNA and the latter decreasing it.[136] COX-2 inhibitors have also been suggested to rebalance a disrupted immune response[74,137] and have demonstrated beneficial effects for patients with schizophrenia[80,138]; however, the latter notion may be influenced by publication bias.[139]

Another strategy is activation of central KMO and its downstream enzymes along the quinolinic acid (QUIN)-producing branch, which may be decreased in schizophrenia.[70] Doing so may shift brain KYN degradation towards QUIN and away from KYNA production. However, this would increase production of potentially harmful neurotoxins.[32,53,54]

Finally, nonspecific reduction of KYNA through TRP depletion has been attempted. Thus far, it has produced mixed results with respect to symptoms in patients with schizophrenia.[140–142]

Limitations of Present Study

The present work should be considered in light of its limitations. First, the primary aim may have been too narrow in that other KYN pathway metabolites were not evaluated. Second, some studies included patients with SA and psychosis NOS, which may have alternate pathophysiologies. Third, since some included studies did not report upon certain variables, such as duration of illness, antipsychotic dose, and symptom severity, and multiple measurement scales were utilized for the latter, the present study was unable to include these variables in meta-regression analyses. Fourth, some included studies did not account for the influence of food, smoking, or drug use. Fifth, compared to other major meta-analyses, our sample size was small. This may be especially relevant for the interpretation of subgroup analyses, as accumulating evidence may also reveal disruptions in peripheral KYNA levels. Finally, the possibility of publication bias should not be discounted.

Conclusion

The present meta-analysis found increased KYNA levels in patients with schizophrenia, a phenomenon that appears to be localized to the CNS. While age, antipsychotic status, and sex may have modulating effects, elevated central KYNA might help to explain disruptions in behavior and neurotransmission in patients with schizophrenia, thereby providing further clarity towards the understanding of schizophrenia pathophysiology and contributing to the development of novel potential treatment targets.

Future Directions

Future clinical studies should aim to replicate preclinical findings by testing the relationships between KYNA levels and measures of behavior and neurotransmission. The former can be achieved by utilizing well-characterized symptom (eg, PANSS[143]) and neuropsychological (eg, MATRICS[144]) batteries while the latter can be studied using in vivo brain imaging. Moreover, the regional

distribution of KYNA levels should be explored in these relationships. Specifically, the investigation of possible relationships among KYNA levels, elevated striatal presynaptic dopamine synthesis, and increased subcortical glutamatergic neurometabolites early in the illness is warranted. Furthermore, measuring KYNA longitudinally over the course of illness would help define its role in schizophrenia pathophysiology. Additionally, future investigations should clarify the relationship between CSF, brain, plasma, and saliva KYNA levels, while ensuring that methodological issues such as fasting status are accounted for. This may elucidate whether studies in patients with schizophrenia should employ a particular KYNA sampling method. It may also be beneficial for future work to concurrently measure KYNA with other KYN pathway components to further examine pathway dysregulation. Overall, a better understanding of the cause and consequences of elevated KYNA in patients with schizophrenia may lead to the development of improved diagnostic and therapeutic strategies.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* online.

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