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Biochemical Correlation Between KYNA and Glutamate Concentrations in Schizophrenia: Evidence from Clinical Serum Analysis

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ABSTRACT

Background: Different from other neuropsychiatric diseases, schizophrenia is defined by negative, cognitive, and psychotic symptoms. Recent neurobiological theories link glutamatergic dysfunction to kynurenic acid (KYNA), a metabolite of tryptophan. The relationship between KYNA and glutamate suggests pathogenic processes including excitotoxicity and NMDA receptor hypofunction. This study assessed the relationship between serum concentrations of KYNA and glutamate in individuals diagnosed with schizophrenia.
Methods: This study was a cross-sectional observational investigation involving 99 individuals with schizophrenia treated at Prof. Dr. HB Saanin Psychiatric Hospital in Padang, Indonesia. Serum levels of KYNA and glutamate were quantified via ELISA. The statistical analysis encompassed univariate distribution and Spearman's correlation test.
Results: The median KYNA concentration was 14.6 nmol/L (IQR: 12.3–19.5), and the median glutamate concentration was 10.5 µg/mL (IQR: 9.2–12.5), both significantly higher relative to normative values. A robust positive connection was identified between KYNA and Glutamate Concentrations s (Spearman r = 0.701; p < 0.001).
Conclusion: This study demonstrates a strong positive association between glutamate and KYNA in schizophrenia, suggesting that they may serve as interacting neurochemical indicators. These findings corroborate the significance of KYNA–glutamate dysregulation in the pathogenesis of schizophrenia and propose the kynurenine pathway as a viable target for prospective treatment approaches.

Keywords: schizophrenia, glutamate, kynurenic acid

INTRODUCTION

Although it affects roughly 1% of people globally, the frequency of schizophrenia, a severe and chronic neuropsychiatric disorder, varies depending on region and demographic group (1,2). Positive symptoms comprising hallucinations and delusions, negative symptoms including social isolation and anhedonia, and major cognitive deficits define the illness. These expressions cost patients, families, and healthcare systems a lot of money, which helps to explain higher rates of disability and early death.(3)
With a lifetime prevalence calculated at 0.3–0.7% and a point prevalence of over 0.28–

0.40%, schizophrenia affects over 24 million people globally (1,4). Incidence ranges from 15 to 30 per 100,000 person-years. Mostly due to associated physical diseases and suicide, persons with schizophrenia have a two to thrice higher early death relative to the general population. (1,5). In Asia, where more than half of the world's population resides, prevalence estimates are generally consistent with global figures, but may range from 0.2% to 1% depending on the country and urban versus rural context(6,7). Diagnosis and treatment delivery are influenced by cultural differences, accessibility of mental health services, and stigma; hence, there are significant treatment inequities in many countries.

For Indonesia, schizophrenia is a major public health concern. The 2018 Riset Kesehatan Dasar (Basic Health Research, RISKESDAS) projects schizophrenia prevalence at 0.7% per 1,000 people. (8,9) Constant challenges include stigmatization, limited resources, and unfair access to mental health services. Less than 20% of Indonesians with severe mental illness seem to receive appropriate treatment, which emphasizes how urgently systematic improvements in mental health infrastructure and awareness are needed.(9)

The dopamine hypothesis has been the accepted theory for decades to explain the pathophysiology of schizophrenia. It suggested that whilst hypoactivity in prefrontal circuitry causes negative and cognitive symptoms, hyperactivity of mesolimbic dopamine pathways is responsible for pleasant sensations. About 20–30% of people do not get a sufficient reaction to dopamine antagonist; so, cognitive and negative symptoms often follow.(10,11)

Recent developments underline the importance of disturbance in glutamatergic neurotransmission, especially with relation to N-methyl-D-aspartate receptors (NMDARs). The glutamate theory is supported by research demonstrating that NMDAR antagonists, such as ketamine and phencyclidine (PCP), can induce symptoms in individuals with schizophrenia and symptoms similar to those of schizophrenia in healthy individuals. This has focused attention on endogenous modulators of glutamatergic signaling—more especially, KYNA).(12,13)

With KYNA mostly produced by astrocytes via kynurenine aminotransferases (KATs), the kynurenine pathway becomes the main metabolic route for tryptophan in the brain. At the glycine site of the N-methyl-D-aspartate receptor (NMDAR), KYNA works as an endogenous antagonist; at α7 nicotinic acetylcholine receptors, it operates as a noncompetitive antagonist.(14) KYNA thereby reduces glutamatergic neurotransmission and is linked to the NMDAR hypofunction observed in schizophrenia. First-episode and drug-naïve patients as well as those with schizophrenia have shown higher concentrations of KYNA in their cerebrospinal fluid and postmortem brain tissue.(15,16)

Higher KYNA levels have been linked to poorer cognitive and deleterious effects as well as to possible treatment resistance. Inflammatory signals carefully control the pathway: pro-inflammatory cytokines stimulate IDO and TDO enzymes, so producing increased kynurenine levels and a metabolic change towards KYNA and so linking immunological dysregulation with glutamatergic abnormalities in schizophrenia.(17)

Preclinical studies show that via antagonizing NMDARs and blocking α7nAChRs, high KYNA results in reduced extracellular glutamate.(18,19) On the other hand, reduction of KYNA synthesis improves glutamate release. Human imaging investigations confirm this reciprocal relationship by showing that stress-induced increases in salivary KYNA match reduced glutamate levels in the anterior cingulate cortex of schizophrenia patients.(20) KYNA could affect synaptic pruning driven by microglia as well as neurodevelopmental processes. Possibly caused by elevated KYNA and inflammatory signaling, excessive synaptic pruning has been linked to

cortical thinning and connection anomalies seen in schizophrenia.(21)

Although these pathways are acknowledged, significant knowledge gaps remain about the relationship between KYNA and glutamate in the brains of schizophrenia patients, the impact of inflammation and hereditary factors, and their correlations with clinical symptoms and cognitive performance. Though need further clinical validation, therapeutically the inhibition of KAT II, increase of KMO, or use of anti-inflammatory medications to target the kynurenine pathway has shown promise in preclinical trials (22). This work aims to clarify the relationships between KYNA and blood glutamate levels in schizophrenia as well as their links with neurobiological and clinical features, thereby supporting the search of creative therapy targets and improved outcomes in this crippling illness.

MATERIALS & METHODS

Conducted at an outpatient facility of Prof. Dr. HB Saanin Psychiatric Hospital in Padang, Indonesia. The study was a cross-sectional and analytical observational. Under significant research into indicators of neurochemical dysfunction in schizophrenia, the project ran from March to August 2024. Comprising 99 individuals diagnosed with schizophrenia in line with the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), the study involved participants using consecutive sampling technique. The inclusion criteria were a verified diagnosis of schizophrenia by an expert psychiatrist, an age between 18 and 60 years, and written informed consent. Considered exclusory were (1) acute agitation or violent conduct requiring sedation, (2) current systemic infection, (3) pregnancy or lactation, and (4) simultaneous serious physical illness (e.g., liver or renal failure).

Authorized the study plan is the Health Research Ethics Committee of Universitas Andalas Faculty of Medicine. Every procedure was carried out in compliance with the Declaration of Helsinki's ethical guidelines. Every participant completed an informed permission form before registration. After recruitment, each participant had a 3 mL venous blood sample taken using a sterile procedure. In order to separate the serum, the samples let coagulate for a while at room temperature then centrifuged at 3,000 rpm for ten minutes. Serum levels of glutamate and kynurenic acid (KYNA) were ascertained by use of commercially sold enzyme-linked immunosorbent assay (ELISA) kits. The study took place in Universitas Andalas' Biomedical Laboratory under the Faculty of Medicine.

STATISTICAL METHODS

We gathered sociodemographic information—age, gender, education, marital status, and occupation—using structured questionnaires. KYNA and glutamate levels were assessed using descriptive statistics such as median, interquartile range, minimum, and maximum, KYNA and glutamate levels were evaluated. We used a Kolmogorov–Smirnov test to assess normalcy. Given non-parametric distribution of the data, Spearman's rank correlation test was used to evaluate the association between serum KYNA and glutamate levels. The statistical work was done using SPSS version 26.0. The p-value of less than 0.05 defined statistical significance.

RESULT

Based on Table 1, the demographic profile provides essential context for interpreting the observed correlation between KYNA and glutamate. The sample had a median age of 37 years (range: 18-55 years), with a male predominance (62.6% male, 37.4% female). Regarding marital status, half of the participants (50.5%) were unmarried, 34.3% were married, and 15.2% were widowed. Educational attainment varied, with most participants having completed the second cycle of secondary education (47.5%), followed by first cycle of secondary education (18.2%), elementary school or bachelor's degree (15.2% each), and a small

proportion (4.0%) without formal education. Employment status was distributed among those not working (38.4%), those who were employed or self-employed (42.4%), housewives (16.2%), and students (3.0%).

Table 1. Feature of Research Subjects

Variable	**N=99**
Age (years), median (min-max)	**37 (18 – 55)**
Gender, n (%)	
Man	62 (62,6)
Woman	37 (37,4)
Marital status, n (%)	
Unmarried	50 (50,5)
Married	34 (34,3)
Widow	15 (15,2)
Last education, n (%)	
No formal education	4 (4,0)
Elementary School	15 (15,2)
Secondary education's first cycle	18 (18,2)
Secondary education's second cycle	47 (47,5)
A degree from college	15 (15,2)
Occupation, n (%)	
Not working	38 (38,4)
Housewifes	16 (16,2)
Students	3 (3,0)
Employee/self-employed	42 (42,4)

Table 2 presents the distribution of KYNA and glutamate level among 99 individuals diagnosed with schizophrenia. KYNA levels in plasma were found to have a median value of 14.6 nmol/L, with an interquartile range from 12.3 to 19.5 nmol/L. Glutamate concentrations had a median of 10.5 μg/mL, with an interquartile range (IQR) of 9.2 to 12.5 μg/mL.

Table. 2. Distribution of Micropolin Levels, Kynurenic Acid (KYNA), and Glutamate Concentrations in People with Schizophrenia

Variabel	**N=99**	
	Median (IQR)	**Min – Max**
KYNA concentrations (nmol/L)	14,6 (12,3 – 19,5)	3,7 – 119,3
Glutamate concentrations (μg/mL)	10,5 (9,2 – 12,5)	0,5 – 65,2

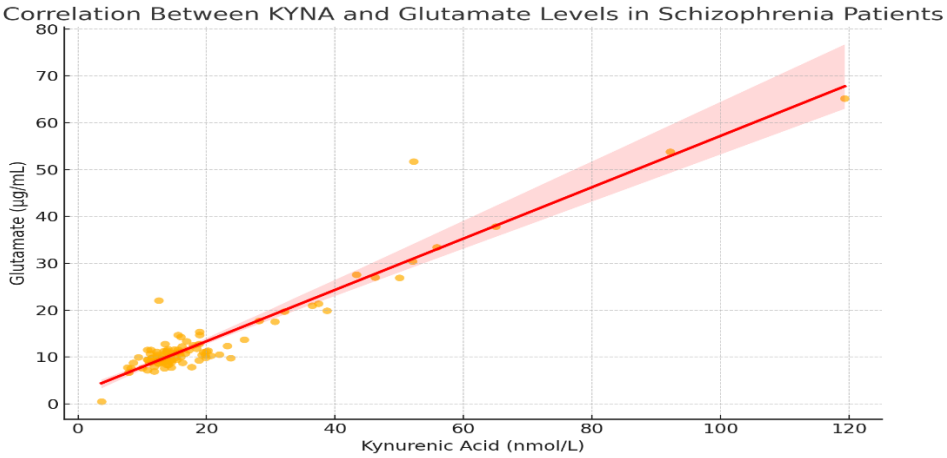
Description: IQR=Inter Quartile Range

Table 3 showed a bivariate correlation analysis examining the relationship between KYN levels (nmol/L) and glutamate concentrations (μg/mL) in individuals with schizophrenia, using Spearman's rank correlation. The analysis yielded a Spearman correlation coefficient (r) of 0.701, indicating a strong positive correlation between KYNA and glutamate concentrations. The corresponding p-value is less than 0.001, suggesting that the association is statistically significant at the conventional alpha level ($p < 0.05$).

Figure 1 showed a statistically significant positive correlation between serum kynurenic acid (KYNA) and glutamate concentrations among individuals diagnosed with schizophrenia. As depicted in the scatter plot, increasing levels of KYNA are associated with higher concentrations of glutamate. This relationship is supported by Spearman's correlation coefficient ($r = 0.701$; $p < 0.001$), indicating a strong monotonic association. The observed co-elevation of KYNA and glutamate supports the theory holds that the pathophysiology of schizophrenia is mutually related with

abnormalities in the kynurenine pathway and glutamatergic transmission. It potentially contributes to NMDA receptor hypofunction, excitotoxicity, and neuroinflammatory mechanisms.

Picture 1. Bivariate Analysis of Correlation of Proline Levels, Kynurenic Acid (KYNA) Levels, and Glutamate concentrations in People with Schizophrenia



DISCUSSION

The median age of 37 years (range 18–55) indicates that the majority of patients are in the productive age group. This is consistent with research at Dr. Soeharto Heerdjan Hospital in 2022, which reported that 92.6% of schizophrenic patients were between 18–60 years old. High productive age in schizophrenia patients is a concern because it can have an impact on productivity and economic burden on families and communities.(23)

As many as 62.6% of patients were men, in line with a study at the Bali Provincial Hospital which found that 66% of schizophrenic patients were male. Male dominance in cases of schizophrenia can be attributed to biological and social factors, including differences in responses to stress and seeking medical help.(24) As many as 50.5% of patients were unmarried, which supports the findings of Dr. Soeharto Heerdjan Hospital, where 64.7% of schizophrenic patients are unmarried. Unmarried status may reflect the impact of schizophrenia on an individual's ability to form and maintain interpersonal relationships.(25)

The majority of patients had their last education in high school (47.5%), followed by junior high school (18.2%) and elementary school (15.2%). Lower education is often associated with limited access to mental health information and services. A study by Wafa & Cahyanti (2023) shows that low education and economic stress are significant risk factors in the development of schizophrenia. (26) As many as 38.4% of patients are not working, while 42.4% work as employees or self-employed. The high unemployment rate among schizophrenic patients reflects the challenges of maintaining a job due to symptoms of the disease. Research at the Bali Provincial Hospital reported that 88% of schizophrenic patients did not work.(27)

Normal levels of kynurenic acid (KYNA) in the general population typically range from 1.0–5.0 nmol/L, while glutamate levels in healthy individuals range from 5.0–9.0 µg/mL (28,29) In this study, it was found that the median KYNA level was 14.6 nmol/L (IQR: 12.3–19.5 nmol/L) and the median glutamate concentration was 10.5 µg/mL (IQR: 9.2–12.5 µg/mL). These figures show that KYNA and glutamate concentrations in schizophrenic patients are much higher compared to the general population.

The difference in KYNA and glutamate concentrations in this study compared to normal values could be caused by several factors. First, elevated levels of KYNA are

associated with overactivation of the kynurenine metabolic pathway which often occurs in chronic inflammatory conditions, oxidative stress, or immune system disorders commonly found in schizophrenic patients (12). These factors collectively increase the production of KYNA through the enzyme KAT, which in charge for the synthesis of KYNA.(13)

Second, increased glutamate concentrations in schizophrenic patients may be due to disruptions in the regulation of the glutamatergic system, including overactivity of glutamatergic neurons or decreased glutamate transport function (EAAT), resulting in extracellular glutamate accumulation. This increase in glutamate causes neuronal excitotoxicity and contributes to cognitive deficits and psychotic symptoms (30). Previous studies have also reported increased levels of KYNA and glutamate in schizophrenic patients. These significant differences may also be influenced by the duration of the disease, the type of therapy the patient receives, or even the genetic characteristics that vary between populations. In addition, environmental factors such as chronic stress, unhealthy lifestyles, and dietary patterns also play a role in the modulation of KYNA and glutamate metabolism.(31)

The results of this study showed a significant strong relationship between kynurenic acid (KYNA) and glutamate concentrations in patients with schizophrenia, with a Spearman correlation coefficient of $r=0.701$ ($p<0.001$). These findings suggest that the higher the KYNA levels, the higher the glutamate concentrations in schizophrenic patients. These results are particularly relevant in understanding the pathophysiology of schizophrenia, given the central role of these two biomarkers in the neurobiology of the disease.

Biologically, KYNA is a neuroactive metabolite derived from the kynurenine pathway, which is the main degradation pathway of the amino acid tryptophan. KYNA is known to be a competitive endogenous antagonist at the glycine site of the glutamate N-methyl-D-aspartate (NMDA) receptor, which is an important receptor in the processes of synaptic excitation and synapse plasticity. Pathologically elevated levels of KYNA in schizophrenia lead to decreased NMDA receptor activity known as NMDA hypofunction, a condition believed to be a key mechanism in the etiology of schizophrenia's positive, negative, and cognitive deficit symptoms(28,29).

The results of this study, which showed a simultaneous increase in KYNA and glutamate concentrations, can be explained through specific biological mechanisms. NMDA receptor hypofunction due to increased KYNA triggers overcompensation of the neurotransmitter glutamate, especially in the prefrontal cortex and hippocampus, which are the main brain areas involved in the regulation of cognitive and affective functions. As a result of this NMDA hypofunction, glutamatergic neurons undergo compensatory hyperactivation, resulting in excessive release of glutamate into synapse and extracellular spaces.(30)

Pathologically, this extracellular accumulation of glutamate causes neuronal excitotoxicity, that is, neuronal damage due to overactivation of glutamate receptors, especially NMDA and AMPA receptors. Neuronal excitotoxicity is one of the neurodegeneration mechanisms that contribute to brain atrophy, impaired connectivity between neurons, and significant cognitive deficits in schizophrenia patients (32,33).

Furthermore, this relationship between KYNA and glutamate also has far-reaching implications in the clinical aspects of schizophrenia. These findings are consistent with a meta-analysis study by Plitman et al. (2017), which consistently found that high levels of KYNA are closely related to cognitive function deficits and more severe negative symptoms in schizophrenic patients. In the review, it was noted that patients with high levels of KYNA also tended to show a poorer response to conventional antipsychotic therapy,

especially in addressing negative and cognitive symptoms that are often persistent despite routine treatment (12).

A recent study by Hatzimanolis et al. (2024) also confirmed the link between high levels of KYNA and resistance to antipsychotic treatment in the first episode of psychosis. Patients with high levels of KYNA show more persistent negative symptoms, as well as a slow recovery in social and functional aspects after therapy. This condition underscores the importance of assessing KYNA levels as a potential biomarker in the clinical management of schizophrenia, especially in predicting the prognosis and response of individual treatment (34).

The regulation of the kynurenine pathway is strongly influenced by inflammatory factors. Research by Noyan et al. (2021) shows that chronic inflammatory processes, which are common in schizophrenic patients, can boost the activity of the kynurenine pathway by stimulating the indoleamine-2,3-dioxygenase (IDO) enzyme with pro-inflammatory cytokines including tumor necrosis factor-alpha (TNF-α) and interleukin-1β (IL-1β). This activation of IDO increases the conversion of tryptophan to kynurenine and subsequently KYNA, creating a neuroinflammatory condition that exacerbates glutamatergic dysfunction as well as clinical symptoms of schizophrenia patients (35).

Research by Kindler et al. (2020) adds that dysregulation of kynurenine metabolism not only increases KYNA but can also disrupt the balance of other metabolites in this pathway, such as quinolinic acid which is a potent and neurotoxic NMDA agonist. This condition causes an excitation-inhibition imbalance in the brain, amplifies impaired glutamatergic transmission, and increases the risk of excitotoxicity and chronic brain tissue disorders (31).

The identification of strong associations between KYNA and glutamate opens up the opportunity for innovative therapeutic approaches in the management of schizophrenia. The development of a specific inhibitor for the enzyme KAT, which is responsible for the synthesis of KYNA, has been the focus of recent research. Preclinical studies show that KAT inhibitors can significantly lower KYNA levels, improve glutamatergic function, and show potential to improve cognitive deficits as well as negative symptoms in animal models of schizophrenia (18,20).

The findings of this work help us to better grasp the intricacy of the relationship among the kynurenine pathway and glutamate control in the development of schizophrenia. Because KYNA and glutamate are closely linked, these two biomarkers are important as possible biological indicators that can be used to track the disease, guess the prognosis, and tailor treatment for schizophrenic patients. More thorough investigation of the glutamatergic system and kynurenine pathway control is required to support the creation of more focused and potent therapeutic interventions.

CONCLUSION

Our findings challenge accepted ideas obtained mostly from preclinical research by showing a high positive connection between KYNA and glutamate concentrations in persons with schizophrenia. This finding shows the complicated nature of neurochemical interactions in schizophrenia and implies that in clinical populations rather than experimental models the link between the kynurenine pathway and glutamatergic neurotransmission may be different. Knowing this link might help to create more successful therapies aiming at these neurochemical systems in schizophrenia.

Declaration by Authors

Ethical Approval: Approved

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