The correlation of the serum kynurenine level with P50 in first-episode patients with schizophrenia

Yunlong Tan (✉ yltan21@126.com)
Peking University HuiLongGuan Clinical Medical School, Beijing Huilongguan Hospital, Beijing, P. R. China

Qingyan Yang
Peking University HuiLongGuan Clinical Medical School, Beijing Huilongguan Hospital, Beijing, P. R. China

Yong Zhang
Peking University HuiLongGuan Clinical Medical School, Beijing Huilongguan Hospital, Beijing, P. R. China

Kebing Yang
Peking University HuiLongGuan Clinical Medical School, Beijing Huilongguan Hospital, Beijing, P. R. China

Yajuan Niu
Peking University HuiLongGuan Clinical Medical School, Beijing Huilongguan Hospital, Beijing, P. R. China

Fengmei Fan
Peking University HuiLongGuan Clinical Medical School, Beijing Huilongguan Hospital, Beijing, P. R. China

Song Chen
Peking University HuiLongGuan Clinical Medical School, Beijing Huilongguan Hospital, Beijing, P. R. China

Xingguang Luo
Department of Psychiatry, Yale University School of Medicine, New Haven, CT

Shuping Tan
Peking University HuiLongGuan Clinical Medical School, Beijing Huilongguan Hospital, Beijing, P. R. China

Zhiren Wang
Peking University HuiLongGuan Clinical Medical School, Beijing Huilongguan Hospital, Beijing, P. R. China

Jinghui Tong
Peking University HuiLongGuan Clinical Medical School, Beijing Huilongguan Hospital, Beijing, P. R. China

Fude Yang

Peking University HuiLongGuan Clinical Medical School, Beijing Huilongguan Hospital, Beijing, P. R. China

Chiang-Shan R. Li

Department of Neuroscience, Yale University School of Medicine, New Haven, CT

Research Article

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Abstract

Background: Increasing facts demonstrated the occurrence of sensory gating defects in schizophrenic sufferers, which had relation to the weakening of P50 response inhibition and had association with α7 nicotinic acetylcholine receptor (α7nAChR). Nevertheless, as a noncompetitive antagonist of α7nAChR, Kynurenic acid (KYNA) cannot cross the blood-brain barrier (BBB). In contrast, Kynurenine (KYN), as a precursor of KYNA metabolism, is capable of crossing the BBB. The exploration focused on investigatating the relation of the serum KYN level with P50 among first-episode patients with schizophrenia (FEPS).

Methods: In the exploration, measurement of P50 sensory gating was conducted among 82 FEPS and 73 healthy controls (HC). Positive and Negative Syndrome Scale (PANSS) was used for assessing the psychopathology; and liquid chromatography-tandem mass spectrometry was utilized for measuring the the serum KYN level. Spearman rank correlation coefficient was used to test the correlation between P50 index and serum KYN level and PANSS score. Pearson correlation coefficient was used to test the correlation between serum KYN level and PANSS score.

Results: The serum KYN levels[(251.46 ± 65.93) ng/ml vs. (320.65 ± 65.89) ng/ml, t = -6.38, p < 0.001], S1 amplitude [(2.88(1.79, 3.78) μV vs. 3.08(2.46, 4.56) μV , Z = -2.17, p =0.030] and S1 minus S2 amplitude [1.60(0.63, 2.49) μV vs. 1.92(1.12, 2.93) μV , Z = -2.23, p = 0.026] in FEPS were apparently lower than those in the HC. An obviously inverse correlation was seen between S1 minus S2 amplitude and the serum KYN levels (r = -0.32, p = 0.004) in the FEPS.

Background

Among the core symptoms of schizophrenia, cognitive impairment is found to lead to social functioning deficit (1–3) and correlate with the prognosis of the disease(4–6). According to several researches, cognitive impairment may emerge prior to the onset (7), and will persist even if psychotic symptoms have been under control.

As an aspect of cognitive function, sensory gating means the capability of reduction in trivial or redundant sensory input (8–10). Decreased sensory gating is likely to cause cognitive impairment and life functioning (11, 12). Neurophysiological approaches of auditory double-clicking could be utilized for measurement of sensory gating (13). All the testees were required to make paired clicks at an interval of 500ms under double click mode. After stimulation, measurement of two positive potentials was done, and the P50 waveform of the second (S2) decreased contrast with the first (S1). Generally, the measured S2/S1 ratio or S1-S2 difference means P50 inhibition, so it gives a reflection on sensory gating function.

In line with various facts, schizophrenic patients have P50 inhibition defect, accompanied by attention disorder, bad working memory and slow processing speed (14). As a reflection of sensory gating deficits(15), the P50 repression defect was likely to be a sensitive biological marker for identification of

schizophrenia(16–19). In addition, sensory gating defects is related to the chromosome 15q14 locus of the α7 nicotinic receptor gene, which has relation with the weakening of P50 response inhibition (20–27).

Kynurenine (KYN) and its metabolites are associated with mental diseases, like depression and schizophrenia (28). Primarily generated by the peripheral system, 60% of KYN can enter the central nervous system through the blood-brain barrier (BBB). The degradation of KYN in the central nervous system can be claasified into astrocytes and microglia (29). Microglia produce quinolinic acid (QUIN), an N-methyl-D-aspartate receptor (NMDAR) agonist. Astrocytes can produce kynurenic acid (KYNA), an NMDAR and α 7 nicotinic acetylcholine receptor (α7nAChR) antagonist. QUIN and KYNA are dysregulated in schizophrenia (28, 30). Some studies have shown that KYN and KYNA concentrations in prefrontal cortex (PFC) (31, 32) and cerebrospinal fluid (CSF) (33–35) are increased in schizophrenia sufferers.

In contrast with the healthy control group, a decrease could be seen in the hippocampal and cortical regions of schizophrenic patients α 7nachr activity (36, 37). There is a KYNA hypothesis in schizophrenic patients, that is, the level of KYNA increases through blocking α7nAChR leads to positive symptoms and cognitive deficits (38–40). The nicotine cholinergic system and the kynurenine pathway in the brain are significantly functionally interacted (41). Mathai et al found the effects of smoking upon blood KYN levels and P50 in patients with schizophrenia (42). Since KYNA cannot pass through BBB, our study was intended to explore the relation of serum KYN level with P50 in patients with first-episode schizophrenia.

Methods

Participants

According to the structured clinical interview of DSM-IV, 82 FEPS were registered from Beijing Huilongguan Hospital. They met the diagnostic criteria of schizophrenia; 18–45 years old; Course of disease ≤ 3 years; Time of previous antipsychotic medication ≤ 2 weeks. 73 age and sex matched healthy controls (HC) were recruited through advertising in the local community and were excluded if they had a history of mental disorders or psychosis in their first-degree relatives. All participants were Han Chinese. The exclusion criteria were cardiovascular or nervous system diseases, history of head injury with loss of consciousness, physical abnormalities, substance dependence (including drugs or alcohol or tobacco), or emotional or anxiety disorders. All participants had normal hearing acuity (subjective hearing threshold of 40 dB).

Clinical Assessment

All subjects were asked to have complete medical history, physical examination and laboratory examination. Positive and Negative Syndrome Scale (PANSS) was used to evaluate their clinical symptoms. The intraclass correlation coefficient (ICC) between raters was more than 0.80.

P50 Testing

We used the signal generator and data acquisition system of the fully functional digital 64 channel EEG system (Brain Products, Germany) for electrophysiological examination. We assessed sensory gating by recording P50 waves of auditory evoked response in the conditioned reflex test paradigm. The test was conducted in a shielded sound insulation room. The subjects sat down, relaxed their whole muscles, remained awake and focused, and waited for stimulation.

P50 inhibition was recorded in the conditional test mode. According to the international EEG 10 / 20 system, the recording electrode was located in the central midline (CZ), the reference electrode was located in the right ear (A2), the forehead (FPZ) was grounded, the impedance between electrodes was < 5K, the analysis time was 600ms, the non target stimulation frequency was 1000Hz, which was 80%, and the rule intensity was 80dB. The target stimulation frequency is 4000Hz, the probability is 20%, and the intensity is 90dB. It appears randomly, mixed with non target stimulation.

The regulatory P50 wave (S1) was determined as the most positive peak between 40 and 90 ms after regulatory stimulation. The test P50 wave (S2) was determined as the positive peak after test stimulation, which was closest to the regulated P50 wave in the incubation period. Amplitude is defined as the difference between the positive peak of two waves (S1 amplitude and S2 amplitude) and the previous negative trough. Use P50 gating ratio (S2 amplitude / S1 amplitude × 100) further analyze P50 inhibition. Lower ratios or higher P50 differences indicate stronger SG. The data from the apex (CZ site) are reported because this site has been determined as the best site to distinguish schizophrenic patients from healthy participants when using this electrode array (43).

Biochemistry

Blood samples were collected from 7 a.m. to 8 a.m. after fasting overnight, centrifuged at 3000 rpm at 4 ° C for 10 minutes, then the serum was separated and stored at − 80 ° C. Measurement of serum KYN levels was done by high performance liquid chromatography (HPLC) and tandem mass spectrometry (MS / MS), and then quantified using standard protocols. In order to minimize the difference, the same technician was unaware of the clinical data and analyzed all samples. The identity of the participants was coded and saved by the investigator until all biochemical analyses were completed.

Statistical Analysis

We performed T-test on normal continuous variables of inter group comparison. Shapiro-Wilk was used to confirm normality. Serum KYN levels were in line with the normal distribution. Hence, t-test and ANCOVA (the covariates of ANCOVA analysis were age and gender) were utilized for comparing the differences between schizophrenic patients and HC. P50 indexes (S1 amplitude, S2 amplitude, S1 minus S2 amplitude difference, S2 / S1 ratio) are seriously skewed and are not easy to transform into normal distribution. As a result, the inter group differences of P50 index were analyzed by Mann Whitney test. χ^2 test was utilized for comparing the classification variables between schizophrenic patients and HC patients. All P values were two tailed, and the significance level was set to < 0.05.

Spearman rank correlation coefficient was used to test the correlation between P50 index and serum KYN level and PANSS score. Pearson correlation coefficient was used to test the correlation between serum KYN level and PANSS score.

Results

Demographics, Clinical characteristic

Table 1 showed demographics. There were no significant differences between the patients and controls in age, gender and educational level (all $p > 0.05$).

Table 1
Demographical, clinical, and metabolic characteristics

	FEPS(n = 82)	HC (n = 73)	t/χ2/Z	*p*value
Male/Female	40/42	36/37	< 0.01	1.000
Age, years	27.95 ± 7.52	28.71 ± 6.07	-0.69	0.493
Education degree, years	13.66 ± 3.11	14.32 ± 2.08	-1.56	0.121
Age at onset, years	26.58 ± 7.56	NA	NA	NA
Duration of illness, months	6.36 ± 8.47	NA	NA	NA
PANSS				
Total score	76.07 ± 11.93	NA	NA	NA
Positive subscale	21.94 ± 5.04	NA	NA	NA
Negative subscale	17.71 ± 5.54	NA	NA	NA
General psychopathology subscale	36.42 ± 6.86	NA	NA	NA
Kynurenine (ng/ml)	251.46 ± 65.93	320.65 ± 65.89	-6.38	**< 0.001**
P50				
S1 amplitude (μV)	2.88(1.79, 3.78)	3.08(2.46, 4.56)	-2.17	**0.030**
S2 amplitude(μV)	1.20(0.63,1.97)	1.19(0.81, 1.80)	-0.08	0.937
S1 minus S2 amplitude(μV)	1.60(0.63, 2.49)	1.92(1.12, 2.93)	-2.23	**0.026**
S2/S1 ratio	0.43(0.24, 0.69)	0.41(0.23, 0.52)	-1.14	0.178

Abbreviations: FEPS, first-episode patients with schizophrenia; HC, healthy controls; NA, not applicable; PANSS, Positive and Negative Syndrome Scale.

Group comparisons on P50 indexes and serum KYN levels

In contrast with healthy controls, schizophrenia sufferers displayed apprarently lower S1 amplitude (Z = -2.17, p = 0.03) and S1 minus S2 amplitude (Z = -2.23, p = 0.026). No difference was seen between the two groups in S2 amplitude (Z = -0.08, p = 0.937), and S2/S1 ratio (Z = -1.14, p = 0.178). Lower serum KYN (t = -28.726.38, p < 0.001) was found in schizophrenia sufferers versus HC. After further adjusting for age and gender, there was a significant difference in KYN levels between patients and controls (F = 44.93, p < 0.001) (Table 1).

Relations of P50 indexes (S1 amplitude and S1 minus S2 amplitude) with serum KYN levels

The amplitude of S1 minus S2 had apprarently negative correlation with the patient's serum KYN level (r = -0.32, p = 0.004) (Fig. 1), while the amplitude of S1 was not correlated with the patient's serum KYN level (r = -0.15, p = 0.194).

Relation of serum KYN levels with PANSS

Pearson correlation outcomes revealed the nonexistence of significant correlation between KYN level and PANSS positive (r = -0.04, p = 0.711), negative (r = -0.06, p = 0.578), the general psychopathology symptom scale scores (r = 0.03, p = 0.773), or total score (r = -0.03, p = 0.808).

Relation of P50 indexes (S1 amplitude, S1 minus S2 amplitude) with PANSS

There was no significant correlation between S1 amplitude and PANSS positive (r = -0.18, p = 0.099), negative (r = 0.21, p = 0.062), the general psychopathology symptom scale scores (r = -0.17, p = 0.124), or total score (r = -0.10, p = 0.291). No significant correlation was found between S1 minus S2 amplitude and PANSS positive (r = -0.17, p = 0.122), negative (r = 0.11, p = 0.339), general psychopathology symptom scale score (r = -0.09, p = 0.442) or total score (r = -0.09, p = 0.418). PANSS subscale scores and total scores were independent of P50 index (S1 amplitude, S1 minus S2 amplitude) (all ps > 0.05).

Discussion

According to this exploration, FEPS has a lower level of KYN in contrast with HC, which may have relation with the effect of inflammation upon indoleamine-2,3-dioxygenase (IDO) activity, leading to a large amount of KYN consumption in plasma (44). Proinflammatory cytokines may induce the conversion of tryptophan (TRP) to KYN and increase KYNA by increasing kynurenine aminotransferase (KAT) mRNA and possibly more enzyme synthesis activity in brain astrocytes. The study revealed that in contrast with the healthy control group, the activities of kynurenine 3-monooxygenase [KMO] and 3-hydroxyanthranilate dioxygenase [3-HAO] decreased, but the activities of kynurenine enzyme, quinolinic acid phosphoribosyltransferase [QPRT] and kynurenine aminotransferase II [KAT II] decreased, and the activities in the brain of patients with schizophrenia did not change. Changes in KYN metabolism lead to increased KYNA levels in the brain of schizophrenic patients (45–47).

We also found that the sensory gating function represented by P50 was significantly impaired, which was consistent with many earlier explorations (28). Sensory gating function was highly correlated with 7nachrs. KYNA is an effective α 7nachrs antagonists, right α Inhibition of 7nachrs function leads to impaired P50 sensory gating in schizophrenic patients (48). Additionally, high concentrations of KYNA may lead to decreased glutamate energy function, thereby interfering with cognitive function (49).

In this exploration, serum KYN and S1 minus S2 amplitude were negatively correlated, suggesting the possible relation of KYN concentration with sensory gating and α7NACHRs function. Meta analysis showed that the lower the plasma KYN level, the higher the cerebrospinal fluid KYNA concentration in patients with schizophrenia. High KYNA concentration inhibition α7nAChR/sensory gating, which is reflected in the inhibition of P50 in electrophysiological indexes (50).

PANSS score is independent of P50 parameter, which shows consistency with other explorations (51, 52). As one of the P50 parameters, the high P50 gating ratio indicates that the sensory gating function is weak, and the P50 index can also be used as a supplementary index to reflect the curative effect (53). Unfortunately, in this exploation, there was no difference in S2 / S1 ratio between FEP and HC, which may be related to the relatively small sample size of this study.

This study has some limitations. First, the cross-sectional design of the study will limit the inference of causality. Prospective and longitudinal studies should be conducted to clarify the causal relationship between KYN and P50. Antipsychotic treatment was not involved, which is another limitation of the study. Because the participants in this study are FEP and the medication time is short, the impact of antipsychotics on the research results is relatively small.

In conclusion, to our knowledge, so far, no research has focused on the relationship between KYN and p50. We collected smokeless FEP and added it to this study, which can eliminate some confusing factors. According to the results of this study, canine urinary ammonia pathway may be involved in P50 inhibition deficiency in schizophrenia. Our findings provide new insights into the possible causes of cognitive impairment in patients with schizophrenia.

Declarations

Availability of data and materials

The datasets generated during the current study are not publicly available due to this study is still going on, but are available from the corresponding author on reasonable request.

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Author information

Affiliations

Peking University HuiLongGuan Clinical Medical School, Beijing Huilongguan Hospital, Beijing, P. R. China

Qingyan Yang, Yong Zhang, Kebing Yang, Yajuan Niu, Fengmei Fan, Song Chen, Shuping Tan, Zhiren Wang, Jinghui Tong, Fude Yang, Yunlong Tan

Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA

Xingguang Luo

Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA

Department of Neuroscience, Yale University School of Medicine, New Haven, CT, USA

Chiang-Shan R. Li

Author contribution

Dr Yunlong Tan is responsible for the integrity of the data and the accuracy of data analysis and had full access to all data in the study. Concept and design: Yunlong Tan. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Qingyan Yang, Yong Zhang. Critically revise manuscripts of important intellectual content: Xingguang Luo, Shuping Tan, Chiang-Shan R. Li, Yunlong Tan. Statistical analysis: Qingyan Yang, Yong Zhang, Fengmei Fan, Yunlong Tan. Obtained funding: Yong Zhang, Song Chen and Yunlong Tan. Administrative, technical, or material support: Yunlong Tan.

Corresponding author

Correspondence to Yunlong Tan.

Ethics declarations

Ethics approval and consent to participate

The ethics committee of Beijing Huilongguan Hospital approved the study. After fully explaining the procedure to them, all subjects signed informed consent and agreed to participate in the study. All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable.

Competing interests

We declare no competing interests in this research.

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Figures

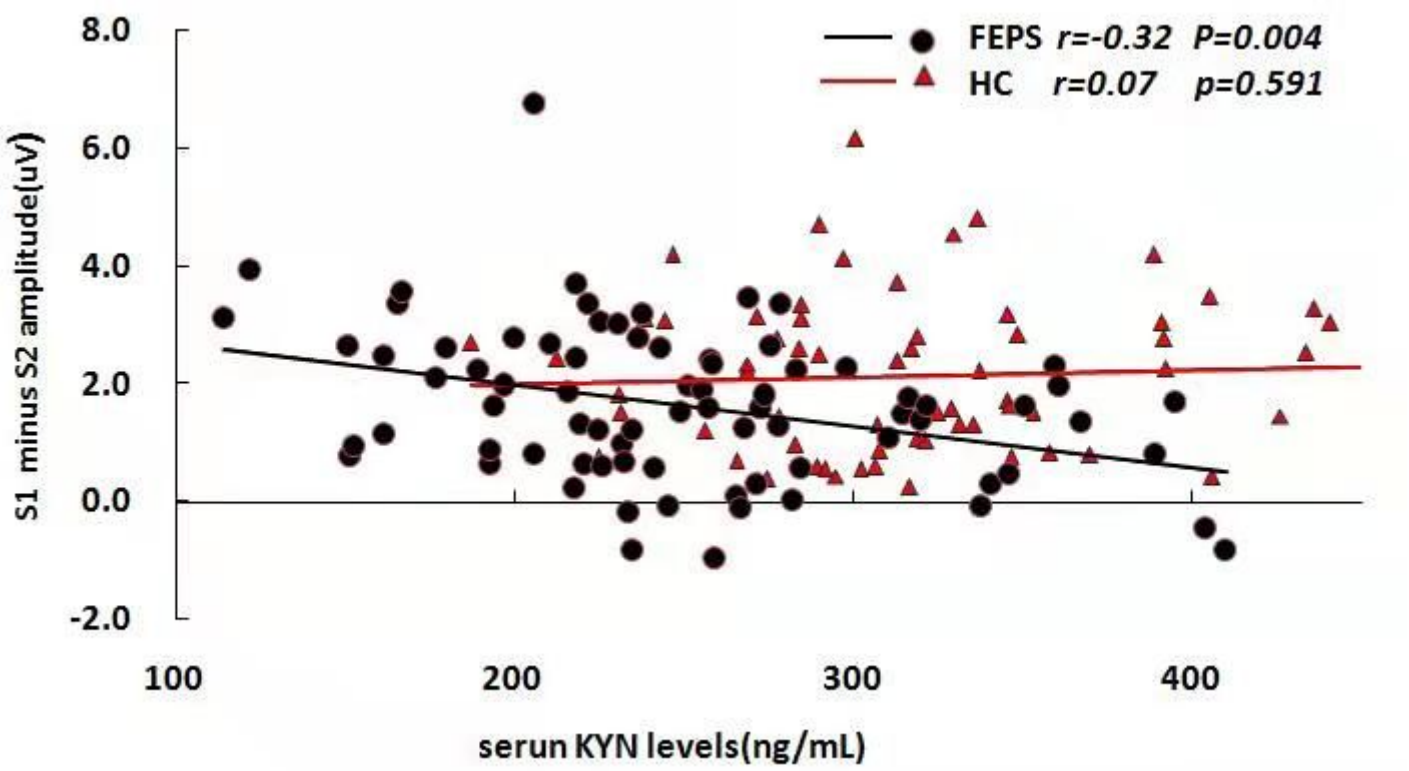

Figure 1

Correlation between S1 minus S2 amplitudeandserum KYN levels

S1 minus S2 amplitudewere significantly inversely correlated with the serum KYN levelsin FEPS.