Evaluation Serum Levels of G Protein-Coupled Estrogen Receptor and Its Diagnostic Value in Patients with Schizophrenia

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Abstract

Background: Estrogens not only play a role in the reproductive system of the female but also have a significant role in modulating the activities of serotonin, dopamine, glutamate, and GABA, important neurotransmitters involved in schizophrenia. The physiological effects of estrogen-related components are mostly regulated by Estrogen receptor alpha (Erα), Estrogen receptor beta (Erß), and G Protein-Coupled Estrogen Receptor (GPER-1), which are subtypes of estrogen receptors. This study aimed to examine the possible role of GPER-1 in schizophrenia by comparing schizophrenia patients with sex – and age-matched healthy controls and examining the association between symptom severity and GPER-1.

Methods: The study sample consisted of 36 people with schizophrenia and 30 age – and sex-matched healthy control subjects. Demographic and clinical characteristics were recorded by pre-designed questionnaires for participants, and all required laboratory tests and physical examinations were performed; the Positive and Negative Syndrome Scale (PANSS) was administered to all schizophrenia patients.

Results: We found that male schizophrenia patients had higher GPER-1 levels than male controls. However, we found no difference in the levels of GPER-1 between female patients and female controls. No significant correlation was found among age, PANSS score, duration of illness, and GPER-1 levels.

Conclusions: This study demonstrated that male patients with schizophrenia had high serum GPER-1 levels compared with healthy male controls, and that the levels of GPER-1 had good diagnostic value in patients with schizophrenia.

INTRODUCTION

Schizophrenia is a brain disease characterized by positive and negative symptoms; it affects about 0.7% of the population throughout life [1, 2]. Male patients with schizophrenia generally exhibit poorer premorbid functioning [3], earlier age of onset [4], lower global functioning [5], more negative symptoms, and poorer cognition [6, 7] compared with females. Previous studies found that female patients with schizophrenia were more likely to have affective symptoms and had an older age of onset than males. Females also displayed a second peak between the ages of 55 and 64 [8, 9]. Importantly sex differences in the clinical presentation are now thought to strengthen the hypothesis that gonadal steroid hormones have a role in both the treatment and the etiology of schizophrenia [10, 11].

Estrogen is primarily considered a female sex hormone, but it exists in both males and females. Estrogens are synthesized peripherally by the ovaries, liver, skeletal muscle, fat and centrally by the brain [12]. Estrogens not only play a role in the reproductive system of the female but also display a significant role in modulating the activities of serotonin, dopamine, glutamate, and GABA, important neurotransmitters involved in schizophrenia [13]. Rat studies have demonstrated estrogen-dependent decreased dopamine receptor D2 (D2R) sensitivity and increased D2R density in the striatum [14], and estradiol was reported to modulate many components of the brain's serotonin system [15]. More recently, an estrogen-related elevation in glutamatergic neurotransmission via the up-regulation of NMDA receptors was noted [16].

Similarly, another study showed that treatment with estradiol could significantly reverse psychomimetic states

induced by the separate administration of a 5HT1A agonist, D2R agonist, and an NMDA receptor antagonist in female ovariectomized rats [14]. A number of clinical studies have shown that there is a correlation between circulating estrogen levels and cognitive performance in women with schizophrenia [17, 18]. Moreover, several studies focusing on the effect of estradiol in hippocampus-based spatial memory reported that estradiol was not only essential for the frontal cortex, hippocampal, basal forebrain, and cerebellar-based learning but also for spatial memory in rats [19-21].

The physiological effects of estrogen-related components are mostly regulated by Erα, Erß, and GPER-1 which are subtypes of estrogen receptors [13]. Receptors for estrogen (Erα, Erß, and GPER-1) are widely distributed across many areas of the central nervous system, including the cerebral cortex, amygdala, and hippocampus, increasing the probability that Erα and Erß mediate the known effects of estrogen on cognition and mood, both of which change in major mental illnesses [22-25]. Erα not only plays a role in the reproductive, skeletal, and cardiovascular systems, but studies also suggest that it mediates the neuroprotective role of estrogen in the brain[26]. Erß is thought to be significant in regulating nonreproductive neurobiological systems involved in fear, anxiety, learning, and memory [27]. GPER-1 is particularly expressed in the central nervous system (CNS), including the hippocampus, frontal cortex, substantia nigra, and hypothalamus [28, 29]. GPER-1 has been identified as crucial to rapid, nongenomic estrogen activity, typically involving regulation of cytoplasmic and membrane-bound regulating proteins [30]. GPER-1 seems to modulate many of the effects of estrogen on the nervous system, with the inclusion of luteinizing hormone-releasing activity and calcium oscillations in primate neurons [31, 32]. Recently, some studies have demonstrated the roles of GPER-1 in neuronal plasticity and learning, as well as memory [33, 34].

A recent clinical trial showed increased serum GPER-1 levels in patients with euthymic bipolar disorder compared with controls, and serum GPER-1 level significantly predicted the presence of bipolar disorder [35]. However, to our knowledge, there has been no study about measuring serum GPER-1 levels in patients with schizophrenia. The aim of this study was to examine the possible role of GPER-1 in schizophrenia by comparing schizophrenia patients with sex – and age-matched healthy controls and examining the association between symptom severity and GPER-1. The potential use of GPER-1 as a diagnostic tool is also considered.

METHODS

The study protocol was approved by the Scientific Research Ethics Committee of Kahramanmaras Sütcü Imam University (approval date: 24.10.2018, number: 20). The procedure was explained and each participant submitted written informed consent.

Patients

Power analysis was used to determine the number of samples. Accordingly, taking into account the statistical parameters in the reference study[36] (Mean 1: 4561.12 ± 2478.30 Mean 2: 6298.07 ± 2300.64) alpha 0.05 first type error level, beta: 0.20 second type error level (a power of 0.80), it was planned to recruit a total of 60 individuals with at least 30 individuals in each group. A total of 36 patients with schizophrenia were recruited along with 30 age – and sex-matched healthy controls. Clinical diagnostic interviews were performed by a qualified psychiatrist using the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) Structured Clinical Interview. PANSS was used for evaluating symptom severity. The inclusion criteria were as follows; 1. age 18-65 years and 2. being diagnosed with schizophrenia according to DSM-5 for patients with schizophrenia. Patients with current psychotic attack, concurrent DSM-5 diagnoses other than schizophrenia and recent alcohol/substance abuse were excluded from the study. Additionally, we excluded participants receiving hormone replacement therapy, with irregular menstrual cycles, who were postmenopausal or pregnant, impaired thyroid hormone level, or history of diabetes mellitus.

Demographic and clinical characteristics were recorded with pre-designed questionnaires for participants, and all required laboratory tests and physical examinations were performed.

Procedure

Between 8:30 am and 12:30 pm blood samples were collected from all schizophrenia patients and controls to prevent changes in hormone levels due to daily variations. The obtained blood samples were centrifuged, and serum samples were stored at – 20 degrees centigrade until they were assayed. The levels of GPER-1 were measured using a commercial kit (SEG045Hu; Cloud-Clone Corp., Houston, TX, USA) using the quantitative sandwich enzyme immunoassay according to the manufacturer's instructions.

Statistical Analysis

Normal distribution was examined using the Shapiro-Wilk test. Comparative analysis between independent groups was done by using the Mann-Whitney U test. Independent samples t-test was performed for the comparison of variables with normal distribution. The Chi-Square test was applied for intergroup comparisons. The relationship between variables was tested using the Pearson correlation test. The ROC (receiver operating characteristic) curve was plotted to determine the diagnostic performance of GPER-1 in patients of schizophrenia. Values were accepted statistically significant with $p<0.05$ in this study. Statistical parameters are expressed as median (25% quartile, 75% quartile) and mean ± standard deviation. Data analysis was performed with IBM SPSS version 22 (IBM SPSS for Windows version 22, IBM Corporation, Armonk, New York, United States).

RESULTS

Demographics

For sociodemographic information of participants and symptom severity of the patients with schizophrenia, see Table 1.

Table 1. Demographic summary for participants and symptom severity of patients

Samples-Tests			GROUP		
			Schizophrenia (n:36)	Control (n:30)	P
Age[a]			36.78±7.22	32.93±9.62	0.069
Gender[b]	Male	n(%)	25.00(69.40)	20,00(66.70)	0.809
	Female	n(%)	11.00(30.60)	10,00(33.30)	
Smoke[b]	Yes	n(%)	15.00(41.70)	7,00(23.30)	0.116
	No	n(%)	21.00(58.30)	23,00(76.70)	
Antipsychotics	Typical	n(%)	1.00(2.80)		
	Atypical	n(%)	14.00(38.90)		
	Combined	n(%)	21.00(58.30)		
Duration of illness (years)	Median(Q1-Q3)		13.00(7.00-15.50)		
Number of hospitalizations	Median(Q1-Q3)		2.00(1.00-4.00)		
PANSS positive	Mean±SD		15.53±5.75		
PANSS negative	Mean±SD		17.77±6.01		
PANSS general	Mean±SD		31.91±8.64		
PANSS total	Mean±SD		65.22±15.65		

[a]Independent samples t-test; [b]Chi-Square test; α:0.05, PANSS: Positive and Negative Syndrome Scale

No differences in age or sex were found between the two groups. The patients with schizophrenia were receiving primarily atypical (second generation) and combined antipsychotic medication. According to PANSS scores, mild to moderate symptoms were present in patients with schizophrenia (Table 1).

Comparison of Blood Levels of Healthy Controls and Patients

Data about the blood levels of estradiol and GPER-1 in the male and female patients with schizophrenia and control groups were compared (Table 2).

Table 2. Independent t-test for GPER-1 levels and Mann-Whitney U test for Estradiol levels in patients and controls

		GROUP		
		Schizophrenia	Control	p
E2[b]	Median(Q1-Q3)	30.70 (20.20-46.15)	23.20 (12.10-47.30)	0.155
Male		32.10 (14.40-38.70)	15.10 (6.75-23.20)	**0.001***
Female		29.20 (23.80-101.20)	79.00 (47.30-134.80)	0.132
GPER-1[a]	Mean±SD	0.82±0.18	0.61±0.08	**p<0.001***
Male		0.85±0.17	0.59±0.08	**p<0.001***
Female		0.76±0.19	0.66±0.05	0.133

α:0.05; *difference is statistically significant, GPER-1: G-protein-coupled estrogen receptor 1, E2: Estradiol

There were no significant differences between estradiol levels in the schizophrenia and control groups. But we found that male patients had significantly higher levels of estradiol compared with male controls. When compared with the control group, the patients with schizophrenia had significantly higher serum GPER-1 levels (Table 2, Fig. 1). We made a gender comparison to detect the source of this difference for GPER-1 and found that male patients had significantly higher levels of GPER-1 compared with male controls (Table 2).
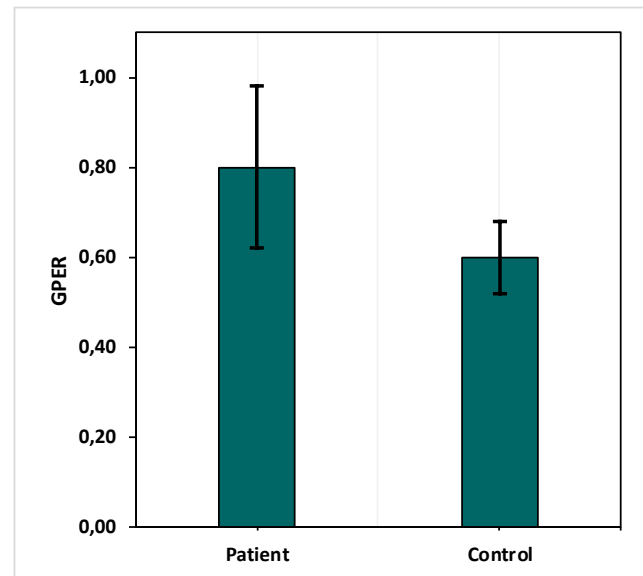

Figure 1. GPER-1 levels in patients with schizophrenia and controls. GPER-1, G-protein-coupled estrogen receptor 1.

Correlation Between GPER-1 and Symptom Severity

Correlations between age, PANNS score, duration of illness and GPER-1 levels were evaluated (Table 3).

Table 3. Pearson Correlation test results between PANSS scores, Age, Duration of illness and GPER-1 levels

	GPER-1	
	R	P
PANSS positive	0.260	0.126
PANSS negative	0.288	0.088
PANSS general	0.157	0.360
PANSS total	0.293	0.083
Duration of illness	0.084	0.626
Age (Patient)	-0.152	0.375
Age (Control)	-0.327	0.078

Pearson Correlation test; α:0,05, GPER-1: G-protein-coupled estrogen receptor 1, PANSS: Positive and Negative Syndrome Scale

No significant correlation was found between age, PANSS score, duration of illness, and GPER-1 levels (Table 3).

The ROC analysis revealed that GPER-1 levels significantly predicted the presence of schizophrenia (area under the curve, 0.857 *p* < 0.001). When the GPER-1 value was

0.7175, the sensitivity and specificity were 77.8 and 93.3% for the presence of schizophrenia, respectively (Figure 2). The GPER-1 level was below this cutoff point in all control group subjects. In the post-hoc power analysis of the study, the statistical power of the test for estradiol in men was 0.92, and effect size: 0.83. The statistical power of the test for GPER-1 was 0.99, effect size: 1.50. For GPER-1, the statistical power of the test in men was 0.99, effect size: 1.95.
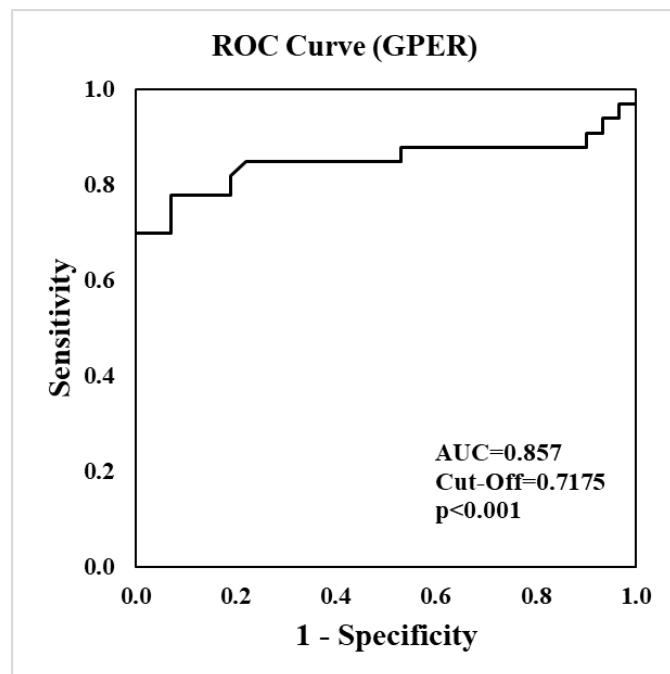

Figure 2. ROC curve for GPER-1. This curve combines information for the true-positive rate and the true-negative rate, and AUC is a measure of the overall discriminative power of GPER-1. AUC, area under curve; GPER-1, G-protein-coupled estrogen receptor-1; ROC, receiver operating characteristic.

DISCUSSION

We found that the GPER-1 levels were higher in patients with schizophrenia compared with healthy controls. Our study is the first to assess GPER-1 levels in patients with schizophrenia. Mahe et al. [37] showed a correlation between a low amount of estrogen in plasma and the risk of psychotic symptoms in patients with schizophrenia. When we investigated GPER-1 differences in terms of sex, we found that male schizophrenia patients had higher GPER-1 levels than male controls. In contrast, we found no difference in the levels of GPER-1 between female patients and female controls. In addition, we found that male schizophrenia patients had higher estradiol levels than their healthy counterparts.

Estrogen is considered preventive for some psychiatric disorders, including schizophrenia, depression, and anxiety [38]. It was suggested that schizophrenia symptoms may

appear in susceptible individuals when estrogen levels begin to decline [39]. However, we found no difference in the levels of estradiol between female patients and female controls in the present study. We found that male schizophrenia patients had higher estradiol levels than male controls. Studies concerning the serum estradiol levels of patients with schizophrenia yielded conflicting results, generally with lower, normal or elevated levels[40, 41]. A recent clinical trial showed that daily oral adjunctive raloxifene (a first-generation selective estrogen receptor modulator) increased brain activity and improved attention and verbal memory during learning in patients with schizophrenia [42, 43]. The clinical studies mentioned lead to the conclusion that estrogen is protective of the dopaminergic system, particularly in females [11]. However, the molecular mechanisms by which estrogen may play a role in resisting schizophrenic symptoms remain uncertain.

Studies in male and female schizophrenia patients have reported reduced mRNA levels and decreased density of wild-type Erα mRNA in the frontal cortex and reduced Erα mRNA levels in the hippocampus [44, 45]. While the effect of 17ß-estradiol on the human nervous system is known to be associated with Erα and Erß, recent evidence has shown that GPER-1 (formerly known as GPR30) has many roles in the neurological functions of 17ß-estradiol [46]. Gingerich et al. [47] suggested that GPER-1 and Erα were involved in the protective effect of 17ß-estradiol in glutamate-related injury.

A recent in vivo study found that GPER agonist G-1 treatment replicated the 17ß-estradiol-related effects in promoting neuronal survival after global brain ischemia [48]. Another study in female rats showed that GPER-1 agonists strengthened, and a GPER-1 antagonist inhibited, reference memory after tasks that involved the hippocampus [49]. We think that the protective effect of estrogen against schizophrenic symptoms may be mediated by GPER-1 receptors. But we couldn't find a significant correlation between symptom severity and GPER-1 levels. Recent studies found that GPER-1 levels were increased in cases with generalized anxiety and major depressive disorder compared with controls. In these studies, the levels of GPER-1 were found to be high in both female and male patients [50, 51]. However, our results show that GPER-1 is a more selective biomarker for schizophrenia in males than in females. Schizophrenia is more prevalent in males than in females [52]. Hence, we think that our findings may play a considerable role in identifying sex differences in the onset, outcome, symptom severity, and incidence of schizophrenia.

Clinical studies examining diagnostic biomarkers for psychiatric disorders have been reported. Studies by Selek [53, 54] found that the levels of catalase (AUC: 0.989) and prolidase (AUC: 0.989) had very good diagnostic values in bipolar patients. Another study reported good diagnostic value for prolidase in patients with schizophrenia (AUC: 1.0) [55]. Gadelha et al. found that the level of angiotensin I-converting enzyme had fair diagnostic value

for the presence of schizophrenia, with an AUC of 0.701. Furthermore, a study by Xiong et al. [56] found diagnostic value for both serum IL-2 (AUC: 0.866) and NGF (AUC: 0.781) in patients with schizophrenia. Our findings indicate that GPER-1 has good diagnostic value (AUC: 0.857) in patients with schizophrenia; however, we do not claim that it is a selective biomarker, as GPER-1 was recently shown to have good diagnostic value for the presence of bipolar and generalized anxiety disorders [35, 50]. It seems GPER-1 has good diagnostic value for different psychiatric disorders. The beneficial effects of estrogens are well known in psychiatric disorders, and selective activation of GPER-1 can reproduce the favorable effects of 17ß-estradiol[46]. The higher GPER-1 serum levels in these diseases may be secondary to insufficient beneficial effects of 17ß-estradiol. Thus, future studies should be done including more homogeneous and larger samples that include patients with generalized anxiety disorder and bipolar disorder to identify whether GPER-1 can be used as a specific biomarker for schizophrenia.

Limitations of this study include the cross-sectional design and small sample size, poor generalizability to all patients with schizophrenia, ongoing medication of patients with schizophrenia, lack of cognitive measures, and failure to consider the menstrual cycle in female patients. Furthermore, GPER-1 levels were determined based on serum samples, which may not reflect brain levels of GPER-1. Despite these limitations, this is the first study to measure the blood levels of GPER-1 in patients with schizophrenia.

In summary, this study demonstrated that male patients with schizophrenia had high serum GPER-1 levels compared with healthy male controls. Moreover, the levels of GPER-1 had good diagnostic value in patients with schizophrenia. These results suggest that, beyond estrogen itself, other estrogen-related signaling molecules such as GPER-1 might have a role in the etiology of schizophrenia. These results should be considered to be preliminary. They require confirmation by further studies, which should involve drug-naïve patients with schizophrenia and large sample size. Additionally, future studies should focus on whether GPER-1 agonists reduce symptom severity in patients with schizophrenia.

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