Neuropsychiatric Disease and Treatment

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ORIGINAL RESEARCH

Serum levels of GPER-1 in euthymic bipolar patients

This article was published in the following Dove Press journal:
Neuropsychiatric Disease and Treatment

Fatma Özlem Orhan[1]
Ergül Belge Kurutaş[2]
Adem Doğaner[3]
Ebru Türker[1]
Safiye Şeyma Taner Özcü[4]
Meltem Güngör[5]
Seyfettin Çakmak[1]

[1]Department of Psychiatry, Faculty of Medicine, Kahramanmaraş Sütçüimam University, Kahramanmaras, Turkey; [2]Department of Biochemistry, Faculty of Medicine, Kahramanmaraş Sütçüimam University, Kahramanmaras, Turkey; [3]Department of Biostatistics and Medical Informatics, Faculty of Medicine, Kahramanmaraş Sütçüimam University, Kahramanmaras, Turkey; [4]Department of Bioengineering, Institute of Science, Kahramanmaraş Sütçüimam University, Kahramanmaras, Turkey; [5]Vocational High School, Toros University, Mersin, Turkey

Introduction: Estrogen and its receptors have been suggested as playing a role in the pathogenesis of bipolar disorder (BD). Estrogen functions through the estrogen receptors alpha and beta and the recently discovered G-protein–coupled estrogen receptor-1 (GPER-1). The aim of this study was to evaluate serum GPER-1 levels in euthymic BD patients.

Patients and methods: The study population consisted of 38 euthymic outpatients meeting the criteria for BD in the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition and 35 age- and gender-matched healthy controls. Medical histories were obtained and physical examinations and laboratory tests conducted.

Results: Serum GPER-1 levels were measured in both patients and controls and found to be significantly higher in the BD patients than in controls. These results were not influenced by the medications in use.

Conclusion: The results of this study demonstrated that GPER-1 may play a role in BD pathophysiology.

Keywords: estrogen receptor, sex hormones, GPER-1, bipolar, euthymic

Introduction

Bipolar disorder (BD) is a severe, recurrent mood disorder that affects millions of people worldwide, yet the etiology of the illness remains unclear.[1,2] It has been found that some women with BD are more vulnerable to developing mood instability during periods of hormone fluctuation. It appears that reproductive events and hormonal treatments may affect the course of BD in women.[3] There is a robust relationship between gonadal hormones, including estrogens, and mood disorders in women.[4] There are some gender differences in patients with BD, even though the results are conflicting. The gender differences support further investigation of the possible interaction between BD and reproduction-related hormonal changes, particularly changes in the main female sex hormone estrogen.[3] Although the role of estrogen in cycle-dependent mood disorders such as premenstrual syndrome or postpartum and menopausal depressive disorders is not entirely clear,[5,6] a broad range of interactions with neuronal signaling has been demonstrated.[7] However, the role of estrogen in BD patients is not fully understood.

Estrogens encompass steroid hormones that not only display physiologic roles in the female reproductive system, but also affect several other systems in the body, including the cardiovascular, musculoskeletal, immune, and central nervous system (CNS).[8,9] Estrogens are synthesized in the brain[10,11] and are known to exhibit widespread neurologic effects ranging from cognition to emotional status to sensory processing.[12] Mood changes occurring due to the effects of estrogen on the CNS have been extensively investigated in studies on rats.[13–18] A correlation has been observed between decreased estrogen levels (eg, premenstrually, during the postpartum period, and perimenopausally) and increased anxiety and depressive symptoms.[19–21] Estrogen appears

Correspondence: Fatma Özlem Orhan
Department of Psychiatry, Faculty of Medicine, Kahramanmaraş Sütçüimam University, 46100 Kahramanmaras, Turkey
Tel +90 344 300 3369
Fax +90 344 300 3409
Email fozlemorhan@yahoo.com

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http://dx.doi.org/10.2147/NDT.S158822

to function as an agonist on the serotonergic system, by decreasing the monoamine oxidase activity (the enzyme catabolizing serotonin and dopamine)[5] and affecting the interneuronal serotonin transport – both processes increasing the level of serotonin in the synapse, leading to possible mood enhancement.[22] Additionally, estrogen is involved in regulating serotonin receptor number and function,[23–25] thus controlling the activity of serotonergic neurons. Also, estrogen has been shown to affect many neurotransmitter systems in addition to the serotonergic system. For example, estrogen generally increases the activity of noradrenaline, acts as a cholinergic agonist in particular areas of the brain, decreases dopamine D2 receptor sensitivity, and appears to act as an adjunct agonist of gamma-aminobutyric acid.[26] While estrogens can modulate serotonin and noradrenaline neurotransmission, they appear to play an important role in neuroprotection[27] and anti-inflammation in the brain.[28]

Estrogen mediates its effects mostly by binding to estrogen receptors (ERs). There are two different types of ERs: one is a member of the nuclear hormone family of intracellular receptors and the other one is a membrane-bound G-protein–coupled estrogen receptor (GPER).[29] The membrane-bound G-protein–coupled estrogen receptor-1 (GPER-1), or GPR-30, was identified by several groups in the late 1990s.[30] GPER has been found to be responsible for the rapid actions of estrogen.[31] Revankar et al reported that estradiol binds to and signals through GPER-1 with high affinity and potency in vitro, leading to the classification of GPER-1 as a membrane-bound ER.[32] GPER-1 was shown to act independently of ERα and Erβ, but likely stimulates the same second-messenger pathways and has genomic actions.[33] Thus, the effects of estrogens in the brain likely depend on the relative expression and cellular locations of multiple ERs. Immunohistochemical studies have revealed that GPER is expressed in both the CNS and peripheral nervous system; throughout the nervous system, the GPER regulates its own expression in regionally distinct ways, and it has increasingly been shown to mediate estrogen's physiologic and pathologic functions, with expression found in the brain of both adult male and nonpregnant female rats.[34] ERs are expressed in a variety of areas in the brain, where they predominate in limbic-related areas known to be important for emotion, cognition, and behavior.[35,36] In animal model experiments, GPER has been found in male and female rodents throughout the CNS and peripheral nervous system, including the hypothalamus, hippocampus, midbrain, spinal cord, and dorsal root ganglia.[34,37–39] GPER-1 is expressed in neurons and microglia.[28,40] In addition, ERs have been identified in the leukocytes isolated from peripheral blood and the blood vessel endothelia of both men and women.[41,42] GPER-1 in macrophages is associated with the anti-inflammatory action of estrogens.[43,44] Till now, the physiologic functions for GPER have been described in almost every organ system.[45]

Several studies have investigated the possible involvement of ERs in the etiology of psychiatric disorders.[29] To the best of our knowledge, there has been no study to date examining serum GPER-1 levels in BD patients. The aim of this study was to evaluate the potential role of GPER-1 in euthymic BD patients and compare their GPER-1 levels with those of healthy controls.

Patients and methods

Patients

The study included 38 BD patients and 35 age- and gender-matched healthy controls. The patients included in the study had already received the diagnosis of BD according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition.[46] The study protocol was approved by the Scientific Research Ethics Committee of Kahramanmaraş Sütçüimam University, and detailed written informed consent was obtained from each patient and control subject.

The study excluded those who were pregnant or postmenopausal, having irregular menstrual cycles (anovulatory cycle), receiving hormone replacement therapy (eg, oral contraceptives), having endocrine disorders (diabetes mellitus or impaired levels of thyroid-stimulating hormone), addicted to alcohol and/or other substances, and having a psychiatric disorder other than BD or a concomitant physical disease.

The demographic and clinical characteristics, including gender, age, and comorbid conditions, were recorded for all participants, and physical examinations and all required laboratory tests were performed.

Procedure

Blood samples were collected from all patients in the BD and the control groups between 9:00 am and 11.00 am Samples were centrifuged and the serum samples stored at –20°C until analysis. The GPER-1 levels were analyzed in the Biochemistry Laboratory at Kahramanmaraş Sütçüimam University School of Medicine using a quantitative sandwich enzyme-linked immunosorbent assay technique and a commercial kit (SEG045Hu; Cloud-Clone Corp.; Houston, TX, USA) according to the manufacturer's instructions.

Statistical analysis

The normal distribution fitness of the data was examined using the Shapiro–Wilk test. An independent samples *t*-test was used to compare the groups for variables that had normal

distributions. Descriptive statistics were specified with mean ± SD. Mann–Whitney *U* test was used to compare the groups for variables that did not have normal distribution. Descriptive statistics were expressed in median (Quartile 1–Quartile 3). Chi-square test and Fisher's exact test were applied to categorical variables. The relationship between variables was examined using Pearson's correlation test. Statistical significance was accepted as $p<0.05$. Analysis of the data was conducted using IBM SPSS version 22 (IBM SPSS for Windows version 22; IBM Corporation; Armonk, NY, USA). A receiver operating characteristic (ROC) curve was plotted to obtain a cut-off value of GPER-1 for predicting the presence of BD.

Results

This study included 38 patients with euthymic BD and 35 age- and gender-matched healthy control subjects. The groups did not differ significantly in age (patients: 37.61±12.16, controls: 33.51±9.59 [mean ± SD], $p=0.117$) or gender (patients male/female: 15/23, controls male/female: 17/18, $p=0.434$). Table 1 shows the sociodemographic characteristics of the sample.

Table 2 shows the BD patients' duration of illness and the medication data. The levels of estradiol were found to be similar in both groups (patients: 41.27 pg/mL, controls: 38.17 pg/mL, [mean ± SD], $p=0.774$). However, the serum GPER-1 level was significantly higher in patients with euthymic BD compared to healthy controls (0.55±0.14 and 0.23±0.09 ng/mL [mean ± SD], respectively, $p<0.001$), as shown in Table 3 and Figure 1.

Table 1 Sociodemographic variables of the groups

	Group		*p*-value
	Bipolar (n=38)	Control (n=35)	
Age[a] (mean ± SD)	37.61±12.16	33.51±9.59	0.117
Gender[b]			0.434
Male, n (%)	15 (39.5)	17 (48.6)	
Female, n (%)	23 (60.5)	18 (51.4)	
Marital status[c]			0.984
Married, n (%)	24 (64.9)	22 (62.9)	
Single, n (%)	11 (29.7)	11 (31.4)	
Divorced, n (%)	2 (5.4)	2 (5.7)	
Education level[c]			0.205
Illiterate, n (%)	3 (10.0)	0 (0.0)	
Primary school, n (%)	5 (16.7)	11 (34.4)	
Secondary school, n (%)	2 (6.7)	1 (3.1)	
High school, n (%)	8 (26.7)	10 (31.3)	
University, n (%)	12 (40.0)	10 (31.3)	
Job[b]			0.001*
Working, n (%)	14 (40.0)	26 (83.9)	
Not working, n (%)	21 (60.0)	5 (16.1)	

Notes: [a]Independent samples *t*-test, [b]chi-square test, [c]Fisher's exact test; $\alpha=0.05$. *Distribution of groups is statistically significant.

Table 2 Duration of illness and medication in use of the patient group

Duration of illness (mean ± SD)	12.03±10.70
Atypical antipsychotics	
Yes, n (%)	34 (87.2)
No, n (%)	5 (12.8)
Typical antipsychotics	
Yes, n (%)	3 (7.7)
No, n (%)	36 (92.3)
Lithium	
Yes, n (%)	19 (48.7)
No, n (%)	20 (51.3)
Anticonvulsants	
Yes, n (%)	22 (56.4)
No, n (%)	17 (43.6)
Antidepressants	
Yes, n (%)	6 (15.4)
No, n (%)	33 (84.6)

Subgroup analysis found significantly higher GPER-1 levels in all patients, regardless of gender (see Table 4). This result indicates the possible diagnostic potential of GPER-1 in BD, independent of gender. No significant difference was found between the BD and control groups in the levels of estradiol in males and females (Table 4). Pearson's correlation analysis showed no significant correlation of the levels of estradiol and GPER with the duration of illness ($p>0.05$). Additionally, the laboratory results were not influenced by the medications in use (Table 5). The ROC analysis revealed that GPER-1 had a predictive value for the presence of BD (area under the curve, 0.977; 95% CI, 0.948–1.000; $p<0.001$). When the GPER-1 value was ≥0.3850, the sensitivity and specificity for the presence of BD were 92.1 and 97.1%, respectively (Figure 2). The GPER-1 level was under the cut-off point in all subjects in the control group.

Discussion

The main finding of this study was that serum GPER-1 levels were higher in euthymic BD patients than in healthy control subjects. In addition, the results showed that these increased

Table 3 Laboratory results of patients and healthy controls

	Group		*p*-value
	Bipolar (n=38)	Control (n=35)	
GPER,[a] ng/mL (mean ± SD)	0.55±0.14	0.23±0.09	$p<0.001$[b]
Estradiol,[a] pg/mL median (Q1–Q3)	41.27 (31.37–94.02)	38.17 (30.48–61.34)	0.774

Notes: [a]Mann–Whitney *U* test, $\alpha=0.05$; [b]difference is statistically significant.
Abbreviation: GPER, G-protein–coupled estrogen receptor.

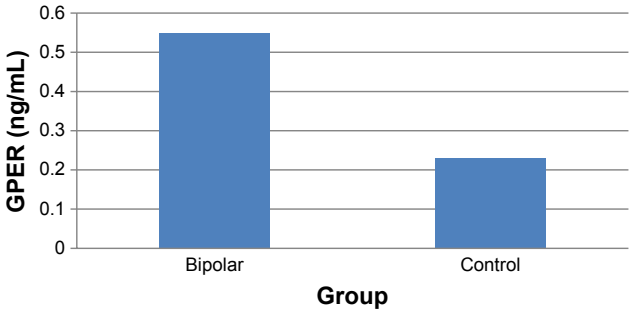

Figure 1 GPER-1 levels in the euthymic BD and control groups.
Note: GPER-1 levels were significantly higher in BD patients.
Abbreviations: BD, bipolar disorder; GPER-1, G-protein–coupled estrogen receptor 1.

GPER-1 levels were independent of gender. Additionally, in ROC analysis, it was found that the diagnostic value of GPER-1 levels for BD was significantly high. This finding indicates that GPER-1 could play a potential role in the pathogenesis of BD. To the best of our knowledge, this is the first study to evaluate serum GPER-1 levels in BD patients.

A significant proportion of women with BD face emotional challenges during periods of normal hormonal fluctuation.[47] In addition, numerous studies have reported that periods of hormonal fluctuation (eg, premenstrually, postpartum, and postmenopausally) are associated with increased risk of affective dysregulation and vulnerability to developing depression.[5,48–50] Several studies have shown that periods of depression often correlate with hormonal fluctuations in women with BD or major depression.[5,26,48–52] It has been suggested that estrogen participates in coordinating synaptic plasticity in the nervous system,[53] and it is thought to play a significant role in neuropsychiatric disorders. Recent data suggest estrogen can serve as a short-term adjuvant to selective serotonin reuptake inhibitors.[54] In most humans, high and constant levels of estrogen are described as anxiolytic and "emotionally positive". In contrast, low and/or fluctuating levels correlate with dysphoric emotional states and increased anxiety.[16]

There has been extensive research into the role of estradiol and the activation of ERs in the neuroprotective and neurodegenerative processes, using various animal models of neurodegeneration, cognitive impairment, and affective disorders.[19,55] Two studies of possible involvement of the ERα and ERβ genes in BD found no association with the disease.[56,57] However, Weickert et al[58] reported that differences in the ERα gene and its mRNA expression contributed to the risk of developing schizophrenia. Another study found that persons committing suicide had decreased levels of ERβ mRNA.[36] The detection of both ERα and ERβ mRNAs in the human hippocampus, amygdala, and cerebral cortex[59–63] raises the possibility that ERs may directly mediate the known effects of estrogen on mood.[64,65] It has been reported that favorable effect of estrogen on mood is associated with ERβ signaling, and that estrogen leads to a decrease in glucocorticoid activity via ERβ and has antidepressant activity.[66]

Although the cellular activities of GPER have been examined in a number of systems, the physiologic functions of GPER are just beginning to be investigated. Based on the extensive effects of estrogen in a vast array of physiologic systems, the contributions of GPER to estrogen-mediated effects could be substantial.[12] Recently, GPER stimulation was shown to attenuate serotonin receptor signaling in the paraventricular nucleus, as demonstrated by reduced oxytocin and adrenocorticotropic hormone responses, suggesting that GPER may play a role in mood disorders.[67] GPER-1 is expressed in the hypothalamus,[67] pituitary gland,[68] hippocampal formation, and amygdala[69] in both male and female rodents, which indicates a role for GPER-1 in controlling emotions and regulating endocrine responses. In addition, a role of GPER-1 in mood disorders has been reported.[12,69] Experimental studies on animals have suggested that antidepressant-like effect of estradiol is mediated by ERβ and GPER-1, and that GPER-1 might be a new target in the treatment of depression.[70,71] Furthermore, the GPER-1 level was increased in the serum of patients with generalized anxiety disorder, significantly and positively correlating with the severity of the anxiety, and it has been suggested that increased serum GPER-1 levels may play a role in the

Table 4 Subgroup laboratory results by gender in patients and healthy controls

	Gender					
	Male (n=32)			Female (n=41)		
	Bipolar	Control	*p*-value	Bipolar	Control	*p*-value
GPER[a] (mean ± SD)	0.56±0.14	0.22±0.10	$p<0.001$[c]	0.55±0.14	0.24±0.008	0.006[b]
Estradiol[c] median (Q1–Q3)	36.05 (24.11–41.58)	32.19 (27.96–38.06)	0.865	85.61 (34.98–118.46)	61.34 (38.27–131.48)	0.843

Notes: [a]Independent samples *t*-test; [b]difference is statistically significant; [c]Mann–Whitney *U* test, $\alpha=0.05$.
Abbreviation: GPER, G-protein–coupled estrogen receptor.

Table 5 Laboratory results by class of medication in use

	Estradiol	*p*-value	GPER	*p*-value
	Median (Q1–Q3)		Median (Q1–Q3)	
Atypical antipsychotics	41.16 (28.45–94.02)	0.982	0.54 (0.46–0.67)	0.255
	41.83 (25.84–96.90)		0.54 (0.51–0.69)	
Typical antipsychotics	39.77 (13.33–193.05)	0.959	0.51 (0.46–0.67)	0.862
	41.27 (28.45–94.02)		0.54 (0.45–0.67)	
Lithium	44.04 (28.45–118.10)	0.361	0.54 (0.42–0.69)	0.967
	39.23 (31.17–63.74)		0.54 (0.48–0.59)	
Anticonvulsants	41.58 (34.98–100.72)	0.403	0.53 (0.46–0.58)	0.371
	38.68 (28.45–70.73)		0.54 (0.47–0.71)	
Antidepressants	33.89 (22.75–81.12)	0.317	0.48 (0.43–0.51)	0.138
	41.43 (29.91–97.37)		0.54 (0.47–0.67)	

Notes: Mann–Whitney *U*-test; α=0.05.
Abbreviation: GPER, G-protein–coupled estrogen receptor.

etiology of generalized anxiety disorder.[72] GPER-1 level has been examined in tissue in rat models,[37,73] and recently, serum has been studied to correlate GPER-1 level with various diseases.[72]

According to our hypothesis, it is expected that GPER-1 is a more selective biomarker for BD in females than in males. But both male and female BD group had higher GPER-1 levels than that of each control group. In rat studies, there is a controversial effect of GPER-1 on mood according to the gender. Some studies show equal effect in both genders,[13–15] and others show gender differences.[16]

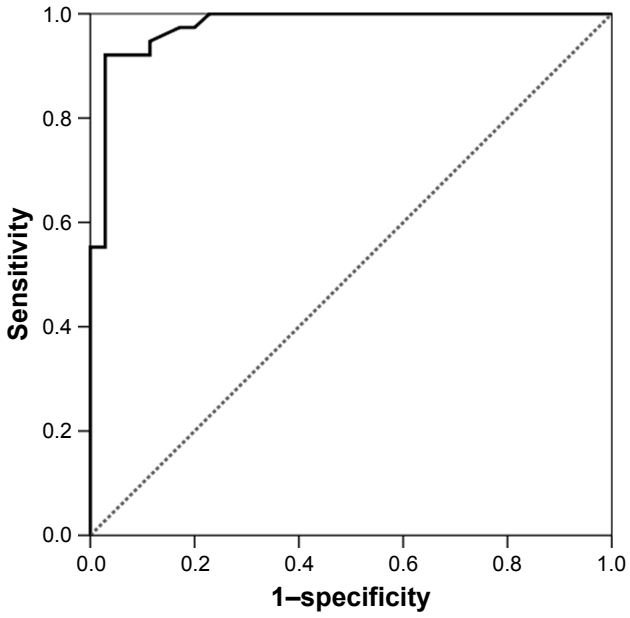

Figure 2 ROC curve for GPER-1.
Notes: AUC was 0.977 for GPER-1. Cut-off point was detected as 0.3850 ng/mL. This curve combines the information of the true-positive rate and the true-negative rate, and the AUC is a measure of the overall discriminative power of GPER-1.
Abbreviations: AUC, area under curve; GPER-1, G-protein–coupled estrogen receptor-1; ROC, receiver operating characteristic.

There is evidence that neuroinflammation underlies BD.[74] Dysfunction still occurs in the brain of euthymic patients, while no BD symptoms appears in euthymic state,[75] implying that neuroinflammation persists in BD patients with euthymic state. Serum GPER-1 level is higher in euthymic patients compared with controls, while there is no difference in serum estradiol level between the two groups. Accordingly, it is possible that GPER-1 signal is increased to attenuate neuroinflammation in BD patients with euthymic state. Improved GPER-1 signal may also occur in the brain.

GPR30 mediates estrogen-induced G-protein activation of several signaling cascades, such as protein kinase cascades-phosphatidylinositol 3 kinase and calcium signaling,[32] at its locations in the plasma membrane, Golgi apparatus, and endoplasmic reticulum.[76] Additionally, estrogen treatment increases the expression of protein kinase C (PKC), an important intracellular messenger.[77] Biochemical data support the potential involvement of PKC and its substrates in BD patients,[2] and mood stabilizers such as lithium and valproate have been shown to inhibit PKC.[78] In this context, two small, randomized controlled trials have revealed robust anti-manic effects with tamoxifen, which is an ER and PKC antagonist and a selective estrogen receptor modulator.[77,79] However, in this study, the laboratory results were not influenced by the medications in use (Table 5).

The limitations of this study include its small sample size, its cross-sectional design, and the ongoing medication of the BD patients. Because it is unethical to stop patients' treatments, medications were not suspended during the study. In addition, the study measured serum levels, which offer insight into global alterations of GPER-1 levels in BD, but may not reflect the levels in the brain. In contrast, the study's

strength is that it is the first to investigate blood GPER-1 levels in BP patients, as far as we know.

Conclusion

This study demonstrated that serum GPER-1 levels were significantly higher in BP patients than in control subjects. Moreover, it was observed that GPER-1 level had a good diagnostic value for the presence of BD. Therefore, GPER-1 receptor activity may be a candidate biomarker for BP. These results should be considered preliminary and need to be confirmed by future studies.

Acknowledgments

The authors are grateful to Mehmet Karadöl for data collection.

Disclosure

The authors report no conflicts of interest in this work.

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