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ORIGINAL ARTICLE

Decreased Levels of G Protein-Coupled Estrogen Receptor in Bipolar Patients

Bipolar Tanılı Hastalarda Azalmış GPER düzeyleri

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ABSTRACT

Objective: There is increasing evidence in the literature that estrogen and its receptors play an essential role in the etiopathogenesis of bipolar disorder due to gender differences in the course, severity, and peak periods of the disease. In this context, g protein-coupled estrogen receptor (GPER), defined in the reproductive system as well as the nervous system, endocrine system, and cardiovascular system, mediates the neurological benefits of estradiol; It is crucial to understand its role in this disease better.
Method: This study aimed to compare serum GPER levels in euthymic bipolar disorder patients and healthy controls matched for age, sex, and body mass index.
Results: In this study, we found decreased serum GPER levels in both genders separately and in total in the patient groups compared to the controls.
Conclusion: Our results should be considered preliminary and should be repeated in more homogeneous groups with larger samples. In addition, we believe that further studies should be conducted on the therapeutic efficacy of G1 in depressive bipolar patients.

Keywords: GPER, Estrogen Receptors, Estradiol, Gender

ÖZ

Amaç: Literatürde östrojen ve reseptörlerinin, hastalığın seyri, şiddeti ve pik dönemlerindeki cinsiyet farklılıklar nedeniyle bipolar bozukluğun etyopatogenezinde önemli rol oynadığına dair artan kanıtlar bulunmaktadır. Bu bağlamda üreme sisteminin yanı sıra sinir sistemi, endokrin sistem ve kardiyovasküler sistemde de tanımlanan ve östradiolün nörolojik faydalarına aracılık eden GPER'in bu hastalıktaki rolünü daha iyi anlamak önemlidir.
Yöntemler: Bu çalışmada, ötimik dönemdeki bipolar bozukluk hastaları ile yaş, cinsiyet ve vücut kitle indeksi açısından eşleştirilmiş sağlıklı kontrollerde serum GPER düzeylerini karşılaştırmayı amaçladık.
Sonuçlar: Bu çalışmada hasta gruplarında kontrol gruplarına göre her iki cinsiyette ayrı ayrı ve toplamda serum GPER düzeylerinin düşük olduğunu saptadık.
Tartışma: Sonuçlarımız ön çalışma olarak değerlendirilmeli ve daha büyük örneklemlerle daha homojen gruplarda tekrarlanmalıdır. Ek olarak, G1'in depresif dönemdeki bipolar hastalarda terapötik etkinliği konusunda daha fazla araştırma yapılması gerektiğine inanıyoruz.

Anahtar kelimeler: GPER, Östrojen Reseptörleri, Estradiol, Cinsiyet

Introduction

Bipolar disorder (BD) is a mood disorder with depressive and manic episodes which etiology is still not fully determined [1]. Although the disease is seen approximately equally in men and women, there are gender differences. Rapid cycling and hypomania are more common in women, and mania episodes are more common in men [2, 3]. In the estimation of the effect of birth events on the course of the disease, the risk of having a bipolar attack in the first month after birth is estimated to be 23 times higher than the pregnancy period, which shows the importance of gender difference and the effect of sex hormones in the course of the disease [4]. Literature data on gender differences in (BD) show that sex hormones, especially estrogen and related receptors, should be investigated further in this disease.

Besides having essential roles in the menstrual cycle and pregnancy, estrogen has important roles in the central nervous system. It has been reported that estrogen increases the serotonin level by decreasing the monoamine oxidase activity, reduces the sensitivity of the D2 receptor, and has an agonistic effect on the cholinergic system [5, 6]. Estradiol is the most common and most potent form of estrogen, while estrone and estriol are other forms of estrogen. Estrogen receptors mediate the effects of estrogens [7]. ERa and ERβ, known as nuclear transcription factors from estrogen receptors, are primarily found in the cytoplasm and nucleus but are present in tiny amounts in the cell membrane [8, 9]. Furthermore, G protein-coupled estrogen receptor 1(GPER), a new estrogen receptor, has been identified in the reproductive system and almost every system, including the cardiovascular, endocrine, and nervous systems [10, 11]. While estradiol plays an essential role in nervous system diseases and is associated with ERa and ERβ, interest in GPER has increased after it has been determined that GPER is expressed throughout the nervous system and mediates neurological benefits related to

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estradiol [12, 13]. GPER mediates various mechanisms, including suppressing neuroinflammatory processes, inhibiting apoptosis-related pathways, and enhancing neurotrophic factors [11].

In the literature, there is evidence in clinical and preclinical studies that estrogen and estrogen receptors are essential in understanding the etiopathogenesis of mood disorders [14-16]. A survey by Dias et al. reported that women with premenstrual exacerbations experience more frequent mood episodes than women who do not [17]. There are limited studies on serum GPER levels in psychiatric disorders, including BD and schizophrenia [18, 19]. Only one study in the literature investigates the potential role of GPER in patients with bipolar disorder [18]. Our study aimed to compare serum GPER levels in non-smoking euthymic bipolar patients with healthy controls matched for age, sex, and body mass index.

Methods

Participants

Our study included 64 participants; 32 in the patient and 32 in the control groups. A Structured Clinical Interview (SCID), according to DSM-5 diagnostic criteria, was applied by a psychiatrist to patients with BD diagnosis before being included in the study. The patients had not experienced mania or depressive episodes, and their medical treatment was the same in the last year. At enrollment, the patients had no affective symptoms and were clinically stable. The control group consisted of hospital workers who were matched for gender, age, and body mass index and had no previous psychiatric admission. Before inclusion in the study, SCID was applied to the control group according to DSM-5 diagnostic criteria.

The inclusion criteria applied are as follows; Being between the ages of 18-65, not having any significant medical disease including endocrine disorders, having a regular menstrual cycle, not taking hormone replacement therapy, not having any comorbid psychiatric illness for the patient group, not having received psychiatric diagnosis and treatment in the past and still for the control group. We obtained written informed consent from all participants included in the study. Ethics committee approval of the present study was made by Ataturk University Faculty of Medicine (approval date/number: 01.12.2022/19).

Measurements

We applied a sociodemographic data form to record sociodemographic variables and clinical data. Hamilton Depression Scale was used to evaluate depressive symptoms, and the Young Mania Rating Scale was used to assess mania symptoms.

Biochemical Analysis

Blood samples were collected from the patient and control groups after fasting between 9.00 and 11.00 in the morning. The samples were quickly taken to the biochemistry laboratory, and immediately after centrifugation at 4000 g for 15 minutes, the serum samples were separated. Separated serum samples were stored at −28 □ until biochemical analysis. To measure serum GPER-1 levels, a commercial kit (SEG045Hu; Cloud-Clone Corp) was used with the quantitative sandwich enzyme immunoassay method, following the manufacturer's instructions.

Statistical Analysis

We evaluated whether the continuous variables were normally distributed, with kurtosis and skewness values. Mean ± standard deviation and percentage values were used to present descriptive statistics. Differences between patient and control groups were examined using independent sample t-tests (when normally distributed) or Mann-Whitney U tests (when not normally distributed). The chi-square test was used to compare binary variables between groups. Pearson correlation test was used to test the relationship between continuous variables (clinical characteristics-GPER) in the patient group. We used IBM SPSS 23.0 program. A p-value less than 0.05 was considered significant.

Results

The patient and control groups consisted of 32 participants in each. Both groups were matched for gender, age, and body mass index. The characteristics of the groups and the additional data of the patient group are shown in Table 1. In this study, we found decreased serum GPER levels in both genders separately and in total in the patient groups compared to the control groups (Table 2).

Table 1. Sociodemographic variables of ali the participants

		Bipolar (n =32)	Control (n =32)	p
Age	Mean ± SD	32.90±8.37	33.21±7.37	0.87
Gender	Female/Male (n/n)	16/16	16/16	1
Education years	Mean ± SD	10.81±2.52	11.84±2.65	0.11
BMI (kg/m2)	Mean ± SD	25.61±2.09	24.86±1.97	0.31
Disease duration (Years)	Mean ± SD	9.50±5.81		
Disease onset	Mean ± SD	23.31±5.06		
Manic episode	Mean ± SD	2.81±2.10		
Depressive episode	Mean ± SD	1.65±1.31		
Hospital stay	Mean ± SD	3.28±2.36		
Treatment (AP+MS)	n, %	14, 43.8		

AP: Antpsychotic; MS: Mood Stabilizator

Table 2. Comparison GPER level between bipolar and control groups

	Bipolar (n =32) Mean ± SD	**Control (n =32)** Mean ± SD	P
GPER	4.24 ± 1.37	10.11 ± 2.69	< 0.01
GPER female	4.13 ± 1.13	9.90 ± 2.42	< 0.01
GPER male	4.35 ± 1.60	10.31 ± 2.99	< 0.01

Discussion

To our knowledge, this is the second study evaluating serum GPER levels in BD. In the first study by Orhan et al., increased serum GPER levels were found in patients with BD compared to the controls, and it was suggested that GPER might play an essential role in the pathogenesis of BD [18]. We found decreased GPER levels in BD compared to the controls, which does not support the previous study. Our study compared the patient and control groups regarding age and gender, as in the first study examining GPER levels in BD. In addition, unlike the previous study, we compared the control group regarding body mass index and determined smoking as an exclusion criterion. In this context, matching non-smoking BD patients with the control group regarding age, sex, and body mass index will provide sufficient homogeneity. Body mass index comparison is important since it was reported in another study that GPER regulates body fat and body weight [20].

Before the literature data on GPER, studies showed the critical role of estradiol in psychiatric diseases. It was believed that ERa and ERβ[11] primarily mediated the benefits of estradiol in the nervous system. With the increasing data on GPER as a new estrogen receptor, it has been revealed that it is expressed in the entire central nervous system and has essential contributions to estradiol-related neurological benefits [13, 21]. Maintaining vascular functions and the blood-brain barrier, reducing neuroinflammation, mediating the increase of neurotrophic factors, and inhibiting the pathways that cause apoptosis can be counted as some of these benefits [11]. As one of the most important pieces of evidence for this, it was reported in the study by Alexander et al. that activating the GPER agonist G1 improves cognitive functions, including memory and learning [22]. G15, the selective antagonist of GPER, has been shown to inhibit the antidepressant effects of G1 in a animal study [23]. Another study by Xu et al. reported that G1 reduced the signal of the serotonin receptor in the paraventricular nucleus in the hypothalamus, supporting the idea that GPER may play an essential role in mood disorders[24].

GPER is required in E2-induced changes in desensitization at the serotonin 1A receptor, which is essential for antidepressant therapy. It has been suggested that GPER may enhance the therapeutic effect of antidepressants [25]. A study conducted with ovariectomized rodents reported that long-term treatment with G1 caused an antidepressant-like impact by increasing the phosphorylation of trkB, ERK, and Akt receptors in the brain [26]. To our knowledge, there are no studies of GPER or G1 in animal models of BD. We found decreased GPER levels in euthymic BD patients compared to the control group. However, a previous human study stated that increased GPER levels might be an essential biomarker [18]. The depressive phase of BD is a complex treatment process, as antidepressant drugs can cause a manic shift. In this context, we believe that further studies should be conducted on the effectiveness of G1 in the depressive period of bipolar disorder, which is the data in the literature on antidepressant efficacy.

A rat study conducted in the context of elucidating the hippocampal functions of GPER showed that the binding of the antagonist weakened the reference memory to GPER. In contrast, the binding of the agonist strengthened the reference memory. Thus, activation of GPER affects cognitive functions [27]. Another animal study showed that estradiol improved social learning, and this process was accelerated because of GPER activation [28]. It is known that patients with BD experience cognitive impairments due to recurrent mood attacks [29]. The patients included in our study showed relative chronicity and had recurrent episodes. The decreased GPER levels we obtained in the patient group compared to the controls may explain the cognitive impairments seen in BD, even if the mood attack is over.

In this study, we applied strict protocols during the blood collection period, such as taking fasting blood at certain times of the day, and non-smoker patients were compared for gender, age, and body mass index; However, the significant limitations of our study should not be ignored when evaluating the decreased GPER levels we obtained. The most important of these limitations is the small sample size. For this reason, another sufficiently strong study needs to be done. Secondly, because it was the venous blood samples we collected, they may be affected by the blood-brain barrier and may not represent values in the central nervous system. Thirdly, since it is a study conducted only in euthymic patients, it does not provide information about different disease periods or establish a causal relationship. Finally, the patients participating in our study continued their current medical treatment, which can be considered an important confounding factor.

In conclusion, our study found decreased GPER levels in non-smoking BD patients compared to healthy controls matched for age, sex, and body mass index. Our results should be considered preliminary and should be repeated in more homogeneous groups with larger samples. In addition, we believe that further studies should be conducted on the therapeutic efficacy of G1 in depressive bipolar patients.

Author Contributions

Conception: O.H, Data Collection and Processing: OH.ÖFU., Design: O.H, ÖFU, Supervision: EBK., Analysis and Interpretation: NÖ, EBK, Literature Review: OH,ÖFU, Writer: O.H, ÖFU, Critical Review: O.H,Ö.F.U, E.B.K, N.Ö

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