Expression of ESR1 and ESR2 oestrogen receptor encoding gene and personality traits – preliminary study

Monika E. Talarowska1, Janusz Szemraj2, Su Kuan-Pin3

1Department of Personality and Individual Differences, Institute of Psychology, University of Lodz, Poland
2Department of Medical Biochemistry, Medical University of Lodz, Poland
3Department of General Psychiatry, China Medical University Hospital, Taichung City, Taiwan

Abstract

Introduction: The main objective of the study is to examine the hypothesis claiming a correlation between personality traits measured with the use of the Minnesota Multiphasic Personality Inventory (MMPI-2) personality questionnaire and the expression of the ERα (ESR1) and ERβ (ESR2) encoding gene in patients suffering from depression.

Material and methods: The experiment was carried out on a group of 44 individuals with depression. The Polish variant of the MMPI-2 was applied with the aim of assessing personality traits. Furthermore, the authors evaluated the expression of the genes encoding the oestrogen receptors (ERα and ERβ) at the mRNA level and protein level in the studied population.

Results: No significant differences in the expression of ERα and ERβ encoding genes were found and confirmed in the patients with the first episode of depression and those suffering from subsequent episodes of the disease. No differences were found between women and men, either. In women a positive relationship was found between the scale of psychopathy (p = 0.04), paranoia (p = 0.01), and mania (p = 0.03) and expression for the ERα encoding gene at the mRNA level. A negative relationship was found between the mania scale and ERβ encoding gene expression at mRNA (p = 0.03) and protein (p = 0.04) levels. In males a positive relationship between anxiety as a personality trait and expression of the ERβ receptor encoding gene at mRNA level (p = 0.03) and protein level (p = 0.03) was found.

Conclusions: Personality traits may be linked with the expression of genes encoding oestrogen receptors (ERα and ERβ) among patients with depressive disorders.

Key words: oestradiol, ERs, depression, personality traits.
The direction of action of oestrogens is largely dependent on their concentration. In low oestrogen concentrations (e.g. in men or in women during menstruation or menopause), proinflammatory cytokines are stimulated and produced, leading to an enhanced cellular response. In women the number of Th2 and B lymphocytes decreases significantly during menopause, while the number of Tc lymphocytes increases, and the application of hormone replacement therapy reverses this phenomenon. In turn, high oestrogen levels, such as those observed in women during ovulation and pregnancy, result in increased antibody production as well as enhancement – depending on Th2 lymphocytes – of the humoral immune response and increased release of Treg lymphocytes. Oestrogens also inhibit NK cells and reduce the influx of neutrophils and monocytes, hindering their chemotaxis and migration to the inflammatory focus, hence protecting the body against long-term inflammation [19-21].

Oestrogen receptors α (ERα, NR3A1 – nuclear receptor subfamily 3, group A, member 1) and β (ERβ, NR3A2 – nuclear receptor subfamily 3, group A, member 2) are steroid hormone receptors found in the nuclear receptor subfamily NR3 [22, 23]. They are encoded by separate genes, and expression of both these receptors occurs in cells of multiple tissues; however, ERα predominance is found in the cells of the mucous membrane of the uterus, ovary, hypothalamus, and ducts of testes, while ERβ predominates in the cells of kidney, brain, heart, bone, lung, intestinal mucosa, prostate gland, and vascular endothelium [24]. ER receptors are located in cells in both cytoplasm and nucleus. Their location is not permanent, but the process is rather dynamic – a result of translocation from and to the cell nucleus [25, 26]. Both ERα and ERβ regulate the synthesis and metabolism of many neurotransmitters and neuropeptides, their receptors, and transporters, and also play a role in non-genomic cell signalling (the so-called rapid mechanism of action) [3, 27]. This makes ER essential for CNS development by regulating neuronal and glial proliferation, migration, differentiation, activation, and apoptosis of neurons [28, 29]. Oestrogen receptors can also be found in the immune system cells, e.g. in/on B lymphocytes, Th and Tc lymphocytes, NK, monocytes, macrophages, and dendritic cells [30].

With the neurodevelopmental theory of depression [31] (which underlines the importance and impact of earlier stages of human life, including the prenatal period, on the occurrence of depressive disorders) being the starting point for our considerations, and referring to the results of our earlier studies, in which we showed a correlation between personality traits and active inflammatory process indicators in depressed patients [32, 33], we adopted – as the aim of the presented paper – the hypothesis that personality traits measured by the Minnesota Multiphasic Personality Inventory (MMPI-2) personality questionnaire and the expression of the gene encoding ERα (ESR1) and ERβ (ESR2) in patients treated due to a depression episode are related.

Material and methods

Patients

Forty-four individuals diagnosed with depression took part in the experiment. Qualification to participate in the study was based on random selection principles. All the qualified subjects were native Poles, inhabitants of central Poland, aged 20-60 years. They were not related to one another. The inclusion clinical criteria in the research study were in accordance with the ICD-10 guidelines (F32.0-7.32.2, F33.0-F33.8) and based on the diagnostic criteria determining a depressive episode as well as recurrent depressive disorders [34]. The process of qualifying subjects for the experiment was performed by a psychiatrist.

The exclusion criteria in the research study were as follows: history of psychiatric disorders other than depression; somatic diseases that may affect depression; central nervous system trauma; history of autoimmune and inflammatory diseases and cancer; excessive use of, or addiction to, psychoactive substances; and lack of consent to participate in the experiment.

The study was carried out while the patients were hospitalised. The fact that the experiment was conducted had no impact on the treatment modalities applied by the specialists during the patients’ hospital stay (pharmacotherapy, psychotherapy).

All patients were asked to give written consent for participation in the study, in compliance with the report approved by the Bioethics Committee of the Medical University of Lodz (approval no. RNN/534/10/KB of 07/09/2010).

Methods

The Hamilton Depression Rating Scale (HDRS, HAM-D), developed and introduced by Hamilton in 1960, served as a tool for the evaluation of the dynamics of intensity of recurrent depressive disorder symptoms. Cronbach’s α (t-equivalent reliability) calculated for this scale totalled on average 0.70; the sensitivity coefficient was 0.78, and test relevance coefficient was 0.75 [35]. When analysing the severity of depressive episode symptoms, a special scoring system worked out by Demyttenaere and De Fruyt was used [36].

Furthermore, the Composite International Diagnostic Interview (CIDI) questionnaire (version 3.0) was used in the experiment. This tool is based on the diagnostic criteria of the ICD-10 and DSM-IV classifications and is recommended by the WHO and WMH for epidemiological studies in psychiatry. It enables the estimation of disem-
Statistical analysis

When analysing the collected materials, specific methods of descriptive statistics and statistical reasoning were applied. A two-tailed critical area was assumed for the statistical verification of the hypotheses stated in the introduction.

Appropriate structure indicators, for example the existence of a specific trait expressed in percentage terms, were used to describe qualitative features in both the affected patients and the control subjects. The arithmetic mean (M) was calculated with the intention to describe average quantitative features. The range of values (minimum and maximum values) as well as standard deviation (SD) were adopted as measures of dispersion.

The Shapiro-Wilk test served as a tool for the examination of the nature of the distribution of all the variables. The hypothesis on the normality of distribution was rejected. Non-parametric variables were examined using the Mann-Whitney U test in order to make statistical comparisons between the examined groups. The authors used Spearman’s rank correlation coefficient to examine the relationships between the analysed variables. The materiality level with regard to all the statistical methods applied totalled \( p < 0.05 \) [40]. All statistical calculations were performed in STATISTICA PL (version 12).

Results

Table 1 includes all the social and demographic characteristics of the experiment group. It also contains relevant data on the course of the disease. The subjects were divided into patients diagnosed with the first episode of depression (ED-I) and those with recurrent depressive disorders (rDE). No statistically significant differences in the age of the subjects in both groups were found and confirmed.

Descriptive statistics of the variables

Tables 2 and 3 include descriptive statistics of the variables analysed by the authors: scales of the MMPI-2 questionnaire and expression for the gene encoding ER\( \alpha \) and ER\( \beta \) receptors at the level of mRNA and protein level. We also compared the variables analysed between patients with the first and subsequent episodes of depression (Table 2) and between women and men (Table 3).
In the first case, differences of statistical significance were found and confirmed in only two scales of the MMPI-2 test, i.e. the scale of schizophrenia and the scale of anxiety (Table 2). These results, significantly higher in the patients with subsequent episodes of depression, indicate the intensification of symptoms related to the sense of social and emotional alienation, lack of ego control in the cognitive and volitional spheres (these features are measured by the scale of schizophrenia), as well as an increased level of anxiety as a constant personality trait, which in turn translates into anxiety sensitivity and consequently leads to subsequent episodes of the disease. In the second case of sex-differentiated comparisons (Table 3), statistically significant differences concern only the scale of masculinity-femininity, which assesses the intensity of personality traits consistent with female and male social roles. Nevertheless, no significant differences were observed or found in the expression of the genes encoding ERα and ERβ receptors in the subjects with the first episode of depression and with subsequent episodes (Table 2). The differences between men and women were not confirmed (Table 3).

### Table 1. Demographic features and the course of the disease in the studied group (n = 44)

| Feature                                      | All subjects n = 44 | ED-I n = 17 | rDE n = 27 |
|----------------------------------------------|---------------------|-------------|------------|
| Age (years) M (SD)                          | 45.54 (10.74)       | 44.37 (12.52) | 46.15 (9.94) |
| Women/men n (%)                             | 31/13 (70.45/29.54) | 13/4 (81.25/18.75) | 18/9 (66.67/33.33) |
| HDRS-I M (SD)                                | 22.41 (6.88)        | 21.37 (8.02) | 22.48 (5.69) |
| HDRS-II M (SD)                               | 7.03 (4.59)         | 6.67 (4.72) | 7.25 (4.61) |
| Number of depressive episodes M (SD)         | 3.38 (4.11)         | –           | 5.13 (4.91) |
| Duration of disease (years) M (SD)           | 5.07 (4.67)         | 1.71 (1.21) | 7.51 (4.02) |

HDRS I – Hamilton Depression Rating Scale on the day of qualification for the study, HDRS II – Hamilton Depression Rating Scale after response to pharmacotherapy, ED-I – patients with the first episode of depression, rDE – patients with recurrent depressive disorders.

### Analysis of correlations

The results of the correlation analysis carried out separately for the examined women and men revealed the following relationships:

- **Women** – positive relationship between the scale of psychopathy ($R = 0.36, p = 0.04$), paranoia ($R = 0.43, p = 0.01$), and mania ($R = 0.38, p = 0.03$) and expression at the mRNA level for the gene encoding the ERα receptor. Negative relationship between the mania scale and ERβ receptor encoding gene expression at mRNA ($R = -0.39, p = 0.03$) and protein ($R = -0.36, p = 0.04$) levels.
- **Men** – positive relationship between anxiety as a personality trait and expression of the ERβ receptor encoding gene at mRNA level ($R = 0.69, p = 0.03$) and protein level ($R = 0.72, p = 0.03$).

### Table 2. Descriptive statistics of the analysed variables – number of episodes of the disease

| Variable                                | All subjects n = 44 | ED-I n = 17 | rDE n = 27 | ED-I vs. rDE Mann-Whitney U test |
|-----------------------------------------|---------------------|-------------|------------|----------------------------------|
| Hypochondria scale (Hd)                 | 73.682 (15.08)      | 71.125 (14.77) | 74.667 (15.41) | 0.889                           |
| Depression scale (D)                    | 78.068 (14.21)      | 75.125 (13.74) | 80.185 (14.52) | 0.842                           |
| Hysteria scale (Hy)                     | 72.773 (15.97)      | 69.813 (16.91) | 73.519 (14.91) | 0.556                           |
| Psychopathic deviate scale (Pd)         | 67.318 (13.54)      | 64.813 (13.19) | 69.037 (13.94) | 0.842                           |
| Femininity/masculinity scale (Mf)       | 50.636 (9.29)       | 47.625 (9.06) | 52.037 (9.14) | 1.000                           |
| Paranoia scale (Pa)                     | 72.205 (13.29)      | 68.250 (10.71) | 74.593 (14.51) | 0.221                           |
| Psychasthenia scale (Pt)                | 74.114 (10.51)      | 71.875 (11.46) | 75.296 (10.08) | 0.551                           |
| Schizophrenia scale (Sc)                | 74.841              | 70.125 (9.37) | 77.815 (11.81) | 0.052*                          |
| Mania scale (Ma)                        | 56.455 (11.37)      | 54.750 (15.97) | 57.407 (12.29) | 0.233                           |
| Social introversion scale (Si)          | 69.233 (13.49)      | 65.200 (11.78) | 72.185 (10.28) | 0.529                           |
| Anxiety scale (A)                       | 73.735 (11.49)      | 70.308 (9.71) | 76.450 (5.91)  | 0.051*                          |
| Repression scale (R)                    | 62.029 (8.14)       | 63.462 (13.47) | 61.300 (14.07) | 0.900                           |
| ERα mRNA (2−ΔΔct)                       | 0.254 (0.05)        | 0.251 (0.05)  | 0.254 (0.06)  | 0.338                           |
| ERα protein (pg/ml)                     | 4.658 (0.55)        | 4.583 (0.49)  | 4.687 (0.58)  | 0.510                           |
| ERβ mRNA (2−ΔΔct)                       | 0.231 (0.04)        | 0.231 (0.03)  | 0.231 (0.04)  | 0.782                           |
| ERβ protein (ng/ml)                      | 4.624 (0.71)        | 4.601 (0.69)  | 4.649 (0.75)  | 0.712                           |

ED-I – first depression episode, rDE – recurrent depressive episodes, Me – mean, SD – standard deviation, *p statistically significant, ERα – oestrogen receptor α, ERβ – oestrogen receptor β.
Discussion

This paper is the first to evaluate the relationship between personality traits measured by the MMPI-2 questionnaire and the expression of the genes encoding α and β receptors in patients diagnosed with depression. Although the study group was not numerous, we were able to confirm the interrelations described in the literature (in most cases, however, referring to animal models).

In the literature there are few studies evaluating the relationship between polymorphisms of the genes encoding oestrogen receptors and traits of emotional functioning of the subjects. Consequently, the A-351G gene polymorphism responsible for encoding oestrogen receptor α was found to be correlated with the pre-menstrual syndrome (PMS; or premenstrual dysphoric disorder – PMDD). In women with PMS/PMDD the GG allele was found to be eight times more common and was connected with the intensity of the symptoms reported by the examined subjects [41]. In addition to somatic ailments, the following behavioural and emotional symptoms are also present in the case of PMS/PMDD [42, 43]: low mood and self-acceptance and sense of hopelessness; increased level of anxiety, sensitivity, increased tension; affective instability – frequent and easy change of affect; persistent strong feeling of anger or significantly increased irritability; reduced interest in doing everyday work and duties; sense of hindered concentration; lack of enthusiasm (delight, enthusiasm, joy), easy fatigue; eating disorders – overeating or starvation; sleep disorders – excessive sleepiness or insomnia; the feeling of lack of control or being overburdened; physical symptoms – breast tenderness, distension with gas, body weight increase, headaches, joint and muscle pains [44]. Yen et al. [42] recorded interesting results from the perspective of our study. The level of oestradiol measured prior to menstruation was negatively correlated with anxiety and fear levels experienced by the women with PMDD. According to Miller et al. [45], selected polymorphisms of the ESR1 gene in women diagnosed with PMDD correlate with personality traits such as: lower Emotional Stability (L0058), lower Impression Management (L0058) (higher scores serve as an indication for a greater chance to project a socially desirable image), higher Harm Avoidance (L0026, L0060, L0061), higher Neuroticism (L0026), and lower Impression Management (L0058) (idea-oriented and imaginative thinking is reflected by higher scores, whereas low scores indicate concrete practical thinking) [45]. Gade-Andavolu et al. [46] observed, however, that the SS allele of the gene encoding ESR1 is associated with the tendency to compromise, and Prichard et al. [47] found that in men it may be combined with anti-social personality traits. Alternatively, Feng et al. [48], when assessing the relationship between the rs9340799 polymorphism of the ESR1 gene and the occurrence and severity of depression symptoms among teenagers, victims of natural disasters (earthquakes), found that the possession of the AA allele of the evaluated gene was the risk factor of depression in the group of women. Furthermore, Keyes et al. [49] confirmed the association of the AA al-
lele of the ESR2 rs4986938 gene with an increased risk of depression symptoms during life (in the group of women). Doi et al. [50] observed that severities in the impairment of social interaction and emotional regulation were linked to SNPs in ESR1 rs11155819 and ESR2 rs1152582 in a group of 96 individuals with autism spectrum disorder (ASD). However, Giegling et al. [51] did not validate any link or connection between the indicated polymorphisms of the ESRs encoding gene (rs827421, rs1913474, rs1801132, rs722207, rs974276, and rs910416) and an elevated rate of suicidal or aggressive behaviour.

Oestrogen receptors were found to be present in the area of the prefrontal cortex and the hippocampus [52], as well as within the hypothalamus and the amygdala [53]. These brain regions are not only associated with the risk of depression [31] but are also involved in social cognition processes and regulation of aggressive behaviour [31]. The presence of oestrogen receptors was also confirmed in the dorsal part of the raphe nucleus, i.e. the brain area crucial for the production of neurotransmitter serotonin [54]. In their animal model study, Yang et al. [54] examined the influence of changeable oestriadi doses (10 and 50 μg/rat per day for 11 consecutive days) on the behaviour of the animals and on the expression of tryptophan hydroxylase (TPH) and glucocorticoid receptor in the raphe nucleus of ovariectomised rats that were undergoing a forced swim test. According to the quoted authors, the physiological dose of oestriadi decreased the incidence of depressive behaviour in the examined animals and increased the expression of TPH – an enzyme involved in the serotonin biosynthesis pathway. Interestingly, a high dose of oestriadi showed no antidepressant effect. In such cases the level of corticosterone increases simultaneously, which may reverse tryptophan hydroxylase expression of in the raphe nucleus [54].

Oestriadi participation in the aetiology of depressive disorders may be associated not only with the regulation of tryptophan hydroxylase 2 but also with the expression of monoamine oxidase A and B, serotonin transporter, and serotonin-1A receptor. This effect is related to the binding of oestriadi to the intracellular oestrogen receptor, which interacts with oestrogen response elements in the tryptophan hydroxylase 2 promoter sequences, the transporter of serotonin and monoamine oxidase B [55].

Oestrogen receptor α is important for the proper course of sexual behaviour, while both ERα and ERβ modulate the anxiety response by influencing the level of arousal [56, 57]. According to Sharma and Thakur [58] and Le Moêne et al. [59], ERβ in the central amygdala is responsible to a certain extent for the well-established anxiolytic effects of oestrogens and may modulate the level of arousal. On the other hand, in aversive or threatening situations, ERα in the ventromedial nucleus of the hypothalamus has an anxiogenic action. ERβ phosphorylates and activates intracellular second messenger proteins and regulates protein expression of genes involved in neurological functions. It also promotes neurogenesis, modulates the neuroendocrine regulation of stress response, confers neuroprotection against ischaemia and inflammation, and reduces anxiety- and depression-like behaviour [3]. These results correspond with the results recorded by us for the examined women: a positive relationship between the scale of psychopathy (R = 0.36, p = 0.04), paranoia (R = 0.43, p = 0.01), and mania (R = 0.38, p = 0.03) and the expression the ERα receptor encoding gene at the mRNA level. There is a correlation between these scales and an elevated sense of experienced anxiety. In contrast, a negative relationship was found and confirmed between the scale of mania and ERβ receptor gene expression at the level of mRNA (R = –0.39, p = 0.03) and at the protein level (R = –0.36, p = 0.04), which indicates that higher ERβ expression was linked with the calming down of the patients.

Sharma and Thakur [58] observed a significant (p < 0.05) increase in ERα mRNA and protein expression levels in response to a mild yet chronic stress stimulus, while the expression of ERβ in the prefrontal cortex, hippocampus, and amygdala was significantly reduced. These changes affected both the prefrontal cortex region, the area of the hippocampus, and the amygdala and were associated with increased anxiety and depressive symptoms. At the same time, the quoted authors reported a decrease of dendritic complexity with concomitant increase in spine density in the medial prefrontal cortex, CA3 area of the dorsal hippocampus, and basolateral complex of the amygdala [58]. ERβ and oxytocin are thought to modulate the action of the hypothalamic–pituitary–adrenal axis (HPA) by reducing ACTH and corticosterone levels [60].

In addition, male mice devoid of the α oestrogen receptor became less sensitive to social stimuli [61], which is also consistent with the biopsychosocial model of depression [31]. According to Franklensztajn et al. [29], oestriadi may modulate synaptic plasticity in the central part of the amygdala, thus affecting the ability to process social information. These findings are also confirmed by Hyer et al. [62]. Interesting research results are presented by a team led by Adzic et al. [63]. The authors explored the impact of fluoxetine on mitochondrial ERα and ERβ (total and phospho-pERβ) together with their link with the activity of cytochrome c (cyt c) oxidase and apoptotic Bcl2/Bax-molecules in the mitochondria of the hippocampus in female and male rats subject to chronic isolation. No influence of chronic isolation on the expression of mitochondrial ERα in both sexes was found, with simultaneous decrease of mitochondrial ERβ expression and increase of pERβ expression in both sexes. The antidepressant treatment applied reversed these processes [63]. In other experiments, a team led by Losch et al. [64] considered the ex-
pression at the protein level of the gene encoding ERα in the accumbens nucleus region as a protective factor reducing the risk of depression development in the examined animals. The accumbens nucleus is part of the human reward system, the main motivating system of behaviour, and the overexpression of ESR1 in this area was associated with increased stress resilience.

In addition, Findkin et al. [65] observed that a relatively recently discovered oestrogen receptor, i.e. G protein-coupled oestrogen receptor 1 (GPER1), may be relevant in the aetiology of depressive disorders. The level of GPER1 in 56 new patients diagnosed with depression was significantly higher compared with an equivalent group of healthy subjects. Furthermore, it positively correlated with depression symptom intensity as measured with the use of the Hamilton Depression Rating Scale. The mechanism of its action may both increase and decrease the probability of anxiety behaviour [66].

To sum up, it is possible to conclude that there is a close link between the HPA (hypothalamic–pituitary–adrenal) axis, which has a significant role in stress response, and the HPG (hypothalamic–pituitary–gonadal) axis [67]. Undoubtedly, this matter still requires further and thorough research.

Conclusions

Personality traits may be linked with the expression of the genes encoding the oestrogen receptors ERα and ERβ among patients with depressive disorders.

Limitations

In the analysis of the results, the number of respondents should be taken into account. The analysis was carried out on a group of people treated for depression. The biochemical evaluation used venous blood.

Disclosure

The authors report no conflict of interest.

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hydroxylase expression in the dorsal raphe nucleus of rats subjected to

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