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Interaction estrogen receptor polymorphism associates with psychosocial stress on menopausal women☆

Elizabet Catherine Jusuf[a,*], Nusratuddin Abdullah[a], Andi Mardiah Tahir[a], Jayalangkara Tanra[b], Muhammad Hatta[c]

[a] *Department of Obstetrics and Gynecology, Hasanuddin University, Indonesia*
[b] *Department of Psychiatry, Hasanuddin University, Indonesia*
[c] *Department of Microbiology, Hasanuddin University, Indonesia*

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Abstract
Objective: This research aimed to evaluate the interaction between polymorphisms of ERα & ERβ and associated with psychosocial stress on menopausal women.
Methods: It was a cross-sectional study, subject were 102 women aged 40–70 years who meet the inclusion criteria at the Obstetrics and Gynecology Education Hospital of Hasanuddin who agreed on filling questioner which have been determined. Then proceed with blood taking for the ERα and ERβ receptor polymorphisms. Genomic DNA was isolated from 1 mL of EDTA anticoagulation edge blood sample using a salting-out procedure and examined interaction of polymorphisms receptors ERα and ERβ. The data were statistically analyzed using the chi-square test with p-value < 0.05.
Results: This research showed that subjects who experienced psychosocial stress have the most ERα Pvull heterozygous Pp polymorphism, ERα Xbal homozygous recessive xx, and homozygous dominant ERβ AA. There is ERβ polymorphism relationship with the occurrence of psychosocial stress in menopausal women. But there is no relationship between polymorphisms ERα Pvull, ERα Xbal, as well as the interaction between polymorphisms of ERα and ERβ with the occurrence of psychosocial stress in menopausal women.
Conclusion: ERβ polymorphism relationship the occurrence of psychosocial stress in menopausal women.

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* Corresponding author.
E-mail address: elizabet.jusuf@gmail.com (E.C. Jusuf).

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Introduction

Improved progression in medical science and health care, especially preventive medicine, led to a median increase in life expectancy, which was around the age of 65, is currently on average at the age of 75. Therefore, most women will spend one-third of their lifetime in the postmenopausal period. The transition period of menopause and the length of life spent during this period can lead to the quality of life problems and an increase in degenerative diseases.[1–3]

In Indonesia, the life expectancy of women has increased until the age of 70 years from 2000 until now. This has an impact on the increasing number of menopausal women in Indonesia. The age of women entering the menopausal period ranges from 45 to 55 years. Specifically, at the US census of 2010, there were nearly 42 million women aged 55 years and older. And it is estimated that the number of menopausal women will increase to 80 million by 2025 (about 400 times compared to 1990). Thus, when the age of menopause about 50 years, it is estimated that an Indonesian woman will experience menopause about 20 years in his life, which is almost a third of the whole life.[3,4]

Many factors can affect estrogen levels in a woman. The activity of estrogen in the brain is mediated through the activation of intracellular estrogen receptors, transmembrane, and membranes that remember receptors through non-genomic mechanisms. The estrogen receptor (ER) has 2 subtypes namely subtype α (ERα) and subtype β (ERβ). These two receptors are located in areas of the brain associated with cognitive and emotional functions. The predominant ERA is expressed in the hypothalamus and amygdala, an area involving autonomic function, emotional regulation and associated emotional memory. The predominant ERβ is expressed in the hippocampus and the entorhinal cortex, the area of the brain involving memory. So it can be said ERβ is associated with cognitive function. The involvement of estrogen receptor is still controversial as well. Currently research on mental status focuses more on the ERα gene, but attention to the ERβ gene also begins much.[5]

Population-Based cohort research of Caucasians aged 55 and older found that Xbal and PvuII polymorphisms were associated with anxiety in women but were not associated with depressive symptoms or DSM-IV depressive disorders in women or men. The XP haplotype was associated with an increased risk of anxiety symptoms in dose-dependent women.[5,6] Research in China, patients with Major Depressive Disorders (MDD) and healthy controls reported that three times more risk for MDD occurrence in women with homozygous P alleles than Pvull variants compared with women with Pp or pp genotypes.[5,7] No evidence relationship was found in men. In adult males treated drug abuse, ER-α TA-recurring polymorphisms were significantly associated with anxiety symptoms.[5,8] While research on the work of ERβ is more associated with anxiety.[1]

In menopausal women often experience physical and emotional problems where this occurs because of decreased estrogen levels and psychosocial factors that cannot be overcome, to cause psychosocial stress. Psychosocial stress that cannot be resolved will cause anxiety even can cause depression symptoms. But this situation does not occur in all menopausal women.[9] Research on the relationship of psychosocial stress with estrogen receptor polymorphism is still lacking, so researchers are interested in assessing the possible relationship between ERα polymorphism and ERβ polymorphism and how their interaction with psychosocial stress on menopausal women.

Method

It was conducted at the educational hospital in Makassar, BLU RS Dr. Wahidin Sudirohusodo and other government and private hospitals that are included in the educational networking hospital. The research population was all 40–70 years old women who came to the educational hospital and its network in Makassar, and no history of psychiatry diseases.

The patients who agreed to participate were then asked to sign the consent papers in the research. Afterward, do a record of patient's data, and filling questioner which have been determined. Then proceed with blood taking for the ERα and ERβ receptor polymorphisms. Genomic DNA was isolated from 1 mL of EDTA anticoagulation edge blood sample using a salting-out procedure. DNA is isolated from the blood using the Genomic DNA Purification kit (Promega) Wizard. DNA Genomics (100 ng) reinforced in 100 l of reaction mixture containing 0.2 M forward prime (5′-CTGCCACCCTATCTGTATCTTTTCCTATTCTCC-3′), 0.2 M reverse prime (5′-CTTTCTCTGCCACCCTGGCGTCGATTATCTGA-3′), 0.2 mM each dATP, dCTP, dGTP, dTTP, 1× PCR buffer, 2 mmol/l $MgCl_2$ and 3.5 U Taq polymerase (Promega Corp., Madison, WI). The PCR reaction was performed in 30 cycles at 94 °C for 30 s, 61 °C for 40 s, and 72 °C for 90 s (Peltier Thermocycler: MJ Research Inc., Watertown, MA). Product 1.3, a portion of intron 1 and exon 2 of the estrogen receptor gene digested with restriction endonucleases XbaI and PvuII (Amersham Pharmacia Bio-Tech, New Jersey), electrophoresis, and analyzed on 1% agarose gel. Genotyping of PvuII and XbaI polymorphisms named PP, Pp, and pp and XX, Xx, and xx respectively.

The sample data obtained are recorded in the research form, then analyzed by using the chi-square test, then the results are presented in the form of tables and narrations accompanied by an explanation.

Results

Estimation of estrogen alpha pvull receptor polymorphism with psychosocial stress in menopausal women shows that respondents who experienced psychosocial stress had the most polymorphism of ERα Pvull heterozygous Pp (36.2%). While respondents who do not experience psychosocial stress most have polymorphism of ERα Pvull homozygous dominant PP (66.7%). Chi-square test results obtained p-value = 0.979 ($p < 0.05$) which shows no relationship polymorphism ERα Pvull with the occurrence of psychosocial stress in menopausal women (Table 1).

Relation of beta-receptor polymorphisms with psychosocial stress in menopausal women shows that respondents experiencing psychosocial stress most had dominant homozygous ERβ polymorphism AA (64.3%). While respondents who do not experience psychosocial stress, most have

Table 1 Estimation of estrogen alpha Pvull receptor polymorphism with psychosocial stress in menopausal women.

Alpha Pvull receptor	Psychosocial stress				Total		*p*
	Yes		No				
	n	%	*n*	%	*n*	%	
PP	5	33.3	10	66.7	15	100.0	
Pp	17	36.2	30	63.8	47	100.0	0.979*
pp	14	35.0	26	65.0	40	100.0	
Total	36	35.3	66	64.7	102	100.0	

* Chi-square test.

Table 2 Relation of beta receptor polymorphisms with psychosocial stress in menopausal women.

Beta Receptor	Psychosocial stress				Total		*p*
	Yes		No				
	n	%	*n*	%	*n*	%	
GG	23	32.9	47	67.1	70	100.0	
GA	4	22.2	14	77.8	18	100.0	0.035*
AA	9	64.3	5	35.7	14	100.0	
Total	36	35.3	66	64.7	102	100.0	

* Chi-square test.

Table 3 Relationship interaction of alpha Pvull receptors, alpha Xbal receptors, and beta receptors against psychosocial stress occurrences in menopausal women.

Alpha Pvull receptor + alpha Xbal receptor + beta receptor interaction	Psychosocial stress				Total		*p*
	Yes		No				
	n	%	*n*	%	*n*	%	
PP,XX,Xx,xx,GG,GA,AA	25	32.9	51	67.1	76	100.0	
Pp,Xx,xx,GA,AA	10	43.5	13	56.5	23	100.0	0.647*
pp,xx,AA	1	33.3	2	66.7	3	100.0	
Total	36	35.3	66	64.7	102	100.0	

* Chi-square test.

dominant homozygous ERβ GA polymorphism (77.8%). Chi-square test results obtained p-value = 0.035 ($p < 0.05$), which shows there is a relationship of polymorphism of ERβ with the occurrence of psychosocial stress on menopausal women (Table 2).

Relationship interaction of alpha pvull receptors, alpha xbal receptors and beta receptors against psychosocial stress occurrences in menopausal women shows that respondents experiencing psychosocial stress most commonly have interaction with polymorphism of ERα Pvull, ERα Xbal and ERβ heterozygous Pp, heterozygote Xx, homozygous recessive xx, homozygous dominant GA, homozygous dominant AA (43.5%). The respondents who did not experience psychosocial stress had the most polymorphisms of ERα Pvull, ERα Xbal and dominant homozygous ER, XX, hexozygot XX, homozygous recessive xx, homozygous dominant GG, homozygous dominant GA, homozygous dominant AA (67.1%). Chi-square test results obtained $p = 0.647$ ($p < 0.05$) which showed no interaction relationship between the polymorphism of ERα Pvull, ERα Xbal and ERβ with the occurrence of psychosocial stress in menopausal women (Table 3).

Discussion

This research showed that subjects who experienced psychosocial stress have the most ERα Pvull heterozygous Pp polymorphism, ERα Xbal homozygous recessive xx, and homozygous dominant ERβ AA. There is ERβ polymorphism relationship with the occurrence of psychosocial stress in menopausal women. But there is no relationship between polymorphisms ERα Pvull, ERα Xbal, as well as the interaction between polymorphisms of ERα and ERβ with the occurrence of psychosocial stress in menopausal women.

Estrogen facilitates synaptogenesis, induces production of growth factors, protects against oxidative stress, and

regulates neurotransmission (in this case serotonin, norepinephrine, and acetylcholine) in brain systems associated with cognition and mood. The effects of estrogen regulation on cholinetyltransferase and acetylcholinesterase are related to cognitive and mood changes, in this case contributing to cholinergic transmission in learning, memory, and Alzheimer's disease. The activity of estrogen in the brain is mediated through intracellular activation, transmembrane, and membrane-bound estrogen receptor (ER) along with non-genomic mechanisms. There are two subtypes of estrogen receptor, ERα, and ERβ. The subtypes of ER receptor are encoded by two different genes.

In this research, respondents who experienced psychosocial stress had most of the xα homozygous xα xα (38.6%) homozygous XY polymorphisms while the respondents who did not experience psychosocial stress had the most dominant XDA homozygous Xα polymorphism (100.0%). No correlation of Alpha Xball estrogen receptor polymorphism with the occurrence of psychosocial stress in menopausal women. This is probably due to the lack of variation in the distribution of cases of the polymorphisms of ERα Pvull and ERα Xbal in this research.

In several previous studies that examined the relationship of polymorphisms of ERα Pvull and Xbal with mood disorders using several different measurement scales were found to be related to stress and anxiety events.[5–8]

Regarding the neuroendocrine response, ERα and ERβ work opposite to diverse neuron populations within or near PVN. There is some evidence supporting the regulation of neuropeptide promoters directly by ERβ, such as Crh. For behavioral response, ERβ seems to work through a brain circuit involving the amygdala. However, further research is needed to confirm the cellular and molecular mechanisms used by ERα and ERβ to regulate the stress response.[9,10]

In this research, it was found that respondents who experienced psychosocial stress had the most dominant homozygous beta estrogen receptor polymorphism AA (64.3%) whereas respondents who did not experience psychosocial stress had the most dominant beta polymorphism beta homozygote GA (77.8%). Relationship of estrogen receptor polymorphism with the occurrence of psychosocial stress in menopausal women was statistically significant.

Previous studies looking at the relationship of ERβ polymorphism with stress incidence in a person are still lacking, most of which examine the relationship of ERβ polymorphism with anxiety, research got anxiolytic estrogen action mediated by ERβ in mice that have been oophorectomy, These findings suggest that the anxiolytic estrogen properties are mediated by ERβ.[11]

From the result of the research, Pvull alpha receptor relationship did not appear to be statistically correlated with psychosocial stress incidence in menopausal women seen in PP, Pp, and pp. The distribution of psychosocial stress incidence is not much different, as well as with Alpha Receptor (ERα) Xbal where XX, Xx, and xx do not seem to be much different so researchers consider it important to analyze the interaction of polymorphisms of ERα Pvull and Xbal on psychosocial stress events as shown in Table 6 where respondents experiencing psychosocial stress most on interaction of polymorphisms of ERα Pvull and Alpha Xball homozygous recessive pp And homozygous recessive xx (50.0%). Respondents who did not experience the most psychosocial stress on the interaction of polymorphisms of ERα Pvull and Xbal homozygous dominant PP, homozygous dominant XX, heterozygote Xx, homozygous recessive xx (68.7%). No relationship between the interaction of polymorphisms of ERα Pvull and alpha Xbal with the occurrence of psychosocial stress in menopausal women.

Several animal studies have shown a direct link between estrogen physiology and serotonin, but these findings have a number of differences with each other. For example, studies on Makakus show there are mRNAs and ER-β proteins in serotonin neurons.[12–15] Immunocytochemical localization in rat and rats' brains also found the presence of labeled (and some labeled, ER-β labeled ER-α cells) in nuclear raphe neurons, although the labeled ER cells were not exactly the same as cells which releases serotonin most likely there is an interneuron connection between the two.[16]

Conclusion

There is no relationship of polymorphism of ERα Pvull with the occurrence of psychosocial stress in menopausal women. There is no correlation between ERα Xball polymorphism with the occurrence of psychosocial stress in menopausal women. There is a relationship of ERβ polymorphism with the occurrence of psychosocial stress in menopausal women. There is no interaction relationship between ERα and ERβ polymorphism with the occurrence of psychosocial stress in menopausal women.

Conflict of interest

The authors declare no conflict of interest.

References

1. Lund TD, Rovis T, Chung WC, Handa RJ. Novel actions of estrogen receptor on anxiety-related behaviors. Endocrinology. 2005;146:797–807.
2. Williams JW, Hoffman BL. Williams gynecology. 2nd ed. New York, NY: McGraw-Hill Education LLC; 2012.
3. Kemenkokesra. Usia Harapan Hidup Penduduk Indonesia. Jakarta: Kemenkokesra; 2010.
4. Alexander LL, LaRosa JH, Bader H, Garfield S, Alexander WJ. New dimensions in women's health. 6th ed. USA: Jones & Bartlett Learning; 2013.
5. Sundermann EE. A review of estrogen receptor α gene (ESR1) polymorphisms, mood, and cognition. Menopause. 2010;17:874–86.
6. Tiemeier H, Schuit SC, Heijer TD, van Meurs JB, van Tuijl HR, Hofman A, et al. Estrogen receptor alpha gene polymorphisms and anxiety disorder in an elderly population. Mol Psychiatry. 2005;10:806–7.
7. Tsai SJ, Wang YC, Hong CJ, Chiu HJ. Association study of estrogen receptor alpha gene polymorphism and suicidal behaviors in major depressive disorder. Psychiatr Genet. 2003;13:19–22.
8. Comings DE, Muhleman D, Johnson P, MacMurray JP. Potential role of the estrogen receptor gene (ESR1) in anxiety. Mol Psychiatry. 1999;4:374–7.
9. Malacara JM, Pérez-Luque EL, Martínez-Garza S, Sánchez-Marín FJ. The relationship of estrogen receptor-alpha polymorphism with symptoms and other characteristics in post-menopausal women. Maturitas. 2004;49:163–9.

10. Handa RJ, Mani SK, Uht RM. Estrogen receptors and the regulation of neural stress responses. Neuroendocrinology. 2012;96:111–8.
11. Bethea CL, Gundlah C, Mirkes SJ. Ovarian steroid action in the serotonin neural system of macaques. Novartis Found Symp. 2000;230:112–30.
12. Bethea CL, Lu NZ, Gundlah C, Streicher JM. Diverse actions of ovarian steroids in the serotonin neural system. Front Neuroendocrinol. 2002;23:41–100.
13. Bethea CL, Pecins-Thompson M, Schutzer WE, Gundlah C, Lu ZN. Ovarian steroids and serotonin neural function. Mol Neurobiol. 1998;18:87–123.
14. Rubinow DR, Schmidt PJ, Roca CA. Estrogen–serotonin interactions: implications for affective regulation. Biol Psychiatry. 1998;44:839–50.
15. Gundlah C, Lu NZ, Mirkes SJ, Bethea CL. Estrogen receptor beta (ERbeta) mRNA and protein in serotonin neurons of macaques. Mol Brain Res. 2001;91:14–22.
16. Alves SE, Weiland NG, Hayashi S, McEwen BS. Immunocytochemical localization of nuclear estrogen receptors and progestin receptors within the rat dorsal raphe nucleus. J Comp Neurol. 1998;391:322–34.