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Interaction estrogen receptor polymorphism associates with psychosocial stress on menopausal women

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Abstract

Objective: This research aimed to evaluate the interaction between polymorphisms of ER α & ER β 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 ER α and ER β receptor polymorphisms. Genomic DNA was isolated from 1 mL of EDTA anticoagulation edge blood sample using a lysis out procedure and examined interaction of polymorphisms receptors ER α and ER β . 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 ER α PvuII heterozygous Pp polymorphism, ER α XbaI homozygous recessive xx, and homozygous dominant ER β AA. There is ER β polymorphism relationship with the occurrence of psychosocial stress in menopausal women. But there is no relationship between polymorphisms ER α PvuII, ER α XbaI, as well as the interaction between polymorphisms of ER α and ER β with the occurrence of psychosocial stress in menopausal women.

Conclusion: ER β polymorphism relationship the occurrence of psychosocial stress in menopausal women

KEYWORDS: Polymorphism; estrogen receptor; psychosocial stress; menopause

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 now 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.^{1,2,3}

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 45-55 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 total life.^{3,4}

Many factors can affect estrogen levels in a woman. The activity of estrogen in the brain is mediated through activation of intracellular estrogen receptors, transmembrane and

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

Population-Based cohort research of Caucasians aged 55 and older found that XbaI 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 3 times more risk for MDD occurrence in women with homozygous P alleles than PvuII 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 ER β 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 can not be overcome, so as to cause psychosocial stress. Psychosocial stress that can not 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 ER α polymorphism and ER β 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 ER α and ER β 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 μ l of reaction mixture containing 0.2M forward prime (5'-CTGCCACCCTATCTGTATCTTT TCCTATTCTCC-3'), 0.2M reverse prime (5'-CTTTCTCTGCCACC GCGTCGATTATCTGA-3'), 0.2mM each dATP, dCTP, dGTP, dTTP, 1 \times PCR buffer, 2 mmol/l MgCl₂ and 3.5U Taq polymerase (Promega Corp., Madison, WI). The PCR reaction was performed in 30 cycles at 94°C for 30 s, 61°C for 40 seconds, and 72°C for 90 seconds (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 PvuII receptor polymorphism with psychosocial stress in menopausal women shows that respondents who experienced psychosocial stress had the most polymorphism of ER α PvuII heterozygous Pp (36.2%). While respondents who do not experience psychosocial stress most have polymorphism of ER α PvuII homozygous dominant PP (66.7%). Chi-square test results obtained p-value = 0.979 ($p < 0.05$) which shows no relationship polymorphism ER α PvuII with the occurrence of psychosocial stress in menopausal women (Table 1).

Table 1 Estimation of Estrogen Alpha PvuII Receptor Polymorphism With Psychosocial Stress In Menopausal Women.

Alpha PvuII Receptor	Psychosocial Stress				Total		p
	Yes		No		n	%	
	N	%	n	%			
PP	5	33.3	10	66.7	15	100.0	0.979*
Pp	17	36.2	30	63.8	47	100.0	
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	0.035
GA	4	22.2	14	77.8	18	100.0	
AA	9	64.3	5	35.7	14	100.0	
Total	36	35.3	66	64.7	102	100.0	

*Chi-Square Test.

Relation of beta-receptor polymorphisms with psychosocial stress in menopausal women shows that respondents experiencing psychosocial stress most had dominant homozygous ER β polymorphism AA (64.3%). While respondents who do not experience psychosocial stress, most have dominant homozygous ER β 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 ER β with the occurrence of psychosocial stress on menopausal women (Table 2).

Table 3 Relationship Interaction of Alpha PvuII Receptors, Alpha XbaI Receptors, and Beta Receptors Against Psychosocial Stress Occurrences in Menopausal Women.

Alpha PvuII Receptor + Alpha XbaI 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	0.647*
Pp,Xx,xx,GA,AA	10	43.5	13	56.5	23	100.0	
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.

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 ER α Pvull, ER α Xbal and ER β 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 ER α Pvull, ER α 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 ER α Pvull, ER α Xbal and ER β with the occurrence of psychosocial stress in menopausal women (Table 3).

Discussion

This research showed that subjects who experienced psychosocial stress have the most ER α Pvull heterozygous Pp polymorphism, ER α Xbal homozygous recessive xx, and homozygous dominant ER β AA. There is ER β polymorphism relationship with the occurrence of psychosocial stress in menopausal women. But there is no relationship between polymorphisms ER α Pvull, ER α Xbal, as well as the interaction between polymorphisms of ER α and ER β 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, ER α , and ER β . The subtypes of ER receptor are encoded by two different genes.

In this research, respondents who experienced psychosocial stress had most of the xx homozygous xx xx (38.6%) homozygous xy polymorphisms while the respondents who did not experience psychosocial stress had the most dominant XDA homozygous X α 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 ER α Pvull and ER α Xbal in this research.

In several previous studies that examined the relationship of polymorphisms of ER α 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, ER α and ER β work opposite to diverse neuron populations within or near PVN. There is some evidence supporting the regulation of neuropeptide promoters directly by ER β , such as Crh. For behavioral response, ER β seems to work through a brain circuit involving the amygdala. However, further research is needed to confirm the cellular and molecular mechanisms used by ER α and ER β to regulate the stress response.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 ER β polymorphism with stress incidence in a person are still lacking, most of which examine the relationship of ER β polymorphism with anxiety, one of which Lund TD (2005), research got anxiolytic estrogen action mediated by ER β

in mice that have been oophorectomy, These findings suggest that the anxiolytic estrogen properties are mediated by ER β .

From the result of the research, PvuII 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 (ER α) XbaI where XX, Xx, and xx do not seem to be much different so researchers consider it important to analyze the interaction of polymorphisms of ER α PvuII and XbaI on psychosocial stress events as shown in table 6 where respondents experiencing psychosocial stress most on interaction of polymorphisms of ER α PvuII and Alpha XbaI homozygous recessive pp And homozygous recessive xx (50.0%). Respondents who did not experience the most psychosocial stress on interaction of polymorphisms of ER α PvuII and XbaI homozygous dominant PP, homozygous dominant XX, heterozygote Xx, homozygous recessive xx (68.1%). No relationship between the interaction of polymorphisms of ER α PvuII and alpha XbaI 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.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 ER α PvuII with the occurrence of psychosocial stress in menopausal women. There is no correlation between ER α XbaI polymorphism with the occurrence of psychosocial stress in menopausal women. There is a relationship of ER β polymorphism with the occurrence of psychosocial stress in menopausal women. There is no interaction relationship between ER α and ER β polymorphism with the occurrence of psychosocial stress in menopausal women.

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