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Estrogen effect to expression of calcitonin gene related peptide, protein gene product 9.5, and tyrosine hydroxylase in vaginal epithelial mucous of wistar mouse with ovariectomy bilateral



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ABSTRACT

Background: To know role of CGRP, PGP 9.5, and TH to pathogenesis mechanism of change in vaginal epithelial mucous of Wistar mouse with decreases estrogen level.

Method: Randomized posttest only control group design. Treatment group is wistar mouse post bilateral ovariectomy that given estrogen. Control group is wistar mouse post bilateral ovariectomy that not given estrogen.

Results: We use 34 sample of Wistar mouse (*Rattus norvegicus*) and divided further to 2 group of 17 treatment mouse and 17 control group.

We analyzed expression CGRP, PGP 9.5, and TH in both group. It shown CGRP expression in control group significantly different compared with treatment group, PGP 9.5 expression in control group higher compared to treatment group, TH expression of control group higher compared to treatment group.

Conclusion: Estrogen decreased expression of CGRP, PGP 9.5, and TH. CGRP is the most affected by estrogen compared to PGP 9.5 and TH.

Keyword: Bilateral ovariectomy, Estrogen, CGRP, PGP 9.5, TH.

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INTRODUCTION

Bilateral ovariectomy is procedure of ovarian removal by laparotomy with specific indication. This procedure will affect decreased estrogen level that lead to menopause. Furthermore, Menopause is women's health problem related to anatomical and physiology of vaginal mucose. Menopause cause thinning of vaginal mucose dispareunea, decreased vaginal lubrication, and subjective complaint like emotional instability, night sweat, heat, insomnia, palpitation and low focus.

Estrogenic effect to vagina were vaginal dryness, loss of elasticity, irritation, hyperalgesia, dispareunia. Because of decreased in estrogen, it have direct effect to target cell in vagina. Estrogen receptors are abundant in the vagina, and estrogen stimulates proliferation of epithelial cells in the vagina and remodeling of blood vessels. Therefore, the decrease in estrogen levels causes vaginal dysfunction.¹

Various attempts have been made to relieve complaints and symptoms related to the hormonal deficit, either through the topical and systemic therapy with hormone replacement therapy. But the results are still not satisfactory and even controversial. In addition, topical therapy success also depends on the accuracy of the dose for therapeutic

targets is directly on epithelial cells; not the controller activates protein. Additionally, estrogen is also thought to be carcinogenic.^{2,3}

Mechanism of action of estrogen involve protein gene product 9.5 (PGP 9.5) contained in nerve tissue, post-translational proteolytic function in collaboration with CGRP-like immunoreactivity with a lot of nerve fibers supporting blood vessels and nonvascular smooth muscle. Mechanism of action of estrogen also involves TH where genes are located on the short arm of chromosome 11p15.5 consisting of 10k base pairs.^{4,5,6}

Mechanism of action of estrogen in hormone replacement therapy are unclear and allegedly involving nerve. Hormone replacement therapy itself is using for a long term even decades during menopause so it could potentially cause other health problems such as increased risk of cancer, infections, anxiety and depression.³ That's why research on CGRP, PCG 9.5, and TH in relation to the mechanism of action of estrogen in connection with the anatomy and physiology of the vagina, especially the structure and integrity of the vaginal mucosa.

It takes molecular level study to improve effectiveness and minimize the risk of long-term estrogen

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use. Furthermore, is expected to explain the mechanism of action of estrogen and its relationship with clinical symptoms, especially in the vagina. If it can be proven the role of CGRP, PGP 9.5 and TH on the results of this research will be able to explain how the new mechanism of steroid hormone estrogen on the vaginal anatomy and physiology. The mechanism mainly involving innervation, vascularization and psychological. This research can then also be used as a data further research in humans either menopause or andropause, in addition to determining the bio-molecular indicators for the prediction, diagnosis and therapy in conditions of low estrogen levels; especially at menopause.

METHOD

This study design is randomized post test only control group design. The treatment group was post ovariectomy bilateral mice given estrogen. The control group was post ovariectomy bilateral mice that were not given estrogen bilateral

RESULTS

In this study is used as much as 34 Wistar rats (*Ratus norvegicus*) and the samples are divided into two

groups each totaling 17 rats treated group and the control group of 17 mice. Further discussion will describe the expression of CGRP relationship, PGP 9.5 and TH in the treatment group and the control.

Test above shows that the expression of CGRP in the control group significantly different compared to the treatment group.

Test above shows that the expression of PGP 9.5 in the control group higher compared to the treatment group.

Test above shows that the expression of TH in the control group higher compared to the treatment group.

DISCUSSION

Blacklock et al (2004) get the results in different studies where it was said that after ovariectomy and then given estrogen increased nerve fibers containing CGRP, this means that a proliferation of nerves during the administration of estrogen.⁷ On this study, the expression of CGRP in the control group significantly different compared to the treatment group. Estrogen administration significantly decreased the expression of CGRP in rat vaginal mucosa epithelium. In this study were also compared between the control and treatment groups with the normal group, namely the group of mice that did not do ovariectomy and are not given estrogen with the results of an increase of 0.04 times between the control and the normal group. There's no difference between the treatment group and the normal group. This is consistent with the theory that after ovariectomy there will be an increase in the expression of CGRP and then given estrogen after the expression of CGRP is going down.⁸

Research by Elena et al (2000) and Qin Fan et al (2000) found decreased expression of PGP 9.5 when given estrogen and increased expression of PGP 9.5 when not given estrogen. The basis of this is said to be unclear. The possibility that the case is the occurrence of degenerative and regenerative. Axonal degenerative occurs when the continuity with the cell body disturbed, but other things can also be influential. The structural changes related neurodegenerative said to occur in the uterus during pregnancy, supports the possibility that the degeneration related to some form of nerve remodeling. This reflects the normal variations that will be followed by a phase of nerve degeneration restoration and regeneration of nerve fibers. Another thing that may happen is the retraction of nerve fibers. This retraction is normal during development and in adult animals. It said nerve retraction is associated with reduced nerve growth.^{9,10}

It was found the expression of PGP 9.5 in the control group higher compared to the treatment

Table 1 Mean Expression of CGRP relationship in Treatment Group and Control

Subject Group	n	Mean Expression of CGRP	SD	t	p
Control	17	23,102	0,291	3,774	0,001
Treatment	17	21,984	0,519		

Note: *t-independent test*

Table 2 Comparison of PGP 9.5 Relationship in Treatment Group and Control

Group	PGP 9.5 Expression		χ^2	p
	High	Low		
Treatment	5	12	12,14	0,001
Control	15	2		

Note: *chi-square test*

Table 3 Comparison of TH relationship in Treatment Group and Control

Group	TH Expression		χ^2	p
	High	Low		
Treatment	6	11	12,88	0,001
Control	16	1		

Note: *chi-square test*

group. Estrogen administration significantly decreased the expression of PGP 9.5 in the vaginal mucosa epithelium. In this study were also compared between the control and treatment groups with the normal group, namely the group of mice that did not do ovariectomy and are not given estrogen with the results of an increase of 0.06 times between the control group and the normal group and no difference between the treatment group and the normal group. This is consistent with the theory that after ovariectomy there will be an increase in the expression of PGP 9.5 and later given estrogen after the expression of PGP 9.5 will go down.⁸

Research by Ting et al (2005) found that ovariectomy in animal experiments increase expression of TH. TH relatively little in animal experiments but can raise significantly when the levels decline after ovariectomy. Sympathetic axons releasing norepinephrine cause smooth muscle contraction, vasoconstriction and increase vaginal muscle tone. Finally increase of sympathetic nerve fibers in low estrogen state causes a decrease in blood flow and a decrease in lubrication. This is consistent with the vasoconstriction, decreased blood flow, decreased lubrication in menopause and after ovariectomy surgery in humans and experimental animals. Estrogen causes a decrease in the expression of TH and reduced complaints occur.¹ It was found TH expression in the control group higher compared to the treatment group. Estrogen administration significantly decreased the expression of TH in vaginal mucosa epithelium. In this study were also compared between the control and treatment groups with the normal group, namely the group of mice that did not do ovariectomy and are not given estrogen with the results of an increase of 0.04 times between the control group and the normal group and no difference between the treatment group and the normal group. This is consistent with the theory that after ovariectomy there will be an increase in the expression of TH and after given estrogen the expression of TH is going down.⁸

CONCLUSION

Expression of CGRP in the vaginal mucosa epithelium of Wistar rats were performed ovariectomy in the treatment group were given estrogen lower than the control group who were not given estrogen.

Expression of PGP 9.5 in the vaginal mucosa epithelium of Wistar rats were performed ovariectomy in the treatment group were given estrogen lower than the control group who were not given estrogen.

TH expression in vaginal mucosa epithelium of Wistar rats were performed ovariectomy in the treatment group were given estrogen is lower compared to the control group who were not given estrogen.

Expression of CGRP most affected by administration of estrogen in the treatment group compared with PGP 9.5 and TH expression in the same group.

SUGGESTION

Further research in humans to see if ovariectomy and estrogen administration will give the same effect.

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