Effects of Estrogen Deprivation on Depressive-Like Behavior and Noradrenergic Neurotransmitters in Ovariectomized Rats

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Background: *The rate of depression increases in menopausal women. Possible reasons may involve the effects of ovarian steroid hormones, including estrogen, on the function of the brain.*
Objective: *This study aimed to investigate the effects of long-term estrogen deprivation on depressive-like behavior and noradrenergic neurotransmitters in the brain areas involved in the regulation of emotional behavior.*
Material and Method: *Adult female Wistar rats were ovariectomized and randomly assigned into 2 groups, ovariectomized (Ovx) rats and Ovx rats treated with estrogen (E2) (10 μg/kg BW, subcutaneously into the dorsal region of the neck, once daily). Four weeks after ovariectomy, the rats were tested in open field and forced swim tests. After the behavioral tests, their brains were removed for measurement of norepinephrine (NE) and 3-methoxy-4-hydroyphenylglycol (MHPG) levels.*
Results: *Four weeks after ovariectomy, the Ovx rats showed longer immobility time in the forced swim test than the E2 rats. NE levels in the hippocampus and the adrenal gland weights tend to be increased after ovariectomy.*
Conclusion: *Long-term estrogen deprivation for four weeks promoted depressive-like behavior in female Wistar rats and also altered NE levels in the hippocampus. This finding indicated that long-term estrogen deprivation alters noradrenergic neurotransmission and the HPA axis.*

Keywords: *Depression, Estrogen, Forced swim test, Ovariectomized-rat*

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Depressive illness is a major psychological disorder affecting people around the world, with an approximation of 5.5-5.9% of the world's population having the symptoms[1]. The prevalence rates of depressive patients in Thailand were found to be 345.08 people per 100,000 population[2]. Consideration by gender showed that 20% of women suffer from depression compared to 10% of men[3]. Some studies found that the onset of major depression may increase after menopause and estrogen (E2) replacement can alleviate this symptom[4]. This may imply that decreased estrogen levels contribute to increased depression in this age group. Therefore, possible mechanisms may be involved in the different mood-related effects of steroid hormones on neurotransmitters and enzyme functions in depressive persons.

The classical hypothesis of depression is that it arises from a functional deficit of norepinephrine (NE) in the brain that is involved in mood regulation, including the hippocampus, amygdala, frontal cortex, and hypothalamus[5]. Several studies showed that depletion of NE leads to depressogenic effects[6,7]. These results are consistent with the effects of antidepressant drugs, including tricyclic antidepressants, selective NE reuptake inhibitors, serotonin, NE reuptake inhibitors, monoamine oxidase inhibitors, and miscellaneous antidepressants, which work by blocking the reuptake mechanism, leading to an increase in NE in the synaptic terminal and improve the depressive symptom[8]. However, the selective NE reuptake inhibitor has an effect in some but not all cases[9]. Some studies reported that depletion of the catecholamine in control volunteers does not promote a depressed mood[10]. These findings indicated the involvement of NE neurotransmission in depression. However, alterations of noradrenergic

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neurotransmission in depressive disorders are unclear. Abnormalities in noradrenergic function in depression may be the result of varied processes, including deficient innervations to key structures or cellular mechanisms resulting in abnormal neurotransmission.

Many reports found a relationship between estrogen and the noradrenergic system[11,12]. Estradiol can modulate the activity of the noradrenergic system in basal condition. For example, estradiol-elevated tyrosine hydroxylase (TH) and/or dopamine β-hydroxylase (DBH) mRNA levels in the locus coeruleus (LC) and adrenal medulla of ovariectomized (Ovx) rats[12,13]. Ovariectomy in adult rhesus monkeys produced a net increase in the DBH mRNA levels in the pre-frontal cortex and estrogen replacement can reverse the effect[14]. These results indicated that alteration of estrogen affects the function of noradrenergic neurotransmission and may have contributed to depression.

This study aimed to investigate the effects of long-term estrogen deprivation on depressive-like behavior and noradrenergic neurotransmission in brain areas related to depression.

Material and Method

Animals

Female Wistar rats weighing 170-190 gm at the beginning of the experiments were obtained from the National Laboratory Animal Center, Mahidol University (NLAC-MU), Thailand. All animals were housed in pairs per cage under 12 h light/dark cycles (lights on at 06.00 h) at room temperature (25±2°C). Standard rat chow and water were supplied ad libitum. Body weights and food intakes were measured daily and uterine weights were determined on the day of sacrifice. After a 7-day adaptation period, each rat was anesthetized with isoflurane and both ovaries were removed. For the E2-treated rats, a replacement regimen was started 1 day after ovariectomy by injecting 17β-estradiol (10 μg/kg) subcutaneously into the dorsal region of the neck, once daily for four weeks. In the Ovx group, rats were injected by an equivalent volume of propylene glycol. Each rat was tested by a forced swim test at four weeks after ovariectomy to measure depression levels.

All procedures were done according to the National Institutes of Health Guide for the Care and Use of Laboratory Animals and with the approval of the Animal Use Committee, Faculty of Veterinary Science, Chulalongkorn University (Protocol numbers 1531015).

Measurement of body weights, food intakes, uterine and adrenal gland weights

Body weights and food intakes of the animals were determined daily. Uterine weights, used as an indirect parameter of estrogen deficiency and replacement, were determined immediately after sacrifice. The left and right adrenal gland were weight, used as classical indices of chronic stress via Hypothalamic-Pituitary-adrenal gland (HPA) axis and also determined immediately after sacrifice.

Behavioral assessments

1) Forced swim test

The forced swim test was used in accordance with the methods described by Frye and Walf [15]. The apparatus was a cylindrical container (40 cm depth, 27 cm in diameter) filled with water (23-25°C) to a depth of 19.6 cm. The rats were placed in the cylindrical container for 5 min. The amount of time the rats spent immobile was recorded and considered to be a measure of depressive-like behavior. Swimming was defined as movement of the forelimbs and hind limbs without the front paws breaking the surface of the water. Immobility was counted when there was absence of any movement other than that necessary to keep the head and nose above the water when rats were floating in a vertical position. The experiments were conducted between 09.00 and 12.00 h and recorded using a video camera for later analysis.

2) Open field test

The open field was used to assess the effects of drugs on the motor activity of the rats. After the forced swim test, the animals were tested in an open field for 5 min to measure their locomotive activity. The open field was a wooden box (76 cm long x57 cm wide x35 cm high) with a 48-square grid floor (6x8 squares, 9.5 per side). The test was used in accordance with the methods described by McCarthy et al[16]. The numbers of total crosses that the rats made during the 5 min in this task were recorded as the locomotive activity. The experiments were recorded by a video camera for later analysis.

3) Norepinephrine analysis

Following day after behavioral test, all rats were sacrificed and their brains were removed, frozen in the liquid nitrogen and stored at -80°C. The midbrain, amygdala, frontal cortex and hippocampus were isolated in all groups from frozen brain following the instructions of Heffner et al[17]. The isolated brains were sonicated

in cold 0.1 M perchloric acid containing 3, 4-dihydroxy-benzyl-amine hydrobromine (DHBA) as an internal standard. Thereafter, samples were centrifuged at 5,000 g for 30 min at 4°C. The supernatants were collected for analysis of norepinephrine (NE) and its metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) neurotransmitters using HPLC with an electrochemical detector (HPLC-EC) (sensitivity 2 nA and oxidative potential +0.70 V).

HPLC-EC

HPLC-EC, a glassy carbon working electrode, and amperometric control (Bioanalytical systems, West Lafayette, IN, USA) were used to quantify neurotransmitter levels. A Shimadzu Model LC-10 AD pump (Kyoto, Japan) was connected to a Rheodyne (Cotati, CA, USA) injector, equipped with a 20 µl fixed loop and a 15-cm phenomenex® column packed with 5-µm particles. The mobile phase solution was composed of 1 mM Heptane sulfonate, 100 mM Sodium dihydrogen phosphate, 1 mM Na2-EDTA, and 5% Methanol, adjusted to pH 4.1 with saturated citric acid. The mobile phase was filtered through a 0.22-µm filter, degassed by ultrasonic agitation, and pumped at a flow-rate of 1 ml/min. The supernatant (40 µl) from the brain was injected into the HPLC-EC system to detect NE and its metabolites, 3-methoxy-4-hydroxy-phenylglycol (MHPG), respectively.

Analytical procedures

Standard solutions at concentrations were injected into the HPLC system. The retention time was evaluated by injecting the standard NE and its metabolites individually and by the injection of a standard mixture. The concentrations of transmitters and metabolites were calculated by reference to an internal standard using peak integration and wet weigh of brain tissue samples and expressed as ng/g tissue. The turnover rate (activity) of noradrenergic system was expressed as ratio of MHPG/NE.

Data analysis

All data were presented as means and standard errors of mean (SEM). Student's unpaired t-test was used for comparison between the 2 groups. Differences were considered statistically significant at $p<0.05$.

Results

Effects of estrogen deficiency on body weights, food intakes, and uterine weights

At the beginning of the experiment, the body weights of the two groups of the rats were not different ($p = 0.9333$) (Table 1). Four weeks after ovariectomy, the average body weight of the vehicle treated-Ovx rats was higher than that of the 17β-estradiol treated rats (E2, 10 µg/kg) ($p<0.0001$) (Table 1). Further, the average weight gain and the percent change of body weight in the Ovx rats were also higher than those of the E2 rats ($p<0.0001$) (Table 1). The average daily feed intake (DFI) in the Ovx rats was more than that of the E2 rats ($p<0.001$) (Table 1).

The lack of ovarian hormones was confirmed by the reduction in average uterine weight (UW) and the ratio of uterine weight to body weight (% UW/BW) in the Ovx rats ($p<0.0001$) (Table 1).

Adrenal gland weight

Average adrenal gland weight and the ratio of adrenal gland to body weight (% ADW/BW) were

Table 1. Body weights, percent changes of body weights, daily feed intakes, uterine weights, and ratios of uterine weights to body weights of the ovariectomized rat treated with either vehicle (Ovx) or 17β-estradiol at the dosage of 10 µg/kg (E2)

Parameters	Ovx	E_2 (10 µg/kg)	*p*-value
Beginning weight (g)	184.50±2.13	185.00±1.97	0.9333
End weight (g)	277.75±2.22	227.50±3.03***	<0.0001
Weight gain (g)	93.25±2.84	42.50±2.14***	<0.0001
Percent change of body weight	50.71±1.99	22.99±1.16***	<0.0001
Daily feed intake (g/d)	15.21±0.19	13.62±0.27**	0.0001
Uterine weight (g)	0.112±0.007	0.442±0.015***	<0.0001
Ratio of uterine to body weight	0.040±0.003	0.194±0.006***	<0.0001

Data presented as mean ± SEM, **$p<0.005$ and ***$p<0.0001$, significantly different from corresponding Ovx groups using Student's unpaired t-test, n = 10 in each group.

Table 2. Adrenal gland weights, percent of adrenal gland weights to body weights (%AGW/BW), brain weights, percent adrenal gland weights to brain weights of the ovariectomized rats treated with either vehicle (Ovx) or 17β-estradiol at the dosage of 10 μg/kg (E2)

Parameters	Ovx	E_2 (10 μg/kg)	*p*-value
Adrenal gland weight (g)	0.093±0.002	0.083±0.004*	0.0341
% AGW/BW	0.033±0.0008	0.036±0.001	0.0844

Data presented as mean ± SEM, *p<0.05, **p<0.005 and ***p<0.0001, significantly different from corresponding Ovx groups using Student's unpaired t-test, n = 10 in each group.

measured as classical indices of chronic activation of HPA axis. After the lack of ovarian hormones for 4 weeks, the average adrenal gland weight in the Ovx rats was higher than that of the E2 rats (p<0.05). However, the ratio of adrenal gland to body weight was not different between the groups (p>0.05) (Table 2).

Depression-like behaviors in the force swim test

The depression levels of the Ovx rats as measured by the forced swim test are shown in Fig. 1. It can be observed that the Ovx rats significantly increased immobility time (p<0.05) with a concomitant decrease in swimming behavior (p<0.05) and no change in climbing (p>0.05).

The locomotive activity, the total number of lines crossed in the open field test during 5 min, was not different between the groups (p>0.05; Fig. 2), indicating that the behaviors seen in the forced swim test were not affected by treatments.

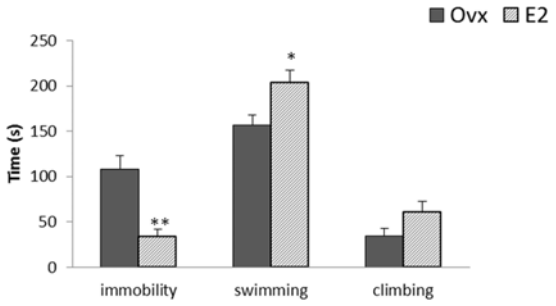

Fig. 1 Immobility, swimming, and climbing in forced swim test of the ovariectomized rats treated with either vehicle (Ovx) or 17β-estradiol (E2). Data presented as mean ± SEM, * p<0.05 and ** p<0.005, significantly different from corresponding Ovx groups using Student's unpaired t-test, n = 10 in each group.

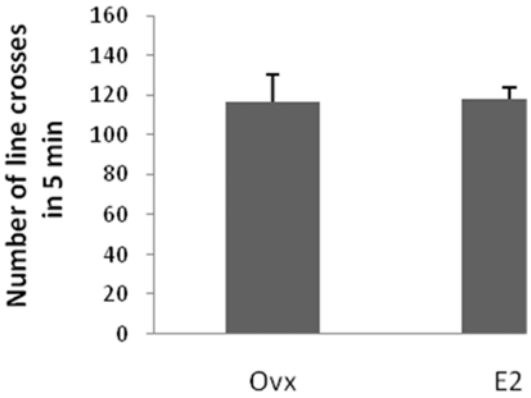

Fig. 2 Number of 5 minute-line crossings in the open field of the ovariectomized rats treated with either vehicle (Ovx) or 17β-estradiol (E2). Data presented as mean ± SEM, * p<0.05, significantly different from corresponding Ovx groups using Student's unpaired t-test, n = 10 in each group.

Effects of estrogen deprivation on noradrenergic activity in the brain associated with depression

After the behavioral tests, the rat's brains were removed for measurement of NE and its metabolite MHPG by the HPLC technique. The results of NE and MHPG levels after estrogen deprivation are summarized in Table 3. In the hippocampus, the levels of NE in the estrogen-treated group were significantly lower than the ovariectomized group, while the levels of MHPG and MHPG/NE ratio were not different between the groups. In the amygdala, frontal cortex, and midbrain, the levels of NE, MHPG, and MHPG/NE ratio were not different between the groups.

Discussion

The study found that the Ovx rats showed increases in immobility time, adrenal gland weight, and NE levels in the hippocampus compared to the E2 rats. These results indicated that long-term estrogen deprivation for four weeks can induce depressive-like behavior in female rats. Increased adrenal gland weight

Table 3. Effects of estrogen deprivation on NE, MHPG levels, and MHPG/NE ratio in amygdala, frontal cortex, hippocampus, and midbrain. Data presented as mean ± SEM, * $p<0.05$ significantly different from Ovx group, unpaired t-test.

Structure	Ovx	E2	*p*-value
Amygdala			
NE	4.03±0.64	3.25±0.40	0.3280
MHPG	12.93±8.06	5.78±1.76	0.4064
MHPG/NE	2.46±1.08	2.34±0.98	0.9403
Frontal cortex			
NE	2.55±0.17	2.00±0.29	0.1225
MHPG	8.60±3.99	5.68±1.48	0.5419
MHPG/NE	3.03±1.15	3.22±0.96	0.9045
Hippocampus			
NE	4.15±0.36	2.49±0.53	0.0249*
MHPG	6.75±2.59	6.69±3.81	0.9902
MHPG/NE	1.54±0.51	3.10±1.45	0.3032
Midbrain			
NE	3.65±0.63	2.66±0.75	0.3353
MHPG	11.19±5.15	4.98±1.91	0.3246
MHPG/NE	2.54±0.67	4.27±2.62	0.5045

and NE levels in the Ovx rats may indicate the activity of the HPA axis and LC/NE system which may imply that estrogen deprivation results in the Ovx rats being more stressed than the E2 rats.

Several studies reported that depressive-like behaviors as indicated by use of the forced swim test and tail suspension test were observed in rodents after ovariectomy for 1-5 weeks[18-20]. However, Estrada-Camarena et al[21] found that only one week but not 3 or 12 weeks after ovariectomy can induce depressive-like behavior in mice. In the current study, the depressive-like behaviors were found at four weeks after ovariectomy. These inconsistent findings may be due to differences in the behavioral test periods. Therefore, the present study's findings indicated that a long-term lack of estrogen can induce depressive-like behavior in female rats. However, the development of depressive-like behavior may depend on animal species/strains, behavioral test paradigms, and test periods that may affect the brain function.

The limbic system, including amygdala, hippocampus, and frontal cortex, is involved in the regulation of emotional behavior and the regulation of the HPA axis response to stress. In addition, there is information indicating that the limbic system is innervated by the noradrenergic system. The present study revealed that long-term ovariectomy elevated the NE levels in the hippocampus but the MHPG and MHPG/NE ratio were not different to the E2 group. However, the levels of NE, MHPG, and MHPG/NE ratio in amygdala, frontal cortex and midbrain did not change. The present study's results were consistent with a previous study involving this experiment[22]. Pandaranandaka et al[22] showed that NE levels in the caudate putamen increased four weeks after ovariectomy. On the other hand, Bowman et al[23] reported that levels of NE in the hippocampus decreased 21 days after ovariectomy. These results indicated that time after ovariectomy may differently affect the function of neurotransmission in the brain. Evidence in both clinical and animal studies showed that the noradrenergic system has a role in modulating affective disorder. Patients who received an α2-adrenergic receptor antagonist had increased levels of NE in the synapse, which may initiate anxiety[24]. On the other hand, administration of an α2-adrenergic receptor agonist produced less anxiety[25]. Therefore, it may be concluded that increased activity of the noradrenergic system may lead to affective behavior, which may cause depression disorders. Not surprisingly, in the present study, the Ovx rat showed a more depressed state than the E2 rats and had higher levels of NE in the hippocampus. These findings indicated that estrogen deprivation alters the noradrenergic system in the brain and may lead to depression.

Conclusion

Long-term estrogen deprivation for four weeks promotes depressive-like behavior in female Wistar rats

as shown by increased immobility time in the forced swim test and altered NE levels in the hippocampus.

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What is already known on this topic?

Previous studies reported that the estrogen hormone may be involved in depression disorders in both animal and clinical studies. Some studies showed the alteration of the noradrenergic system to be associated with depression disorders.

What this study adds?

This study found that long-term estrogen deprivation for four weeks can promote depressive-like behavior in female Wistar rats and it also increased NE in the hippocampus. The enlargement of adrenal gland in the Ovx rats suggested alteration in the HPA axis activity after ovariectomy as indicated by the increase in the adrenal gland weight. These results indicated that estrogen deprivation increases the activity of the HPA axis and noradrenergic activity, which may lead to increased levels of depression.

Potential conflicts of interest

None.

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ผลของการขาดเอสโตรเจนต่อพฤติกรรมซึมเศร้าและสารสื่อประสาทนอร์อีพิเนฟรินในหนูแรทที่ถูกตัดรังไข่

สุวภรณ์ แดนดี, จารุวรรณ์ วงบุตดี, ปรารถนา โฉมเฉลา, รัตติยา ทองรุ่ง, วัลวิสาข์ สุวรรณเลิศ, สฤณี กลันทกานนท์ ทองทรง

ภูมหลัง: เพศหญิงมีอัตราการเกิดภาวะซึมเศร้าเพิ่มขึ้นเมื่อหมดประจำเดือน ซึ่งกลไกการเกิดเชื่อว่าน่าจะเกี่ยวข้องกับผลของฮอร์โมนเพศจากรังไข่รวมทั้งเอสโตรเจนต่อการทำงานของสมอง

วัตถุประสงค์: เพื่อศึกษาผลของการขาดฮอร์โมนเอสโตรเจนเป็นระยะเวลานานต่อพฤติกรรมซึมเศร้าและสารสื่อประสาทนอร์อีพิเนฟริน ในสมองส่วนที่เกี่ยวข้องกับการเกิดพฤติกรรมอารมณ์

วัสดุและวิธีการ: หนูเพศเมียพันธุ์ Wistar ที่ถูกตัดรังไข่นำมาแบ่งเป็น 2 กลุ่ม คือ 1) กลุ่มที่ถูกตัดรังไข่และ 2) กลุ่มตัดรังไข่แล้วได้รับฮอร์โมนเอสโตรเจนทดแทนที่ขนาด 10 ไมโครกรัมต่อน้ำหนักตัว 1 กิโลกรัม เป็นเวลา 4 สัปดาห์ เมื่อครบกำหนด ทำการทดสอบพฤติกรรมซึมเศร้าโดย forced swim test (FST) และ open field test หลังทดสอบพฤติกรรมทำการเก็บสมองเพื่อวัดระดับสารสื่อประสาทนอร์อีพิเนฟรินและ MHPG

ผลการศึกษา: ภายหลังตัดรังไข่ 4 สัปดาห์ ในการทดสอบ FST หนูกลุ่มที่ถูกตัดรังไข่ใช้เวลาอยู่นิ่ง (immobility time) นานกว่าหนูที่ได้รับฮอร์โมนเอสโตรเจนทดแทน แสดงว่าหนูที่ถูกตัดรังไข่มีระดับความซึมเศร้ามากกว่าหนูที่ได้ฮอร์โมนทดแทน เมื่อวัดระดับสารสื่อประสาทนอร์อีพิเนฟรินพบว่ามีระดับสูงขึ้นในสมองส่วน hippocampus นอกจากนี้ต่อมหมวกไตในหนูที่ตัดรังไข่มีแนวโน้มขนาดโตกว่าหนูที่ได้รับฮอร์โมนเอสโตรเจนทดแทน แสดงให้เห็นว่า HPA axis มีการทำงานเพิ่มขึ้น

สรุป: การขาดฮอร์โมนเอสโตรเจนเป็นเวลานาน 4 สัปดาห์ มีผลทำให้เกิดพฤติกรรมซึมเศร้าในหนูแรทพันธุ์ Wistar และทำให้มีการเปลี่ยนแปลงของสารสื่อประสาทนอร์อีพิเนฟรินในสมองส่วนที่เกี่ยวข้องกับการเกิดพฤติกรรมอารมณ์ ผลการทดลองแสดงให้เห็นว่าการขาดเอสโตรเจนเป็นเวลานานมีผลทำให้เกิดการเปลี่ยนแปลงของสารสื่อประสาทนอร์อีพิเนฟรินและ HPA axis ซึ่งอาจจะเป็นปัจจัยหนึ่งที่ทำให้เกิดภาวะซึมเศร้าในหญิงที่หมดประจำเดือน