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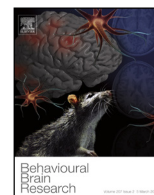

Research report

Inflammation and increased IDO in hippocampus contribute to depression-like behavior induced by estrogen deficiency

Yongjun Xu [a,1], Hui Sheng [a,1], Zhiping Tang [b], Jianqiang Lu [b,*], Xin Ni [a,*]

[a] Department of Physiology, Second Military Medical University, 800 Xiangyin Road, Shanghai 200433, China
[b] School of Kinesiology, The key Laboratory of Exercise and Health Sciences of Ministry of Education, Shanghai University of Sport, 399 Changhai Road, Yangpu District, Shanghai 200438, China

HIGHLIGHTS

- Estrogen ameliorates depression-like behavior in ovariectomized rats.
- Ovariectomy results in increased IDO expression and decreased 5-HT in hippocampus.
- Ovariectomy increases TLR-4 expression and inflammation in hippocampus.
- Serum E_2 level correlates to phosphorylated p65, IFN-γ and IL-6 in hippocampus.

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ABSTRACT

Estrogen deficiency is involved in the development of depression. However, the mechanism underlying estrogen modulates depression-like behavior remains largely unknown. Inflammation and indoleamine-2,3-dioxygenase (IDO) have been shown to play pivotal roles in various depression models. The objective of the present study was to investigate whether estrogen deficiency-induced depression-like behavior is associated with inflammation and IDO activation in brain. The results showed that ovariectomy resulted in depression-like behavior in female rats and caused a decrease in 5-HT content and an increase in levels of IDO, IFN-γ, IL-6, toll like receptor (TLR)-4 and phosphorylated NF-κB (p65 subunit) in hippocampus but not in prefrontal cortex (PFC). 17β-Estradiol (E_2) treatment ameliorated depression-like behavior and restored above neurochemical alternations in hippocampus in ovariectomized rats. Partial correlation analysis showed that the levels of phosphorylated p65, IFN-γ and IL-6 in hippocampus correlated to serum E_2 level. Our study suggests that estrogen inhibits inflammation and activates of IDO and maintains 5-HT level in hippocampus, thereby ameliorating depression-like behavior.

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1. Introduction

Depression is a commonly-occurring, debilitating, and life-threatening psychiatric disorder. Interestingly, it was found that women may be more vulnerable to develop depression disorders than men, with the prevalence being approximately 2–3 times higher in women [1]. Moreover, among the patients with depression, depressive episodes are more protracted and recur more frequently in women than in men [2]. The gender difference in the development of depressive disorders is attributed to, at least in part, sex hormones [1,3,4].

The effects of estrogen on mood and emotion have well been documented. For example, it has been demonstrated that menopausal reduction in circulating estrogen levels are associated with an increase in mood disturbances, including symptoms of anxiety and depression in women [5]. Administration of estrogen sufficiently improves depressive symptoms, which meets the definition of clinical recovery [6]. Rodents show increased depression-like behavior during the diestrus phase of the estrous cycle when the level of estrogen is low [7]. Ovariectomy in rats elicits a reliable increase in depression-like behavior, which can be

Abbreviations: 5-HT, serotonin; ACTH, corticotrophic hormone; BDNF, brain derived neurotrophic factor; CORT, corticosterone; E_2, 17β-estradiol; ERs, estrogen receptors; HPA, hypothalamic–pituitary–adrenal; IDO, indoleamine-2,3-dioxygenase; IFN-γ, interferon-γ; IL, interleukin; KYN, kynurenine; MDD, major depressive disorder; MyD88, myeloid differentiation factor 88; NF-κB, nuclear factor-kappaB; OVX, ovariectomized; OFT, open field test; p-p65, phosphorylated p65; PFC, prefrontal cortex; TLR-4, toll like receptor-4; TNF-α, tumor necrosis factor-α; TRP, tryptophan.

* Corresponding author. Tel.: +86 21 51253318; fax: +86 21 81870978.
E-mail addresses: lujianqiang@sus.edu.cn, lujianqiang@medmail.com.cn (J. Lu), nixin@smmu.edu.cn (X. Ni).

[1] Both the authors contributed equally to this work.

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reversed by administration of estrogen [8]. Together, it suggests that estrogen is involved in the development of depression. However, the mechanism by which estrogens regulate depression-like behavior remains largely unknown.

Recently, neuroinflammation is viewed as central to the development of depressive symptoms in some cases [9]. Some studies has demonstrated that neuroinflammation in some depression models is characterized by the activation of toll like receptor (TLR)-4 and downstream nuclear factor-kappaB (NF-κB), and the release of proinflammatory cytokines [10,11]. Gárate et al. [11] have shown that TLR-4 signaling pathway is activated in brain cortex of the rats exposed to a model of depression, with increased levels of the proinflammatory cytokines. The study by Goshen et al. [12] have shown that mice subjected to chronic mild stress exhibits depression-like behavior, with increased interleukin(IL)-1β level in the hippocampus. Additionally, postmortem gene analyses of major depressive disorder (MDD) patients have suggested an upregulation of a variety of proinflammatory cytokines in the prefrontal cortex (PFC) [13]. Although the association between depression and neuroinflammation is established [14,15], the specific mechanisms by which activation of the neuroinflammation and appearance of specific depressive symptoms are poorly understood.

Recently evidence implicates that proinflammatory cytokines can cause impaired serotonergic systems [16,17] and hypothalamic–pituitary–adrenal (HPA) axis hyperactivity [18]. The enzyme indoleamine-2,3-dioxygenase (IDO) could be a potential link between inflammatory processes and serotonergic systems [17]. IDO can be induced by proinflammatory cytokines and functions as a catalyst to degrade tryptophan (TRP) into kynurenine (KYN) [18]. The depletion of TRP, in turn, can reduce the production of serotonin (5-HT) in brain [19]. Overexpression of IDO leads to depletion of plasma TRP and reduces synthesis of 5-HT in the brain, which may eventually induce depression [20], while inhibition of IDO abrogates depression-like behavior induced by acute or chronic inflammation [21]. Besides impaired 5-HT system in brain, excessive activation of HPA axis also contributes to development of depression [22]. As mentioned, proinflammatory cytokine-induced activation of IDO may contribute to HPA axis hyperactivity in depression [18].

Estrogen has been shown to inhibit inflammatory response in brain [23]. We therefore hypothesized that estrogen deficiency leads to increased inflammatory state in brain, in turn activates IDO and then reduces 5-HT production, thereby leading to depression-like behavior. To test it, we examined the depression-like behavior in ovariectomized (OVX) rats and OVX rats with 17β-estradiol (E_2) replacement. Since hippocampus and PFC are critical for modulation of emotion, 5-HT, IDO contents, levels of proinflammatory cytokines, and TLR-4 and NF-κB expression in these brain regions were determined.

2. Materials and methods

2.1. Animals

Adult Female Sprague-Dawley rats, weighing 220 ± 20 g, were obtained from Shanghai SLAC Laboratory Animal Co (Shanghai, China) and housed with regular light–dark cycles (lights on at 7:00 a.m., lights off at 7:00 p.m.) under controlled temperature (22 ± 2 °C) and humidity (50 ± 10%), and were given standard diet and water ad libitum. They were allowed to acclimatize for 7 days before use. All animal procedures were carried out in accordance with the guidelines for the use of laboratory animals published by the People's Republic of China Ministry of Health (January 25, 1998), with the approval of the Ethical Committee of Experimental Animals of Second Military Medical University. Procedures were designed to minimize the number of animals used and their suffering.

2.2. Ovariectomy and E_2 replacement

Twenty four rats were randomly assigned to Sham, OVX and OVX + E_2 groups ($n = 8$ for each group). Sham operation or bilateral ovariectomy was performed under anesthesia with sodium pentobarbital. After one week of operation, OVX rats were subcutaneously administered with E_2 (Sigma–Aldrich, St Louis, MO) (OVX + E_2 group) at a dose of 30 μg/kg/day or with same volume of sesame oil (Sigma–Aldrich) as placebo (OVX group) as previously described. Twelve weeks after E_2 or sesame oil treatment, rats were examined by behavioral tests and then sacrificed. For sham rats, behaviors were examined on the first or second day of diestrus phase, and the animals were then sacrificed on the second day after behavior examination.

Rats were decapitated at 12:00 p.m. to 13:00 p.m. on the day of sacrifice. Blood was kept in room temperature, and then was centrifuged at $3000 \times g$ for 10 min to separate the serum and blood cells. Simultaneously, hippocampus and PFC were rapidly and carefully separated on ice according to anatomical structure of rat brain [24]. Serum, hippocampus and PFC were stored at −80 °C until assays, respectively. Body and uterus weight were also monitored.

2.3. Sucrose consumption test

The procedure was performed as described by Willner et al. [25]. Briefly, 72 h before the test rats were acclimatized to 1% sucrose solution (w/v): two bottles of 1% sucrose solution were placed in each cage, and 24 h later 1% sucrose in one bottle was replaced with tap water for 24 h. After adaptation, rats were deprived of water and food for 24 h, followed by the sucrose preference test, in which rats housed in individual cages had free access to two bottles containing 200 ml of sucrose solution (1% w/v) and 200 ml of water, respectively. At the end of 24 h, sucrose and water consumption (ml) was measured and the sucrose preference was calculated as a percentage of the consumed 1% sucrose solution relative to the total number of liquid intake.

2.4. Open field test (OFT)

The test was performed as described previously with minor modifications [26]. Each rat was placed at the center of the open field (60 cm × 60 cm × 60 cm chamber, with 16 holes in its floor) for 5 min in a quiet room. A video-computerized tracking system was used to record the behavior of the animals. Parameters assessed were the number of poking into holes and rearing, and the distance traveled in the center. The number of poking into holes and the distance in the center were traced by infrared sensor, while the number of rearing was recorded through a mirror on the wall. Next test was performed after cleaning the chamber.

2.5. Tail suspension test (TST)

The test was performed as described previously with minor modifications [27]. Each rat was suspended by the tail with bands and hung from a mounted hook. The duration of immobility during the total 6 min was measured. Immobile time was defined as a lack of all movement except for whisker movement and respiration.

2.6. Hormone assays

Concentrations of adrenal corticotrophic hormone (ACTH), corticosterone (CORT) and E_2 were assayed using commercially

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