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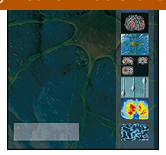

Exercise ameliorates depression-like behavior and increases hippocampal BDNF level in ovariectomized rats

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HIGHLIGHTS

- Ovariectomy induced depression-like behavior in rats.
- Ovariectomy downregulated BDNF level in hippocampus.
- Exercise ameliorated depression-like behavior in OVX rats.
- Exercise increased BDNF level in hippocampus.

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ABSTRACT

The aims of the present study were to investigate whether exercise can improve the depression-like behavior caused by estrogen deficiency. Given that decreased level of brain-derived neurotrophic factor (BDNF) in many brain areas including hippocampus and prefrontal cortex is associated with estrogen deficiency-induced depression-like behavior, we also determined whether exercise affects the levels of BDNF and its receptor in hippocampus and prefrontal cortex (PFC). It was found that ovariectomy (OVX) caused an increase in depression-like behavior in rats and a decrease in BDNF level in hippocampus but not in PFC. The expression of TrkB, a high affinity BDNF receptor in hippocampus and PFC was not affected by OVX. 17β-estradiol (E_2) treatment ameliorated depression-like behavior and increased BDNF level in hippocampus in OVX rats. Serum E_2 level inversely correlated to depression-like behavior and positively correlated to BDNF level in hippocampus. Exercise ameliorated depression-like behavior, increased serum E_2 level and BDNF level in hippocampus in OVX rats. The increased E_2 level did not correlate to BDNF level but correlated with some of the behaviors in the rats subjected to exercise. Our results suggested that E_2 maintains BDNF in hippocampus, thereby ameliorating depression-like behavior. Exercise amelioration of depression-like behavior in OVX rats is partly due to increased serum E_2 level.

1. Introduction

Depression is a significant public health problem due to both its high prevalence and its devastating impact on individuals and society. It was found that ovarian hormones, particularly estrogens, have profound effect on incidence and/or symptomology of depression [1]. Menopausal declines in circulating estrogen levels are associated with increased susceptibility to develop major depressive disorder (MDD) [2]. Rodents have also shown an increase in depression-like behavior during the diestrus phase of the estrous cycle when the levels of estrogens are low [1]. Ovariectomy (OVX), which removes the primary source of estrogens, elicits depression-like behavior in rats [3].

Several reports have indicated that estrogen replacement therapy can produce antidepressant effects in both clinical and pre-clinical studies [3,4]. Given that estrogen therapy results in some severe side effects including thrombotic events, breast cancer and dementia [5], there is obvious interest in developing better and safer therapeutic approaches. Increasing evidence suggests that exercise may play a protective role in mood disorders [6]. Clinical data has shown that physical exercise can reduce depressive

Abbreviations: BDNF, brain-derived neurotrophic factor; E_2, 17β-estradiol; MDD, major depressive disorder; OFT, Open field test; OVX, ovariectomy; PFC, prefrontal cortex; TrkB, tropomyosin-related kinase B; TST, Tail suspension test; ERs, estrogen receptors.

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symptoms and prevent depression relapse [6]. Animal studies have also suggested exercise amelioration of depression-like behavior [7]. Our previous study has demonstrated that swimming exercise reduces depressive behavior in two rat models of depression [8,9]. However, there are few studies about the effect of exercise on depression-like behavior caused by estrogen deficiency.

Exercise can modulate some neurotransmitters and neurotrophin expression in clinical and rodent studies [10,11]. Changed expression of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), is associated with depression in both humans and animal models [12]. The levels of BDNF and its receptor were decreased in hippocampus of MDD patients [13]. Studies in rodents have indicated that decreased BDNF level in many brain regions is associated with the development of depression-like behavior in OVX rats [3]. Administration of BDNF into the hippocampus of depressive animal model ameliorates the behavioral changes as antidepressant treatment does [14]. In the present study, we therefore investigated the effect of OVX on depression-like behavior and the levels of BDNF and its high-affinity tropomyosin-related kinase B (TrkB) receptor in hippocampus and prefrontal cortex (PFC) in female rats, and then determined whether exercise alleviates the depression-like behavior induced by this paradigm and the expression of BDNF and TrkB. Our study would extend the knowledge of the mechanisms underlying exercise amelioration of depression.

2. Materials and methods

2.1. Animals

A total of 56 adult female Sprague–Dawley rats (Shanghai SLAC Laboratory Animal Co.), weighing 200 ± 20 g, were housed with regular light-dark cycles under controlled temperature (22 ± 2 °C) and humidity (50 ± 10%), and were given standard diet and water ad libitum. All animal protocols were approved by the Ethical Committee of Experimental Animals of Second Military Medical University and Shanghai University of Sport.

2.2. Groups, surgical procedure and exercise training

We firstly used 24 rats which were randomly assigned to Sham, OVX and OVX-E_2 groups (n = 8 for each group) to examine the depression-like behavior and the levels of BDNF and TrkB. Sham operation or bilateral OVX was performed under anesthesia with sodium pentobarbital (60 mg/kg, i.p.). After recovery for 1 week, OVX rats were divided into two groups OVX-E_2 and OVX groups. OVX-E_2 rats were subcutaneously administered with E_2 (Sigma–Aldrich, St Louis, MO) (dissolved in 0.1 ml sesame oil) at a dose of 30 μg/kg/day for 8 weeks. OVX rats were administered with 0.1 ml sesame oil as placebo for 8 weeks.

To determine the effects of exercise on depression-like behavior, we set up another independent experiment using 32 rats which were randomly assigned to Sham-sedentary (Sham), Sham-exercise (Sham-Ex) groups, OVX-sedentary (OVX) and OVX-exercise (OVX-Ex) groups (n = 8 for each group). One week after OVX operation, rats were adapted to the treadmill for 1 week (15 min/day at 15 m/min on a 0% slope) and then gradual increase in running time and speed to 60 min/day at 18 m/min on a 0% slope, 5 days/week for the next 7 weeks (supplement Fig. S1).

2.3. Behavioral tests

Rats were examined by behavioral tests after 8-week E_2 treatment or exercise. Open field test (OFT) and tail suspension test (TST) were performed as described previously [7,15] at 14:00 p.m. to 17:00 p.m. In OFT, each rat was placed at the center of the open field (60 × 60 × 60 cm chamber) for 5 min. A video-computerized tracking system was used to record the behavior of the animals. Parameters assessed were total distance (meters), number of crossing squares and immobile episodes. In TST, 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.

2.4. Blood and tissue sample collection

Rats were decapitated at 12:00 p.m. to 13:00 p.m. Sham rats were sacrificed at the diestrus phase. Trunk blood was collected. Simultaneously, hippocampus and PFC were rapidly separated as described by O'Leary et al. [16]. Serum, hippocampus and PFC were stored at −80 °C until assays.

2.5. Determination of E_2 and BDNF

17β-estradiol (E_2) content in serum was assayed using radioimmunoassay kit (Sino-UK Institute of Biological Technology, Beijing, China), and BDNF levels in hippocampus and PFC were determined using ELISA kit (R&D, Minneapolis, USA), following the manufacturer's instructions.

2.6. Western blotting analysis

Tissues were homogenized in cold T-Per lysis buffer (Pierce Biotechnology, USA). The protein concentration was determined using a BCA protein Assay Kit (BioTeke, Beijing, China). The samples were quickly sonified in ice bath, boiled 5 min at 95 °C. 50 μg protein of each sample was loaded and separated by 10% SDS–PAGE and subsequently transferred to nitrocellulose membranes. The membranes were then incubated with antibodies against TrkB (Santa Cruz, CA) at a dilution 1:500 overnight at 4 °C. After washes, the membrane was incubated with the secondary antibodies of horseradish peroxidase-conjugated antibody. Immunoreactive proteins were detected using the enhanced chemiluminescence Western blotting detection system (Santa Cruz, CA) and visualized using Sygene Bio Image system and analyzed following by GeneSnap and GeneTools software (Synoptics Ltd., UK).

2.7. Statistics

Data were presented as mean ± SEM. All data were tested for homogeneity of variance by the Bartlett test at first and then analyzed using one-way or two-way ANOVA followed by Dunnett's or LSD post hoc test. Pearson's correlation analysis was used to examine the relationship between E_2 and BDNF level as well as the parameters of behaviors. All statistics were carried out using SPSS software version 16.0 (SPSS Inc., USA). $P < 0.05$ was considered significant.

3. Results

3.1. The effects of OVX and E_2 replacement on depression-like behavior

OVX rats showed increased depression-like behavior including decreased total distance ($P < 0.01$) and number of crossing squares ($P < 0.01$) in OFT, and increased number of immobile episodes ($P < 0.01$) in OFT and immobile time ($P < 0.01$) in TST compared to Sham group. E_2 replacement significantly reduces depression-like behavior in OVX rats ($P < 0.01$) (Fig. 1A–D).

The level of E_2 in serum correlated to several behavioral indexes including total distance ($R^2 = 0.717$, $P < 0.01$), number of immobile

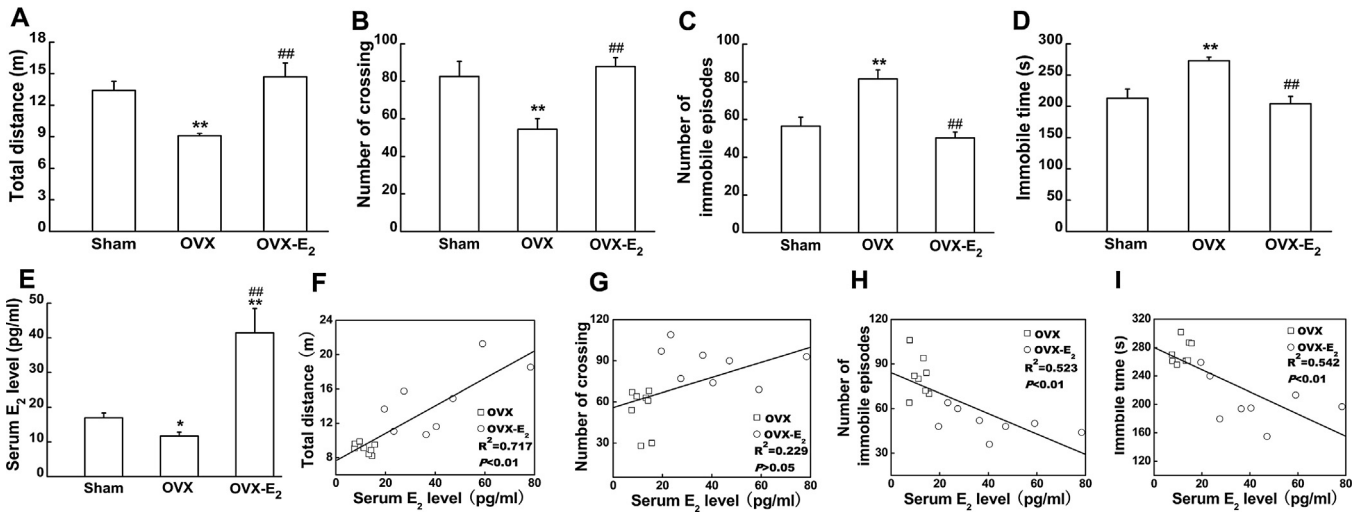

Fig. 1. The effects of OVX and E_2 replacement on depression-like behavior. Sham operation or bilateral OVX was performed, and then OVX rats were subcutaneously administered with E_2 (30 μg/kg/day) or placebo for 8 weeks. Behavior was determined using OFT and TST. Data shows total distance (meters) (A), the number of crossing squares (B) and immobile episodes (C) in OFT, the immobile time (D) in TST. The level of serum E_2 was determined by radioimmunoassay (E). Pearson's correlation analysis was performed to analyze the correlation between serum E_2 levels and total distance (meters) (F), number of crossing squares (G) and immobile episodes (H) in OFT, and immobility time (I) in TST. Data are presented as means ± SEM ($n = 8$ in each group). $^{*}P < 0.05$, $^{**}P < 0.01$ vs. Sham, $^{\#\#}P < 0.01$ vs. OVX. *R*: Pearson's correlation coefficient.

episodes ($R^2 = 0.523$, $P < 0.01$) as well as immobility time ($R^2 = 0.542$, $P < 0.01$) (Fig. 1F–I). No significant correlation was found between E_2 level and the behavioral index, the number of crossing squares.

3.2. The effects of OVX and E_2 replacement on BDNF level and TrkB expression in hippocampus and PFC

Decreased BDNF and its receptor are involved in depression-like behavior [3]. Some brain areas, such as PFC and hippocampus, have been known to be responsible for depression-like behavior [17]. As shown in Fig. 2, BDNF level in hippocampus was significantly decreased in OVX rats compared to Sham rats ($P < 0.01$), which was reversed by E_2 treatment ($P < 0.01$). Moreover, BDNF level in hippocampus correlated to serum E_2 level ($R^2 = 0.304$, $P < 0.05$). BDNF level in PFC was not significantly differed among Sham, OVX and OVX-E_2 groups.

There was no significant difference in TrkB protein expression in hippocampus and PFC among Sham, OVX and OVX-E_2 groups.

3.3. Exercise ameliorates depression-like behavior and increases BDNF level in hippocampus of OVX rats

Exercise ameliorated depression-like behavior in OVX rats, including increasing total distance ($P < 0.01$) and number of crossing squares ($P < 0.01$) and decreasing number of immobile episodes ($P < 0.01$) and immobile time in TST ($P < 0.05$) (Fig. 3A–D). Exercise did not affect the above behaviors in Sham rats.

Exercise could increase serum E_2 level in OVX rats ($P < 0.05$) (Fig. 3E). E_2 level correlated to total distance ($R^2 = 0.500$, $P < 0.05$) and the number of immobile episodes ($R^2 = 0.273$, $P < 0.05$), but did not correlate to the number of crossing squares and immobility time (Fig. 3F–I).

Exercise significantly increased BDNF level in hippocampus but not in PFC in both Sham ($P < 0.05$) and OVX rats ($P < 0.01$) (Fig. 4A and B). BDNF level in hippocampus did not correlate to E_2 level in OVX rats with or without exercise (Fig. 4C).

There was no significant difference in TrkB protein expression in hippocampus and PFC among the experimental groups (Fig. 4D and E).

4. Discussion

The present study has demonstrated that OVX induced depression-like behavior by showing decreased total distance and number of crossing squares, as well as increased number of immobile episodes in OFT and immobile time in TST in rats. Both E_2 treatment and exercise ameliorated depression-like behavior in OVX rats. OVX resulted in a decrease in BDNF level in hippocampus but not in PFC, which can be restored by E_2-replacement as well as exercise.

OVX rats exhibit depression-like behavior and estrogen treatment can decrease depression-like behavior or facilitate antidepressant action [18]. The present study showed E_2 treatment ameliorated depression-like behavior including a decrease in locomotor activity and behavioral despair in OVX and serum E_2 level correlated to some parameters of depression-like behavior, confirming the antidepressant effect of E_2.

Infusion of BDNF into brain or hippocampus has antidepressant-like effects [14]. Many antidepressant drugs exert their effects through modulation of BDNF expression in the hippocampus in humans and animal models [12]. The present study showed that OVX decreased BDNF expression in hippocampus while caused depression-like behavior, which was restored by E_2 replacement. E_2 level positively correlated to BDNF level in hippocampus. These data are consistent with previous studies that estrogen replacement increases BDNF expression in many brain regions including hippocampus in OVX rats [3]. Activation of TrkB has been implicated to play a role in antidepressant action [19]. We found that OVX and E_2 replacement did not affected TrkB protein expression in hippocampus and PFC. However, whether E_2 affect the level of phosphorylated TrkB remains to be elucidated.

Several brain regions including the PFC, amygdala, and hippocampus have been implicated in mood disorders [17]. Hippocampus has been considered as an important component of the limbic system and the target of estrogens [1,20]. It has been shown that E_2 is concentrated in hippocampus after administration of E_2 into female rats [1,21]. Our data that OVX and E_2 replacement caused changed BDNF level in hippocampus support that hippocampus is a putative focal area for estrogens. In the present study, it is hard to explain why estrogen has no effect on BDNF in PFC. Classically estrogen binding to estrogen receptors (ERs) enhances the

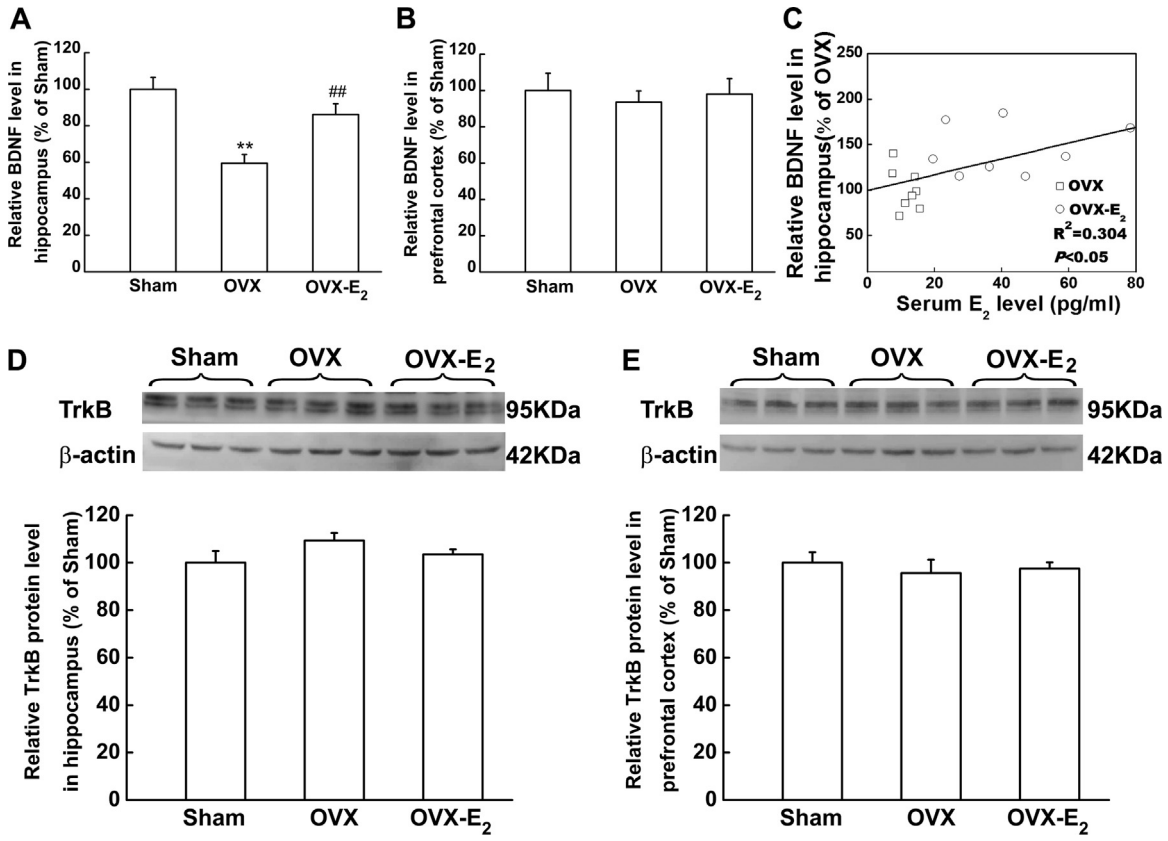

Fig. 2. The effects of OVX and E_2 replacement on BDNF level and TrkB expression in hippocampus and PFC. Sham operation or bilateral OVX was performed, and then OVX rats were subcutaneously administered with E_2 (30 μg/kg/day) or placebo for 8 weeks. The hippocampus and PFC of rats were collected for determination of BDNF level and TrkB expression as described in Section 2. A, BDNF level in hippocampus; B, BDNF level in PFC. C, Pearson's correlation analysis was performed to analyze the correlation between serum E_2 levels and BDNF level in hippocampus. D, TrkB protein expression in hippocampus; E, TrkB protein expression in PFC. Representative protein bands were presented on top of histogram. All data are presented as means ± SEM ($n = 8$ in each group). $^{**}P < 0.01$ vs. Sham, $^{\#\#}P < 0.01$ vs. OVX. *R*: Pearson's correlation coefficient.

ability of receptors to bind to estrogen response elements (EREs) in the promoter many, though not all, estrogen-response genes [22]. Once at the promoter, estrogen-bound ER, interacts with coregulator proteins to form a multiprotein complex that modulates the expression of target genes [23]. It is known that the differences in subtype of ERs and the coregulator proteins are responsible for the tissue-specific effects of estrogen. Both of ERα and ERβ have been identified in hippocampus and PFC [1,24]. However,

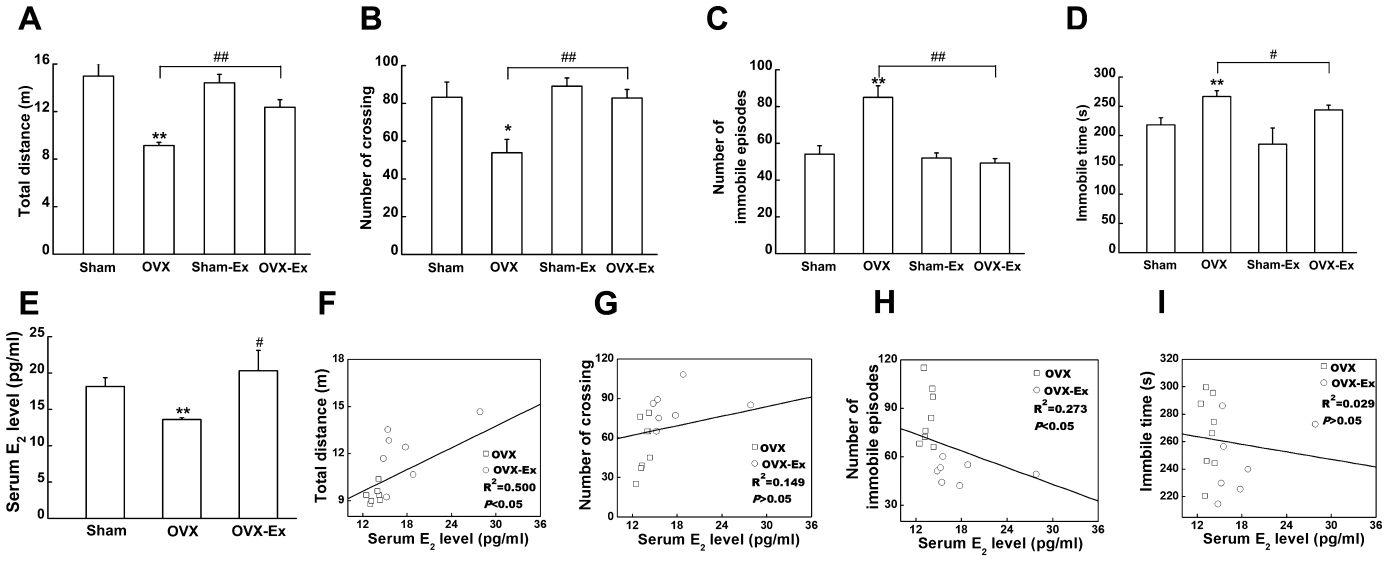

Fig. 3. The effects of exercise on depression-like behavior. Sham operation or bilateral OVX was performed. After 8 weeks exercise, behavior was determined using OFT and TST. Data shows total distance (meters) (A), the number of crossing (B) and immobile episodes (C) in OFT, the immobile time (D) in TST. The level of serum E_2 was determined by radioimmunoassay (E). Pearson's correlation analysis was performed to analyze the correlation between serum E_2 levels and total distance (meters) (F), number of crossing squares (G) and immobile episodes (H) in OFT, and immobility time (I) in TST. Data are presented as means ± SEM ($n = 8$ in each group). $^{*}P < 0.05$, $^{**}P < 0.01$ vs. Sham, $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ vs. OVX. *R*: Pearson's correlation coefficient.

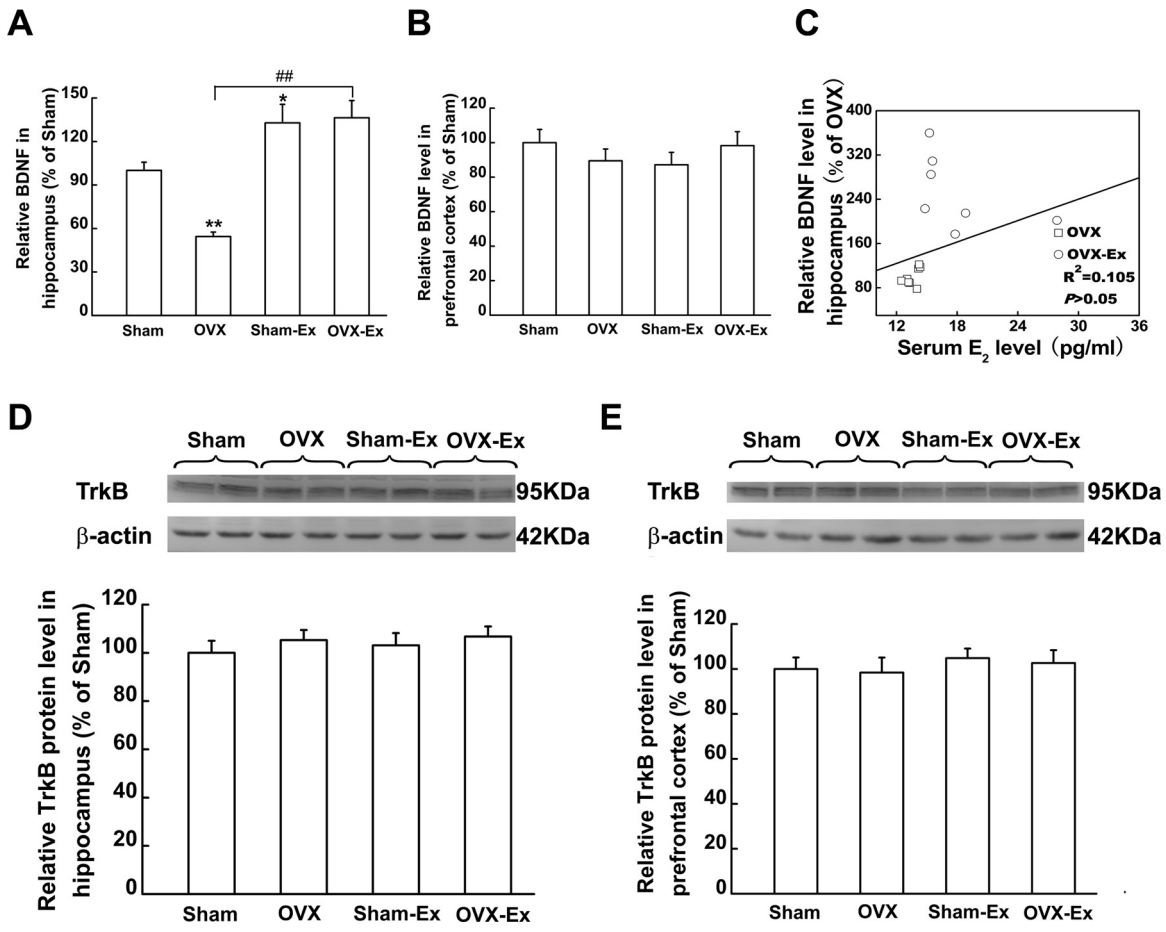

Fig. 4. The effects of exercise on BDNF level and TrkB expression in hippocampus and PFC. Sham operation or bilateral OVX was performed. After 8 weeks exercise, the hippocampus and PFC of rats were collected for assay of BDNF level and TrkB expression as described in Section 2. A, BDNF level in hippocampus of Sham and OVX groups with or without exercise; B, BDNF level in PFC of Sham and OVX groups with or without exercise; C, correlation between serum E_2 levels and BDNF level in hippocampus; D, TrkB protein expression in hippocampus of Sham and OVX groups with or without exercise; E, TrkB protein expression in PFC of Sham and OVX groups with or without exercise. Representative protein bands were presented on top of histogram. All data are presented as means ± SEM ($n = 8$ in each group). $^{*}P < 0.05$, $^{**}P < 0.01$ vs. Sham, $^{\#\#}P < 0.01$ vs. OVX. *R*: Pearson's correlation coefficient.

the coregulators responsible for estrogen actions in hippocampus and PFC remain unknown. Moreover, we could not exclude other possibilities for the discriminative effect of estrogen on BDNF in different brain regions. Such as, duration of estrogen treatment in the present study might be not enough to cause significant influence on BDNF in PFC.

So far, few studies have focused on the effect of exercise on estrogen deficiency-induced depression. We showed that exercise ameliorated depression-like behavior including a decrease in locomotor activity and behavioral despair in OVX rats, indicating that exercise is effective as antidepressant treatment does. However, the mechanisms underlying exercise improve depression remain largely unknown. Exercise can increase estrogen level in the peripheral circulation of OVX rats [25]. Although we demonstrated that exercise increased serum E_2 level, the serum E_2 level only correlated to some behavior parameters such as locomotor activity in these rats. Thus, it suggests that serum E_2 level may be associated with certain aspects of depression-like behavior. And in addition to increasing serum E_2 level, other mechanisms might also be involved in exercise amelioration of depression. Meeusen [26] has demonstrated that exercise promotes the secretion of neurotransmitters including 5-HT, which may partly explain the beneficial effect of exercise on depressive symptoms.

Exercise can enhance hippocampal function by increasing the production of BDNF, which is associated with antidepressive effect of exercise [27]. Consistently, the present study showed that exercise resulted in a significant increase in BDNF level in hippocampus. However, we also found that increased E_2 level did not correlate to BDNF level in hippocampus in the rats with exercise. It may suggest that other factors might also be involved in the stimulatory effect of exercise on BDNF. For example, it has been shown that exercise can induce hippocampal BDNF by increasing the expression of fibronectin type III domain-containing protein 5 [28].

In conclusion, OVX induces depression-like behavior and downregulates BDNF level in hippocampus. Estrogen replacement and exercise ameliorate depression-like behavior and reverse BDNF level in hippocampus. Exercise amelioration of depression is partly due to increasing E_2 level in circulation.

Disclosure

All authors have nothing to disclose.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neulet.2014.04.053.

References

[1] A.A. Walf, C.A. Frye, A review and update of mechanisms of estrogen in the hippocampus and amygdala for anxiety and depression behavior, Neuropsychopharmacology 31 (2006) 1097–1111.
[2] P. Llaneza, M.P. García-Portilla, D. Llaneza-Suárez, B. Armott, F.R. Pérez-López, Depressive disorders and the menopause transition, Maturitas 71 (2012) 120–130.
[3] A. Kiss, A.M. Delattre, S.I. Pereira, R.G. Carolino, R.E. Szawka, J.A. Anselmo-Franci, S.M. Zanata, A.C. Ferraz, 17β-estradiol replacement in young, adult and middle-aged female ovariectomized rats promotes improvement of spatial reference memory and an antidepressant effect and alters monoamines and BDNF levels in memory- and depression-related brain areas, Behav. Brain Res. 227 (2012) 100–108.
[4] J.W. Studd, A guide to the treatment of depression in women by estrogens, Climacteric 14 (2011) 637–642.
[5] S. Rozenberg, J. Vandromme, C. Antoine, Postmenopausal hormone therapy: risks and benefits, Nat. Rev. Endocrinol. 9 (2013) 216–227.
[6] A.L. Dunn, M.H. Trivedi, J.B. Kampert, C.G. Clark, H.O. Chambliss, Exercise treatment for depression: efficacy and dose response, Am. J. Prev. Med. 28 (2005) 1–8.
[7] H. Zheng, Y. Liu, W. Li, B. Yang, D. Chen, X. Wang, Z. Jiang, H. Wang, Z. Wang, G. Cornelisson, F. Halberg, Beneficial effects of exercise and its molecular mechanisms on depression in rats, Behav. Brain Res. 168 (2006) 47–55.
[8] W. Liu, H. Sheng, Y. Xu, Y. Liu, J. Lu, X. Ni, Swimming exercise ameliorates depression-like behavior in chronically stressed rats: relevant to proinflammatory cytokines and IDO activation, Behav Brain Res. 242 (2013) 110–116.
[9] W. Liu, Y. Xu, J. Lu, Y. Zhang, H. Sheng, X. Ni, Swimming exercise ameliorates depression-like behaviors induced by prenatal exposure to glucocorticoids in rats, Neurosci. Lett. 524 (2012) 119–123.
[10] E. Stenman, A. Lilja, Increased monoaminergic neurotransmission improves compliance with physical activity recommendations in depressed patients with fatigue, Med. Hypotheses 80 (2013) 47–49.
[11] J. Wang, X. Chen, N. Zhang, Q. Ma, Effects of exercise on stress-induced changes of norepinephrine and serotonin in rat hippocampus, Chin. J. Physiol. 56 (2013) 5.
[12] R.S. Duman, L.M. Monteggia, A neurotrophic model for stress-related mood disorders, Biol. Psychiatry 59 (2006) 1116–1127.
[13] A.E. Autry, L.M. Monteggia, Brain-derived neurotrophic factor and neuropsychiatric disorders, Pharmacol. Rev. 64 (2012) 238–258.
[14] Y. Shirayama, A.C. Chen, S. Nakagawa, D.S. Russell, R.S. Duman, Brain-derived neurotrophic factor produces antidepressant effects in behavioral models of depression, J. Neurosci. 22 (2002) 3251–3261.
[15] L. Steru, R. Chermat, B. Thierry, P. Simon, The tail suspension test: a new method for screening antidepressants in mice, Psychopharmacology 85 (1985) 367–370.
[16] O.F. O'Leary, X.F. Wu, E. Castren, Chronic fluoxetine treatment increases expression of synaptic proteins in the hippocampus of the ovariectomized rat: role of BDNF signalling, Psychoneuroendocrinology 34 (2009) 367–381.
[17] A. Tanti, C. Belzung, Open questions in current models of antidepressant action, Br. J. Pharmacol. 159 (2010) 1187–1200.
[18] M. Singh, E.M. Meyer, J.W. Simpkins, The effect of ovariectomy and estradiol replacement on brain-derived neurotrophic factor messenger ribonucleic acid expression in cortical and hippocampal brain regions of female Sprague-Dawley rats, Endocrinology 136 (1995) 2320–2324.
[19] Y. Li, B.W. Luikart, S. Birnbaum, J. Chen, C.H. Kwon, S.G. Kernie, R. Bassel-Duby, L.F. Parada, TrkB regulates hippocampal neurogenesis and governs sensitivity to antidepressive treatment, Neuron 59 (2008) 399–412.
[20] H. Mukai, T. Kimoto, Y. Hojo, S. Kawato, G. Murakami, S. Higo, G. Murakami, Y. Komatsuzaki, M. Ogiue-Ikeda, T. Kimoto, H. Mukai, Modulation of synaptic plasticity by brain estrogen in the hippocampus, Biochim. Biophys. Acta 1800 (2010) 1030–1044.
[21] D. Pfaff, M. Keiner, Atlas of estradiol-concentrating cells in the central nervous system of the female rat, J. Comp. Neurol. 151 (1973) 121–158.
[22] P. Diel, Tissue-specific estrogenic response and molecular mechanisms, Toxicol. Lett. 127 (2002) 217–224.
[23] C.L. Smith, B.W. O'Malley, Coregulator function: a key to understanding tissue specificity of selective receptor modulators, Endocr. Rev. 25 (2004) 45–71.
[24] J.M. Westberry, M.E. Wilson, Regulation of estrogen receptor alpha gene expression in the mouse prefrontal cortex during early postnatal development, Neurogenetics 13 (2012) 159–167.
[25] A. Pighon, J. Gutkowska, M. Jankowski, R. Rabasa-Lhoret, J.M. Lavoie, Exercise training in ovariectomized rats stimulates estrogenic-like effects on expression of genes involved in lipid accumulation and subclinical inflammation in liver, Metabolism 60 (2011) 629–639.
[26] R. Meeusen, Exercise and the brain: insight in new therapeutic modalities, Ann. Transplant. 10 (2005) 49–51.
[27] C.R. Sartori, A.S. Vieira, E.M. Ferrari, F. Langone, E. Tongiorgi, C.A. Parada, The antidepressive effect of the physical exercise correlates with increased levels of mature BDNF, and proBDNF proteolytic cleavage-related genes, p11 and tPA, Neuroscience 180 (2011) 9–18.
[28] C.D. Wrann, J.P. White, J. Salogiannnis, D. Laznik-Bogoslavski, J. Wu, D. Ma, J.D. Lin, M.E. Greenberg, B.M. Spiegelman, Exercise induces hippocampal BDNF through a PGC-1α/FNDC5 pathway, Cell Metab. 18 (2013) 649–659.