Effects of exercise on mature or precursor brain-derived neurotrophic factor pathways in ovariectomized rats

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Abstract. Ovariectomy (OVX) is a method used to block estrogen in female rats that induces hippocampal dysfunction and affects brain-derived neurotrophic factor (BDNF) pathways. The majority of previous studies investigating OVX focused on BDNF expression in the hippocampus and cognitive function. The present study focused on the pathways of each BDNF type, precursor (proBDNF) and mature (mBDNF), and the effects of regular exercise in the hippocampus of ovariectomized rats. Female Sprague-Dawely rats were used and OVX surgery was performed. After 1 week of recovery from surgery, two groups of rats that received OVX surgery were subjected to regular treadmill exercise for 8 weeks. The results of protein levels by western blotting indicated that the expression of proBDNF, p75 neurotrophin receptor (p75NTR) and c-Jun N-terminal protein kinase (JNK) was increased, and mBDNF, tropomyosin-related kinase B (TrkB) and nuclear factor-κB expression was significantly reduced in the OVX control group compared with the sham control group SC ($P<0.05$). Thus, the survival pathway by mBDNF was impaired and the pro-apoptotic response was activated by increased JNK expression due to proBDNF-p75NTR binding in the hippocampus of ovariectomized rats. By contrast, exercise reduced activation of the pro-apoptotic response and increased mBDNF-TrkB expression in the hippocampus of ovariectomized rats. Thus, regular exercise may increase the activation of survival pathways via mBDNF and reducing the activation of the pro-apoptotic pathway of proBDNF in the hippocampus of ovariectomized rats.

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Introduction

An animal model of ovariectomy (OVX) previously demonstrated that OVX induced blockade of estrogen (1). The resulting estrogen deficiency has been reported to be closely associated with brain dysfunction in the hippocampus (2). After binding to estrogen receptor α (ERα) or β (ERβ), estrogen promotes mitogen-activated protein-kinase (MAPK), phosphatidylinositol 3-kinase (PI3K) and phospholipase C γ (PLCγ) pathways (3), which influence synaptic formation, neuronal plasticity, cognition and neuroprotection in neurodegenerative diseases (4-7). In addition, estrogen has an important role in the synthesis and expression of brain-derived neurotrophic factor (BDNF), which regulates neuronal function in the hippocampus (8). BDNF exists as two forms in tissues: Precursor BDNF (proBDNF) and mature BDNF (mBDNF). mBDNF is synthesized from proBDNF following cleavage by tissue plasminogen activator (tPA) (9). In general, mBDNF acts by binding to the tropomyosin-related kinase B (TrkB) receptor in the MAPK and PI3K-Akt pathways (10-14), which has positive effects for neuronal proliferation, differentiation and the development of synapses associated with hippocampal function (15,16). ProBDNF also acts positively for neuronal function by binding to the p75 neurotrophin receptor (p75NTR). However, the proBDNF-p75NTR pathway also includes pro-apoptotic activation (10-14). BDNF expression is reduced by OVX, which induces an estrogen block (17,18). In an animal model of OVX, BDNF was reduced markedly and hippocampal function declined (2). Previous studies investigating hippocampal function in OVX focused on mBDNF pathways alone (17,18). Contrary to the previous OVX results, regular exercise has been previously demonstrated to have positive effects on brain function (19,20), and affects the proliferation, differentiation and survival of neuronal cells, and aids neuronal plasticity by promoting neurotrophins (21). Exercise enhances BDNF expression by positively affecting tPA, which is associated with the synthesis of mBDNF in the hippocampus (22) and the TrkB pathway (16,23,24). Chronic exercise has neuroprotective effects on hippocampal dysfunction, dementia and neurodegenerative diseases (25-28). In addition, exercise improves cognitive decline induced by OVX (1). The majority

of previous studies regarding the effects of exercise on brain function by OVX focused on BDNF expression and cognition in the hippocampus (29-31). A limited number of studies have sought to determine the underlying mechanism of proBDNF and mBDNF pathways associated with hippocampal function in OVX. The present study investigated whether regular exercise increased mBDNF synthesis from proBDNF in the OVX rat model, and determined the underlying molecular mechanisms of proBDNF and mBDNF signaling pathways.

Materials and methods

Animals. Female, 6-week-old Sprague-Dawley rats (n=50; 160-200 g; Samtako Bio Korea Co., Ltd., Republic of Korea) were adapted to the laboratory environment (temperature, 22±1˚C; relative humidity, 55±3%; 12-h light/12-h dark photoperiod) for 2 weeks. All rats were housed in pairs, given free access to water and fed a standard chow diet (protein, 21%; fat, 5%; nitrogen-free extract, 55%; fiber, 4%; adequate mineral and vitamin content). Studies were performed in accordance with Chung-Nam University standards for the Care and Use of Laboratory Animals (publication no. CNU-00203). Rats were allocated to the following groups: Sham control group (SC; n=10); OVX control group (OC; n=10); OVX low-exercise group (OLE; n=10); and OVX moderate-exercise group (OME; n=10).

Ovariectomy. Following anesthetization using ketamine/xylazine (8 mg/kg body weight), the dorsal mid-lumbar area between the first and third lumbar was shaved and the midline was incised. A single 5.5-10 mm long incision was made in the muscle wall on the right and left sides approximately one-third of the distance between the spinal cord and the ventral midline. The ovary was exteriorized through the muscle wall and removed. In the SC group, the ovary was exteriorized but not removed.

Exercise protocol. After a 1-week recovery from surgery, rats in the OLE and OME groups were subjected to treadmill exercise for 8 weeks, 5 days a week. The speed of treadmill exercise was 8 m/min (grade 0%) in weeks 1-4 and 10 m/min (grade 0%) in weeks 5-8 for the OLE group, and 12 m/min in weeks 1-4 and 18 m/min (grade 0%) in weeks 5-8 for the OME group (32). The duration was gradually increased from 30 to 60 min. OLE and OME groups were subjected to 30 min for in weeks 1 and 2, 40 min in weeks 3 and 4, 50 min in weeks 5 and 6, and 60 min in weeks 7 and 8. The non-exercise groups, including SC and OC, were exposed to environmental stress similar to that experienced with treadmill use, including noise and vibration, and restricted food and water during treadmill exercise. To minimize the stress of exercise, treadmill exercise was performed without external stimuli and electronic shock.

Tissue preparation. Upon completion of the 8-week exercise program, the rats were anesthetized at 48 h after the final exercise session by intraperitoneal injection of xylazine (8 mg/kg) and ketamine (40 mg/kg). For protein analyses, brains of rats from each group were extracted and the hippocampus was dissected and stored at -80˚C.

Western blotting. To prepare protein for western blotting, each hippocampus was crushed in a solution containing 150 mM NaCl, 5 mM EDTA, 50 mM Tris-HCl (pH 8.0), 1% NP-40, 1 mM aprotinin, 0.1 mM leupeptin and 1 mM pepstatin, and centrifuged at 15,294 x g for 15 min at 4˚C. Proteins were quantified by a Bradford assay and 30 μg was loaded onto a 10% gel, subjected to SDS-PAGE and transferred to a polyvinylidene difluoride membrane (EMD Millipore, Billerica, MA, USA). The membrane was blocked in TBS containing 0.001% Tween-20 (TBS-T) and 5% bovine serum albumin (Bovogen Biologicals Ltd., Victoria, Australia) at 4˚C for 90 min. After washing, the membrane was incubated overnight at 4˚C with the following primary antibodies: Rabbit anti-GAPDH (1:1,000; catalog no. ABS16; EMD Millipore, Billerica, MA, USA), rabbit anti-proBDNF (1:1,000; catalog no. sc-546; Santa Cruz Biotechnology, Inc., Dallas, TX, USA), rabbit anti-mBDNF (1:1,000; catalog no. sc-546; Santa Cruz Biotechnology, Inc.), rabbit anti-tPA (1:1,000; catalog no. sc-15346; Santa Cruz Biotechnology, Inc.), rabbit anti-TrkB (1:1,000; catalog no. sc-119; Santa Cruz Biotechnology, Inc.), rabbit anti-p75NTR (1:1,000; catalog no. 4201S; Cell Signaling Technology, Inc., Danvers, MA, USA), rabbit anti-total (t)-JNK (1:1,000; catalog no. sc-571; Cell Signaling Technology, Inc.), rabbit anti-phosphorylated (p)-JNK (1:1,000; catalog no. sc-135642; Cell Signaling Technology, Inc.) and rabbit anti-nuclear factor-κB (NF-κB; 1:1,000; catalog no. 3031S; Cell Signaling Technology, Inc.). Subsequently, membranes were washed 3 times with TBS-T for 10 min and incubated with a goat anti-rabbit IgG secondary antibody conjugated to alkaline phosphatase (1:2,000; catalog no. sc-2007; Santa Cruz Biotechnology, Inc.) for 1 h at room temperature. The membrane was washed 3 times with TBS-T for 10 min. Membranes were exposed to Luminata™ (EMD Millipore, Billerica, MA, USA) and protein bands were imaged using a Kodak Image Station 440CF (Kodak, Rochester, NY, USA) and were quantified using Kodak ID version 3.5 densitometry software (Kodak). Membranes were stripped with stripping buffer [20 ml 10% SDS, 12.5 ml 0.5 M Tris HCL (pH 6.8), 67.5 ml ultra pure water, 0.8 ml beta-mercaptoethanol] for 45 min at 50˚C and washed 5 times with TBS-T for 10 min. Following stripping, membranes were blocked and re-probed with the appropriate primary antibody 3-4 times. This was performed at least twice, and the results demonstrate blots from one representative experiment.

Statistical analysis. All data was analyzed using SPSS software version 16.0 (SPSS, Inc., Chicago, IL, USA) by one-way analysis of variance followed by Tukey's post hoc test to compare among the experimental groups. Results are presented as the mean + standard deviation. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Effects of exercise on mBDNF, TrkB and tPA in the hippocampus. The OC group exhibited reduced mBDNF, TrkB and tPA protein expression in the hippocampus compared with the SC group (Fig. 1). By contrast, in the OLE and OME groups, significantly increased mBDNF, TrkB and tPA protein expression was observed in the hippocampus compared with

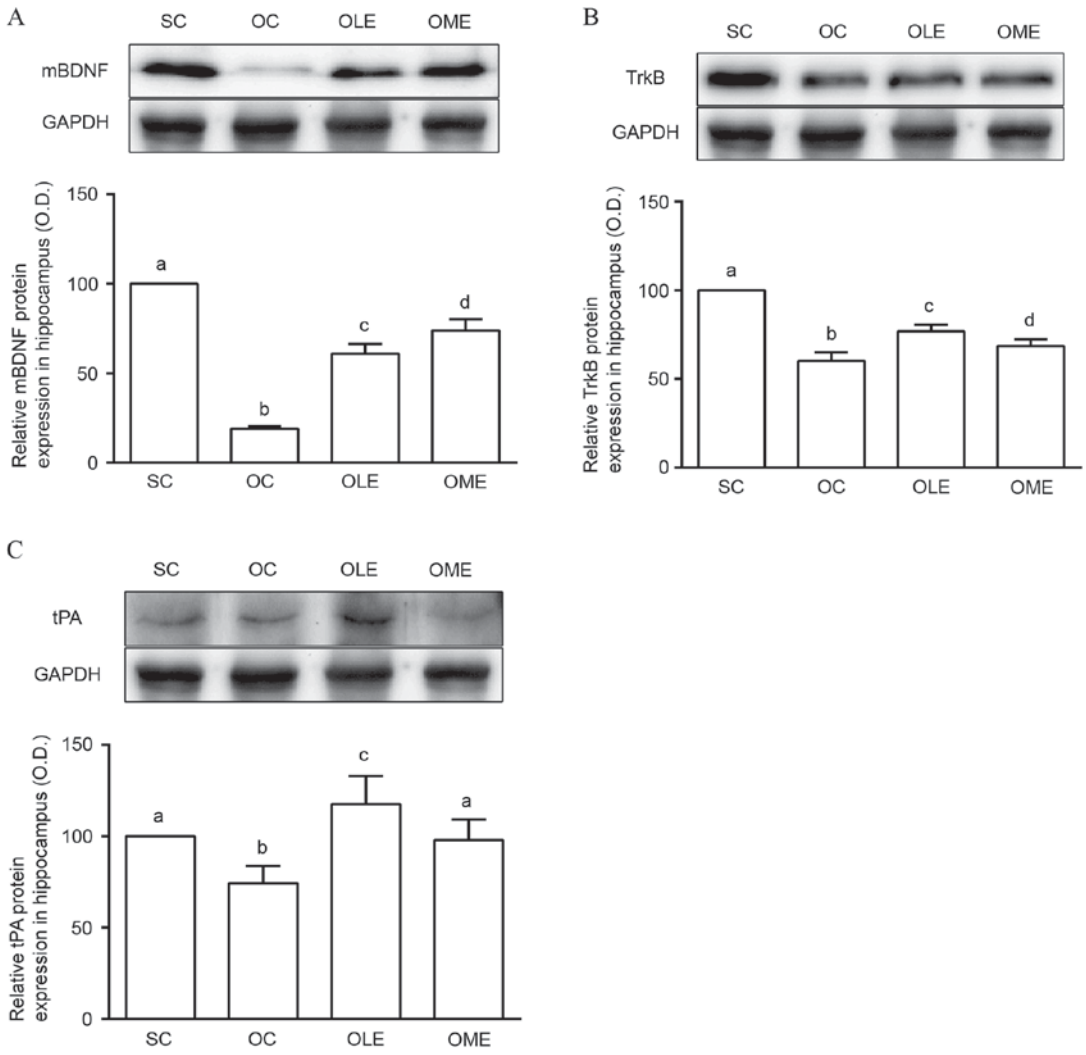

Figure 1. Expression of (A) mBDNF, (B) TrkB and (C) tPA protein in the hippocampus of control and OVX rats. Results are presented as the mean + standard deviation. Different letters represent significant differences compared with the other groups (P<0.05). mBDNF, mature brain-derived neurotrophic factor; TrkB, tropomyosin-related kinase B; tPA, tissue plasminogen activator; OVX, ovariectomy; SC, sham control; OC, OVX control; OLE, OVX + low-exercise; OME, OVX + moderate-exercise; O.D., optical density.

the OC group (Fig. 1). Exercise intensity differences were also apparent as expression levels were significantly different between the OLE and OME groups (Fig. 1).

Effects of exercise on proBDNF and p75NTR in hippocampus. The OC group exhibited significantly increased proBDNF and p75NTR protein expression in the hippocampus compared with the SC group (Fig. 2). Furthermore, the OLE and OME groups had reduced proBDNF and p75NTR protein expression in the hippocampus compared with the OC group (Fig. 2). There were significant differences in exercise intensity between the OLE and OME groups (P<0.05; Fig. 2).

Effects of exercise on t-JNK, p-JNK, and NF-κB in the hippocampus. A significantly increased p-JNK/t-JNK ratio and reduced NF-κB protein expression was observed in the hippocampus of OC rats compared with the SC group (Fig. 3). In addition, a reduced p-JNK/t-JNK ratio and increased NF-κB protein expression was observed in the hippocampus of OLE and OME groups, compared with the OC group (Fig. 3). There were significant differences in NF-κB expression between the OLE and OME groups (P<0.05; Fig. 3).

Discussion

The present study investigated the effects of exercise on BDNF pathways in the hippocampus of ovariectomized rats and demonstrated that tPA, mBDNF and NF-κB protein expression was reduced, and the proBDNF, p75NTR and p-JNK level was increased by OVX compared with sham rats. The observed alterations in protein expression were reversed by regular exercise.

As a sex hormone, estrogen regulates diverse processes, including bone mineral density and calcium intake. Estrogen also influences intracellular pathways, synaptic structure and physiological functions of neurons in several brain regions (4-6), and regulates neurotrophin expression and has neuroprotective effects against diseases (2). In the hippocampus, estrogen is particularly important in enhanced cognitive functions by supporting neurogenesis and synaptic

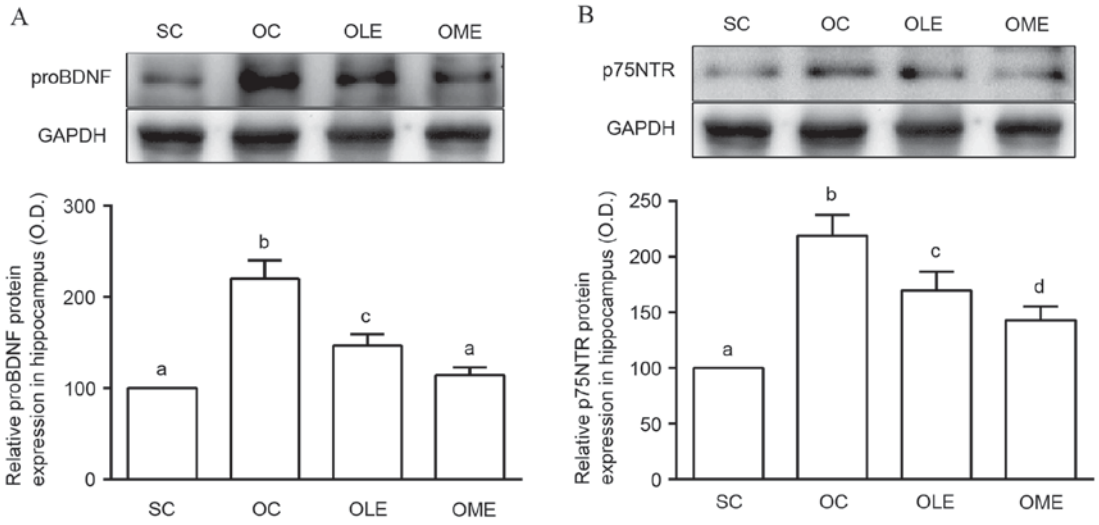

Figure 2. Expression of (A) proBDNF and (B) p75NTR protein in the hippocampus of control and OVX rats. Results are presented as the mean + standard deviation. Different letters represent significant differences compared with the other groups (P<0.05). proBDNF, precursor brain-derived neurotrophic factor; p75NTR, p75 neurotrophin receptor; OVX, ovariectomy; SC, sham control; OC, OVX control; OLE, OVX + low-exercise; OME, OVX + moderate-exercise; O.D., optical density.

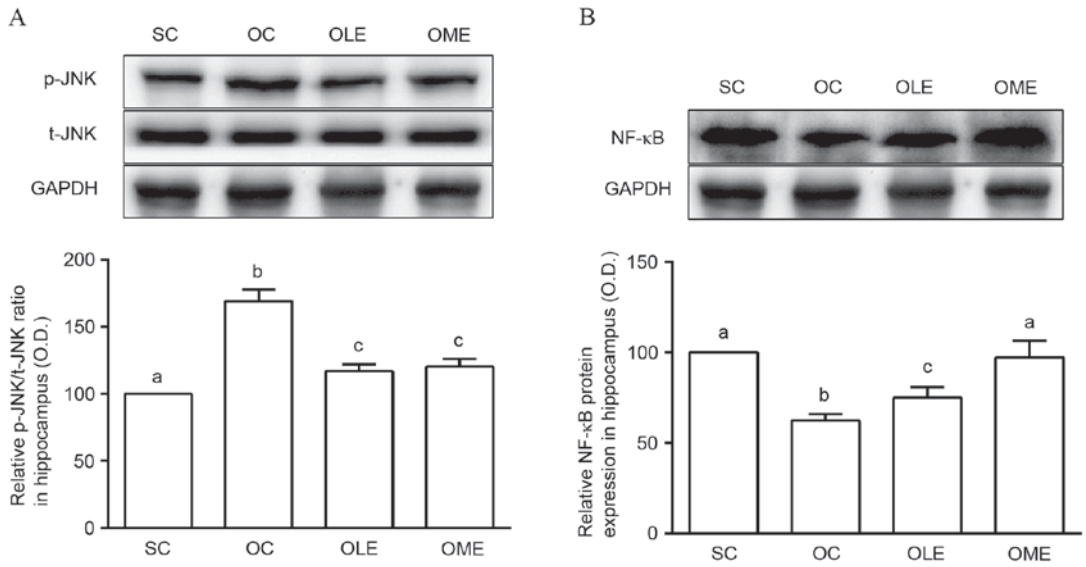

Figure 3. Expression of (A) p-JNK/t-JNK and (B) NF-κB protein in the hippocampus of control and OVX rats. Results are presented as the mean + standard deviation. Different letters represent significant differences compared with the other groups (P<0.05). JNK, c-Jun N-terminal protein kinase; p-JNK, phosphorylated-JNK; t-JNK, total-JNK; NF-κB, nuclear factor-κB; OVX, ovariectomy; SC, sham control; OC, OVX control; OLE, OVX + low-exercise; OME, OVX + moderate-exercise; O.D., optical density.

plasticity, and protects hippocampal function from neurodegenerative disease (2,7). Estrogen has direct effects in various pathways through binding to estrogen receptors (17) or indirect neuronal functions by regulating extrinsic factors, such as neurotrophins (33). In particular, estrogen is associated with BDNF synthesis and expression in the hippocampus (8). The interaction between estrogen and BDNF is crucial for hippocampal functions (3,34).

BDNF released from neuronal cells exists in precursor and mature forms, and mBDNF is synthesized from proBDNF (9,35,36). proBDNF is proteolytically cleaved intracellularly by enzymes, including furin and pro-protein convertase (37-39), or secreted as proBDNF and subsequently cleaved to create mBDNF by extracellular proteases, such as metalloproteases and plasmin (40). Plasmin is converted from plasminogen by tPA as a key regulator of BDNF synthesis, and has a crucial role in BDNF-dependent, late-phase, long-term potential associated with hippocampal plasticity (40). Various studies investigating the interaction between estrogen and BDNF in the hippocampus have demonstrated that BDNF expression is reduced by an estrogen deficit in ovariectomized rats (17,18). In the present study, hippocampal mBDNF was significantly reduced in the OVX treatment group compared with SC rats, and tPA also was reduced by OVX. The results indicate that tPA may be involved in the reduced expression of mBDNF induced by OVX. mBDNF exerts its actions on

neuronal structure, function and synaptic plasticity underlying memory and cognition (41-43) by activation of MAPK, PI3K-Akt, PLCγ, Ca^{2+}/calmodulin-dependent protein kinase and cAMP response element-binding protein pathways following interactions with TrkB (23,44).

While proBDNF was originally considered to be a precursor with no inherent biological function, multiple reports have indicated that proBDNF is secreted from neurons and modulates synaptic functions through certain pathways by binding p75NTR (45,46). The interaction between proBDNF and p75NTR aids neuronal functions through underlying pathways (46). proBDNF-p75NTR functions in prosurvival responses via the NF-κB cascade (13), and is also associated with long-term hippocampal depression (45) and induces pro-apoptotic responses (10-14) via the JNK cascade (47-49). In particular, apoptosis induced by proBDNF-p75NTR has been previously demonstrated in neurodegenerative diseases; Sierksma *et al* (50) noted that hippocampal proBDNF was increased significantly in an animal model of Alzheimer's disease.

In the present study, the OVX group exhibited significantly higher proBDNF, p75NTR and JNK, associated with pro-apoptotic responses, compared with the SC group. Conversely, NF-κB was reduced by OVX. As a result, we hypothesize that the pro-apoptotic response of JNK underlying the proBDNF pathway functions in hippocampal dysfunctions induced by OVX. Estrogen deficit-associated hippocampal dysfunction may be associated with inhibition of the mBDNF pathway and the pro-apoptotic action of proBDNF. Exercise is beneficial for hippocampal functions (19,20), and it is associated with increased mBDNF expression and signaling (22). In addition, exercise has a role in the improvement and protection of the hippocampus in neurodegenerative diseases (51). Jin *et al* (1) reported that exercise improved cognitive functions in a rat model of OVX. To investigate the effects of exercise on OVX, rats were subjected to treadmill exercise following OVX and it was observed that regular exercise improved BDNF pathways in the hippocampus, increasing the levels of mBDNF, TrkB and tPA, and reducing levels of proBDNF, p75NTR and JNK. These results suggested that exercise may suppress the pro-apoptotic response of the proBDNF-p75NTR pathway by increasing synthesis of mBDNF and activating tPA. Thus, exercise may enhance neuronal functions in the OVX rat brain.

The present study has several important implications. First, hippocampal dysfunction induced by OVX was caused by dysfunction of the mBDNF pathway and the pro-apoptotic response associated with the proBDNF pathway. In addition, it was demonstrated that pro-apoptotic action through the proBDNF-p75NTR cascade involved the JNK pathway. Furthermore, dysfunction of BDNF signaling was improved by exercise. Therefore, regular exercise may improve BDNF pathways in the hippocampus of OVX rats. These results may aid future studies investigating the effects of exercise on proBDNF and mBDNF pathways, in addition to hippocampal function, estrogen deficiency and menopause.

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