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Forced running exercise attenuates hippocampal neurogenesis impairment and the neurocognitive deficits induced by whole-brain irradiation via the BDNF-mediated pathway

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ABSTRACT

Cranial radiotherapy induces progressive and debilitating cognitive deficits, particularly in long-term cancer survivors, which may in part be caused by the reduction of hippocampal neurogenesis. Previous studies suggested that voluntary exercise can reduce the cognitive impairment caused by radiation therapy. However, there is no study on the effect of forced wheel exercise and little is known about the molecular mechanisms mediating the effect of exercise. In the present study, we investigated whether the forced running exercise after irradiation had the protective effects of the radiation-induced cognitive impairment. Sixty-four Male Sprague–Dawley rats received a single dose of 20 Gy or sham whole-brain irradiation (WBI), behavioral test was evaluated using open field test and Morris water maze at 2 months after irradiation. Half of the rats accepted a 3-week forced running exercise before the behavior detection. Immunofluorescence was used to evaluate the changes in hippocampal neurogenesis and Western blotting was used to assess changes in the levels of mature brain-derived neurotrophic factor (BDNF), phosphorylated tyrosine receptor kinase B (TrkB) receptor, protein kinase B (Akt), extracellular signal-regulated kinase (ERK), calcium-calmodulin dependent kinase (CaMKII), cAMP-calcium response element binding protein (CREB) in the BDNF–pCREB signaling. We found forced running exercise significantly prevented radiation-induced cognitive deficits, ameliorated the impairment of hippocampal neurogenesis and attenuated the down-regulation of these proteins. Moreover, exercise also increased behavioral performance, hippocampal neurogenesis and elevated BDNF–pCREB signaling in non-irradiation group. These results suggest that forced running exercise offers a potentially effective treatment for radiation-induced cognitive deficits.

1. Introduction

Radiation therapy is an important treatment modality for primary and metastatic brain tumors [1]. However, cranial irradiation may result in debilitating cognitive deficits in both pediatric and adult patients, especially in who survive long enough (>6 months). Although short-term interventions have proved to be effective, there are no proven successful long-term treatments or effective preventative strategies for radiation-induced cognitive deficits. Thus, the search for therapeutic strategies to prevent/ameliorate radiation-induced cognitive deficits has become very important [2]. Data from human [3] and rodents [4] both indicate that decreased hippocampal neurogenesis is one of the most important mechanisms involved in radiation-induced cognitive impairment, although the exact mechanisms under it are not very clear.

Exercise enhances neurogenesis, growth factors expression and synaptic plasticity in the hippocampus of rodents, and these changes have been associated with improved cognitive function, spatial memory, and learning [5]. In humans, physical activity is known to not only improve cognitive function and but also be associated with reduced risk of dementia, Alzheimer's disease and cognitive impairment in elderly individual [6–8].

Brain-derived neurotrophic factor (BDNF) is well known to play an important role in the adult brain in synaptic plasticity, learning, and neurogenesis and is considered to be the most important factor upregulated by exercise [9]. Mature BDNF activates tyrosine receptor kinase B (TrkB) signaling follows the general scheme for receptor tyrosine kinases, and downstream effectors, including protein kinase B (Akt), extracellular signal-regulated kinase (ERK), and calcium-calmodulin dependent kinase (CaMKII), are phosphorylated. Ultimately, the transcription factor cAMP-calcium response element binding protein (CREB) that mediates transcription of genes essential for the survival and differentiation of neurons was phosphorylated and activated [10].

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In previous studies, voluntary exercise (VEx) has been demonstrated to be of great benefit to radiation-induced cognitive impairment both in hippocampus-dependent cognitive performance and hippocampus neurogenesis in rodents [11,12]. However, no one knows the effect of forced running exercise (FEx) and little is known about the molecular mechanisms mediating the effect of exercise. We hypothesized that FEx after irradiation of the rat brain would help to decrease the declines on hippocampus-dependent cognitive function and hippocampal neurogenesis. We also detected the changes in protein expression of BDNF–pCREB signaling pathway in the hippocampus, which may potentially contribute to the effect of exercise.

2. Materials and methods

2.1. Animals

A total of 104 healthy Sprague–Dawley rats (male, one month old) was obtained from the Experimental Animal Center of Soochow University (Suzhou, China). All animals were maintained four per cage with food and water ad libitum, on 12 h light–dark cycles (lights on at 7 AM) at 22 ± 2 °C. The Animal Care and Ethics Committee at the Soochow University, China, approved all experimental procedures. Fig.1 presents the timeline of all experimental procedures.

In the first part of the experiment, we examined the effects of forced running on recognition at different intensities. The animals were divided into 4 groups: the control group (C), the low-intensity exercise group (LE), the moderate-intensity exercise group (ME), the high-intensity exercise group (HE) (n = 10 in each group).

The second part of the experiment was aimed at determining whether the forced wheel running exercise can ameliorate the radiation recognition impairment induced by whole brain irradiation. The animals were divided into 4 groups: the sham group (Sham), the sham and exercise group (EX), the irradiation group (IR), the irradiation and exercise group (IR + EX) (n = 16 in each group).

2.2. Forced wheel running exercise

Animals submitted to forced running were placed into a motor-driven running wheel (diameter = 380 mm, width = 120 mm, Dingda, Beijing, China). The speed and intensity of forced running were determined the velocity of the wheel revolution. Three running intensities (light, moderate and high) were set at a running speed of 6, 8 and 10 rounds/min, respectively. Animals in the exercise group were run on the motor-driven running wheel twice a day (30 min in the morning and 30 min in the afternoon), 5 days a week for a consecutive 3-week period.

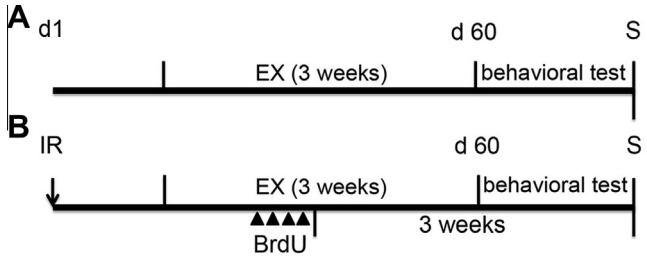

Fig. 1. Experimental design and timeline of procedures. (A) After three kinds of intensities FEx, four groups of animals were subjected to behavioral test. (B) 3 weeks before sacrificed, rats received four twice daily BrdU injections (arrowheads); exercise group rats were given a 3-week FEx before the starting of behavioral test.

2.3. Irradiation

The animals were anesthetized with an intraperitoneal injection of 3.6% chloral hydrate (360 mg/kg). Sham irradiated rats were treated similarly. Rats were irradiated using a linear accelerator (Philips SL − 18) as described previously [13,14]. The whole brain of each rat received a single dose of 0 Gy or 20 Gy of 4 MeV electron beam.

2.4. Behavioral test

The tests used here included open field, Morris water maze. All experiments were performed during 08:00–16:00, and the experimenter was blinded to the treatment of the animals.

2.4.1. Open field test

Performance in learning and memory tests can be affected by different levels of anxiety. Therefore, the open field test was used to assess the anxiety, as described previously [14]. The animals were placed singly in a square open field (OF) arena of 41 × 41 cm, placed inside an isolated box (Jiliang, Shanghai, China). The middle and inner area was called central region. Animals were observed for 10 min to assess spontaneous exploratory behavior. Ambient sound levels, light intensity, and room temperature were maintained at constant levels for all experimental sessions. The path of the animals was recorded by the automated video-tracking system (Jiliang, Shanghai, China). The total distance traveled and the time spent in the central region of the OF were recorded. The apparatus was cleaned thoroughly between trials with 10% ethanol to remove any olfactory cues.

2.4.2. Morris water maze test

Assessment of hippocampus-dependent cognitive performance was conducted using the Morris water maze test, as described previously [14]. A circular water tank (160 cm diameter) filled with water (22 ± 1 °C) was placed in a dimly lit behavioral testing room. Visual cues were placed around the room as spatial references. The place navigation test was conducted on days 1–4. A platform (9 cm diameter) was placed in one of the four maze zones (the target zone) and submerged 1.5 cm below the water surface. All animals conducted 4 trials per day (16 trials total), and the tank insertion point was changed from trial to trial. The maximum trial duration was 60 s. If the animal found the platform within 60 s, it was permitted to rest there for 10 s before finishing the trial. If the animal failed to find the platform in 60 s, it was manually guided to the platform and allowed to remain there for 10 s. The latency (time to find the platform) and swim speed were recorded by the automated video-tracking system (Jiliang, Shanghai, China). Spatial probe test took place on day 5, the platform was removed and animals were allowed to swim freely for 30 s. The time for crossing the target zone, and the total time for crossing all zones were recorded by the automated video-tracking system (Jiliang, Shanghai, China).

2.5. Western blot

Four groups (the second part of the experiment) of rat hippocampus tissues were lysed for total protein extraction. The protein concentration was determined by the BCA method (Beyotime, Nantong, China). 30 μg extracted proteins were separated by SDS–polyacrylamide gel electrophoresis (SDS–PAGE) and transferred onto PVDF membranes (Millipore, Billerica, MA, USA).The membranes were blocked in 5% non-fat milk and incubated overnight at 4 °C with the appropriate primary antibodies. BDNF antibody was purchased from Epitomics (Burlingame, CA, USA). Phospho-TrkB antibody was purchased from BD Biosciences (San

Diego, CA, USA). The antibody phospho-Akt (Ser473), Akt, phospho-p44/42 MAPK (Erk1/2) (Thr202/Tyr204), p44/42 MAPK (Erk1/2), phospho-CaMKII (Thr286), CaMKII, phospho-CREB (Ser133), CREB, and TrkB antibodies were all purchased from Cell Signaling Technologies (Beverly, MA, USA). β-Actin (Abcam, Cambridge, MA, USA) was used as the internal reference. Membranes were then incubated with HRP-conjugated secondary antibody (Abcam, Cambridge, MA, USA). After washing with TBST buffer, membranes were subsequently assayed using the Thermo Scientific Pierce Femto ECL (Rockford, IL, USA).

2.6. 5-Bromodeoxyuridine (BrdU) labeling and tissue processing

BrdU (Sigma, St. Louis, MO, USA) at 50 mg/kg/day was administered intraperitoneally (i.p.) for four consecutive days (twice a day) to SD rats 3 weeks before sacrificed. After the rats were anesthetized, tissue fixation was done by transcardiac perfusion with 0.9% saline, followed by 4% paraformaldehyde. Brains were removed and postfixed overnight in 4% paraformaldehyde at 4 °C, and then equilibrated in 30% sucrose for an additional 24 h. Serial sections of the brains were cut (30 μm sections) through the entire hippocampus on a freezing microtome.

2.7. Immunohistochemistry and immunofluorescence staining

For immunohistochemical detection of BrdU-labeled nuclei, sections placed on slides were incubated for 30 min with 2 N HCl at 37 °C for DNA denaturation, then neutralized in 0.1 M borate buffer (pH 8.5) for 10 min. Slides were soaked in cold methanol for 20 min to increase permeability of fixed tissue and then blocked using 10% normal calf serum for 2 h at room temperature. After blocking, slides were incubated overnight with rat monoclonal anti-BrdU antibody (Abcam, Cambridge, MA, USA) at 4 °C. Co-labeling runs used mouse anti-NeuN (Millipore, Billerica, MA, USA) for the visualization of neurons. After washes, secondary fluorescent antibodies, Alexa Fluor® 555 goat anti-rat, Alexa Fluor® 488 rabbit anti-mouse, were applied for 1 h and visualized with confocal laser scanning microscopy.

For immunohistochemical detection of doublecortin (DCX)-positive cells, slides were soaked in cold methanol for 20 min to increase permeability of fixed tissue and then blocked using 10% normal calf serum for 2 h at room temperature. After blocking, slides were incubated overnight with rabbit anti-DCX antibody (CST, Beverly, MA, USA) at 4 °C. After washes, secondary fluorescent antibodies, Alexa Fluor® 488 donkey anti-rabbit, was applied for 1 h and visualized with confocal laser scanning microscopy.

2.8. Microscopy and cell counting

An olympus microscope equipped with digital camera (Olympus) was used to analyze the sections. Every sixth section throughout the hippocampus was counted for the total number of DCX^+ or $BrdU^+/NeuN^+$ cells (10 sections per animal). The number of positives per a dentate gyrus (DG) of hippocampus was obtained by multiplying the value by 6.

2.9. Statistical analysis

Data are expressed as mean ± SD. One-way analysis of variance (ANOVA) was used to compare the exercise treatment or radiation effect by SPSS16.0 software (SPSS, Seattle, WA, USA). Values of $P < 0.05$ deemed statistically significant. Data were analyzed and graphs were plotted by GraphPad Prism software version 5.0.

3. Results

3.1. General observation

According to previous study [14], whole brain irradiation (WBI) with 20 Gy as used here was tolerated by all animals, can cause hippocampus-dependent cognitive impairment without any gross histologic change. All rats survived after the WBI and showed normal daily activities, including feeding and drinking. Mild depilation was observed in the irradiated area 2–3 weeks after WBI but gradually disappeared. Neither irradiation nor FEx caused a significantly change on body weight (data not shown).

3.2. Moderate-intensity forced running exercise significantly improved learning and memory in intact animals

There was no significant group difference in total distance traveled and the time spent in the central region ($P = 0.118, 0.148$). This indicates that FEx has no effect on locomotor activity or anxiety. There was no significant group difference in average swim velocity ($P = 0.226$). In the place navigation test, all of the three intensity FEx groups decreased latency time compared with the control group but only the moderate-intensity one reached significant ($P = 0.001$, Fig. 2A). In the spatial probe test, no significant group difference was found in the percentage of target quadrant exploring time ($P = 0.804$; Fig. 2B).

3.3. Forced running exercise rescues cognitive deficits induced by whole-brain irradiation

There was no significant group difference in total distance traveled and the time spent in the central region ($P = 0.656, 0.434$).This indicates that neither WBI nor FEx has an effect on locomotor activity or anxiety. In Morris maze test, there was no significant group difference in average swim velocity ($P = 0.843$). In the place navigation test, WBI significantly increased latency time compared with the sham group ($P = 0.014$, Fig. 2C). FEx significantly decreased latency time both in sham group and irradiation group ($P = 0.004$; $P < 0.001$, Fig. 2C). In the spatial probe test, no significant group difference was found in the percentage of target quadrant exploring time ($P = 0.286$; Fig. 2D).

3.4. Forced running exercise enhances neurogenesis and elevates BDNF–pCREB signaling in the hippocampus after whole-brain irradiation

We found irradiation reduced the number of immature neurons (DCX^+) in the DG significantly 2 months after WBI ($P < 0.001$). Our data show that FEx brought a 159% and 211% increase of DCX^+ cells in the DG compared with sham group and irradiated group animals, respectively ($P = 0.001$; $P < 0.001$) (Fig. 3A).

The effect of FEx on neurogenesis was assessed by analysis of BrdU, which is incorporated into the DNA during S-phase, was administrated 3 weeks before perfusion fixation, in combination with the mature neurons marker NeuN. WBI induced a significant reduction (82%) of the total number of new neurons ($BrdU^+/NeuN^+$) compared with the sham group ($P < 0.001$). The total number of $BrdU^+/NeuN^+$ cells was significantly increased (189%) in sham and exercise group compared with the sham group ($P < 0.001$). In irradiation and exercise group, there was a significant increase (226%) in the number of newborn cells becoming neurons compared with irradiation group ($P < 0.001$) (Fig. 3B).

WBI significantly decreased BDNF expression and TrkB receptor phosphorylation in the hippocampus to about 62% and 46%, respectively, compared with the sham group ($P = 0.001$;

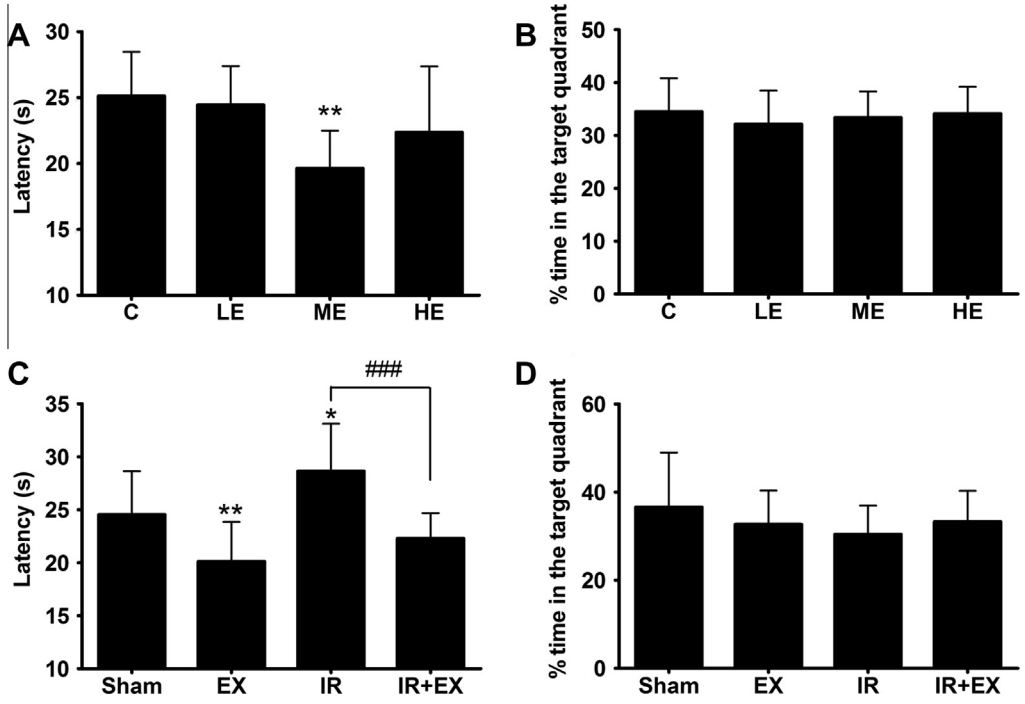

Fig. 2. Morris water maze test. (A) Moderate-intensity FEx significantly decreased the latency in the place navigation test. (B) The percentage of target quadrant exploring time was similar between groups. (C) FEx decreased the latency increased by WBI. (D) No significant group difference was found in percentage of target quadrant exploring time. Data are expressed as mean ± SD, $^{*}P < 0.05$, $^{**}P < 0.01$ vs sham group, $^{###}P < 0.001$ vs irradiation group.

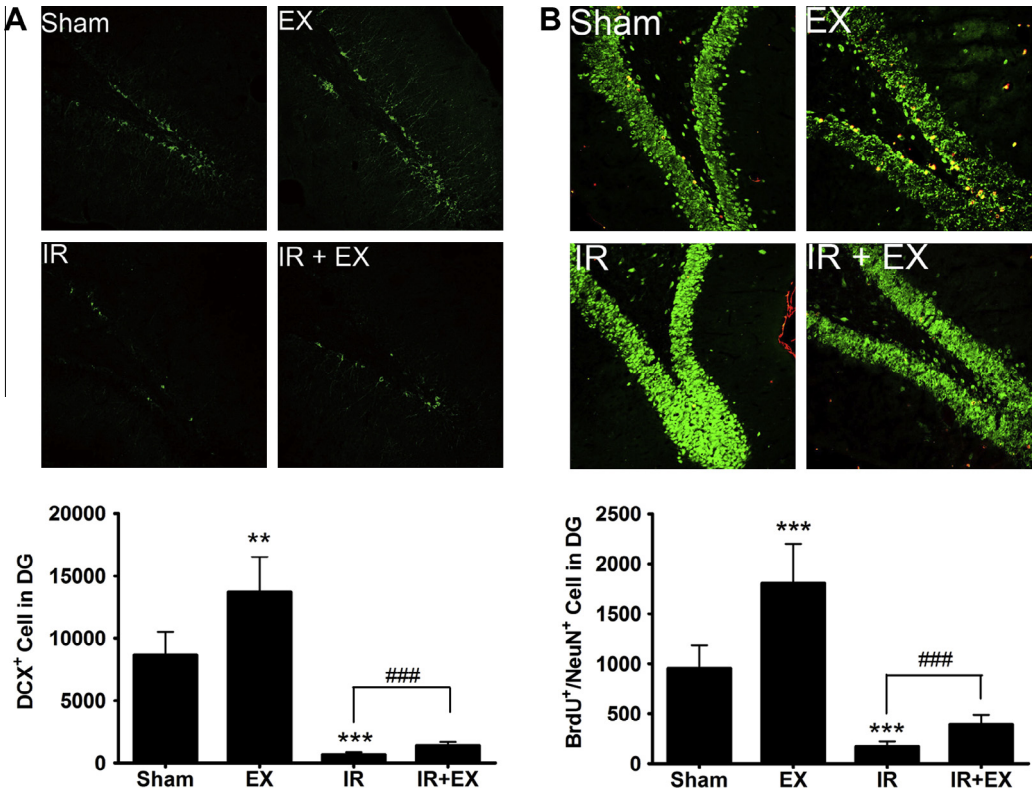

Fig. 3. Forced running exercise increased the neurogenesis in the dentate gyrus (DG) in sham and irradiated animals 2 months after WBI. (A) Representative fluorescence images of DCX^{+} cells in the DG of each group of animals 2 months after irradiation. The total number of DCX^{+} cells in the DG increased after FEx compared with sham and irradiated animals. (B) Representative confocal images [$BrdU^{+}$ cells (red), $NeuN^{+}$ cells (green)] of each group of animals. The total number of newly generated neurons in the DG increased after FEx compared with sham and irradiated animals. All micrographs are at 200× magnification. Data are expressed as mean ± SD, $^{**}P < 0.01$, $^{***}P < 0.001$ vs sham group, $^{###}P < 0.001$ vs irradiation group. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

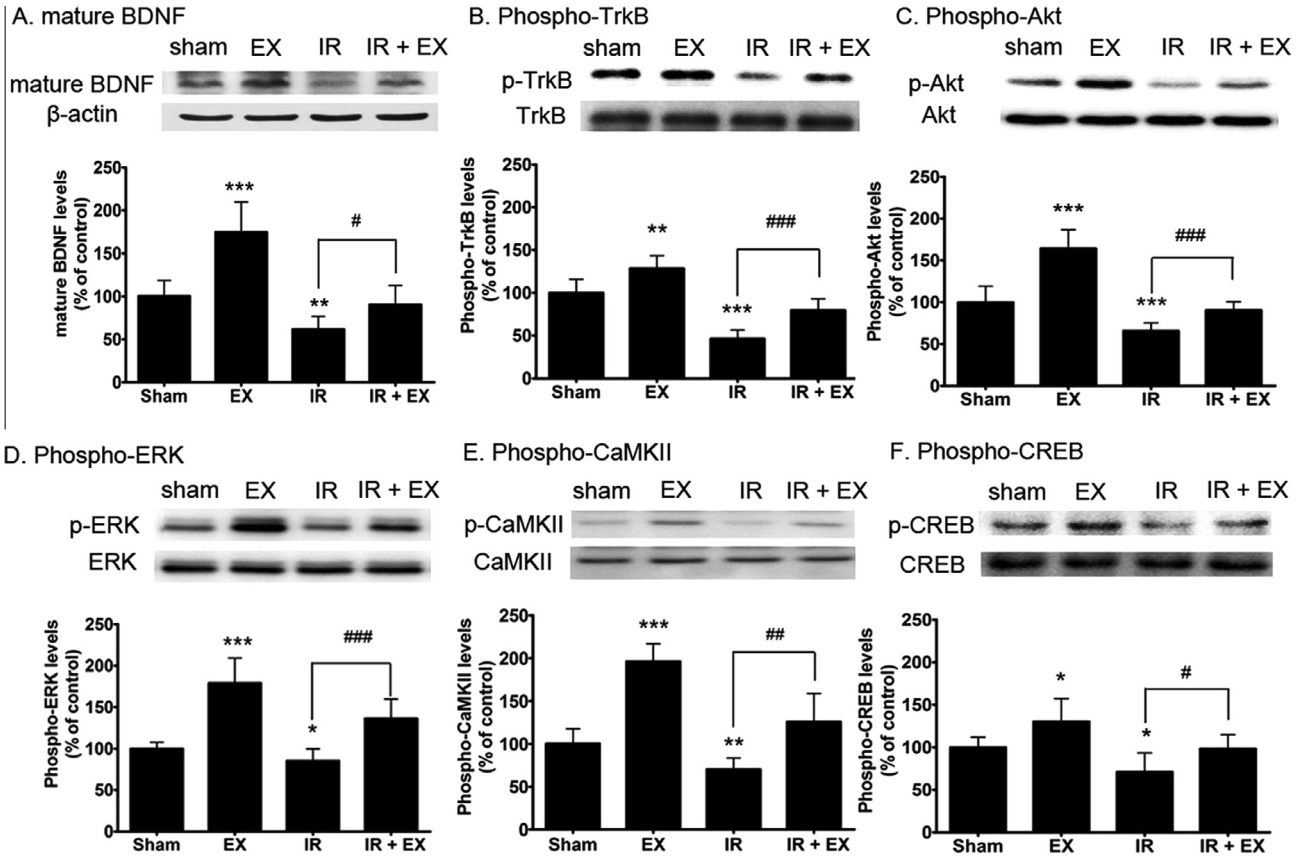

Fig. 4. WBI-reduced mature BDNF (A), phospho-TrkB (B), phospho-Akt (C), phospho-ERK (D), phospho-CaMKII (E) and phospho-CREB (F) were increased by forced running exercise in the rat hippocampus. Data are expressed as mean ± SD, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ vs sham group, $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, $^{\#\#\#}P < 0.001$ vs irradiation group.

$P < 0.001$; Fig. 4A and B). FEx significantly improved BDNF expression and TrkB receptor phosphorylation in the irradiation and exercise group (90% and 80% of sham group, respectively) compared with the irradiation group ($P = 0.016$; $P < 0.001$). BDNF expression and TrkB receptor phosphorylation in the exercise group was increased to about 175% and 128% respectively, compared with the sham group ($P < 0.001$; $P = 0.005$; Fig. 4A and B).

WBI significantly reduced the level of Akt, ERK, CaMKII, and CREB phosphorylation (66%, 85%, 70%, and 71%, respectively) compared with levels in the sham group ($P = 0.001$; $P = 0.036$; $P = 0.001$; $P = 0.012$; Fig. 4C–F). FEx significantly increased the levels of phosphorylated Akt, ERK, CaMKII, and CREB (phosphorylated Akt, 164% of sham, $P < 0.001$, Fig. 4C; phosphorylated ERK, 179% of sham, $P < 0.001$, Fig. 4D; phosphorylated CaMKII, 196% of sham, $P < 0.001$, Fig. 4E; and phosphorylated CREB, 130% of sham, $P = 0.02$, Fig. 4F). FEx prevented reduction in phosphorylation of these proteins (phosphorylated Akt, 91% of control, $P < 0.001$; phosphorylated ERK, 136% of control, $P < 0.001$; phosphorylated CaMKII, 126% of control, $P = 0.001$; and phosphorylated CREB, 98% of control, $P = 0.024$; Fig. 4C–F).

4. Discussion

Our study is the first to demonstrate that FEx for 3 weeks activated Akt, ERK, CaMKII and CREB, the major signaling intermediates of the BDNF-pCREB pathway, via BDNF/TrkB signaling in the hippocampus of rats. The enhanced BDNF–pCREB signaling is beneficial not only in increasing the number of hippocampal newborn neurons but also in reducing functional impairment in irradiated rat. Moreover, FEx significantly increased hippocampal neurogenesis and cognitive function in the sham group via BDNF–pCREB pathway.

Cranial radiation therapy is associated with a progressive decline in cognitive function. Although the exact mechanism(s) of this cognitive decline is unclear, impairment of hippocampal neurogenesis is thought to be an important mechanism underlying it. Consistent with previous studies [4,15], our findings demonstrate that irradiation caused declined cognitive function detected by the Morris water maze test 2 months after WBI was correlated with the inhibited neurogenesis in the hippocampus in our rat model.

Exercise enhances cognitive function in many models of brain disease, such as delaying cognitive decline associated with aging, preventing cognitive deficits in a variety of Alzheimer's disease models, modifying cognitive of Parkinson's disease, modulating cognitive deficits in Huntington's disease models, neuroprotective effects on models of chronic stress, recovery from traumatic brain injury [16]. Previous studies have shown that WBI caused a progressive loss of learning and memory function that can be rescued by VEx [11,12] or environmental enrichment that included shared access to a running wheel [17]. Because of humans cannot spend much time during the day for exercise, in the present study, we used FEx as it is more similar to human exercise training, and allowed animals to run regularly only for a limited time per day. Compared with non-exercise group of animals, hippocampus-dependent spatial learning and memory were significantly improved by FEx both in irradiation and sham groups. The significant increase in both the total population of immature neurons and newborn neurons identified as DCX^{+} and $BrdU^{+}/NeuN^{+}$ cells in FEx animals suggests an enhancement of hippocampal neurogenesis activity in the irradiation and sham groups (Fig. 3).

Previous studies on exercise have revealed that exercise can regulate neurotrophic factors important for brain cognitive function, such as BDNF, vascular endothelial growth factor (VEGF) and insulin-like growth factor-1(IGF-1) [18]. In a lot of studies, hippocampal BDNF is shown as a notable mediator for the effects of exercise on learning and memory, it has been the most important of these factors. Improvements in performance on the spatial learning task Morris water maze in exercised rats were abolished by blocking hippocampal BDNF action, evidenced the strong relationship of BDNF to the link between exercise and synaptic plasticity [19]. Suppressed BDNF and (or) its downstream molecules are enhanced by exercise in aged, stressed, Alzheimer's disease, Parkinson's disease and traumatic brain injury animal models [16]. In our present study, expression of BDNF–pCREB signaling pathway proteins were shown to be down-regulated by WBI, that was consistent with previous studies [12,20]. We found FEx increased hippocampal BDNF levels and the phosphorylation of its downstream signaling molecules both in irradiation and sham groups (Fig. 4).

Several studies had indicated that WBI can lead to vascular damage, microvascular rarefaction [21], or dendritic spine density reduction [22], all of them were closely associated with cognitive function. Meanwhile, exercise had been certificated can improve angiogenesis and spine density. In our further research, we can detect these changes in hippocampus.

In summary, our present study is the first to report that FEx activates BDNF–pCREB signaling, which is impaired in the hippocampus of rats subjected to radiation. Moreover, FEx significantly increased BDNF–pCREB signaling in the sham irradiation. The enhancement of BDNF–pCREB signaling correlates with the effects of exercise on hippocampal neurogenesis and hippocampus-dependent learning and memory. Our results provide a clearer understanding of the molecular changes related to exercise-induced protective effects of radiation-induced cognitive impairment. Furthermore, our findings highlight the importance of physical exercise as a potential therapeutic intervention.

Acknowledgments

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References

[1] S. Scoccianti, U. Ricardi, Treatment of brain metastases: review of phase III randomized controlled trials, Radiother. Oncol. 102 (2012) 168–179.
[2] D. Greene-Schloesser, M.E. Robbins, Radiation-induced cognitive impairment – from bench to bedside, Neuro. Oncol. 14 (Suppl. 4) (2012) iv37–iv44.
[3] M.L. Monje, H. Vogel, M. Masek, K.L. Ligon, P.G. Fisher, T.D. Palmer, Impaired human hippocampal neurogenesis after treatment for central nervous system malignancies, Ann. Neurol. 62 (2007) 515–520.
[4] R. Rola, J. Raber, A. Rizk, S. Otsuka, S.R. VandenBerg, D.R. Morhardt, J.R. Fike, Radiation-induced impairment of hippocampal neurogenesis is associated with cognitive deficits in young mice, Exp. Neurol. 188 (2004) 316–330.
[5] R.M. Arida, F.A. Scorza, S. Gomes da Silva, R.M. Cysneiros, E.A. Cavalheiro, Exercise paradigms to study brain injury recovery in rodents, Am. J. Phys. Med. Rehabil. 90 (2011) 452–465.
[6] A. Verdelho, S. Madureira, J.M. Ferro, H. Baezner, C. Blahak, A. Poggesi, M. Hennerici, L. Pantoni, F. Fazekas, P. Scheltens, G. Waldemar, A. Wallin, T. Erkinjuntti, D. Inzitari, Physical activity prevents progression for cognitive impairment and vascular dementia: results from the LADIS (Leukoaraiosis and Disability) study, Stroke 43 (2012) 3331–3335.
[7] F.M. Coelho, D.S. Pereira, L.P. Lustosa, J.P. Silva, J.M. Dias, R.C. Dias, B.Z. Queiroz, A.L. Teixeira, M.M. Teixeira, L.S. Pereira, Physical therapy intervention (PTI) increases plasma brain-derived neurotrophic factor (BDNF) levels in non-frail and pre-frail elderly women, Arch. Gerontol. Geriatr. 54 (2012) 415–420.
[8] N. Scarmeas, J.A. Luchsinger, N. Schupf, A.M. Brickman, S. Cosentino, M.X. Tang, Y. Stern, Physical activity, diet, and risk of Alzheimer disease, JAMA 302 (2009) 627–637.
[9] C.W. Cotman, N.C. Berchtold, L.A. Christie, Exercise builds brain health: key roles of growth factor cascades and inflammation, Trends Neurosci. 30 (2007) 464–472.
[10] C. Cunha, R. Brambilla, K.L. Thomas, A simple role for BDNF in learning and memory?, Front Mol Neurosci. 3 (2010) 1.
[11] A.S. Naylor, C. Bull, M.K. Nilsson, C. Zhu, T. Bjork-Eriksson, P.S. Eriksson, K. Blomgren, H.G. Kuhn, Voluntary running rescues adult hippocampal neurogenesis after irradiation of the young mouse brain, Proc. Natl. Acad. Sci. USA 105 (2008) 14632–14637.
[12] S.J. Wong-Goodrich, M.L. Pfau, C.T. Flores, J.A. Fraser, C.L. Williams, L.W. Jones, Voluntary running prevents progressive memory decline and increases adult hippocampal neurogenesis and growth factor expression after whole-brain irradiation, Cancer Res. 70 (2010) 9329–9338.
[13] Y. Tian, Z. Shi, S. Yang, Y. Chen, S. Bao, Changes in myelin basic protein and demyelination in the rat brain within 3 months of single 2-, 10-, or 30-Gy whole-brain radiation treatments, J. Neurosurg. 109 (2008) 881–888.
[14] L.Y. Zhang, L.S. Chen, R. Sun, S.J. Ji, Y.Y. Ding, J. Wu, Y. Tian, Effects of expression level of DNA repair-related genes involved in the NHEJ pathway on radiation-induced cognitive impairment, J. Radiat. Res. 54 (2013) 235–242.
[15] J. Raber, R. Rola, A. LeFevour, D. Morhardt, J. Curley, S. Mizumatsu, S.R. VandenBerg, J.R. Fike, Radiation-induced cognitive impairments are associated with changes in indicators of hippocampal neurogenesis, Radiat. Res. 162 (2004) 39–47.
[16] T.Y. Pang, A.J. Hannan, Enhancement of cognitive function in models of brain disease through environmental enrichment and physical activity, Neuropharmacology 64 (2013) 515–528.
[17] Y. Fan, Z. Liu, P.R. Weinstein, J.R. Fike, J. Liu, Environmental enrichment enhances neurogenesis and improves functional outcome after cranial irradiation, Eur. J. Neurosci. 25 (2007) 38–46.
[18] M.W. Voss, C. Vivar, A.F. Kramer, H. van Praag, Bridging animal and human models of exercise-induced brain plasticity, Trends Cogn. Sci. 17 (2013) 525–544.
[19] S. Vaynman, Z. Ying, F. Gomez-Pinilla, Hippocampal BDNF mediates the efficacy of exercise on synaptic plasticity and cognition, Eur. J. Neurosci. 20 (2004) 2580–2590.
[20] S.B. Oh, H.R. Park, Y.J. Jang, S.Y. Choi, T.G. Son, J. Lee, Baicalein attenuates impaired hippocampal neurogenesis and the neurocognitive deficits induced by gamma-ray radiation, Br. J. Pharmacol. 168 (2013) 421–431.
[21] J.P. Warrington, N. Ashpole, A. Csiszar, Y.W. Lee, Z. Ungvari, W.E. Sonntag, Whole brain radiation-induced vascular cognitive impairment: mechanisms and implications, J. Vasc. Res. 50 (2013) 445–457.
[22] A. Chakraborti, A. Allen, B. Allen, S. Rosi, J.R. Fike, Cranial irradiation alters dendritic spine density and morphology in the hippocampus, PLoS One 7 (2012) e40844.