Research Article

Exercise-Enhanced Neurogenesis: A Potential Remedy for Malnourished Rat Brains

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Abstract

Physical exercise has gained attention as a prospective intervention, leveraging its established capacity to augment brain function and cognition through neurogenesis and the production of brain-derived neurotrophic factor (BDNF) facilitated by the FNDC5 pathway. This study aims to evaluate Fndc5 gene expression in malnourished rat brains induced by a low-protein diet coupled with exercise intervention to unravel the interplay of nutrition, exercise, and brain function in addressing malnutrition. The research was conducted from June to September 2022 with total of 20 male wistar rats, aged 6 weeks, were categorized into four groups (control, low-protein diet, normal diet with exercise, and low-protein diet with exercise). The intervention spanned 24 weeks with 8 weeks low-protein diet followed by 16 weeks of moderate-intensity exercise. Brain tissue of wistar rats was collected for brain weight assessment and RNA extraction. The brain weight and Fndc5 mRNA expression were significantly increased in the normal diet and exercise group compared with the control group. The brain weight rose slightly in the low-protein diet plus exercise group compared to the exercise-absent low-protein diet group; however, the difference was not statistically significant (p=0.722). There was no substantial rise in Fndc5 levels in the malnourished rat group subjected to exercise intervention compared to the non-exercising malnourished group (p=0.137). Exercise intervention in the normal diet group can increase brain weight and Fndc5 expression. However, exercise intervention could not increase brain weight and Fndc5 expression in malnutrition model rats.
Keywords: *exercise, FNDC5, malnutrition, neurogenesis.*

Pengaruh Olahraga pada Neurogenesis: Potensial Terapi pada Tikus Model Malnutrisi

Abstrak

Olahraga berpotensi meningkatkan fungsi kognisi otak melalui mekanisme neurogenesis dan produksi brain-derived neurotrophic factor (BDNF) yang dipengaruhi jalur FNDC5. Oleh karena itu, penelitian ini bertujuan untuk menganalisis interaksi antara nutrisi, olahraga, dan fungsi otak. Penelitian dilakukan pada bulan Juni-September 2022. Sebanyak 20 tikus wistar jantan berusia 6 minggu dibagi 4 kelompok (kontrol, diet rendah protein, kontrol dengan olahraga, dan diet rendah protein dengan olahraga). Perlakuan keseluruhan selama 24 minggu dengan 8 minggu diet rendah protein dilanjutkan dengan 16 minggu olahraga intensitas sedang. Jaringan otak tikus diisolasi untuk ditimbang berat dan ekstraksi RNA. Berat otak dan ekspresi mRNA Fndc5 meningkat bermakna pada kelompok diet dan olahraga normal dibandingkan kelompok kontrol. Berat otak sedikit meningkat pada kelompok diet rendah protein dengan olahraga dibandingkan kelompok diet rendah protein tanpa olahraga; namun, perbedaannya tidak signifikan (p=0,722). Tidak ada peningkatan bermakna dalam kadar Fndc5 pada kelompok tikus malnutrisi yang menjalani olahraga dibandingkan kelompok malnutrisi yang tidak berolahraga (p=0,137). Olahraga pada kelompok diet normal dapat meningkatkan berat otak dan ekspresi Fndc5. Namun, olahraga tidak dapat meningkatkan berat otak dan ekspresi Fndc5 pada tikus model malnutrisi.
Kata kunci: *olahraga, FNDC5, malnutrisi, neurogenesis.*

Introduction

Malnutrition stands as a critical public health concern necessitating immediate attention.[1] Insufficient intake of essential nutrition, encompassing both quantitative and qualitative aspects of consumed dietary components, can lead to malnutrition. Among the pivotal manifestations of malnutrition, addressing pediatric undernutrition, colloquially known as stunting, holds paramount significance. The repercussions of malnutrition on health are far-reaching, extending to its profound influence on brain development and cognitive processes.[2,3] Studies have demonstrated the potential of malnutrition to precipitate neurological disorders in humans, encompassing cognitive decline and structural alterations in the brain.[4–6] Therefore, it is important to identify effective interventions to mitigate the negative impact of malnutrition on the nervous system.

Exercise has been identified as a potential intervention to address this issue. Exercise has been proven to have various health benefits, including enhancing brain function and cognition.[7,8] Studies in animals and humans have demonstrated that exercise can stimulate neurogenesis, the process of generating new neurons in the brain.[9–11] Additionally, exercise can increase the production of neurotrophic factors, improve blood flow to the brain, and reduce inflammation.[12–15] However, research on the effects of exercise on neurogenesis in malnourished rats is still limited.

This study defined the malnourished rats' model by providing a low-protein diet. The variables used were the expression of the *Fndc5* gene in the rat brain and their brain weight as a secondary measurement. The *Fndc5* expression has been linked to neurogenesis and brain development. Research using genetic deletion of *Fndc5* has shown abnormalities in brain morphology, transcription, and function. Studies have also indicated that exercise can increase the expression of the *Fndc5* in various organs under normal conditions. However, whether similar effects occur in malnourished rats subjected to exercise is unknown. This study aims to evaluate *Fndc5* gene expression in malnourished rat brains induced by a low-protein diet coupled with exercise intervention to unravel the interplay of nutrition, exercise, and brain function in addressing malnutrition.

Method

This research is a quantitative study with an experimental design using wistar strain rats (*Rattus norvegicus*), conducted from June to September 2022. This research was approved by UNPAD Ethical Committee No. 1024/UN6.KEP/EC/2023.

In this study, the rats, aged 6 weeks, with a baseline body weight range of 225−250 grams, were divided into four groups: a control group receiving a normal diet, a group receiving a normal diet with physical exercise, a group receiving a low-protein diet, and a group receiving a low-protein diet with physical exercise. In the treatment groups, after weaning, rats in the low-protein diet group were given a low-protein diet for 24 weeks. Meanwhile, rats in the low-protein diet with exercise group received 8 weeks of low-protein diet at the beginning of the experiment, followed by an intervention of moderate-intensity exercise for 16 weeks. Rats were exercised on a rodent treadmill (IDEAS, Indonesia), 20 m/min for 30 min/ day, 5 times per week. Moderate-intensity exercise is selected because it has been suggested as the most optimal intensity level to help improve cognitive function.[10,16,17] Five samples were used per group, resulting in 20 samples in total.

During the exercise intervention period, the low-protein diet was provided *ad libitum*. After 16 weeks of exercise intervention, all experimental rat groups were euthanized by administering 5% isoflurane inhalation anesthesia, followed by cervical dislocation performed by a trained individual. The brain tissues were isolated, cleaned from surrounding tissues, and stored in a -80°C freezer. The four groups of rat brain samples were individually weighed on a digital scale and the measurements were recorded for the macroscopic examination.

The total RNA of the brain was extracted using GENEzol reagent (Geneaid, Biotech Ltd., New Taipei, Taiwan); 200 µl of GENEzol was added to 17−20 mg of the sample. The mixture was homogenized for 30 seconds and incubated for 5 minutes at room temperature. The sample was centrifuged for 10 minutes at 11,200 rpm at 4 °C, transferred to a new 1.5 ml RNse-free microcentrifuge tube, and 40 µl of 100% chloroform solution was added. The mixture was homogenized with a vortex for 10 seconds and then centrifuged for 15 minutes. The 100−130 µl upper aqueous phase was transferred to a new 1.5 ml microcentrifuge tube and 100 ml of 100% isopropanol was added, then the mixture was homogenized and incubated at room temperature for 10 minutes.

Following incubation, the mixture was centrifuged for 10 minutes at 11,200 rpm at 4 °C to

form a tight RNA pellet and 200 µl of 70% ethanol was added, then the mixture was centrifuged for 5 minutes. The ethanol solution was discarded and RNAse-free water was added to resuspend the RNA pellet, which was then incubated for 10 minutes at 60 °C to dissolve the RNA pellet. The mRNA was subsequently quantified using a multimode microplate reader at 268/280 nm absorbance spectrophotometry (M200 Po, Tecan, Morrisville, NC). Semi-quantitative PCR was performed using a one-step PCR kit. Beta-actin was measured for each sample as an internal control and normalization. Following electrophoresis, the gel was visualized using a BluPAD Dual LED Blue/White Light Transilluminator (Bio-Helix Co., Taiwan).

The data were analyzed using SPSS V.29. Prior to data analysis, a normality test was conducted using the Shapiro-Wilk test, and a homogeneity test was performed using the Levene test. The differences in gene expression between these groups were analyzed using a one-way analysis of variance (ANOVA), which indicated mean ±minimum standard error (SEM). A significance level of less than 0.05 ($p<0.05$) was used to determine the statistical significance of the findings in this study.

Results

After the various treatments were administered, body weight was measured. All low-protein diet (LPD) groups showed lower body weight than the control group (Figure 1A). It indicated that LPD treatment successfully affected body weight in a rat model. Then, the brain weight was measured and classified into treatment groups. The average brain weight of the control group was 1.26 ±0.02, the LPD group was 1.12 ±0.02, the normal diet with exercise intervention group was 1.34 ±0.01, and the LPD with exercise intervention group was 1.15 ±0.02. The statistical significance of brain weight differences among the various treatment groups is shown in Figure 1B.

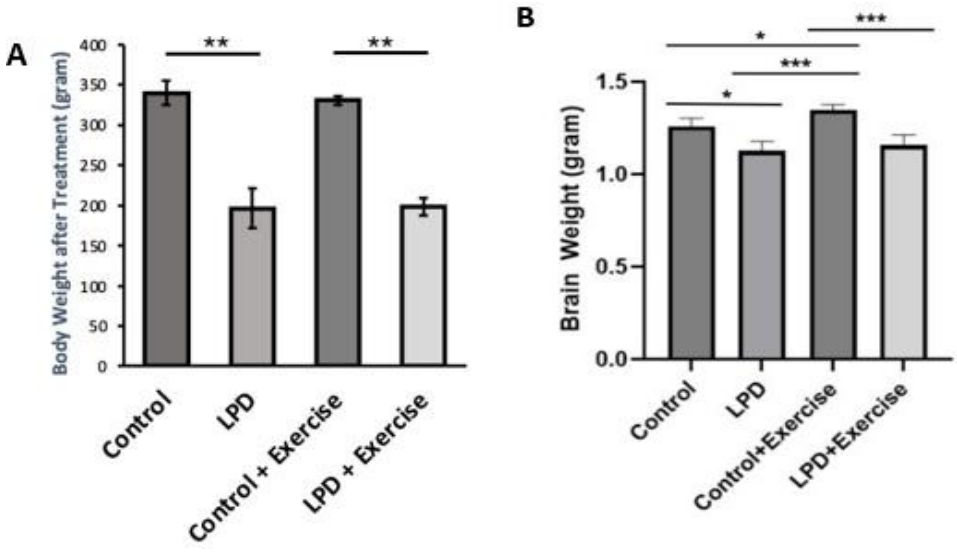

Figure 1. (A) Body Weight after The Treatment Period; (B) Brain Weight of All Groups. Values are expressed as mean ±SEM, *p<0.05; **p<0.01; ***p<0.001.

Compared to the control group, the exercise intervention group showed a significant increase in brain weight (p=0.025). On the other hand, the LPD group exhibited a significant decrease in brain weight (p=0.006). However, the LPD group with exercise intervention compared to the LPD group without exercise showed increased brain weight, but the results were not statistically significant (p=0.722).

The *Fndc5* mRNA expression is illustrated in Figure 2A. The mean expression of *Fndc5* normalized with beta-actin in the control group was 1.06 ±0.03, the LPD group was 0.897 ±0.015, the normal diet with exercise group was 1.313 ± 0.057, and the LPD with exercise group was 0.782 ±0.057. The statistical significance of *Fndc5* expression among the treatment groups can be seen in Figure 2B.

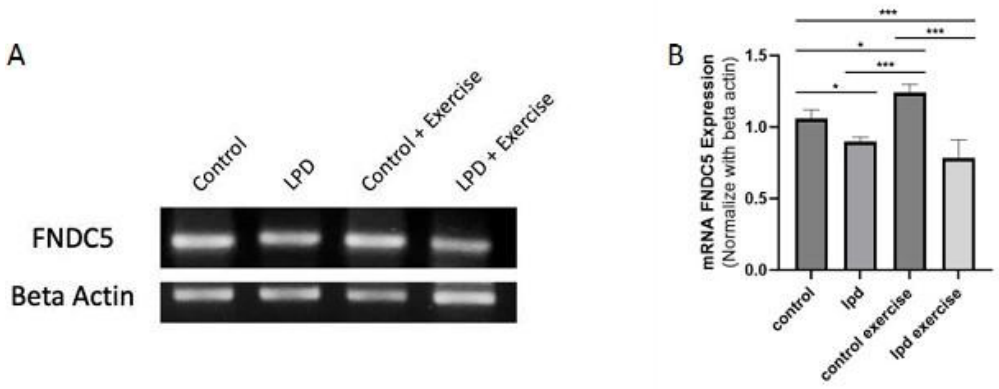

Figure 2. (A) Fndc5 mRNA Expression and (B) Quantification of mRNA Density. Values presented as mean ±SEM, *p<0.05, ***p<0.001

Compared to the control group, the exercise intervention group showed a significant increase in *Fndc5* expression (p=0.011). On the other hand, the LPD group exhibited a significant decrease in *Fndc5* expression (p=0.022). However, the LPD group with exercise intervention did not significantly increase compared to the LPD group without exercise (p=0.137).

Discussion

One of the benefits of being physically active is related to brain development. Various studies have shown increased hippocampal and overall brain volume with regular aerobic exercise.[11,18–22] In animal models subjected to exercise, there is an increase in neurogenesis in the dentate gyrus, which can be interpreted as an enhancement of learning and memory abilities. The mechanism may involved in this process is the upregulation of brain-derived neurotrophic factor (BDNF) synthesis during physical activity.[11] The increased BDNF is known to occur due to the secretion of proteins during muscle contractions, such as cathepsin-B and *Fndc5*/irisin.[11]

Fndc5 is known to interact with various molecules. In the context of exercise-related effects, PGC-1α induces the expression of the *Fndc5* through the availability of ERRα, and exercise leads to increased transcription of PGC-1α and ERRα, thereby increasing *Fndc5* transcription.[23] Additionally, *Fndc5* found in the brain act as a positive regulator of BDNF expression. Irisin also interacts with BDNF to regulate BDNF levels in the brain.

In this study, a statistically significant increase in brain weight was observed in the group of rats subjected to moderate-intensity exercise intervention compared to the control group. Moreover, a significant increase in mRNA gene expression was also found between these two groups. Exercise stimulates the upregulation of the *Fndc5* expression in the hippocampus through the PGC-1α/ERRα transcription.[23] This increased *Fndc5* expression and stimulated the expression of the BDNF gene. BDNF is a major regulator of cell survival, differentiation, and neuronal plasticity in the brain.[24] This leads to improved cognitive function, learning, and memory, known as the benefits of exercise on the brain.[24] The increased brain weight represents increased brain volume due to enhanced neurogenesis from exercise intervention.

In the LPD treatment group, a significant decrease in brain weight was observed compared to the control group. Similarly, a significant reduction in *Fndc5* expression between these two groups was also found. Previous research has revealed that circulating irisin is positively influenced by a high-protein diet, which promotes muscle growth.[25–27] In contrast, the decreased expression of the *Fndc5* in the brain may be influenced by the muscle's inability to produce irisin due to insufficient protein intake. The reduced brain weight may result from impaired neurogenesis, leading to a decrease in the number of neurons in the brain.

Protein malnutrition results in smaller brains with fewer neurons, reduced RNA and DNA content, and lower concentrations of neurotransmitters.[28,29] Studies in animal models have shown that an LPD leads to down-regulated synaptic components and accelerated brain atrophy.[30] Protein deficiency slows down development and impairs cognitive function. Considering that *Fndc5* plays a crucial role in BDNF formation, the decrease in *Fndc5* expression in the LPD group may contribute to the downregulation of synaptic components.

In the group with an LPD and exercise intervention, there was significantly lower body weight than the normal diet. However, there was no significant difference in brain weight compared to the group with an LPD without exercise. The lack of significance was observed in the *Fndc5* expression examination between these groups. This can be explained by severe malnutrition resulting from an LPD in the rat model limits the intake of essential amino acids, including those necessary for protein synthesis, such as histidine and phenylalanine.[31] These amino acids are essential building blocks in protein synthesis, including the proteins involved in the regulation of neurogenesis. Sufficient amino acid presence within cells is a critical requirement for protein synthesis and efficient gene transcription regulation, contributing to the decreased expression of the *Fndc5* in the malnourished rat brain.[32] Exercise may not adequately overcome the negative impact of malnutrition to trigger the expected increase in gene expression.

Moreover, it is essential to consider other factors that might have impacted these outcomes. These factors encompass the type, intensity, duration of exercise, and the potential influence of chronic inflammation. The specific characteristics of exercise, including how long and intense it lasts, could play a pivotal role in shaping this study's findings. Striking the right balance in exercise duration becomes crucial to trigger *Fndc5* expression in malnourished rats effectively. Furthermore, the severity of malnutrition can trigger chronic inflammation within the body. This inflammation could disrupt the intricate signaling pathways responsible for regulating *Fndc5* expression. During malnutrition, shifts in cytokine equilibrium might transpire, leading to elevated levels of interleukin-6 (IL-6) or tumor necrosis factor-α (TNF-α).[33–35] These cytokines, owing to their complex signaling networks, could potentially hinder the activation of the *Fndc5*, thus hampering its expression. In this intricate context, it becomes plausible that chronic inflammation linked with malnutrition might emerge as a counteracting factor, impeding the upregulation of *Fndc5* expression even in exercised malnourished rats. Consequently, the anticipated substantial increase in brain weight might also not manifest as expected.

The findings of this study hold the potential to shed light on the intricate connections between nutrition, exercise, and brain function. This may offer novel perspectives for devising enhanced strategies to treat or prevent the consequences of malnutrition on the nervous system. The limitations of this study are the potential impact of the duration and intensity of exercise on the research outcomes. Further research is needed to determine the appropriate exercise regimen that may provide better results. Additionally, the genetic differences present individually may also influence the research outcomes. Since this study only assessed the *Fndc5* expression, further research is necessary to evaluate neurotrophic factors and other gene interactions to conclude the effects on neurogenesis.

Conclusion

There was no significant increase in brain weight and *Fndc5* expression in the malnourished rat model with exercise intervention. Future histological examinations of the brains of the rats are preferable to observe the morphological changes in the malnourished rat model after exercise.

Conflict of Interest

There is no conflict of interest.

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