2024, Retos, 60, 27-33

Circulating IGF-1 related exercise associated with improved spatial memory in elderly mice
El ejercicio relacionado con el IGF-1 circulante se asocia a una mejora de la memoria espacial en ratones ancianos

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Abstract. This study examined the correlation between the circulating and hippocampal IGF-1 levels in elderly mice after exercise intervention and evaluated the relationship between circulating and hippocampal IGF-1 levels in improving the spatial memory function of elderly mice. Methods: Nine-month-old female mice were divided into treadmill, swimming, and control groups, each consisting of ten mice. Exercises were carried out for six weeks, five times a week. Before and after training, Y-maze spontaneous alternation tests were carried out for spatial working memory. After six weeks of exercise, hippocampal and circulating IGF-1 levels were measured with the ELISA method. ANOVA was performed to analyze differences between groups. Pearson's or Spearman's correlation analysis was performed to assess the correlation of hippocampal and circulating IGF-1 levels with spatial working memory and the correlation between circulating IGF-1 levels and hippocampal IGF-1 levels. Results: The circulating IGF-1 levels significantly increased ($p < 0.05$) in the treadmill and swimming groups compared to the control, while the hippocampal IGF-1 levels only significantly increased ($p < 0.05$) in the swimming group. There was a significant correlation between spatial memory and blood IGF-1 levels ($p = 0.002$), but no significant correlation ($p = 0.122$) existed between spatial memory and hippocampal IGF-1 levels. There was a significant correlation between serum IGF-1 levels and hippocampal IGF-1 levels ($p = 0.028$). Conclusion: Circulating IGF-1 levels were correlated with hippocampal IGF-1 levels. However, hippocampal IGF-1 levels had yet to demonstrate any significant correlation with improved memory function
Keywords: IGF-1, exercise, ageing, memory, healthy lifestyle

Resumen. Este estudio examinó la correlación entre los niveles de IGF-1 circulante e hipocampal en ratones ancianos después de una intervención de ejercicio y evaluó la relación entre los niveles de IGF-1 circulante e hipocampal en la mejora de la función de memoria espacial en ratones ancianos. Métodos: Se dividieron ratones hembra de nueve meses de edad en grupos de cinta rodante, natación y control, cada uno compuesto por diez ratones. Los ejercicios se llevaron a cabo durante seis semanas, cinco veces por semana. Antes y después del entrenamiento, se realizaron pruebas de alternancia espontánea en el laberinto en Y para evaluar la memoria de trabajo espacial. Después de seis semanas de ejercicio, se midieron los niveles de IGF-1 hipocampal y circulante mediante el método ELISA. Se realizó un ANOVA para analizar las diferencias entre los grupos. Se realizó un análisis de correlación de Pearson o Spearman para evaluar la correlación de los niveles de IGF-1 hipocampal y circulante con la memoria de trabajo espacial y la correlación entre los niveles de IGF-1 circulante y los niveles de IGF-1 hipocampal. Resultados: Los niveles de IGF-1 circulante aumentaron significativamente ($p < 0.05$) en los grupos de cinta rodante y natación en comparación con el control, mientras que los niveles de IGF-1 hipocampal solo aumentaron significativamente ($p < 0.05$) en el grupo de natación. Hubo una correlación significativa entre la memoria espacial y los niveles de IGF-1 en sangre ($p = 0.002$), pero no existió una correlación significativa ($p = 0.122$) entre la memoria espacial y los niveles de IGF-1 hipocampal. Hubo una correlación significativa entre los niveles de IGF-1 en suero y los niveles de IGF-1 hipocampal ($p = 0.028$). Conclusión: Los niveles de IGF-1 circulante estuvieron correlacionados con los niveles de IGF-1 hipocampal. Sin embargo, los niveles de IGF-1 hipocampal aún no han demostrado una correlación significativa con la mejora de la función de la memoria.
Palabras clave: IGF-1, ejercicio, envejecimiento, memoria, estilo de vida sano

Fecha recepción: 24-04-24. Fecha de aceptación: 03-08-24
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Introduction

Insulin-like Growth Factor-1 (IGF-1) is a small family of single-chain polypeptides secreted and involved in metabolism, development, and growth (Yakar & Adamo, 2012). The liver is the primary source of IGF-1 secretion, with around 75% of IGF-1 in the bloodstream coming from the liver. IGF-1 serves as an endocrine, paracrine, and autocrine mediator. In small amounts, around 25-30% IGF-1 is synthesized locally in various cells, including neurons and glial cells (Morel et al., 2017). After being secreted, IGF-1 is transferred to different organs to modulate its effect on them (Yakar & Adamo, 2012). Serum IGF-1 levels can be quantified using Enzyme-Linked Immunosorbent Assay (ELISA), the same method utilized with reliable findings to quantify IGF-1 levels in the brain tissue (Kizhakke Madathil et al., 2010; Yan et al., 2011). IGF-1 performs neuroprotective and neurogenesis roles. Peripheral injection of IGF-1 has been demonstrated to induce neurogenesis in the rat hippocampus (Åberg et al., 2000). IGF-1 suppresses inflammatory factor expression and promotes other nerve growth factor expression (Arjunan et al., 2023). Additionally, IGF-1 facilitates Amyloid Beta Peptide (Aβ) clearance from the brain by inducing the endocytosis of Aβ carriers into the brain via the choroid plexus (Carro et al., 2005).

Exercise-induced elevation of circulating IGF-1 levels has been demonstrated to enhance cognitive function (Kang et al., 2020). Several studies showed that resistance and physical straining increased circulating IGF-1 levels and improved cognitive performance in the elderly (Berelleza et al., 2021; Marcos-Pardo et al., 2024; Stein et al., 2018). Furthermore, some studies indicated that the decrease in circulating IGF-1 levels was associated with low cognitive ability in neurodegenerative patients (Picillo et al., 2017). Hypothetically some studies have proven that IGF-1 can cross the blood-

brain barrier through various pathways, including low-density receptor-related protein-2 (LPPR2) and, in small amounts, non-cognate transporters (Carro et al., 2005; Yu et al., 2006). The levels of IGF-1 in the brain do not always correlate with the levels of IGF-1 in the blood. Animal model studies have shown that a deficiency of IGF-1 in circulation does not affect the levels of IGF-1 in the brain (Adams et al., 2009). It remains uncertain whether the amounts of IGF-1 present in the bloodstream can accurately indicate the levels of IGF-1 in the brain.

This study had several objectives. First, it was to study the correlation between circulating and brain tissue IGF-1 levels in aged mice following six weeks of exercise. Second, it was to determine how accurately circulating IGF-1 reflects IGF-1 levels in the brain tissue. Third, it was to analyze the relationship between circulating IGF-1 and hippocampal IGF-1 in the improvement of spatial memory function in aged mice.

Material and Methods

Animals

Nine-month healthy female Balb/c mice weighing 28–30 grams were obtained from the animal research and development laboratory of Farma Veterinary Centre, East Java. Mice were maintained over a 12-h light/dark cycle (light cycle starting at 7 AM). Food and water access was given freely ad libitum. Thirty female Balb/c mice were randomly divided into swimming (S), treadmill (T), and control groups (C), with ten mice per group. The mice were placed in standard cages, with five mice per cage, except during exercise in the case of mice in the swimming and treadmill groups. Before training, acclimatization was conducted for a week, followed by another week of habituation at the training sites (the treadmill and pool). Each mouse was euthanized in a jar with chloroform the day after a Y-maze test was carried out. Blood was collected from each mouse's heart by cardiac puncture and then put into an Eppendorf tube. The brain was extracted and subsequently washed with PBS. The hippocampus was isolated using a razor blade on a plate chilled using dry ice, complying with a method used by Papouin & Haydon (2018). Hippocampal tissues were stored in PBS-filled Eppendorf tubes at -80°C until analysis. The Health Research Ethics Committee of the Faculty of Medicine, Universitas Airlangga, had approved all of the protocols for this study (No. 86/EC/KEPK/FKUA/2020). The experiments were conducted following the guidelines provided in the NIH Guide for the Care and Use of Laboratory Animals.

Training Protocols

A treadmill with five tracks was utilized for mice in the treadmill group. The mice in this group exercised on the treadmill five times per week for 30 minutes per day. The speed was gradually increased until it reached a speed of 21 cm/second (Purwoto et al., 2020). At the same time, the mice in the swimming group performed a swimming exercise for the same duration and at the same frequency as the exercise duration and frequency applied in the treadmill group (30 minutes, five times a week). Plastic containers filled with 24–27°C water were utilized for mice in the swimming group. Before starting the treatment, the mice in the treadmill and swimming groups were introduced to the treadmill and water for one week to reduce novelty stress. We handled all procedures between 10 and 12 AM for six weeks.

Y-Maze Test

Assessments of the mice's spatial working memory function were undertaken a day before and after exercise using Y-maze spontaneous alternation tests (Prieur & Jadavji, 2019). The Y-maze in this study was made from black plexiglass with three arms 39.5 x 8.5 x 13 cm in dimensions, which were connected to one another at one end of each arm, forming a 120-degree angle between one end of one arm and one end of another arm. Memory function evaluation in mice utilized % alternation. An alternation occurred when a mouse successfully entered three different Y-maze arms in succession. For example, a mouse would leave the upper arm to enter the right arm and then the left arm. The measure of % alternation is defined as the frequency of a mouse visiting three different arms consecutively compared to the total times the mouse visiting the arms. The exploration pattern of each mouse in the Y-maze was recorded for five minutes. The mice were accustomed to the Y-maze one week before treatment to avoid novelty stress (Prieur & Jadavji, 2019).

Tissue and Blood

The mice's hippocampal tissues were homogenized in phosphate-buffered saline (PBS) (pH 7.4, 137 mmol/L of NaCl, 2.7 mmol/L of KCl, 10 mmol/L of Na2HPO4, 1.8 mmol/L of KH2PO4). The ratio of the weight of hippocampal tissue (g) to the volume of PBS (mL) was 1:9. The homogenates were subjected to sonication over a total of five cycles, each lasting for six seconds, while being kept on ice. These homogenates were subsequently subjected to centrifugation at 12,000 RPM for 15 minutes at a temperature of 4°C in order to obtain supernatants. The supernatants were stored at -80°C until further processing. The collected blood was allowed to clot for 10–20 minutes at room temperature before being centrifuged at 3000 RPM for 10 minutes at 4°C. Serums were separated and saved at -80°C until analyzed.

IGF-1 ELISA

The ELISA method was used to assess the levels of IGF-1 in the hippocampus and serum 24 hours after training using the mouse IGF-1 ELISA Kit (Bioassay Technology Laboratory, No. E0037Mo) following Bioassay Technology Laboratory protocols. In brief, the plate was pre-coated with mouse IGF-1 antibody. The IGF-1 present in the sample was added and bound to the antibody coated on the wells. Then, the biotinylated mouse IGF-1 antibody was added and

bound to the IGF1 in the sample, followed by adding and binding streptavidin-HRP to the biotinylated IGF-1 antibody. After incubation, unbound streptavidin-HRP was washed away during a washing step. Substrate solution was then added and color developed in proportion to the amount of mouse IGF-1 applied. The reaction was terminated by adding an acidic stop solution. Absorbance was measured at 450 nm on the ELISA reader (MicroPlate Reader, Bio-Rad, Japan. Serial No.12096). Samples and standards were run in duplicate, and IGF-1 concentrations were calculated using the standard curve. The content is expressed as the equivalent of human recombinant IGF-1 protein in the standards. The IGF-1 standards contain IGF-1 concentrations within the range of 375–6000 pg/mL.

Statistical Analysis

All data were analyzed using the Statistical Package for Social Sciences for Windows (SPSS Inc., Chicago, IL, USA). Kolmogorov-Smirnov and Levene tests were used to ensure that all data were normal and homogeneous. One-way analysis of variance (ANOVA) or Kruskall-Wallis test was used for primary analysis according to the data's normality to analyze differences between groups. ANOVA was followed by LSD post-hoc analysis to compare all reported data. Depending on the linearity and normality of the data, Pearson's or Spearman's correlation analysis was used to assess the (1) correlation of hippocampal and circulating IGF-1 levels with spatial working memory and (2) the correlation between circulating IGF-1 levels and hippocampal IGF-1 levels in elderly mice.

Results

The effect of exercise on spatial memory

Before training, no statistically significant differences ($p = 0.685$) were found in the percentages of spontaneous alteration on the Y-maze test (Figure 1) between the swimming, treadmill, and control groups (59.26 ± 14.37, 63.76 ± 12.18%, and 63.13 ± 10.42%, respectively). After training, the percentages of spontaneous alteration on the Y-maze test showed significant increases ($p = 0.001$) in the swimming and treadmill groups (74.15 ± 7.34% and 66.01 ± 12.34%, respectively).

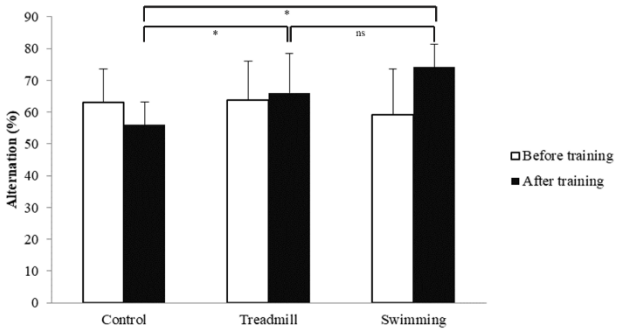

Figure 1. The effect of swimming and treadmill exercises on the spatial memory of female elderly mice. Values are in means ± standard errors. *P < 0.05; ns = not significant.

IGF-1 measurements in the serum and brain in elderly mice

The serum IGF-1 levels in the treadmill and swimming groups (667.3 ± 114.2 pg/mL and 694.5 ± 79.3 pg/mL, respectively) were 37% and 42% higher than the serum IGF-1 levels in the control group (487.9 ± 74.5 pg/ml) (Figure 2A). Meanwhile, the hippocampal IGF-1 levels only showed an increase in the swimming group (414.8 ± 248.6), which was 50% higher compared to the levels in the control and treadmill groups (225.6 ± 75.9 and 225.54 ± 98.1, respectively) (Figure 2B).

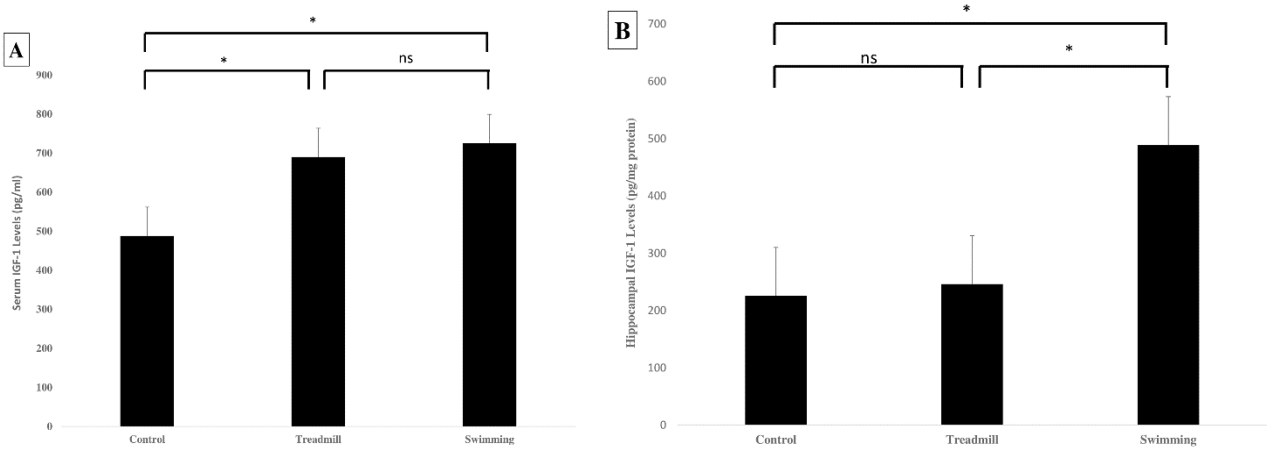

Figure 2. The effect of swimming and treadmill exercises on the IGF-1 levels in the serum (A) and hippocampus (B) in female elderly mice. Values are in means ± standard errors. *p < 0.05; ns = not significant.

Correlation between IGF-1 levels and spatial working memory in elderly mice

The correlation test revealed (Figure 3A.) a significant correlation between spatial memory and blood IGF-1 levels ($p = 0.002$), showing a moderate positive correlation ($r = 0.535$, $n = 30$). However, no significant correlation ($p = 0.122$, $n = 30$) existed between spatial memory and hippocampal IGF-1 levels (Figure 3B).

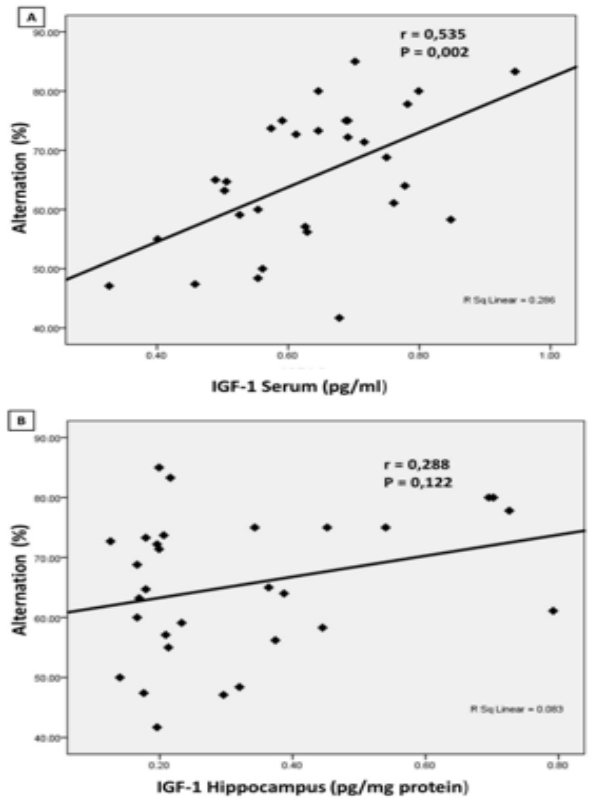

Figure 3. The correlation between spatial memory and (A) serum IGF-1 levels and (B) hippocampal IGF-1 levels in female elderly mice. Statistical analyses were performed using Pearson's correlation test.

Correlation of IGF-1 levels in the serum and hippocampus in elderly mice

The correlation analysis indicated a significant correlation ($p = 0.028$), showing a weak positive correlation between serum IGF-1 levels and hippocampal IGF-1 levels in elderly mice ($r2 = 0.288$, $n = 30$) (Figure 4).

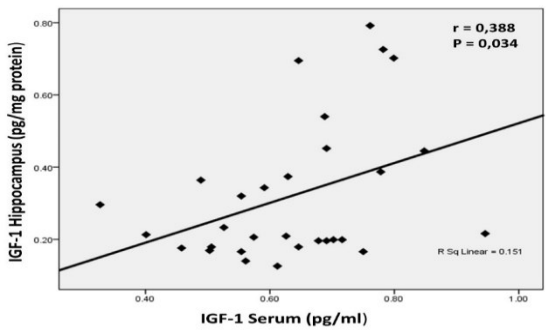

Figure 4. The correlation between serum IGF-1 levels and hippocampal IGF-1 levels in elderly mice. Statistical analyses were performed using Pearson's correlation test.

Discussion

This study examined the correlation between the levels of IGF-1 in circulation and the hippocampus in elderly mice after chronic aerobic exercise. Furthermore, the correlation between IGF-1 levels and cognitive function was also analyzed. This research indicates increases in serum IGF-1 levels in both exercise groups. A previous study showed that acute aerobic physical exercise twice a week for one week in individuals with AD over 40 yielded an acute increase in circulating IGF-1 levels (Stein et al., 2021). Resistance exercise for 24 weeks was able to cause an increase in circulating IGF-1 levels and improved cognitive function in individuals without dementia (Ricardo C. Cassilhas et al., 2007). Furthermore, it was figured out that there was an increase in IGF-1 levels in adults with mild cognitive impairment (MCI) who engaged in aerobic physical activity for six months (Baker et al., 2010). Aerobic exercise was associated with improved cognitive function in adults with MCI (Nunes et al., 2024; Suryadi et al., 2024; Tejada Medina et al., 2020; Yong et al., 2021). Increased IGF-1 levels were also associated with cognitive performance in various elderly groups (Baker et al., 2010; Ricardo C. Cassilhas et al., 2007; Tsai et al., 2015). The same findings were also found in studies involving animal models. Hippocampal IGF-1 levels increased due to exercise, and the increase in IGF-1 levels was associated with improved cognitive function (R. C. Cassilhas et al., 2012; Vanzella et al., 2017). This was also found in studies using Alzheimer's disease animal models (Özbeyli et al., 2017).

This study shows that the increase in circulating IGF-1 levels was followed by an increase in hippocampal IGF-1 levels in the swimming group. However, the increase in circulating IGF-1 levels in the treadmill group was not accompanied by an increase in hippocampal IGF-1 levels. According to previous studies, spatial memory function and hippocampal IGF-1 gene expression were improved after a swimming exercise for 60 minutes per day, six times per week for eight weeks, in female Wistar rats (Habibi et al., 2017). However, the results on the increased levels of IGF-1 in the hippocampus due to treadmill exercise represented inconsistency. Centikaya showed that a regular treadmill exercise five times a week for six weeks in adult rats significantly increased hippocampal IGF-1 levels (Cetinkaya et al., 2013). However, there was no change in hippocampal IGF-1 levels after a treadmill exercise with moderate intensity for two weeks in adult experimental animals (Llorens-martín et al., 2010). The difference in the results might be due to differences in the exercise durations and types of treadmill exercises, i.e., forced treadmill exercise vs. voluntary treadmill exercise. An increase in basal circulating IGF-1 levels occurred after exercising for five weeks or more, whereas exercising for less than five weeks did not increase basal circulating IGF-1 levels (Stein et al., 2018).

Different types of treadmill exercises were known to influence variations in IGF-1 synthesis. One research found that doing a forced treadmill exercise regularly three times

a week for 4.5 weeks could induce a stress response, which showed increased anxiety on open field tests and increased corticosterone levels in mice induced with global ischemia. However, there was no increase in corticosteroid levels in the voluntary treadmill group compared to controls (Svensson et al., 2016). Another research study found that forced treadmill exercise caused anxiety and stress as characterized by increased corticosterone levels, which were not found in experimental animals performing voluntary wheel runs (Niu et al., 2020). Furthermore, it is known that corticosteroids inhibit the effects of IGF-1 synthesis (Yakar et al., 1999). In the current research, the treadmill group did not show any increase in hippocampal IGF-1 levels. This might be because this study used a forced treadmill exercise, which caused stress and increased corticosteroids, thereby inhibiting IGF-1 synthesis or disrupting IGF-1 uptake into the brain. Further studies are, therefore, needed to understand the effects of stress or corticosterone hormone on IGF-1 brain uptake or local IGF-1 synthesis in the brain.

This study also indicates that circulating IGF-1 levels were associated with the improvement of spatial memory function, while hippocampal IGF-1 levels were not. A previous study used a mouse model of GH deficiency and GH restoration through replacement therapy. Gene expression analysis using PCR showed that circulating IGF-1 does not modify the transcription process of IGF-1 and its receptors in the hippocampus. Instead, it regulates other genes involved in microvascular function and structure, brain development, and synaptic plasticity, potentially supporting brain structure and cognitive function (Mitschelen et al., 2011). Other studies indicated that deficiency in circulating IGF-1 does not affect the levels of IGF-1 in the hippocampus. This suggests that the levels of IGF-1 in the brain are regulated through different mechanisms. However, further research is needed to confirm this hypothesis.

Circulating IGF-1 improves neurogenesis in the hippocampus in basal conditions. Hypophysectomized mice with low serum IGF-1 levels showed fewer new neurons, which returned to large numbers as found in normal animals when injected with IGF-1 (Åberg et al., 2000). Although the mechanisms stimulating the passage of IGF-1 through the blood-brain barrier (BBB) remain elusive, some previous studies hypothesized a number of ways in which IGF-1 in circulation gets through the blood-brain barrier. First, IGF-1 is transported to the cerebrospinal fluid (CSF) via low-density lipoprotein-receptor-related protein-2 (LRP2). Second, IGF-1 is carried to neuronal cells via astrocytes or directly to neuronal cells after binding to IGF-1 receptors on endothelial cells. Third, IGF-1 can enter the central nervous system (CNS) directly if not bound to its carrier protein. Making a free form of IGF-1 requires metalloproteinase-9 activity to break the bonds of IGF-1 with insulin-like growth factor binding protein (IGFBP) (Lewitt & Boyd, 2019). Changes in circulating IGF-1 levels, when IGF-1 levels are elevated or reduced in circulation, will change 30% of IGF-1 levels in the brain (Mitschelen et al., 2011; Yan et al., 2011). This explains the results of this study, which showed a moderate correlation on the Spearman's rank correlation test between IGF-1 levels in the hippocampus and circulation.

Conclusions

Exercise cause an increase in circulating IGF-1 levels, and the increase in circulating IGF-1 levels influences the improvement of spatial memory. Circulating IGF-1 levels are correlated with hippocampal IGF-1 levels. However, hippocampal IGF-1 levels have yet to show any significant correlation with the spatial memory function.

Acknowledgments

The authors acknowledge the Master's Study Program in Basic Medical Science, Department of Physiology, Department of Neurology, Embryology Laboratory of Universitas Airlangga, Airlangga Hospital Laboratory, and Research and Innovation Institute (Lembaga Penelitian & Inovasi) of Universitas Airlangga for their financial support and supply of instruments for this research.

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