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Effect of Continuous Environmental Enrichment Exposure and Aerobic Exercise on Rat's Plasma and Hippocampal Brain-Derived Neurotrophic Factor (BDNF)

ABSTRACT

Environmental enrichment (EE) has been shown to affect memory function positively through increased LTP and neurogenesis, which is facilitated by brain-derived neurotrophic factor (BDNF) that mediates exercise-induced structural and functional change in the hippocampus that has been shown to promote blood vessel growth, angiogenesis linked to adult neurogenesis and neuronal survival. This study aims to study the effect of environmental enrichment, aerobic exercise, and their combination on plasma and hippocampal BDNF levels.

An in-vivo experimental study on twenty-four adult male Wistar rats age 7 months, with weight ranging from 300 to 400 grams. The rats were randomly assigned to 4 groups: Control (C), Aerobic (A), Environmental Enrichment (EE), and combination of Environmental Enrichment and Aerobic (EEA). The treatments were given for 8 weeks. Plasma and hippocampal BDNF levels were measured by ELISA.

Our results showed that combination of aerobic exercise and continuous EE exposure increased the levels of hippocampal and plasma BDNF the highest in adult rats. Our results also showed positive correlation ($r = 0.686$, $p = 0.002$, $n = 24$) between the plasma and hippocampal BDNF in adult rats.

In conclusions, the data in our study support the hypothesis which states combination of aerobic exercise and continuous EE exposure increases plasma and hippocampal BDNF in adult rats.

Keywords: *BDNF; Hippocampus; Aerobic Exercise; Environmental Enrichment*

Running Title: Exercise & EE Increases Plasma & Hippocampal BDNF

INTRODUCTION

Human's ability to store information and recall them back is one of the many hallmarks of higher organism's abilities. The underlying mechanism of memory and learning is synaptic plasticity.[1] One proven candidate for modulating synaptic plasticity in learning and memory is brain-derived neurotrophic factor (BDNF), first extracted from mammalian brain due to its action on dorsal root ganglion cells which promotes neuronal survival. BDNF is classified as the second member of the neurotrophic family of growth factors, with nerve growth factor (NGF) as its first member.[1,2] Among neurotrophic factors, in the nervous system, BDNF,along with its main receptor TrkB, is the most abundantly expressed with widespread distribution. Its expression is fundamental for survival of neurons during development and for their integration in the adult mammalian brain.[2] BDNF has been implicated in the modulation of synaptic function and plasticity through increased long term potentiation (LTP) and neurogenesis.[1] The action of BDNF in the adult central nervous system (CNS) is currently one of the most extensively studied in neuroscience, maybe due to its essential role in long-term potentiation (LTP).[2] Besides in the nervous system, expression of BDNF also occurs in liver and skeletal muscles. In the blood, the primary storage for BDNF is thrombocytes and plasma.

BDNF is a protein that plays an important role in neurogenesis, learning and memory through late LTP. A study conducted on mice that deliberately suppressed BDNF gene expression and its receptor (TrkB) showed complete damage to memory and learning processes. Therefore, many attempts were made to increase the level of BDNF expression to improve memory function.[3] Among these efforts to improve cognitive and memory function are aerobic exercise

and environmental enrichment (EE) exposure. These treatments has shown increase in BDNF protein levels both in the brain and in the peripheral organs.[4]

Aerobic exercise is a type of exercise that can improve learning and memory function by inducing neurogenesis and neuroplasticity. Aerobic exercise increases the activity of nerve cell signaling in the form of LTP, which is known through increased expression of neuropeptides especially BDNF.[5] Besides aerobic exercise, some animals studies have shown that EE can affect learning ability and memory function. EE could have long lasting effects on the individual phenotype through developmental plasticity. It has been shown that serum and plasma BDNF concentration increases in EE exposure.[6]

In this study, we investigated the combined effect of 24-hour continuous environmental enrichment (EE) exposure and aerobic exercise on plasma and hippocampal BDNF in adult rats.

MATERIAL AND METHODS

Animals

An in-vivo experimental study on twenty-four adult male Wistar rats age 7 months, with weight ranging from 300 to 400 grams. The rats were randomly assigned to 4 groups: Control (C), Aerobic Exercise (A), Environmental Enrichment (EE), and combination of Environmental Enrichment and Aerobic Exercise (EEA). They were maintained under a 12-hour light and dark cycle. Food and water were available *ad libitum*. Rats were acclimatized 2 weeks before the start experiment. At the end of an 8-week experiment period, rats were sacrificed, intra orbital blood was collected, and hippocampus was isolated. Plasma and hippocampal BDNF levels were measured using ELISA kit (QY-A10582, Qayeebio, China).

Aerobic exercise

Aerobic exercise treatment was implemented to group A and EEA by using a four-lane treadmill for rats. The treatment was given for 8 weeks, 5 days/week, with each session lasting for 30 minutes with treadmill speed of 20 m/min. Before each session, there was a 3-minute warming up session with treadmill speed of 8 m/min.

Environmental Enrichment model (Marlau™ Cage)

The EE model used is a standardized apparatus, the Marlau™ cage. The goal of a 24-hour continuous EE exposure is to improve the quality of life of the animals by providing a combination of physical activity, enhanced social interaction, and natural exploration.[7] The EE model was applied for group EE and EEA. The treatment was given for 8 weeks.[8] The Marlau™ cage size is 800 x 600 x 510 mm, consists of two floors and has various enrichment objects such as running wheels, ladders, labyrinths, plastic houses, tunnels, and nesting materials. The enrichment objects used are in bright colors to provide visual sensory stimulation. Ground floor height is 300 mm with G1 area measuring 296 x 600 mm and G2 area measuring 496 x 600 mm. There is also a labyrinth on the upper floor, connected from G2 area by stairs and there is also a sled tunnel going down to G1 area (Figure 1).

The protocol used changes the labyrinth configuration three times per week, on Mondays, Wednesdays, and Fridays by using 6 labyrinths (A-F), each consisting of 2 different configurations (1 and 2). The maze change begins with the A1 series, B1, C1 and ended with D2, E2, and F2. When the maze change is finished with the F2 series it starts back from the A1 series (Table 1).

BDNF Levels

Hippocampus tissue was homogenized with phosphate buffer saline pH 7.4 and was centrifuged for 10 minutes at the speed of 3000 rpm, and then the supernatant was collected and stored at -80^{0}C. Blood samples were collected and mixed in EDTA for 20 minutes, centrifuged for 30 minutes at the speed of 3000 rpm, and then the supernatant was collected

and stored at -80^{0}C. Whole protein concentration was assessed using Bradford protein assay and then compared to BDNF concentration that has been measured with ELISA kit (QY-A10582, Qayeebio, China).[11]

Statistical analyses

The plasma and hippocampal BDNF levels were analyzed using ANOVA one-way test, while the correlation between plasma and hippocampal BDNF levels was analyzed with Pearson's correlation. Data was considered statistically significant if p <0.05.

RESULTS AND DISCUSSION

Plasma and Hippocampal BDNF

The combination of continuous EE exposure and aerobic exercise induced the highest increase in both plasma and hippocampal concentrations (Figure 2). The plasma BDNF level in control (C) group was the lowest (2.87±0.31), followed by aerobic exercise (A) group (3.09±0.23), environmental enrichment (EE) group (3.34±0.50), and environmental enrichment and aerobic exercise (EEA group) (3.95±0.45). There were significant differences in BDNF plasma levels between EEA and control group (p = 0.001), and between EEA and A group (p = 0.005). This indicates that combination of continuous EE exposure and aerobic exercise is the best in increasing plasma BDNF.

The hippocampal BDNF level in control (C) group was the lowest (34.15±5.06), followed by aerobic exercise (A) group (35.23±5.38), environmental enrichment (EE) group (39.22±6.07), and environmental enrichment and aerobic exercise (EEA group) (45.82±6.01). There were significant differences in hippocampal BDNF levels between EEA and control group (p = 0.011), and between EEA and A group (p = 0.024). This indicates that combination of continuous EE exposure and aerobic exercise is the best in increasing hippocampal BDNF.

Correlation of plasma and hippocampal BDNF

The plasma BDNF levels were correlated with the hippocampal BDNF levels, and a moderate positive correlation between plasma BDNF with hippocampal BDNF was found ($r_s = 0.686$; $p = 0.002$, $n = 24$, Figure 3).

Discussion

BDNF is a member of the neurotrophic family, which play important roles in neurogenesis, long-term potentiation (LTP), protection against neural cell death, and improves learning and memory by increasing neuronal plasticity.[10] BDNF is also a pro-survival signaling molecule that modulates synaptic plasticity and neurogenesis. BDNF is particularly abundant in hippocampus and cerebral cortex. Although BDNF is more concentrated in hippocampal tissue, it is also present in the bloodstream.[12] As mentioned earlier, besides being produced in the brain tissue, especially hippocampus, BDNF can also cross the blood-brain barrier. Expression of BDNF also occurs in liver and skeletal muscles. In blood, the primary storage for BDNF is thrombocytes and plasma.[12] Circulating BDNF in plasma can originate from both the central nervous system and peripheral nervous system, and also from non-neuronal tissues, such as vascular endothelial cells and cells of the immune system.[5]

Several studies have investigated the effect of exercise on the levels of BDNF. Recent studies have shown aerobic exercise's positive impact on plasma BDNF levels. In a study by Pereira et al conducted in women with depression given 10 weeks of physical exercise, significant increase in plasma BDNF levels was found. This plasma BDNF elevation was followed by enhancement in other functional parameters, which includes muscle strength and mobility.[5] This result is in accordance with our findings in this study, in which aerobic exercise program has a positive impact on plasma and hippocampal BDNF levels. Another recent study showed that FNDC5, a previously identified muscle protein that is induced in exercise and is cleaved and secreted as irisin, is also elevated by aerobic exercise in the hippocampus of rats and

mice.[13] Peripheral delivery of FNDC5 to the liver via adenoviral vectors, resulting in elevated blood irisin, induces expression of BDNF and other neuroprotective genes in the hippocampus.[13]

Environmental enrichment (EE) is a complex sensory-motor stimulation that provides animals with increased opportunity to perform physical activity, various learning experiences and also social interaction.[14] These conditions can improve both the development and the function of the brain.[12,15] Running wheels, stairs, and slides are available for voluntary physical exercise. The availability of objects with various shapes and colors also stimulates the sensory system. Environmental enrichment has also been shown to increase plasma BDNF levels in animal studies.[6] BDNF which was secreted by skeletal muscles during motor activation in physical activity and circulate in the blood can cross blood-brain barrier. Thus, BDNF will bind to its receptor, tyrosine receptor kinase B (TrKB) and p75 neurotrophic receptors (p75 NTR).[1] This will lead to the activation of biochemical cascades leads to proliferation and survival of neuronal cells, and their plasticity. This in part explains the effect of environmental enrichment on plasma and hippocampal BDNF levels.[12]

There was positive correlation between plasma and hippocampal BDNF, which shows that increase of plasma BDNF is also resulting in increase of hippocampal BDNF. The hippocampal BDNF levels is however much higher compared to plasma BDNF. From this data, we may assume that the source of hippocampal BDNF does not come solely from plasma BDNF which crosses the blood-brain barrier, but the majority may be from the hippocampal tissue production. Further study on the BDNF genetic expression level in the hippocampus is needed to support this hypothesis.

In conclusions, both aerobic exercise and environmental enrichment by themselves increases plasma and hippocampal BDNF, but combination of continuous EE exposure and aerobic exercise increases plasma and hippocampal BDNF the highest in adult rats.

TABLES

Table 1. Configuration changes of Marlau™ Cage Maze[10]

Marlau™	DAY	MAZE SERIES
Week 1	Monday	A1
	Wednesday	B1
	Friday	C1
Week 2	Monday	D1
	Wednesday	E1
	Friday	F1
Week 3	Monday	A2
	Wednesday	B2
	Friday	C2
Week 4	Monday	D2
	Wednesday	F2
	Friday	A1
Week 5	Monday	B1
	Wednesday	C1
	Friday	D1
Week 6	Monday	E1
	Wednesday	F1
	Friday	A2
Week 7	Monday	B2
	Wednesday	C2

Marlau™	DAY	MAZE SERIES
	Friday	D2
Week 8	Monday	E2
	Wednesday	F2
	Friday	A1

FIGURES

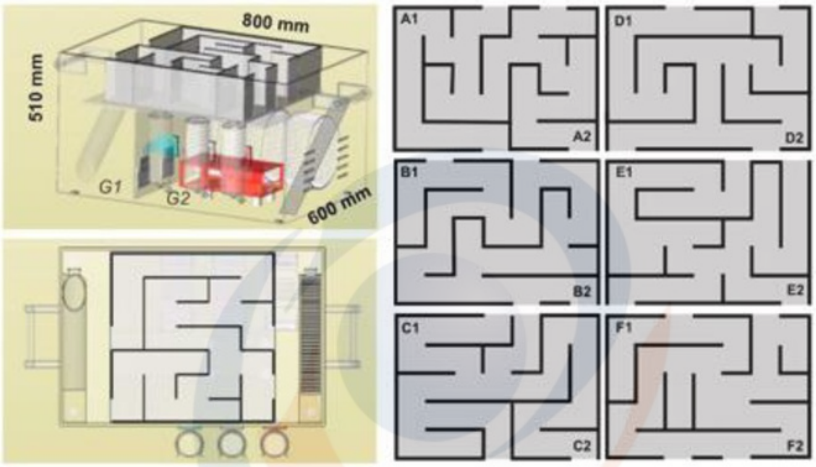

Figure 1. Marlau™ cage[9]

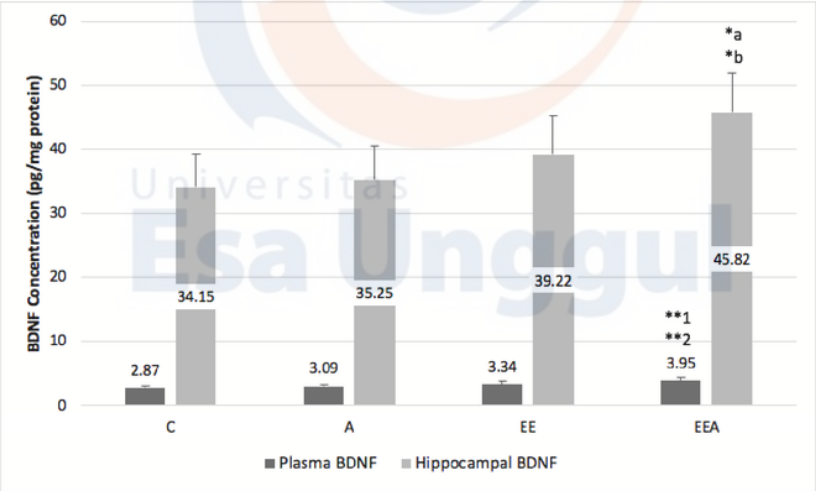

Figure 2. Mean of Plasma and Hippocampal BDNF Concentrations

C=Control; A=Aerobic; EE=Environmental Enrichment; EEA=Combination

$^{**1}p = 0.001$ vs. C; $^{**2}p = 0.005$ vs. A; $^{*a}p = 0.011$ vs. C; $^{*b}p = 0.024$ vs. A

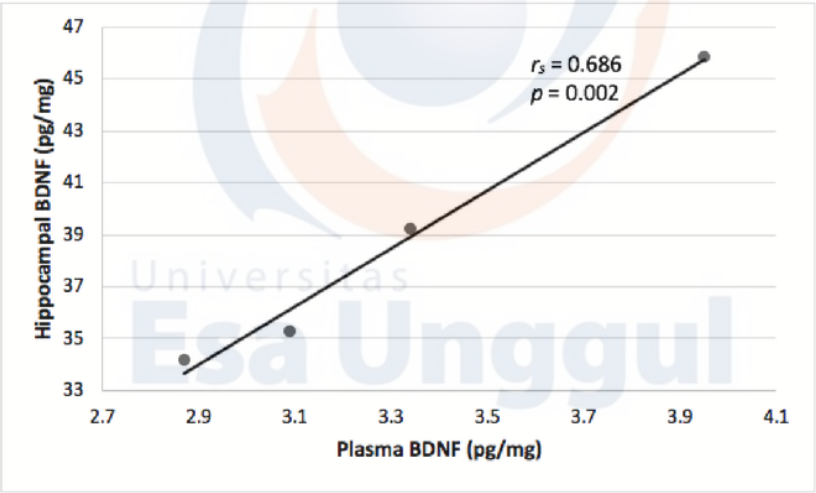

Figure 3. Correlation of plasma BDNF levels with hippocampal BDNF levels

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2	Sheikhzadeh, Farzam, Asieh Etemad, Sahar Khoshghadam, Naser Ahmadi Asl, and Peyman Zare. "Hippocampal BDNF content in response to short- and long-term exercise", Neurological Sciences, 2015. Publication	1%
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of hippocampal neurogenesis following environmental enrichment", European Journal of Neuroscience, 10/2006
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