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Effect of Low Intensity Exercise toward Postsynaptic Density 95 Level and Spatial Memory in Male Swiss Webster Mice Induced by Immobilization Stress

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ABSTRACT

Physical exercise has long been proven as a way to increase metabolic status, synaptic plasticity and protein regulation in order to maintain cognitive function and brain health. There has been a limited study focusing on the protective effect of physical exercise towards cognitive function during stress. This research is quasi experimental studies with post test only control group design, conducted in the animal house and molecular biology laboratory of Medical Faculty of Universitas Sriwijaya. As many as 32 white mice age 10 weeks old weighing 25-35 gr were divided into four groups. The first group was the control group, the second one was treated with immobilization stress 2 hours/daily for 21 days, the third group had been conditioned for 30 minute running at a speed of 11 m/min for 14 days, while the fourth one was treated with physical exercise after being exposure to immobilization stress. The post synaptic density (PSD) 95 level in hippocampus and serum cortisol were measured by using enzyme-linked immunosorbent assay, while spatial memory was assessed by using Morris Water Maze Test. Immobilization stress for 21 days showed significant elevation of serum cortisol as well as decrement of PSD 95 level and spatial memory compared to control group. Low intensity physical exercise showed significant elevation of PSD 95 level and spatial memory compared to control group. Therefore, low intensity physical exercise can prevent the decrement of PSD 95 level and spatial memory due to stress.

Key words: Low intensity exercise, immobilization stress, PSD 95, MWM, neuroplasticity.

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unknown, though it is suspected to have been mediated by complex interactions between age, genetics, and environmental factors such as stress [3, 4].

INTRODUCTION

Alzheimer's and Parkinson's disease are the main cause of dementia among the elderly [1]. The prevalence rate of dementia has been increasing annually along with the rising number of the elderly population and the higher number of living expectation worldwide [2]. The exact cause of these neurodegenerative diseases is still

Stress is a non-specific reaction of body towards various demands physically and psychologically, thereby disturbing homeostasis and urgings physiological and behavioral responses [5, 6]. When a condition is interpreted as a stress, hypothalamus produces corticotropin-releasing hormone (CRH) and arginine-vasopressin hormone (AVP) which will stimulates the

secretion of cortisol [7, 8]. The long-term release level of cortisol due to chronic stress exposure will induce damaging effects in several brain regions [8, 9]. Cortisol induces oxidative stress by causing glutamate excitotoxicity, increasing the level of nitric oxide (NO) and cyclooxygenase (COX), protein oxidation and lipid peroxidation as well as reducing the endogenous antioxidant activity both enzymatic and non-enzymatic [10, 11]. Chronic stress could also lessen reduce the neurotrophin expression such as brain derived neurotrophic factor (BDNF) and synapse proteins like such as synaptophysin (SYP), Post Synaptic Density 95 (PSD 95), neurexin, and neuroligin and post synaptic density 95 (PSD 95)[12, 13].

Physical exercise has been is proven to have been able in improving learning process, memory ability, and hamper the lowering cognitive function in old age, lower the level of depression and protect the body by preventing several neurologic diseases such as Parkinson's disease, Alzheimer's disease and as well as ischemic stroke [14,15]. Physical exercise can induce several stimuli to increase the status of body metabolism and functions, including brain system [16]. A physical exercise mediates the recovery function of neurons cell through via three mechanisms, i.e. comprising neurogenesis, angiogenesis and synaptogenesis [17]. Exercises could also able to modulate numerous neurotrophin that will which regulates the remodeling and the branching of dendrite and axon; increase synaptogenesis at the end of axon terminals; increase the efficacy of synapse transmission and mediate the synapse functional maturation [18]. A proper synaptic activity features the amount of information entering the brain, therefore so any permanent changes to synapse would determine the process of memory learning and building [19]. PSD 95 is the major scaffolding protein and structure in synapse and is an essential structural component in mature dendritic spines. Two-third of the total amount of new and damaged dendritic spines is not equipped with PSD 95 [20, 21]. PSD 95 could intertwine with numerous molecules in the post-synaptic membrane surface such as NMDA receptors, AMPA complex receptors, adhesion molecules, ionic compounds and signal relay molecules so such protein is believed to play an important role in organizing PSD molecularly [22, 23]. PSD 95 could also affect the morphology and functions of dendritic spines. In fact, PSD 95 is one of the causes of in the dendritic spines' morphology changes, volume increase and the

formation of perforated synapses in dendritic spines. Furthermore, PSD 95 strengthens the excitatory postsynaptic process delivered by AMPA receptors by regulating diffusion, trapping, and expressing AMPA receptors to the cell surface, thus would increase the process of synapse strengthening [24, 25].

In this study, we thus investigated the effect of low intensity exercise on spatial memory ability and hippocampal synaptic plasticity, by demonstrating the expression of hippocampal PSD 95 in chronic immobilization stress.

MATERIAL AND METHODS

Animal and Experimental Design

The research subjects were 32 of *Mus Musculus*, 10 to 12-week-old male Swiss Webster strain within 25 to 35 grams, conserved in the Animal House of Medicine Faculty of Universitas Sriwijaya. Each cage housed eight mice fed by food and drinks every day *ad libitum*. The conservation room was well ventilated with maintained room temperature of 25-30 °C, humidity of 50 -60% and dark: light cycle of 12:12 hours.

Seven days after acclimatization, the subjects were randomly divided into four groups consisted of eight mice. Group 1 was the group without physical exercise and stress, group 2 was a group with immobilized stress and no physical exercise. Group 3 had physical exercise without immobilized stress. Finally, physical exercise and immobilized stress were applied for group 4.

The mice that were given physical exercise would run in wheels, aimed so that the training duration and intensity could be controlled. Mice would run for 30 minutes with the velocity of 11 meters per minute for 14 days. As for the group of mice treated with immobilized stress, they were put in a particular plastic canister, specially designed to ensure the mice would stay in dorsal recumbent position without access to food and drink. Such immobilized stress would be applied for two hours (10 am to 12 pm) for 21 consecutive days. Meanwhile, as for the mice grouped to do physical exercise and were given stress, they had been treated with immobilized stress for seven days prior to the experiment. The mice would later be trained to run in wheel after being exposed to two-hour long immobilized stress.

Morris Water Maze Test (MWM Test)

MWM test was conducted to assess the function of spatial and cognitive memory in mice. Mice were put in a 20 cm-deep plastic container with the diameter of 1.5 meter which would later be filled with clean water. The training took four days (day 18 to day 21) and consisted of two phases comprising one day of pre-training and three days of trial. In pre-training, the platform was positioned in the middle of container with the upper part at an inch above water level. As for in trial phase, the container was filled with water laced with food colorant to make the water opaque as to hide the platform which was placed at an inch below water level. Mice were then allowed to swim to find the hidden platform by themselves for one minute. Afterwards, if the mice failed to find the platform, the researcher would direct the mice to the step platform and the mice would stand on the platform for 15 seconds before finally being released back into the pool to their initial position to later be recorded as in the duration it took for the mice to find the hidden platform as latent period in seconds.

Serum Cortisol Measurement

To measure the level of success in the immobilized stress induction, 0.5 ml blood was collected from the lateral tail veins at day 0, 7 and 21 for blood cortisol level measurement. The blood was centrifuged at 2000-3000 rpm for 20 minutes at 25°C. Serum was collected into micro tubes and refrigerated at -20°C in order to measure cortisol levels in all samples. Serum samples were then analyzed by an ELISA kit which was usually utilized specifically for mice. Blood sample was always collected at 8 AM to prevent the effect of circadian rhythm in cortisol.

PSD 95 Measurement

Mice had to be sacrificed 24 hours after the last training session by decapitation to obtain fresh tissues by decapitation procedure without anesthesia as outlined by Institutional Animal Care and Use Committee (IACUC). Hippocampus was then separated from the cerebellum and brain stem manually with a scalpel blade and a micro tweezer, which was then stored at -80°C. The hippocampus was homogenized with blade homogenizer after being added with PBS. Next, the sample was centrifuged at 3,000 rpm for 20 minutes in 4°C. Samples were then analyzed by an ELISA kit.

RESULTS**Cortisol**

The results of mean and one-way ANOVA of Cortisol are summarized in Table 1.

Table 1: Serum Cortisol Level in day 0,7 and 21

Group	Cortisol level Day 0	Cortisol level Day 7	Cortisol Level Day 21
1	6,968±0,442	7,011±0,624	7,090±0,485
2	6,761±0,343	18,314±0,198	21,973±0,615
3	6,971±0,576	7,123±0,139	7,128±0,383
4	6,714±0,3949	18,277±0,185	21,860±0,583
ANOVA test	0,582	0,000	0,000

Table 1 shows no significant differences on the level of cortisol between the mice groups during the initial position. However, as the immobilized stress was applied, there was a noticeable increase of cortisol level in groups 2 and 4, compared to group 1 at day 7 and day 21. Meanwhile, there was no significant difference on the cortisol level of the group of mice with physical exercise (group 3), compared to group 1 at day 7 and day 21. This showed that chronic immobilized stress could raise the level of cortisol while the same cannot be said for the low-intensity physical exercise.

PSD 95

The results of mean and one-way ANOVA of PSD 95 are summarized in Figure 1.

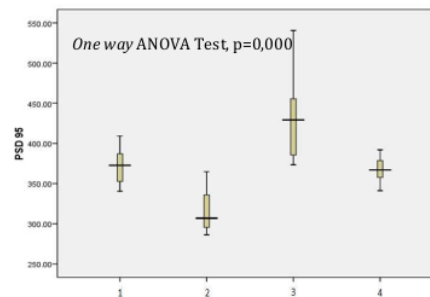
**Figure 1: PSD 95 Level in the Hippocampus.**

Figure 1 indicates a significant difference on the mean level of PSD 95 between all groups whereas the highest level of PSD 95 was in the mice group with low-intensity physical exercise without stress (Group 3). The lowest level of PSD 95 was in the group treated with stress without low-intensity physical exercise (Group 2).

Furthermore, the post hoc test indicated no significant difference between the group with low-intensity physical exercise and stress (Group 4) compared to control (Group 1) ($p > .05$).

MWM Test

The latent period of MWM test was measured for three consecutive days, started from day 19 to day 21. The one-way ANOVA test was conducted to assess whether there was a significant differences of latent time on MWM test at day 19 to day 21. The results of mean and one-way ANOVA of MWM test are summarized in Figure 2.

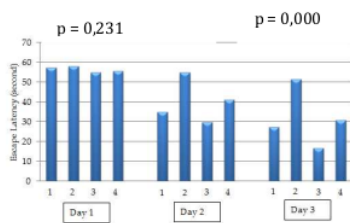


Figure 2: Spatial memory Ability on Day 19, 20 and 21

The result of this study revealed on day 1, there was no significant difference of the mean latent time to find the hidden platform ($p = 0.231$). On day 3 of the MWM test, a significant difference was seen on the mean latent time to find the platform ($p=0.000$), of which the highest latent time was recorded on the mice group treated with stress without low-intensity physical exercise (Group 2) and the lowest was on the group with low-intensity physical exercise without stress (Group 3). Moreover, the study also illustrates the mice group treated with physical exercise and stress (Group 4) had shorter latent time than the group 2.

DISCUSSION

The main finding of the study was that chronic immobilized stress was proven to increase the level of cortisol while low-intensity physical exercise did not. Furthermore, low-intensity physical exercise for 14 days was proven to increase the level of PSD 95 as well as improving the cognitive ability of both groups of mice treated with chronic stress and not treated with immobilized stress.

As for the physical and psychological stimuli such as physical exercise and stress, they could affect

the cortisol level [26]. Chronic immobilized stress as a form of psychosocial stress has been proven to significantly increase the level of cortisol [27-29].

In chronic stress, the increase of cortisol level occurs in a long period of time due to the hyperactivity of HPA system [7]. Continuous exposure of immobilized stress could significantly reduce the protein expression of glucocorticoid receptor (GR) on hippocampus, therefore disrupting GR function in providing negative feedback [28].

Physical exercise is also one of the influencing factors of HPA axis. To respond to physical exercise, the body would activate HPA axis and secrete cortisol. The effect of physical exercise towards cortisol level depends on several factors such as the type, intensity and duration of physical exercise [26, 30, 31]. The lowest limit of physical exercise intensity which could increase cortisol level is that with intensity of 60% of VO_2 max. Meanwhile, physical exercise with the intensity less than 60% VO_2 still could only increase cortisol level if done with the minimum duration of 90 minutes [31, 32]. Such research result provides support for previous studies which reported that low-intensity physical exercise did not increase cortisol level. High-intensity physical exercise do not contribute to the changes in GR, therefore the increased cortisol level can return to normal at 120 minutes post exercise [32].

The increase of cortisol level in chronic stress could reduce the expression of growth factors, particularly BDNF [12, 13, 33]. Cortisol could affect BDNF synthesis including transcription, translation, trafficking and secretion. Cortisol directly affects BDNF promoter and lowers the activity of activator protein-1 (AP-1) and CREB which are essentially required in the transcription of the BDNF gene. However, cortisol disrupts its stability and triggers the degradation of mRNA BDNF. Cortisol is also proven to be able to influence the processes of BDNF signal distribution through TrkB modulation and its intracellular cascade. Moreover, cortisol could reduce the expression of TrkB and activities of Akt and mammalian target of rapamycin (mTOR) which are the essential components in phosphatidylinositol 3-kinase (PI3K/Akt) pathway, activated by BDNF. The decreasing activity of mTOR is believed to be an important factor in the lowering amount of synaptic proteins such as SYP,

PSD 95, neurexin and neuroligin [13, 33, 34]. Chronic stress is also capable of increasing the neuron vulnerability towards oxidative stress. Chronic stress causes glutamate toxicity, Ca²⁺ overload, cytokine release, and reduced activities of endogenous antioxidants so it triggers the neuronal apoptosis process [35, 36].

BDNF along with its specific receptor, TrkB, is the main neurotrophin which mediates the process of synaptic plasticity [18]. BDNF-TrkB plays an important role in the process of maturation and synaptic growth through transport regulation of PSD 95 to dendritic spines. BDNF activates PI3K-AKT pathway and triggers the transfer of PSD 95 to synapse via vesicular transport. The activation of BDNF-TrkB is also required in the palmitoylation process of PSD 95 which is mediated by phospholipase C γ (PLC γ) and protein kinase C (PKC). PSD 95 palmitoylation acts on the sticking of its protein on membrane vesicle and its insertion to synapse. Another intracellular pathway activated by BDNF-TrkB is the pathway of mitogen activated protein kinases/extracellular signal-regulated kinases (MAPK/ERK). The MAPK/ERK and PI3K-AKT pathways in sync would stimulate the activation of mTOR which acts on the acceleration of PSD 95 expression in dendritic spines by increasing the phosphorylation of eukaryotic initiation factor 4E (eIF4E), 4E-binding protein 1 (4E-BP1), and ribosomal protein S6 to later enhance the translation process. The MAPK/ERK pathway also affects the transcription process by CREB phosphorylation which would activate BDNF gene and amplify synaptic maturation as mediated by BDNF. With that said, the direct role of CREB towards PSD 95 synthesis still needs to be explored further [13, 37, 38].

Physical exercise could impact the neuroplasticity process via three main mechanisms. First, physical exercise could enhance the process of neurogenesis and neuroplasticity through the increase of numerous neurotransmitters, neurotrophins, and various intracellular cascades which mediate such process. Next, physical exercise would increase the level of vascular endothelial growth hormone (VEGF) which facilitates the angiogenesis process and vascularization repair in brain. Finally, physical exercise would enhance the durability of neuron cell by affecting the oxidative balance in brain [17, 39, 40].

Low-intensity physical exercise is known to have improved the density of dendritic spines, the amount of synapses, and pre and postsynaptic proteins such as PSD 95 and SYP [13, 41, 42]. Physical exercise is a form of stimulation which could trigger neuroplasticity process [40]. Physical exercise could induce the process of long term potentiation (LTP) by lowering LTP threshold and increasing a number of intracellular cascades such as CREB, CaMKII and MAPK [43,44]. The end turnout of LTP is new proteins synthesis such as several growth factors namely BDNF and Nerve Growth Factor (NGF) [7, 8]. BDNF increase on physical exercise is also mediated by the exercise effect towards a number of neurotransmitters such as norepinephrine and serotonin. The rising level of norepinephrine would enhance the expression of mRNA BDNF. Meanwhile, the positive effect of physical exercise towards serotonin (5-HT) is related to the improvement of 5-HT_{1A} and 5-HT_{2A} receptors which would increase the level of cAMP/PKA to later activate CREB. Physical exercise could also have an impact on TrkB activities through Src tyrosine kinase- G-protein coupled receptor (GPCR) pathway to later directly activate TrkB receptor without involving BDNF [13, 45].

The study has also assessed the mice cognitive function with Morris Water Maze (MWM) method as the output of neurogenesis process. MWM method is utilized to assess the learning and spatial memory of rats [46]. Spatial memory illustrates hippocampus function in the formation of cognitive map which enable an individual to recognize a location. Thus, with the changes of cellular activities in hippocampus could be seen by the changes occurring on the spatial learning process. The study result has shown that the mice group treated with stress had lower cognitive ability while the mice group given low-intensity physical exercise had better cognitive ability. Stress could cause changes in calcium homeostasis, glutamate transmission, increase in the process of long term depression (LTD), and disruption in LTP induction process so that it would reduce the hippocampal excitability which would disturb the process of memory learning and development [8, 47]. Low-intensity physical exercise could improve a number of growth factors such as BDNF which would boost the neurogenesis increase in the hippocampus [48]. Physical exercise would also boost the improvement of short term potentiation and LTP

process as a basic mechanism in the formation of memory and learning [14, 49].

CONCLUSIONS

Low-intensity physical exercise is proven to have been able to improve brain or neuron capability to undergo neuroplasticity. Furthermore, low-intensity physical exercise is also proven to restore the brain's or neuron's neuroplasticity post chronic stress.

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Author Contribution

Irfannuddin Irfannuddin: Conceived and designed the analysis, collected the data, contributed data or analysis tools, performed the analysis, wrote the paper.

Eka Febri Zulissetiana: Conceived and designed the analysis, collected the data, contributed data or analysis tools, performed the analysis, wrote the paper.

Puji Rizki Suryani: Collected the data, contributed data or analysis tools, performed the analysis, edit the paper.

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