Research

The Decrease of Amyloid-Beta Deposit, Increase of Brain-Derived Neurotrophic Factor and Decrease of C-Reactive Protein Levels in the Rat Model of Dementia, Related to the Physical Exercises

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Abstract

Brain plasticity, also known as neuroplasticity, is a term that encompasses both synaptic plasticity and non-synaptic plasticity it refers to changes in neural pathways and synapses due to changes in behavior, environment, neural processes, thinking, emotions, as well as changes resulted from bodily injury.

Dementia is a set of symptoms, which affect the way people think and interact with each other. It can often be linked to a disease of the brain. Very often, short-time memory, mind, personality change, speech and motor skills are affected.

Amyloid-beta (Aβ) is a peptide of 36–43 amino acids, that is crucially involved in Alzheimer's disease (AD). Aβ is the main component of the amyloid plaques found in the brains of AD. Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin, that supports the survival and function of cells compromised in AD. Decreased BDNF causes defects in long-term potentiation and memory and correlates with cognitive decline. In addition to predict the event, C-Reactive Protein (CRP) can also protect dementia. The increase in the volume of cerebral blood flow in physical exercise can improve brain function and retaining plasticity. Physical exercise can reduce the risk and slow the decline in cognitive function of AD patients.

The purpose of this study was to prove the improvement of brain plasticity in the dementia rat model related to the physical exercises. Comparison of Aβ deposit, serum BDNF, cerebrospinal fluid (CSF) BDNF, serum CRP levels, astrocytes BDNF and microglia BDNF expressions between the physical exercise and control groups were performed in a number of 33 male Wistar rats.

The results of this study indicated that the physical exercises can improve brain plasticity. It was found a significant difference (p <0.001) of Aβ, deposition depletion in the 2 series of physical exercise compared with 1 time physical exercise groups and the group without physical exercise. The serum of BDNF, CSF BDNF, serum CRP levels, astrocytes BDNF expression in the 2 series physical exercise group were significantly different compared with 1 time physical exercise group and the group without physical exercise, with p values equal to 0.022, 0.002, 0.720, and <0.001 respectively. No significant difference (p = 0.605) of the microglia BDNF expression in the 3 study groups.

Conclusion

Physical exercises in rats may reduce Aβ deposit, increase serum BDNF, CSF BDNF, reduce serum CRP levels and increase astrocytes BDNF expression. Two set of physical exercises are more effective than 1 time physical exercise or without physical exercise.

Keywords: Brain Plasticity; Aβ; BDNF; CRP; Physical Exercises; Rat Model of Dementia.

Introduction

Brain plasticity is interconnected neural changes, through a new experience in responding to physiological or pathological stimuli. The ability of neural interconnections, can be in the form of interneuron changes and synaptic reorganization, which is the intrinsic development of adult brain tissue in order to keep growing through stimulation [1, 2, 3, 4, 5].

Dementia is a collection of clinical symptoms of progressive decline in intellectual function, which is caused by a variety of backgrounds and disease, characterized by memory loss, accompanied by impaired cognitive function such as language skills, orientation, construction, abstract thinking and problem solving. Dementia can interfere with social functioning, works and activities of daily living (AazI., 2003; Anonymous., 2006; Perani., 2006; Lanska., 2003).

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studies suggest that CRP present in senile plaques and NFT brains under normal circumstances, CRP was not found in the brain. The level will increase 100 times, after 24-48 hours of infection [25]. CRP is an acute phase protein that is found in the blood. The improvement of memory disorders are found after physical exercises [22,23, 24]. and the flexibility of the brain. The increase of serum BDNF, increase of hippocampal and the medial part of the temporal lobe volumes by increased expression of acute phase proteins, proinflammatory cytokines, microglia, astrocytes and neurons [16]. BDNF is a neurotrophin, the marker for brain plasticity. It is secreted by neurons and glial cells [17,18,19 20]. BDNF is synthesized from amino acids 270, started from proneurothropin which is a single amino acids 270, started from proneurothropin which is a single nukleotide with codon 66, BDNF plays a role in the synaptic plasticity and learning [20]. Learning and memory function in the brain is governed by the cerebral cortex, hippocampus and frontal part of the brain [20]. BDNF is found in almost all tissues of the brain with different levels, allegedly the most abundant is in the hippocampus. BDNF work on the central and peripheral nerves, helping the lives of neurons, triggering the growth of new neurons. BDNF receptor. Trk B (tropomyosin Related Kinase B) plays a role in the plasticity of nerve cell regeneration [20, 21, 22]. In adulthood, most of the brain retains its ability to keep generating new nerve cells, known as neurogenesis process. BDNF is one of the most active and important role in the development of nerve cells.

Physical exercise is one of the factors that contribute to increase the flexibility of the brain. The increase of serum BDNF, increase of hippocampal and the medial part of the temporal lobe volumes and the improvement of memory disorders are found after physical exercises [22,23, 24].

CRP is an acute phase protein that is found in the blood. The level will increase 100 times, after 24-48 hours of infection [25]. Under normal circumstances, CRP was not found in the brain. During inflammation, CRP is the most sensitive marker. Several studies suggest that CRP present in senile plaques and NFT brains of people with AD [26, 27]. Increased level of CRP is associated with a decline in cognitive function. High serum level of CRP, is an early sign of AD, vascular dementia, and all types of dementia [26]. Increased level of CRP can predict and protect the incidence of dementia [28]. After 2 years observation to 3000 elderly people in America, it was found a relationship between IL-6 and CRP levels with the worsening of cognitive function. The higher levels of IL-6 and CRP, the more impaired of cognitive function [29]. The increase of proinflammatory cytokines and CRP levels may take place via paracrine and autocrine and then stimulate glial cells to produce Aβ, tau protein and proinflammatory molecules [30]. Irregular and short duration of physical activities will increase the CRP, while sustainable and long duration of physical activities will decrease [31]. In old age, regular physical activity is associated with the decrease of dementia and AD [32]. There is a relationship between the incidence of dementia with high levels of CRP in old age [33, 34]. Through brain plasticity mechanism, physical activity can improve the learning function in experimental animals.

So far, study on the improvement of exercise-induced brain plasticity has not been widely reported (Perrey, 2013). This study has not been performed in Indonesia.

Materials and Methods

This study was conducted at the Laboratory of the Faculty of Veterinary Medicine, Laboratory of Pharmacology Faculty of Medicine Udayana University and laboratory of Veterinary Denpasar, Bali, Indonesia, during a period of 6 months (September 2013 - March 2014), and has received approval from the ethics committee of the Medical Faculty of Udayana University.

Sample of this study consisted of 33 healthy male Wistar rats, aged 3 months, with body weight of 150-200 grams. The independent variable of study was physical exercise, while the dependent variables were Aβ deposition, levels of serum BDNF, CSF BDNF, serum CRP, BDNF expression in astrocytes and microglia. BDNF sample (ug / ml) was taken from serum, CSF and brain extraction, and measured by ELISA [22,34]. Examination of BDNF expression by astrocytes (% of cells) and microglia (% of cells), was performed by using immunohistochemistry anti astrocyte and anti microglia antibodies [35, 36]. Aβ deposit was examined immunohistochemically. The diameter and color intensity of amyloid plaques was assessed by multicolor time-stamp technique with a range of values ranging between 1-3 and plaque sizes ranging from 1-3. Plaque size 1 = ≤ 14, 2 = 14-30; 3 = 30-50 micro meters [37]. Serum CRP level was measured by ELISA.

Physical exercise in rats is a swimming training, that is performed according to the Morris Water Maze (MWM) method. A place to swim is in the form of a plastic tub, diameter 60 cm, height 25 cm, and were filled with water up to 15 cm (temperature 25 ± 1.0 °C). In the middle of the pool, 1 cm below the water surface, put the plate with a length x width x height = 14x14x14 cm). Each rat was trained to swim for 10 minutes. This procedure was observed by researchers. If after 60 seconds of exercise, there was a tired rat and seemed to sink, then the rat was removed from the bath.
and dried with a towel. After a 3-second pause, the exercise was repeated 3 times, then rest. The next day and the next, the exercises were performed again until day 7 (Group 1 series) and up to day 14 (Group 2 series) [13]. The control group did not receive physical exercise.

**Study Procedures**

33 rats were anesthetized with ketamine 100 mg/kg and xylazine 5 mg/kg intra-peritoneal [38]. By using Hamilton micro syringe 10 mL, rats were injected with Aβ (1-40): 2.5 μL/site bilaterally into the lateral ventricle and dorsal hippocampus [39].

Randomly, the rat population is divided into 3 groups. Each group consisted of 11 rats. Diagnosis of rat model of dementia was made on day 21. BDNF and CRP serums of group 1, 2 and 3 were examined on day 21 (pre training). Group 1 is a rat model of dementia without treatment. Serum and CSF was taken on day 28. Then do the euthanasia and necropsy to examine the hippocampus immune histochemically. In the group 2 (exercise 1 series) after continuing training for 7 days, then on day 28 the serum, CSF examinations, euthanasia and necropsy were performed. In the group 3 (exercise 2 series) after 14-day trainings, the same procedures were performed on day 35. Rat brain surgeries were performed by a veterinarian.

**Results**

- Table-1 shows that Physical Exercises on rat model of dementia is very significantly to decrease Aβ deposit.
- Aβ deposit of group 2 (12.20 ± 1.99), is significantly lower than that of group 1 (16.29 ± 0.71).
- Aβ deposit of group 3 (9.94 ± 1.41), is significantly lower than that of group 1 (16.29 ± 0.71).
- Aβ deposit of group 3 (9.94 ± 1.41), is significantly lower than that of group 2 (12.20 ± 1.99).
- ANOVA test shows significant differences of Aβ deposits in all three groups (p < 0.001).
- These data indicates that the series of Physical Exercises on rat model of dementia resulted in the decrease of Aβ deposits. The deposit in group 3 < group 2 < group 1 (control).
- Table-2 shows that Physical Exercises on rat model of dementia is very significantly to increase serum BDNF level
- Serum BDNF level of group 2 (583.63±515.35), is not significantly different with that of group 1 (549.87±552.32).
- Serum BDNF level of group 3 (1144.89±515.84), is significantly higher that of group 1 (549.87±552.32).
- Serum BDNF level of group 3 (1144.89±515.84), is significantly higher that of group 2 (583.63±515.35).

**Table-1:** Physical Exercise Effects on Aβ deposit depletion

<table>
<thead>
<tr>
<th>Groups</th>
<th>Aβ deposit (μm)</th>
<th>95% CI</th>
<th>Aβ difference</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lower</td>
<td>Upper</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1(n=11)</td>
<td>16.29±0.71</td>
<td>15.81</td>
<td>16.78</td>
<td>Ref</td>
</tr>
<tr>
<td>Group 2(n=11)</td>
<td>12.20±1.99</td>
<td>10.85</td>
<td>13.54</td>
<td>-0.49±0.63</td>
</tr>
<tr>
<td>Group 3(n=11)</td>
<td>9.94±1.41</td>
<td>9.00</td>
<td>10.87</td>
<td>-6.34±0.47*</td>
</tr>
</tbody>
</table>

* Significantly difference with 1 series exercise (p = 0.02)  
** Significantly different among the three groups (ANOVA p <0.001)

**Table-2:** Physical Exercise Effects on the Serum BDNF Level

<table>
<thead>
<tr>
<th>Groups</th>
<th>Serum BDNF Level (μg/ml)</th>
<th>95% CI</th>
<th>BDNF difference</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lower</td>
<td>Upper</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1(n=11)</td>
<td>549.87±552.32</td>
<td>944.99</td>
<td>1547.6</td>
<td>Ref</td>
</tr>
<tr>
<td>Group 2(n=11)</td>
<td>583.63±515.35</td>
<td>929.85</td>
<td>237.41</td>
<td>33.75±230.38</td>
</tr>
<tr>
<td>Group 3(n=11)</td>
<td>1144.89±515.84</td>
<td>1491.44</td>
<td>798.35</td>
<td>595.01±230.38*</td>
</tr>
</tbody>
</table>

* Significantly difference with 1 series exercise (p = 0.018)  
** Significantly different among the three groups (ANOVA p <0.022)
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- ANOVA test shows significant differences of serum BDNF level in all three groups (p < 0.022).
- These data indicates that the series of Physical Exercises on rat model of dementia resulted in the increase of serum BDNF levels. The level in group 3 > group 2 > group 1 (control).
- Table-3 shows that physical exercises on rat model of dementia can decrease serum CRP level.
- The decrease of serum CRP level of group 2 (334.65±428.81), is higher than that of group 1 (212.21±446.66).
- The decrease of serum CRP level of group 3 (351.17±393.78), is higher than that of group 1 (212.21±446.66).
- Table-4 shows that physical exercises on the rat model of dementia increase the CSF BDNF level.

### Table-3: Physical Exercise Effects on the Serum CRP Level

<table>
<thead>
<tr>
<th>Groups</th>
<th>Serum CRP Level (µg/ml)</th>
<th>Decreased of CRP level</th>
<th>95% CI</th>
<th>CRP difference</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre Ex</td>
<td>Post Ex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1 (n=10)</td>
<td>1141.34</td>
<td>929.12</td>
<td>212.21±446.66</td>
<td>107.31</td>
<td>531.73</td>
</tr>
<tr>
<td>Group 2 (n=11)</td>
<td>1222.80</td>
<td>888.14</td>
<td>334.65±428.81</td>
<td>46.57</td>
<td>622.73</td>
</tr>
<tr>
<td>Group 3 (n=11)</td>
<td>1206.91</td>
<td>855.74</td>
<td>351.17±393.78</td>
<td>86.63</td>
<td>615.72</td>
</tr>
</tbody>
</table>

* Not significantly different with 1 series exercise (p = 0.843)
** not significantly different among the three groups (ANOVA p < 0.720)

- ANOVA test shows no significant difference of serum CRP level in all three groups (p < 0.720).
- Although no significant difference, these data indicate that the series of physical exercises on rat model of dementia resulted in the decrease of serum CRP levels. The level in group 3 < group 2 < group 1 (control).

### Table-4: Physical Exercise Effects on the CSF BDNF Level

<table>
<thead>
<tr>
<th>Groups</th>
<th>CSF BDNF Level (µg/ml)</th>
<th>95% CI</th>
<th>BDNF difference</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre Ex</td>
<td>Post Ex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1 (n=11)</td>
<td>828.84±238.48</td>
<td>668.63</td>
<td>989.06</td>
<td>Ref -</td>
</tr>
<tr>
<td>Group 2 (n=11)</td>
<td>972.53±166.41</td>
<td>860.74</td>
<td>1084.33</td>
<td>143.68±87.68</td>
</tr>
<tr>
<td>Group 3 (n=11)</td>
<td>1288.17±396.87</td>
<td>1021.55</td>
<td>1554.79</td>
<td>456.32±139.60*</td>
</tr>
</tbody>
</table>

* no significantly difference with 1 series exercise (p = 0.086)
** Significantly different among the three groups (ANOVA p <0.022)

### Table-5: Physical Exercise Effects on Astrocyte BDNF Expression

<table>
<thead>
<tr>
<th>Groups</th>
<th>Astrocyte BDNF Exp %sel</th>
<th>95% CI</th>
<th>BDNF difference</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lower</td>
<td>Upper</td>
<td></td>
</tr>
<tr>
<td>Group 1 (n=11)</td>
<td>48,72±7,68</td>
<td>43,56</td>
<td>53,88</td>
<td>Ref -</td>
</tr>
<tr>
<td>Group 2 (n=11)</td>
<td>63,59±15,52</td>
<td>53,17</td>
<td>74,02</td>
<td>14,35±4,95</td>
</tr>
<tr>
<td>Group 3 (n=11)</td>
<td>77,95±10,24</td>
<td>71,07</td>
<td>84,84</td>
<td>29,23±3,68*</td>
</tr>
</tbody>
</table>

* No significantly difference with 1 series exercise (p = 0.059)
** Significantly different among the three groups (ANOVA p <0.001)
• Astrocyte BDNF expression of group 3 (77.95±10.24), is higher than that of group 2 (63.59±15.52).
• ANOVA test shows significant difference of Astrocyte BDNF expression in all three groups (p <0.001).
• These data indicate that the series of physical exercises on rat model of dementia resulted in the increase of astrocyte BDNF expressions. The expression in group 3 > group 2 > group 1 (control).

Fig-2: Result of Immunohistochemistry Examination of Astrocyte BDNF expression

Astrocyte BDNF expression (bar 300 μm) A = Group 1 (Control); B = Group 2; C = Group 3

Table-6 shows that physical exercises on rat model of dementia increase microglia BDNF expression.
• Microglia BDNF expression of group 2 (140.41±24.68), is higher than that of group 1 (136.50±14.92).
• Microglia BDNF expression of group 3 (144.96±18.06), is higher than that of group 1 (136.50±14.92).
• Microglia BDNF expression of group 3 (144.96±18.06), is higher than that of group 2 (140.41±24.68).
• ANOVA test shows no significant difference of microglia BDNF expression in all three groups (p = 0.605).
• Although no significant difference, these data indicate that the series of physical exercises on rat model of dementia resulted in the increase of microglia BDNF expressions. The expression in group 3 > group 2 > group 1 (control).

Fig-3: Result of Immunohistochemistry Examination of Microglia BDNF Expression

Microglia BDNF expression (bar 30 μm) A = Group 1 (Control); B = Group 2; C = Group 3

Discussion

In this study we have shown the physical exercise effects on several neurobiological substances, that contribute to the onset of dementia. The study conducted in Wistar rats, aimed to assess the effectiveness of physical exercise (swimming training) to the change of brain substance levels and expressions, such as Aβ, BDNF and CRP.

In AD, Aβ deposition will activate caspase, apoptosis, cytoskeletal damage and neuronal death (Rubio and Morillas, 2012). Neuronal damage caused by to apoptosis, occurs through a variety of mediators such as TNF, interleukin-1β-converting enzyme inhibitory protein, and other substances [40,41]. In rat experiments, dementia-like symptoms arise after 2-4 weeks of Aβ injection. Deposition of Aβ mainly occurs in the cerebellum and cerebral cortex [8,10,11,14, 42, 43, 44].

Table-6: Physical Exercise Effects on Microglia BDNF Expression

<table>
<thead>
<tr>
<th>Groups</th>
<th>Microglia BDNF Exp %sel</th>
<th>95% CI</th>
<th>BDNF difference</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lower</td>
<td>Upper</td>
<td></td>
</tr>
<tr>
<td>Group 1(n=11)</td>
<td>136.50±14.92</td>
<td>126.48</td>
<td>146.53</td>
<td>Ref</td>
</tr>
<tr>
<td>Group 2(n=11)</td>
<td>140.41±24.68</td>
<td>12.84</td>
<td>157.00</td>
<td>3.91±8.69</td>
</tr>
<tr>
<td>Group 3(n=11)</td>
<td>144.96±18.06</td>
<td>132.83</td>
<td>157.09</td>
<td>8.64±7.06*</td>
</tr>
</tbody>
</table>

* No significantly difference with 1 series exercise (p = 0.948)
** No significantly difference among the three groups (ANOVA p = 0.605)
The study result (Table-1) shows that the series of physical exercises decreases the \(A\beta\) deposits. The ANOVA test shows significant differences of \(A\beta\) deposits in all three groups (p <0.001). The deposit in group 3 (9.94 ± 1.41) < group 2 (12.20 ± 1.99) < group 1 (control) (16.29 ± 0.71).

In rat Model of AD, reported the addition of \(A\beta\) plaque gradually [37]. So far, no study has reported the volume density or thickness of \(A\beta\) deposit. The main factor to an increase in \(A\beta\) deposits in AD is apolipoprotein E4, which in this study was not evaluated. The decrease of \(A\beta\) deposit in AD may occur due to an increase of anti-amyloid antibody. This situation can reduce the symptoms of the disease [45].

BDNF is a mediator of neurogenesis. The increase of BDNF serum, volume of the hippocampus and the medial part of the temporal lobe after physical exercises can improve memory impairment [23]. BDNF plays an important role in neural development. In normal rat, the physical exercises every day for 7, 14, 28 and 72 days, can significantly increase BDNF levels in the hippocampus. The increase is equal to 150% (day 14), 175% (day 28) and 200% (day 72) [1].

The study result (Table-2) shows that the series of physical exercises significantly increase the serum BDNF levels. The ANOVA test shows significant differences of serum BDNF level in all three groups (p <0.022). The level in group 3 (1144.89±515.84) > group 2 (583.63±515.35) > group 1 (control) (549.87±552.32).

In the brain, BDNF is secreted by neurons and glial cells. BDNF stimulates and controls the plasticity of the brain. Changes in brain plasticity occur due to an increased number of growth factors such as vascular endothelial growth factor (VEGF) and BDNF. BDNF is a key protein in the regulation for the sustainability of growth, for the life of neurons and important activity of synaptic transmission. On physical exercises, BDNF can stimulate neurogenesis in the form of the formation of new neurons [22, 24, 46].

CRP is an acute phase protein. In the event of injury, the level is up 100 times in 24-48 hours (Landenvall et al., 2006). The pathologic changes of AD are thought to be associated with inflammation. It is through the stimulation of glial cells to produce proinflammatory cytokines such as TNF-\(\alpha\), IL-1\(\beta\), IL-6 and CRP. Proinflammatory cytokines stimulate glial cells to produce \(\beta\)A42 and tau protein. CRP could be expected to predict the onset of AD. Increased CRP is a risk of AD [30]. Through inflammation, increased CRP can disrupt cognitive function. (Ge et al., 2013).

The study result (Table-3) shows that the series of physical exercises can decrease serum CRP level. The ANOVA test shows no significant difference of serum CRP level in all three groups (p <0.720). Although no significant difference, these data indicate that the series of physical exercises on rat model of dementia resulted in the decrease of serum CRP levels. The level in group 3 (351.17±193.78) < group 2 (334.65±428.81) < group 1 (control) (212.21±446.66).

Not many explanations of the relation of CRP and AD [33]. Prolong and sustainable physical exercise will reduce levels of CRP, conversely, irregular and short duration physical exercise will increase the CRP [33]. Studies supporting the role of inflammation in the pathogenesis of dementia is still very limited because of the events underlying the inflammatory process is not clearly known. The process is believed to take place through the role of N-methyl-D-aspartate (NMDA) receptors, an increase of Nitric Oxide (NO), intracellular calcium influx, mitochondria disruption, oxidative distress, disruption of energy production and the occurrence of membrane depolarization [47]. Several studies in healthy subjects, found a significant association between increased levels of CRP with improved memory function [48,49]. Neurobiologically, there is a correlation between CRP with \(A\beta\) formation that results in dementia. This is not just happening in humans, but also in animal models. The things mentioned above show that there are still quite a lot of neurobiology mechanisms are unknown. The insignificant value of serum CRP level in this study can be related to the lack of exercise frequency.

The study result (Table-4) shows that the series of physical exercises increases the CSF BDNF level. The ANOVA test shows a significant difference of CSF BDNF Level in all three groups (p <0.002). These data indicates that the series of physical exercises on rat model of dementia resulted in the increase of CSF BDNF level. The level in group 3 (1288.17±396.87) > group 2 (972.53±166.41) > group 1 (control) (828.84±238.48).

This study shows that the series of Physical Exercises on rat model of dementia resulted in the increase of serum and CSF BDNF levels. These results are also in accordance with some previous studies of BDNF and dementia. Many studies on the role of BDNF in the nervous system found that BDNF helps the life of existing neurons, triggering the growth of new neurons, and help function of synapses [20, 21, 22].

Astrocyte is the most predominant glial cell and account for almost half of the adult mammalian brain volume. Greater number of astrocyte found in several brain regions and also in species that have higher cognitive abilities [50]. Related to dementia, along with microglia and proinflammatory cytokines, astrocyte participates in the inflammatory process [16].

The study result (Table-5) shows that the series of physical exercises increase the astrocyte BDNF expression. The ANOVA test shows a significant difference of astrocyte BDNF expression in all three groups (p <0.001). These data indicates that the series of physical exercises on rat model of dementia resulted in the increase of astrocyte BDNF expression. The expression in group 3 (77.95±10.24) > group 2 (63.59±15.52) > group 1 (control) (48.72±7.68). This study also shows a match between the increase of serum, CSF BDNF levels and the increase of astrocyte BDNF expression.

In this study, there is a difference in the expression of BDNF in astrocyte and microglia. The study result (Table-6) shows that
the series of physical exercises increases the microglia BDNF expression. The ANOVA test shows no significant difference of microglia BDNF expression in all three groups (p = 0.605). Although no significant difference, these data indicates that the series of physical exercises on rat model of dementia resulted in the increase of microglia BDNF expression. The expression in group 3 (144.96±18.06) > group 2 (140.41±24.68) > group 1 (control) (136.50±14.92).

In the central nervous system, activated microglia play an important role in the immune process. Astrocytes and microglia together with other immune factors are associated with the synthesis of growth factors and adhesion molecules. These cells produce cytokines. On the Hematoxylin and Eosin (H & E) staining of the normal brain, only a few of the microglia are detected. Related to the rat model of dementia, there has been no report on the immunohistochemistry examination of glial cells quantitatively [35,36,51].

In normal rat, there is a positive correlation between duration of regular physical exercise with brain BDNF levels. The longer the exercise, the higher levels of BDNF [1]. But it is not clear how much the highest levels of BDNF could be achieved by exercise. The insignificant value of microglia BDNF expression in this study, can be related to the lack of exercise frequency.

**Conclusion**

Based on the results of the study, it can be concluded that there are improvements of brain plasticity as a result of a series of physical exercises on the dementia rat model characterized by the presence of:

1. Aβ deposit depletion on the immunohistochemistry examination, compared with controls.
2. The increase in serum BDNF levels, compared with the control.
3. The increase in CSF BDNF levels compared with control
4. The increase in astrocyte BDNF expression, compared with control
5. No significant difference in serum CRP levels, compared with the control.
6. No significant difference in microglia BDNF expression, compared with the control.

Further studies are required to determine the effect of more physical exercises on the serum CRP levels and microglia BDNF expression.

**References**


