Turmeric Extract Administration Increases the Expression of Brain Derived Neurotropic Factor Following Repetitive Traumatic Brain Injuries

Andre Marolop Pangihutan Siahaan 1* , Iskandar Japardi1, Wismaji Sadewo2
1Department of Neurosurgery, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia
2Department of Neurosurgery, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia

Keywords: Repetitive Traumatic Brain Injuries; Turmeric Extract; BDNF.

Abstract: Objective: To demonstrate the role of turmeric extract administration in increasing Brain-Derived Neurotrophic Factor (BDNF). Method: A model of repetitive traumatic brain injury was used on Sprague Dawley mouse, using a 40-gr weight dropped onto the vertex from 1-m height with total frequency of twelve times, divided into four days; three traumas every day. A 500 mg/kg turmeric extract was administered per oral daily. BDNF expression was assessed using immunohistochemistry examination. As a comparison, there were also negative sham control group and trauma only group. Result: There was no significant difference in BDNF expression between the negative sham control group and trauma only group. Instead, there was a significant increase in BDNF expression in the group with turmeric extract administration. Conclusion: Turmeric extract administration increased BDNF expression following repetitive traumatic brain injury.

1 INTRODUCTION

Even though the first long-term effect following repetitive traumatic brain injury (RTBI) was reported almost a century ago, it starts to be a prominent issue in the last decade, especially after Omalu reported this finding in American Football (Omalu et al., 2005). This condition, termed Chronic Traumatic Encephalopathy (CTE), is related to disturbance of behavior, mood, cognitive, and motor function (Montenigro et al., 2015). Following RTBI, the brain will undergo progressive changes consistent with degeneration process, with tau protein as the main pathology (McKee et al., 2016). CTE itself is still a disease of elusive, with varying diagnostic criteria and no proved effective treatment (Hay et al., 2016).

This problem becomes significant if we consider that some people, such as contact sport athletes (i.e., American football, soccer, and martial arts) and military personals are prone to encounter RTBI (McKee et al., 2009). In professional soccer players, for instance, head impacts during playing are various, dependent on the season, from four times up to 125 times in two weeks. A post-mortem examination in American football players confirmed this hypothesis. A report showed that NFT was found in most, if not all retired professional American football players (Perrine et al., 2017). RTBI itself will disturb ionic stability in the neural cell. Following an impact, the released glutamate will initiate hyperactivation of N-methyl-D-aspartate (NMDA)-type receptors, burden the cell with calcium, and induct neuroinflammation (Guerriero et al., 2015). All of these processes will lead to neuronal cell death. To overcome it, neurotrophic factors, especially the brain-derived neurotrophic factor (BDNF), will be released. BDNF serves as a crucial mediator of neuronal plasticity that will lead to neuronal remodeling, the formation of new synapses, or new neurogenesis (Failla et al., 2015). However, this response is lessened following RTBI. Inflammatory cytokines that released following RTBI seem to play a key role by reducing the expression of BDNF (Kaplan et al., 2010). This inhibition is not limited only to BDNF, but also to other trophic factors, such as nerve growth factor (NGF) and neurotrophin-3 (NT-3).
Turmeric (Curcuma longa) plants commonly found in South and Southeast Asia. For centuries, the rhizome of this plant has been used as a spice in daily food and medicinal properties. Curcumin, its active component, has been isolated for decades and proved to have strong anti-inflammation activity (Aggarwal et al., 2013). The aim of this study was to demonstrate the effect of turmeric extract administration on BDNF expression following RTBI.

2 METHOD

2.1 Animal Model and Experimental Groups

Thirty Sprague-Dawley young adult rats were divided randomly into three groups, i.e., the negative sham control group, trauma-only group, and turmeric group. Total traumas were twelve times, divided into four days, i.e. on day 1, 2, 4, and 7, with a no-trauma period on day 3, 5, and 6. This timing was carried out to resemble the real condition in sports. Trauma was applied using a weight model drop, by dropping a 40-gr mass from 1-meter height onto the vertex. A metal helmet was put on the vertex to prevent skull fracture (Xu et al., 2016). This protocol was approved by the Medical Research Committee, Medical Faculty Universitas Sumatera Utara, Medan, Indonesia.

2.2 Turmeric Extract Supplementation

A commercially available turmeric extract (Sido Muncul, curcumin 18.02%) was given orally with 500 mg/kg dose daily to rats in the turmeric group.

2.3 Brain Extraction

Decapitation was done using sharp scissors. Ether was used as an anesthetic agent. Craniotomy was performed started posteriorly from the foramen magnum to the anterior, without preservation of the olfactory bulb. A 10% formalin buffer solution was used as a fixation agent.

2.4 Immunohistochemistry Examination and Cell Count

A 4-micron paraffin block was stained using BDNF antibody (Abcam). Brown-stained nuclear was counted as positive. The observation was carried out using cell count in twenty visual fields at the cortex of the vertex with magnification 400 times.

2.5 Statistical Analysis

Values were expressed as means ± SEM. The results were computed statistically using the independent t-test. A difference was considered significant at the p <0.05 level.

3 RESULTS

3.1 Mortality and Body Weight Change

There was no mortality found in this protocol, either in the negative sham control group, trauma only group, and turmeric group. There was also no significant difference regarding body weight before and after protocols in all three groups (table 1).

Table 1: Change of body weight before and after the protocol

<table>
<thead>
<tr>
<th>Group</th>
<th>Before protocol</th>
<th>After protocol</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative sham</td>
<td>377.22 ± 29.72</td>
<td>378.44 ± 29.66</td>
<td>0.910</td>
</tr>
<tr>
<td>Trauma</td>
<td>351.78 ± 29.89</td>
<td>349.33 ± 38.90</td>
<td>0.482</td>
</tr>
<tr>
<td>TE</td>
<td>367.89 ± 36.70</td>
<td>357.89 ± 39.89</td>
<td>0.950</td>
</tr>
</tbody>
</table>

*paired t-test. Significant if p<0.05.

3.2 BDNF Expression

Compared to the negative sham control group, there was no significant change in BDNF expression following RTBI (p=0.999). BDNF expression in the turmeric group was significantly higher compared to negative sham (p=0.021) and trauma only group (p=0.007; figure 1)
4 DISCUSSION

To the date, there was no generally accepted protocol that can reproduce the situation in RTB in contact sport athletes. The protocol used in this research itself was considered as "mild" TBI, even there are no diagnosis criteria of concussion in the rat (Xu et al., 2016). Even though, we had shown no change in BDNF expression following RTBI. BDNF acts in secondary injury caused by a combination of inflammation, ischemia, cytotoxic process, and apoptosis. Several experimental studies on rat had shown an increase in hippocampal BDNF mRNA days after moderate-severe TBI. Another study showed that BDNF level would decrease in 24 hours following TBI, but not significant again after 36 hours (Yang et al., 2009).

We also found an increase in BDNF expression following turmeric administration. Curcumin is shown to be a potent anti-inflammatory agent in an animal model of TBI. BDNF expression is affected by inflammation (Failla et al., 2015). The mRNA levels of BDNF on hippocampal were reduced following administration of interleukin. Even so, the inflammatory response itself is very
crucial in neural remodeling process and recovery. It makes neuroinflammation is not the only pathway that should be restricted in treating TBI (Lyman et al., 2014).

To the best of our knowledge, this is the first research that demonstrates the effect of turmeric on BDNF expression following RTBI. The main limitation of this research was no evaluation of the status of neuroinflammation itself, even regarding proinflammatory cytokines or either astrogliosis or microglia activation. This aspect can be evaluated in further research.

5 CONCLUSION

Turmeric extract administration increased BDNF expression following repetitive traumatic brain injury.

ACKNOWLEDGMENT

This study was funded by Universitas Sumatera Utara in TALENTA Grant. Authors also thanked Widi Riawan from Department of Biochemistry, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia, for the help in conducting this study.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES


