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Original Article

The Effects of Aerobic Exercises on Memory, Cerebral Edema, and Extracellular Neuronal Discharge in an Experimental Model of Traumatic Brain Injury: The Role of BDNF Expression

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Abstract

Background: Traumatic brain injury (TBI) remains a primary cause of mortality and is a significant contributor to various impairments, including somatosensory and cognitive deficits. The prevention and management of injuries require regular daily exercise. In this research, we examined the impact of eight weeks of aerobic exercise on neurological outcomes, brain water content (BWC), blood-brain barrier (BBB) permeability, electrophysiological characteristics, and concentrations of brain-derived neurotrophic factor (BDNF) in an experimental model of TBI.

Methods: Sixty-four male Wistar rats were divided into four groups: Control, Training, TBI, and Training-TBI. TBI was induced using the Marmarou method. After TBI induction, eight weeks of aerobic exercise were performed using a five-line animal treadmill. Then, the rats' memory and learning were assessed using the Morris water maze. Electrodes were implanted in the skulls of anesthetized rats for single-unit recording. Neurological scores, BWC, BBB permeability, and cerebral tissue BDNF concentrations were measured 48 hours after exercise. Statistical analysis was conducted using one-way ANOVA, followed by Tukey's post hoc test for multiple comparisons. P values < 0.05 were considered statistically significant.

Results: Aerobic exercise significantly reversed the decrement of neurological scores, the neuronal firing rate of the hippocampus, increments of BWC, cognition deficits, and cerebral tissue Evans blue concentration after TBI compared with control. It also increased cerebral tissue BDNF, which had significantly decreased in TBI.

Conclusion: Our results suggest that through BDNF increment, aerobic exercise exerts neuroprotective effects on memory impairment and the decrement of neuronal firing rate caused by TBI.

Keywords: Traumatic brain injury, Aerobic exercise, Edema, BDNF, Rat

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Introduction

Traumatic brain injury (TBI) remains a major contributor to global mortality and disability (1). Each year, TBI impacts the lives of over 50–60 million individuals globally, as evidenced by population-based studies (1). Despite the significant impact of TBI, there are currently no authorized treatments specifically designed to control its immediate and long-term consequences (2). Depending on the severity of the trauma (mild, moderate, and severe), some cerebral injuries can have acute or chronic side effects (3). Overall, TBI could result in acute consequences, such as cerebral edema and hemorrhage (4), or adverse chronic effects, like Alzheimer's disease (5), dementia (6), and persistent pain (7). Impairment in cognitive functions, including memory deficit, and the occurrence of brain edema (7) are among the long-term consequences of the inability to perform executive functions caused by TBI (8).

The initiation of edema is attributed to the breach of the blood-brain barrier (BBB) in TBI models. Astrocyte-induced edema (cytotoxic edema) is an initial occurrence of cerebral edema that arises immediately after a TBI (9); in cases of TBI, the cerebral edema caused by astrocytes results in an elevation of pressure within the skull. This subsequently reduces cerebral blood flow and oxygenation (10).

Understanding the underlying mechanisms of TBI pathophysiology is crucial for preventing this condition.

These mechanisms include apoptosis, inflammation, autophagy, oxidative stress, and neural degeneration (11).

Exercise, especially aerobic exercise training (AET), has many beneficial effects on the neural system (12). AET can be helpful in the treatment or rehabilitation of TBI (13). Previous studies have shown that AET stimulates specific mechanisms and signals in the body. For example, after exercise, chemical mediators such as irisin and BDNF, which benefit memory and hippocampal function, are released in the brain tissue (14,15). Engaging in AET has been linked to several physiological changes that benefit the central nervous system (CNS) and various bodily functions, such as angiogenesis (16) and neurogenesis (17). Evidence from human and animal research suggests that aerobic exercise may enhance cognitive function following TBI (18,19). An experimental model of TBI demonstrated that rats that had undergone aerobic treadmill exercise demonstrated improved cognitive functioning, such as better performance on tasks such as the Morris water maze and reduced latency time in the rotarod task (20).

Research using rats with cerebral contusion has demonstrated cerebral edema and BBB disruption peak within 48 hours (21). Nevertheless, additional investigations are required to elucidate the molecular mechanisms underlying the potential advantages of AET for TBI. Therefore, the current study aimed to evaluate the effects of eight weeks of AET with 90%–95% maximum VO2 intensity on neurological outcomes, cognition deficits, BBB permeability, and cerebral BDNF concentrations in a rat model of TBI.

Methods

Materials

Evans blue (EB) was acquired from Teb Pazhouhan Razi Institute (Tehran, Iran), and the BDNF kit was purchased from ZellBio (Germany).

Animals

Sixty-four adult male Wistar rats (220–250 g, 12–15 weeks old) were acquired from Zahedan Laboratory Animal Reproduction and Breeding Center and allowed one week to acclimatize. Considering the possibility of interference caused by fluctuations in estrogen and progesterone hormone levels during various stages of the female animal's reproductive cycle, male animals were utilized in this study. The rats were group-housed in a temperature-regulated environment (23.0 ± 1.0 °C) with a 12-hour light/dark cycle and unrestricted access to food and water. The study adhered to the protocols outlined by the Ethics Committee of Zahedan University of Sistan and Baluchestan (Zahedan, IRAN) in all experimental procedures (IR.USB. REC.1399.016). The animals were randomly allocated to four primary groups, with 16 subjects in each group, as follows: 1) Control: This group did not receive any exercise protocol and were not subjected to cerebral trauma; 2) Training: Healthy rats that did aerobic exercise with a treadmill for eight weeks, 3) TBI: Rats that underwent concussion induction, 4) Training-TBI; TBI rats that did aerobic exercise on a treadmill for eight weeks after TBI induction.

TBI model

Diffuse TBI was induced using Marmarou's weight drop model, with modifications as previously described, utilizing a TBI induction device constructed in the Department of Physiology at Zahedan University of Medical Science (22). This is a suitable model for simulating head injuries in motor and road accidents.

In brief, the male rats were anesthetized using urethane (1.5 g/kg) (22). After a surgical procedure, which included a midline scalp incision and the removal of the soft tissue between the lambda and bregma sutures, a stainless-steel disc (10 mm diameter, 3 mm thickness) was firmly affixed to the central region of the skull's dorsal area using dental polyacrylamide cement. Subsequently, the rats were positioned on a foam bed directly beneath the device tube. A 200 g weight inside a 1-meter-high Plexiglas tube was dropped onto the disc to induce moderate TBI (22). After stabilization, the animals were transferred to their cages (23). The results show that in this model, diffuse axonal damage occurs from the cerebellum to the brain stem. Depending on the severity of the damage in this model of cerebral edema, neuronal and glial death, inflammation, and bleeding may be observed. Regarding the impact of TBI, initial neuronal cell death occurs at the location of impact, followed by subsequent damage to neurons, starting at the time of impact and continuing for up to 48 hours. Therefore, the subgroups' behavioral, electrophysiological, and biochemical tests were performed two days after the induction of TBI.

Method of performing AET

A motorized treadmill manufactured by Borj Sanat Company was used for AET by rats. The machine has five separate belts for training. Its speed and duration of exercise are adjustable. The adult male rats were first accustomed to the exercise system to minimize the stress of exposure to the new environment before the effects of aerobic exercise were studied. The animals that resisted and did not exercise were excluded from the experiment. Animal adaptation was performed for 15 minutes over two days at a minimum speed (5 m/min). The animals were placed on the device to perform aerobic exercise according to a schedule. The specific slope of the device was determined according to the training program. Aerobic exercise with 90%–95% maximum VO2 intensity began at noon and continued until all the rats had completed their programs. The rats in the Training and Training-TBI groups had running sessions on the treadmill, without

incline, five days/week for eight weeks (24). The training protocol time started from 10 min in the first week with a speed of 12 m/min and gradually reached a training duration of 12 minutes and a speed of 54 m/min in the eighth week (25). The rats exercised until Wednesday and rested on Thursdays and Fridays. Their histories were all recorded based on the numbers on their tails.

Neurobehavioral Assessment

The sensory-motor functions were evaluated using modified neurological severity scores at different points in time (0, 1, 4, 24, and 48 hours) after the induction of TBI, as outlined in Table 1. Scores ranging from 5 to 8 indicate severe damage, and scores between 9 and 12 suggest intermediate damage. Minor damage is implied by scores falling between 13 to 15 (22). An operator blinded to the animal group assignment performed the neural testing.

BBB integrity evaluation

The measurement of EB leakage into brain tissue was used to assess the disruption of the BBB. Concisely, EB (E2129 Sigma, EB 2% in saline, 2 mL/kg) was injected via the jugular vein 1 hour after TBI induction. Thirty minutes after the EB injection and under deep anesthesia, the chest wall was opened, and a saline solution of 200 mL was infused through the heart in order to remove EB from the cerebral circulation. Following this, the rats were euthanized by decapitation. Cerebral tissues were removed and weighed. Each animal's cerebral tissue was homogenized in 2.5 mL PBS, and then 2.5 mL of 60% trichloroacetic acid (Merck, Germany) was added for protein precipitation. Afterward, the samples were centrifuged for 30 minutes at 3500 rpm. The supernatant was measured at 610 nm to measure EB absorbance using a spectrophotometer. Data were presented in units of micrograms per gram of wet brain tissue and calculated via a standard curve. The EB quantity (μg) in brain tissue (g) was calculated using the following formula:

$$EB\ color\ (\mu g)\ in\ brain\ tissue\ (g) = (13.24 \times 20 \times absorbance) / tissue\ weight$$

Determination of cerebral edema

The percentage of brain water content (BWC), indicative of cerebral edema, was evaluated approximately 48 hours after the induction of TBI. In order to obtain a BWC% measurement, the rats were euthanized, and their cerebral tissues were isolated and weighed to obtain the wet weight (WW). Afterward, the cerebral tissues were dehydrated for 24 hours at a temperature of 110 °C to determine their dry weight (DW). The BWC ratio was then considered using the formula:

$$(WW - DW) / WW \times 100$$

Table 1. Veterinary coma scale

	Variable	Score
Motor function	Normal movement	8
	Mildly drowsy with spontaneous, purposeful movements	7
	Lethargic, unable to stand, but maintains sternal recumbency	6
	Lethargic, withdraws to pinch, and lifts head with attention to visual stimuli; no sternal recumbency	5
	Withdraws or pedals to pinch	4
	Spontaneous pedaling	3
	Extensor posturing (spontaneous or to stimuli)	2
	Flaccid to stimuli	1
Eye function	Open	4
	Open on stimulation	3
	Normal eyelid reflexes	2
	No eyelid response to stimuli	1
Respiration	Normal	3
	Ataxic	2
	Apneic	1

Spatial learning and memory

The researchers employed the Morris water maze (MWM) task to assess spatial learning and memory. This task involves a circular pool measuring 180 cm in diameter and 60 cm in height with a smooth, non-reflective inner surface. The pool is filled with water at 26 ± 1 °C. The task is conducted in a dimly lit, soundproof room with consistent external cues. Various parameters such as path length, latency time, and time spent in the target quadrant searching for the hidden platform are recorded, serving as indicators of animal memory and learning, as comprehensively described in prior studies (22).

Electrophysiological study (single-unit recording)

The animals were first given urethane (1.2 g/kg, IP) as an initial anesthesia, with additional doses (0.1 g/kg) given every hour as necessary to ensure a profound and stable state of anesthesia. This was determined by observing the lack of movement in response to a strong tail pinch (26). The body's temperature was kept at 36–36.7 °C with a thermistor-controlled heating pad. The full description of the experiment has been previously described (27). In summary, a single opening 2 mm in diameter was created in the skull above the hippocampal dentate gyrus (HDG: AP = -3.8 mm from bregma; ML = -2.3 mm; DV = -3.5 mm from dura) following the coordinates outlined in a rat brain atlas (Paxinos & Watson, 2007) (22). Extracellular recording from individual neurons was achieved using a tungsten microelectrode (manufactured by Harvad Apparatus, USA). The electrode had a Parylene coating and a shaft diameter of 127 μm with an extra fine tip. The impedance tip was 1 MΩ. During the experiments, data collection was set at 4800 seconds with a bin size of

1000 milliseconds. The collected data were continuously saved on a hard disk. Unit activity, measured as the average frequency in spikes per second, was calculated by a computer. This study considered a signal-to-noise ratio of at least 3 to 1. Unit activity was presented at intervals of 1 or 5 minutes for data visualization.

Measurement of cerebral BDNF content

In another subgroup, two days after TBI induction or cessation of exercise, the rats were administered a lethal dose of Nembutal (IP). They underwent intracardial perfusion with normal saline (pH: 7.4) for 1 minute to eliminate vesicular blood containing potential cytokines from the periphery (28,29). The cerebral tissues were swiftly extracted, immediately frozen in liquid nitrogen, and weighed. The tissues were then homogenized in protein extraction reagent (30) containing 0.5% Triton X-100, 150 mmol/L NaCl, and 50 mmol/L Tris. After homogenization, the samples were placed in a shaker for 90 minutes and then centrifuged at 4 ºC and 4000 rpm for 15 min. The resulting supernatant was collected. A BDNF ELISA kit was purchased from ZellBio (Germany), and the assay was carried out following the manufacturer's instructions. Cytokine concentrations were measured in picograms or nanograms of antigen per milligram of whole brain tissue.

Experimental design

Flow chart presenting the timeline scheme of the experiment (Figure 1).

Statistical analyses

The data was analyzed using GraphPad Prism 7.0 software, and the outcomes are presented as the mean ± standard error of the mean (SEM). One-way ANOVA was employed to analyze data related to BBB, BWC, average spikes, and BDNF concentrations. On the other hand, VCS scores and MWM indices were analyzed through two-way repeated measures ANOVA, followed by Tukey's post hoc test for further examination of significant differences. Results were considered significant at $P < 0.05$.

Results

AET improved TBI VCS scores

VCS scores in all groups are measured according to the classification of TBI clinical scores, according to the indicators listed in the table. The rats were evaluated based on motor, respiratory, and eye performances. The highest score is 15, and the control and training groups achieved a score of 15. The VCS scores showed a notable decrease in the TBI and Training-TBI groups compared to the control ($P < 0.001$). Conversely, the Training-TBI group showed higher VCS scores than the TBI group at 1, 4, 24, and 48 hours after TBI induction ($P < 0.001$, $P < 0.001$, $P < 0.001$, $P < 0.01$ at different time points, respectively) (Figure 2).

AET improved BBB integrity after TBI induction

The impact of AET on BBB disruption post-TBI is depicted in Figure 3. The EB content in the TBI group (29.88 ± 0.4 µg/g tissue) was markedly higher than the control group (23.38 ± 0.12 µg/g tissue, $P < 0.001$) while the EB content in the Training-TBI group (25.33 ± 0.71 µg/g tissue) was lower than the TBI group ($P < 0.001$).

AET improved cerebral edema after TBI induction

In the Control group, the BWC percentage was 77.30 ± 0.7% at 48 hours after surgery. TBI induction considerably enhanced BWC to 79.58 ± 0.7% ($P < 0.001$) at 48 hours after TBI. AET markedly (78.08 ± 0.4%) reduced brain edema formation compared to the control group ($P < 0.001$, Figure 4).

AET improved spatial learning and memory in the rats

During the probe trial, the mean latency time for the rats to reach the hidden platform decreased in all groups during the test trial. Two-way repeated ANOVA showed a significant difference in the mean latency time to find the hidden platform in terms of the training variable ($P < 0.001$) and the time variable ($P < 0.001$). Additionally, a significant day × treatment interaction effect ($P = 0.0008$) was observed across all training trial days. The mean latency time decreased significantly in the control group over the four training days. In contrast, the rats subjected to TBI displayed prolonged latency in finding the platform (day 1: $P < 0.05$, day 4: $P < 0.01$; Figure 5A) compared to the control group. Each animal's swimming path length was meticulously recorded to identify potential differences in water maze behaviors. The swim path length analysis revealed variations between groups during the MWM probe trial. The path length of the experimental groups over the four days of the MWM task is depicted in Figure 5B. The path length

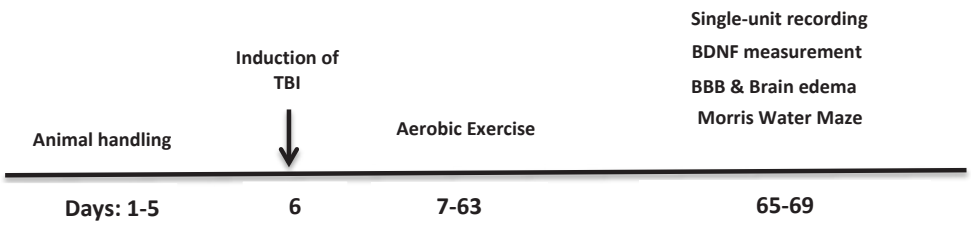

Figure 1. Designing a scheme for the treatment schedule and intervals to estimate various parameters

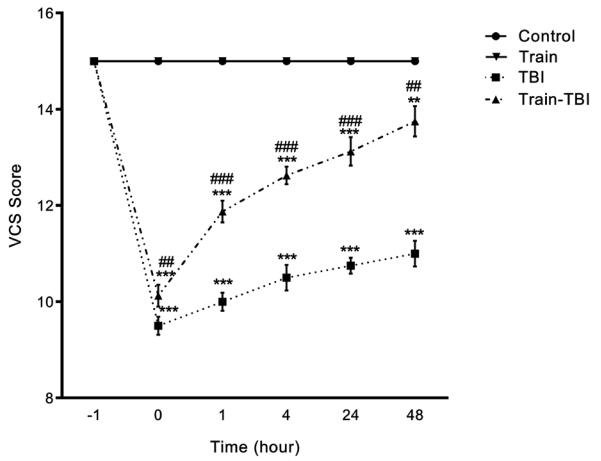

Figure 2. The impact of AET on neurological scores following TBI in male rats. The data is presented as the mean ± SEM, with a sample size of 64. *** Significant difference between the TBI and Control groups ($P < 0.001$). ### Significant difference between the Training+TBI and TBI groups ($P < 0.001$). RM-ANOVA followed by Tukey's post hoc test

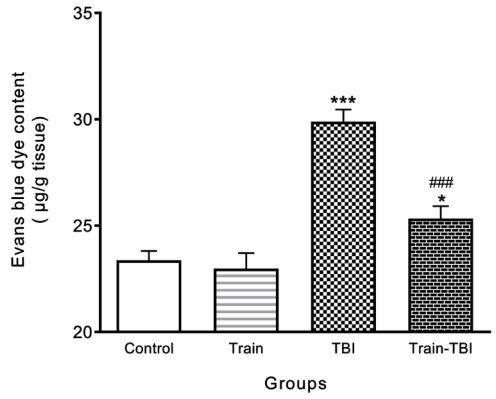

Figure 3. The effect of AET on the content of Evans blue dye in brain tissue after inducing TBI. The data is presented as the mean ± SEM, with a sample size of 32. *** Significant difference between the TBI and Control groups ($P < 0.001$). ### Significant difference between the Training+TBI and TBI groups ($P < 0.001$). RM- ANOVA followed by Tukey's post hoc test

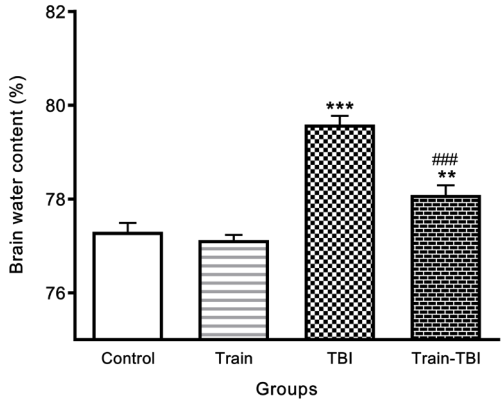

Figure 4. The impact of AET on BWC following TBI in male rats. The data are presented as the mean ± SEM, with a sample size of 32. ** Significant difference between the Training+TBI and Control groups ($P < 0.01$). *** Significant difference between the TBI and Control groups ($P < 0.001$). ### Significant difference between the Training+TBI and TBI groups ($P < 0.001$). RM- ANOVA followed by Tukey's post hoc test

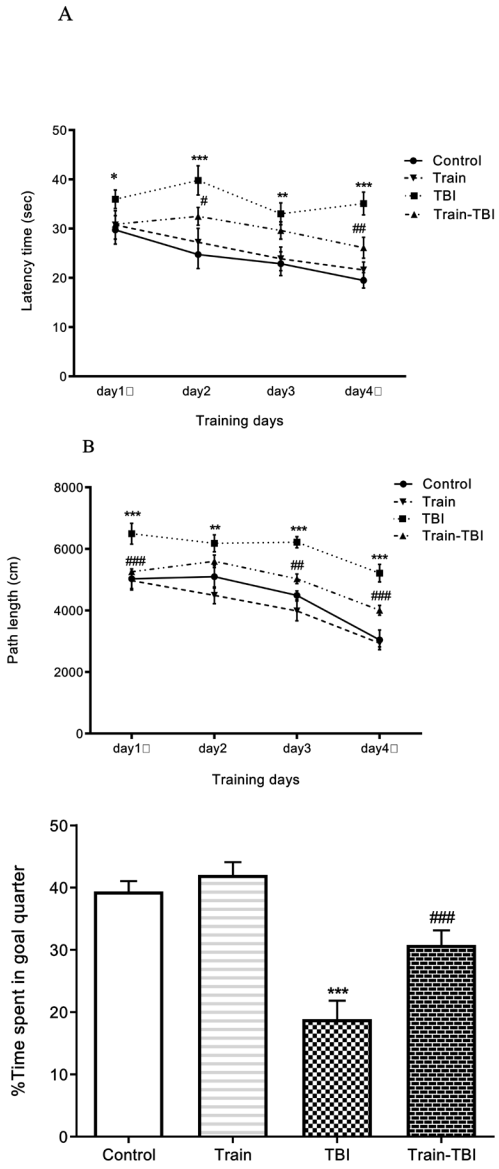

Figure 5. The effect of AET on A) mean escape latency, B) path length, and C) total time spent at the goal quarter in the probe trial during the Morris water maze task in different groups (Control, Training, TBI, and Training+TBI). The data are presented as the mean ± SEM, with a sample size of 8. ** $P < 0.01$, *** $P < 0.001$ vs. control, and # $P < 0.05$, ## $P < 0.01$ and ### $P < 0.001$ vs TBI, mean ± SEM ($n = 8$) two-way repeated measures ANOVA, followed by Tukey's post hoc test)

gradually decreased in the control group during the four training days. In contrast, rats subjected to TBI showed an increased distance traveled to find the platform (day 1, 4: $P < 0.001$, day 3: $P < 0.01$; Figure 5B) compared to the control group.

The probe trials (without a platform) were conducted on test day 5. During this day, the swim time spent in the goal quarter was analyzed for each animal. As illustrated in Figure 5C, there was a significant difference in the percentage of time spent in the goal quadrant between the TBI group (18.89 ± 2.4%) and the control group (39.37 ± 3.1%). Notably, the Training-TBI group

exhibited a substantial increase in swimming time in the goal quarter (30.79 ± 2.4%, $P < 0.001$) compared to the TBI group.

AET's effects on the HDG single-unit recordings in the rats

In vivo, electrophysiological results are shown in Figure 6. Data indicated that TBI induction reduced neuronal firing rate (107 ± 2, $P < 0.01$) in the HDG regions. Aerobic exercise for eight weeks increased the neuronal firing rate in the HDG region in the Training-TBI group, which was evaluated by a single unit recording in the TBI rats (304 ± 12, $P < 0.05$).

AET enhanced cerebral BDNF concentration in the whole brain

The effect of AET administration for eight weeks after TBI on the cerebral concentrations of BDNF 48 hours post-TBI is shown in Figure 7. The BDNF concentrations in TBI rats (11.4 ± 3 mg/mL) were significantly lower than the control group (19.40 ± 3.8 mg/mL) ($P < 0.001$). AET produced a significant increase ($P < 0.05$) in BDNF concentrations (16.62.66 ± 3 mg/mL) compared to the TBI group.

Discussion

This study aimed to evaluate the influence of an eight-week regimen of AET on neurological outcomes, cognitive impairments, BBB permeability, and BDNF levels in rats with TBI.

Considering the findings of the current investigation, eight weeks of AET had protective effects against memory and learning impairments caused by TBI. The decreased expressions of BDNF, VCS scores, neuronal spike frequency, and spatial memory after TBI induction were restored in Training-TBI rats. Improving the effects of AET on memory impairment due to TBI was associated with restored expression of BDNF, BBB integration, and improvement of cerebral edema and neuronal spike frequency in the hippocampus.

Long-term memory impairments resulting from TBI can have severe consequences for individuals, but there has been limited investigation into these issues using rat models of brain injury. The study found that rats with brain injuries exhibited long-term deficits in spatial learning, memory, and behavioral inhibition, which is in line with observations in humans. However, treadmill training improved TBI-induced injury by activating neuroprotective mechanisms that reduce oxidative stress and inflammation following head injury (31,32).

People with TBI have difficulties acquiring signals, recall, and recognition performance (2). Part of the defect is caused by cerebral edema and BBB disruption. In this study, AET prevented the rise in BWC after TBI; furthermore, the reduction in VCS after TBI was less pronounced in the AET group. The neurological disturbance, brain swelling, reduced neuronal activity, and impaired learning and memory observed in this study have also been reported in our previous research (23).

After the weight drop for TBI induction, hyper-excitability develops in the cerebral hemisphere because of the changes in GABAergic functions 48 h post-impact (33). However, in the early acute phase following TBI, the decline in LTP indices in the HDG is notably attenuated. Consequently, synaptic plasticity in the hippocampus is diminished during this acute phase (23).

Neurotrophins are the chief secretory proteins in the cerebral tissue. These endogenous compounds regulate the function, existence, and development of individual cells and neuronal complexes across the entire cerebral tissue (34).

The neurotrophin family, which includes nerve growth factor, neurotrophin-3, neurotrophin-4/5, and BDNF, is pivotal in diverse neuronal functions (35). BDNF, one of the key members, is secreted by neurons and glial cells. It regulates synaptic plasticity, protects neurons

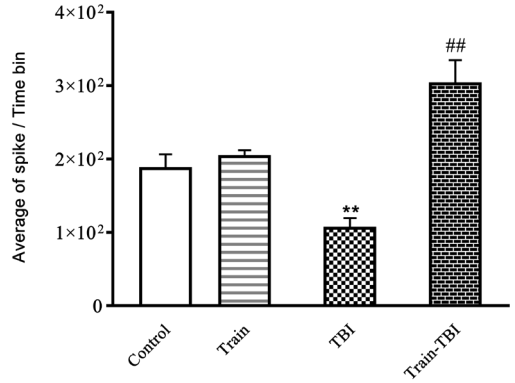

Figure 6. The effects of AET on spike frequency after inducing TBI. Data presented as mean ± SEM, $n = 32$. ** Significant difference between the TBI and Control groups ($P < 0.01$). # Significant difference between the Training-TBI and TBI groups ($P < 0.01$). RM-ANOVA followed by Tukey's post hoc test

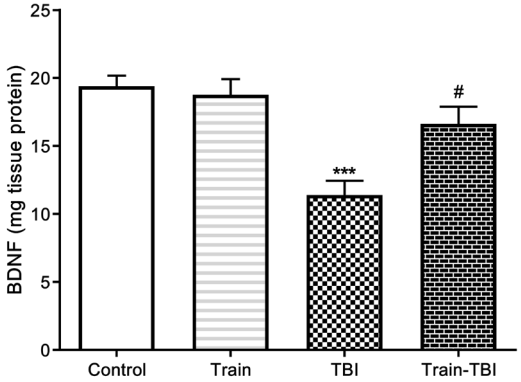

Figure 7. The effects of AET on the cerebral concentration of BDNF after inducing TBI. Data presented as mean ± SEM with a sample size of 32. *** Significant difference between the TBI and Control groups ($P < 0.001$). # Significant difference between the Train-TBI and TBI groups ($P < 0.05$). RM-ANOVA followed by Tukey's post hoc test

from oxidative stress and apoptosis, and promotes neurogenesis (36). Activation of protein kinase B occurs when BDNF binds to its receptors, leading to cell survival by enabling the expression of anti-apoptotic proteins like BcL2 (36). BDNF is a significant regulator of initiating and maintaining LTP in the hippocampus and other brain regions (37). In this study, within 48 hours post-injury, the level of BDNF concentration significantly decreased to very low concentrations in the injured hippocampus. This temporary increment of BDNF following TBI proposes that BDNF acts as an endogenous neuroprotective response to diminish secondary cell injury following TBI. AET was able to greatly increase BDNF concentration.

After TBI, synaptic plasticity for neuronal spike frequency is disrupted, and proteins needed for synaptic tagging and maintenance of spike frequency in the post-synapse are changed (38). Changes in protein expression will reduce the frequencies of the neuronal impulses. Following TBI, the activation of regulatory proteins is often modified through phosphorylation, a process that can be influenced by increased calcium influx after the injury. This ultimately leads to changes in the functioning of protein signaling cascades (38).

The results of this study suggest that AET leads to an elevation in BDNF levels, mainly observed in the Training-TBI group. Thus, exercise improves the frequencies of the impulses and alleviates the TBI-induced VCS score. These inhibitory effects of AET on cognitive deficits are significant, considering that BDNF not only enhances impulse frequency and synaptic plasticity but also affects the rate of edema and disruption of BBB in cerebral tissue. After eight weeks of regular and effective exercise, the neurotrophic agent increased the synthesis and secretion of neurotransmitters, local excitatory postsynaptic potentials, and the likelihood of action potential in postsynaptic neuron terminals to improve cerebral functions (23).

As such, AET applies mechanisms that decrease apoptosis and neural death (39) and increase BDNF concentration and neural growth, differentiation, proliferation, and plasticity. Molecular and cellular events enhance memory and improve the brain's neuronal, muscular, and cognitive function. All of these effects could be helpful to TBI sufferers. However, much research is needed to treat TBI patients.

Conclusion

Cerebral injuries due to TBI activate mechanisms such as cerebral inflammation and edema, which lead to secondary brain injuries, including motor dysfunction, BBB disruption, and memory deficits. Regular aerobic physical activity changes the secretion of chemical mediators. One of the well-known mechanisms by which the cerebral functions act more effectively is the expression of BDNF. BDNF can prevent the adverse effects of TBI, such as cerebral edema, BBB disruption, and changes in the frequency of neuronal spikes.

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Authors' Contribution

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Funding acquisition: Zahra Bazdidi.
Investigation: Zahra Bazdidi.
Methodology: Mohammad Ali Mirshekar.
Project administration: Mohammad Ali Mirshekar.
Resources: Abbas Salehikia.
Software: Mohammad Ali Mirshekar.
Supervision: Mohammad Ali Mirshekar.
Validation: Abbas Salehikia.
Visualization: Zahra Bazdidi.
Writing–original draft: Zahra Bazdidi.
Writing–review & editing: Mohammad Ali Mirshekar.

Competing Interests

None.

Ethical approval

The protocol of this study was approved by the Ethics Committee of Sistan and Baluchestan University with the code IR.USB.REC.1399.016.

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