Review Article

Effects of preconditioning or following exercise on brain-derived neurotrophic factor (BDNF): A systematic review in animal models of multiple sclerosis

Samira Emadi[1], Zahra Hemati Farsani[2*], Mojtaba Dehestani Ardakani[2]

Abstract

Brain-derived neurotrophic factor (BDNF) plays a vital role in the brain. On the other hand, researchers showed that exercise may cause more release of BDNF and thus have a positive effect on the brain. Studies have reported controversial findings in multiple sclerosis, and there are no broad conclusions on this topic. This study aims to systematically investigate the effect of exercise training on BDNF concentration in multiple sclerosis animal models. Searches were conducted in the electronic databases of PubMed, Scopus, Medline, Cochrane Library and Google Scholar search engine to obtain the related articles about the role of exercise training on BDNF levels just in animal models of multiple sclerosis. All of the database searches were limited to the period from inception to February 2021. Two reviewers extracted study details and data. The methodological quality of the studies that used animal models was assessed using the PEDro Scale. Fourteen articles were included in this review with scores from 7/10 to 8/10 according to the PEDro scale. Five articles reported elevation, one article reported a reduction; and eight articles reported no changes in BDNF level following or preconditioning exercise training in model of multiple sclerosis. The findings of this study showed that aerobic exercise increases changes in central BDNF concentration in multiple sclerosis in animal model.

Key Words: **Exercise, Brain-derived neurotrophic factor, Multiple sclerosis**

Introduction

Multiple sclerosis (MS) is known as the disease of the century and affects approximately 2.3 million people around the world. This disease is one of the most common neurological diseases in young people, especially in women, and the prevalence of this disease may be increasing (Sparaco, Lavorgna, Conforti, Tedeschi, & Bonavita, 2018; Xie et al., 2019). Eetiology of MS remains unclear. MS is believed to be caused by T-cell-mediated autoimmunity and inflammation. In this disease, myelin glycoproteins are lost in the CNS (Robinson, Harp, Noronha, & Miller, 2014). MS leads to cognitive and emotional problems, spasms, fatigue, general muscle weakness, balance problems and abnormal walking, which affect the quality of life of people with MS (Rumrill Jr, 2009). There are treatments at modulating inflammation and immune response in MS that are aimed at managing related symptoms; however, have profound side effects and are only moderately effective (Filippi et al., 2018).

Participation in physical activity (PA) is a beneficial rehabilitation strategy in managing MS and it is associated with improved symptoms and quality of life, but this population is generally physically inactive (Fortune J et al., 2020; Motl, Learmonth, Pilutti, Gappmaier, & Coote, 2015). Various mechanisms have been suggested about the salutary effects of physical activity on brain health (Kalinowska-Lyszczarz & Losy, 2012; Wens et al., 2016). It is thought that increasing the regulation of neurotrophins can prevent the progression of this disease (Chao, Rajagopal, & Lee, 2006; C. Rossi et al., 2006). Neurotrophins regulate neural processes and they are critical modifiers of the neuromuscular networks (Huang EJ & Reichardt LF, 2001). BDNF is a member of the family of neurotrophic proteins and is one of the most essential neurotrophics in the brain, which is expressed in the central and peripheral nervous system (Huang EJ & Reichardt LF, 2001). BDNF plays a critical role in the maintenance, development and repair of the nervous system (Wens et al., 2016). It has been shown that BDNF may also have an essential role in regulating

1. Department of Physical Education and Sport Sciences, Faculty of Humanestic, Tarbiat Modares University, Tehran, Iran. 2. Department of Sport Sciences, Ardakan University, Ardakan, Iran.

*Author for correspondence: zhemati@ardakan.ac.ir

H E: 0000-0002-1300-6757; Z H F: 0000-0001-8499-795X; M D A: 0000-0001-8830-1008

Received 2 January 2023; Accepted 20 March 2023

neurogenesis(C. Rossi et al., 2006), neurodegeneration (Xu XM, Guénard V, Kleitman N, & Aebischer P, 1995), neuroprotection (Schäbitz W. R et al., 2007), learning and memory process (Mizuno, Yamada, Olariu, Nawa, & Nabeshima, 2000), behaviors, movements; and a wide range of stress responses in CNS (Berchtold NC, Chinn G, Chou M, Kesslak JP, & CW, 2005).

The level of BDNF in the cerebrospinal fluid and serum of people with MS is lower than that of healthy people (Azoulay D, Urshansky N, & A., 2008; Sorenson M, Jason L, Peterson J, Herrington J, & H., 2014). This decrease leads to impairment in cognitive function and learning, depression, neurodegenerative conditions and mortality (Nagahara AH & MH., 2011; Prokopova et al., 2017). But by doing physical activity, BDNF levels can be increased. Swimming training and treadmill running raises the BDNF levels in the serum and hippocampus and improve clinical disability and intensity of diseases (Naghibzadeh, Ranjbar, Tabandeh, & Habibi, 2018). Some studies have shown that rats who performed aerobic activities had increased levels of BDNF in the hippocampus and improved peripheral metabolism (Johnson RA, Rhodes JS, Jeffrey SL, Garland T Jr, & GS., 2003).

Results from studies on experimental autoimmune encephalomyelitis (EAE), a model of MS, also shows increasing BDNF in the hippocampus after physical activity and enhanced of memory function and hippocampal neuroplasticity (Kim T-W & Y-H., 2017). In addition, treadmill exercise or swimming enhancing with BDNF release; as a result, it protects neurons by delaying the onset of EAE and reducing the inflammatory response associated with reducing demyelination in EAE rats. (Hosseini SM, Fallahmohammadi Z, & V., 2018; Naghibzadeh et al., 2018). Therefore, the results of various researches are conflicting and despite the known positive effects of exercise on BDNF in people with MS, the best exercise protocol is still under discussion (Castellano V & LJ., 2008; HOSSEINI SM, FALLAH MZ, & F., 2017; Mokhtarzade M et al., 2018). Therefore, the purpose of this review is to critically evaluate the available evidence on the effect of exercise on BDNF levels in animal models of multiple sclerosis.

Materials and methods

The present study was a systematic review. The following scientific databases were used: PubMed, Medline, Cochrane Library and Google Scholar search engine. Persian and English were used in the search for articles and terms, which included brain-derived neurotrophic factor, BDNF, exercise, education, sports training, physical activity and multiple sclerosis. The search period was limited to the start period until February 2022.

Inclusion and exclusion criteria

Inclusion criteria included: (1) the primary purpose of the study was to evaluate the randomized; controlled trials of physical exercise on BDNF gene/protein expression in animals and (2) full papers published in English and Persian - The exclusion criteria include: Articles that did not measure BDNF brain factors; studies that evaluated tissue or serum BDNF levels in other conditions rather than multiple sclerosis and articles that physical activity is not part of its interventions; furthermore, reviews, and case studies were excluded.

Data Extraction

The final articles were reviewed based on the checklist that was prepared in advance and the required data were extracted from the articles. Information extracted from each article included: sample size, species evaluated (mice/ rat), disease induction technique, site and type of tissue (whether systemically or locally measured, and in which tissue, for example, serum, plasma, brain, muscle, etc.), the protocol of exercise (training type, time of each session, training frequency and volume). The last item (results) involves the change in BDNF concentrations (increased, decreased or not changed).

Assessment the Quality of Articles

The PEDro scale was used to assess the quality articles. The PEDro is a valid measure of the quality of randomized controlled trials in which the studies rate from the least (zero) to the most (ten) adhered to item; and includes 11 criteria: random and concealed allocation; similarity at baseline groups regarding the most important prognostic indicators; subject, therapist and assessor blinding; more than 85% follow up for at least one key outcome, intention-to-treat analysis, between-group statistical comparison for at least one key outcome, the point estimate, and variability measures for at least one key outcome.

Results

Ninety-three full-text manuscripts fulfilled all of the inclusion criteria. After the duplicates were removed, eighty-six articles were listed; Out of these, 72 articles were excluded primarily because they did not exercise training intervention and lacked of control group. Finally, 14 articles (seven rat studies and seven mouse studies) included in the review was conducted between 2013 and 2021 (Fig. 1). The summary of extracted data from animal studies is presented in Table 1. The total included subjects in this systematic review were 292 male/female Wistar rats and 380 male/female mice. The quality of the animal studies was at least seven and eight according, to the PEDro scale. In addition, brain-derived neurotrophic factor (BDNF) was the primary and critical outcome.

Descriptive of Included Studies

In the study of Nagibzadeh et al. (2018), four weeks low-intensity (LICT) and high-intensity (HIIT) exercise training on a treadmill

were used. In their study, demyelination was induced in mice, and the mice were fed a diet containing 0.2% cuprizone for five weeks. Both training methods increased BDNF gene expression in the hippocampus, although the high-intensity training program was better than the low-intensity training program. Among other results of this research, it can be mentioned that both exercise programs prevent abnormal nerve movements caused by cuprizone (Naghibzadeh et al., 2018). On the other hand, Patel et al. (2016) showed that intramuscular concentrations of BDNF decreased following ten days of treadmill exercise in EAE (D. Patel, White, Lira, & Criswell, 2016).

Klaren et al. (2016) demonstrate no significant effects of forced and voluntary exercise on levels of hippocampal BDNF in EAE. Patel & White. (2013) observed no significant differences in levels of brain BDNF after 10-day forced treadmill training in EAE. Also, in a study by WENS et al. (2015), levels of soleus muscle BDNF were not affected by exercise (Klaren et al., 2016; D. I. Patel & White, 2013; Wens et al., 2015).

Also, in the WENS et al. (2015) study, high intensity aerobic exercise delayed hindquarter paralysis peak. Klaren et al. (2016) demonstrated exercises given to mice during recovery after the onset of the disease had no significant effect on the clinical disability scores in the gastrocnemius and soleus muscles of the mice. Additionally, Hosseini et al. (2017, 2018 & 2020), Zaychik et al. (2020) and Hosseini et al. (2019) evaluated the pretreatment effects of exercise training in animals with EAE and they showed no significant effects of exercise in brain BDNF levels (Hoseini, Falahmohammadi, & Talebi, 2020; HOSSEINI SM et al., 2017; Sayed Mojtaba Hosseini, Fallahmohammadi, & Talebi, 2018; Sayed Mojtaba Hosseini, Fallahmohammadi, Talebi, Mohammadi, & Patel, 2019; Zaychik et al., 2020). Also, in the study by Hosseini et al. (2018 & 2020), in trained rats clinical signs appeared delayed. In Zaychik et al. (2020) study, high-intensity continuous training reduced the severity of clinical disease by reducing loss of myelin and axons, attenuation of T cells and macrophage infiltration. Additionally, Vatandoust et al. (2018) found that aerobic exercise increased BDNF protein expression in the brain tissue of the animal model with MS. In addition, Kim & Sung (2017) found that treadmill exercise significantly increased the BDNF protein expression of the hippocampus of EAE mice (Kim & Sung, 2017). In addition, in the study by Xie et al. (2019), EAE was induced in female rats and they swam in two groups with moderate and high intensity for six weeks. In the high-intensity exercise group, BDNF was increased in the EAE CNS (Xie et al., 2019). In study by Bernardes et al. (2013) observed that six weeks of swimming exercise before MS disease progression increases the concentration of BDNF in the CNS of EAE mice (Bernardes et al., 2013).

Discussion

This study aimed to find the effects of preconditioning or following exercise on BDNF levels in animal models of MS.

The results of the two preconditioning training studies, two exercise training studies after induction of model of diseases and one study combination of preconditioning and exercise training after induction of model of diseases have reported increased BDNF levels in animal models of MS.

In another study have shown decreased BDNF levels after exercise training induction of model of diseases. Four preconditioning training studies and four exercise training studies after induction of model of diseases and four studies preconditioning training and four studies after induction of model of diseases.

MS has a destructive effect on the CNS due to the increase of inflammatory cytokines, and as a result, leads to dementia and impaired cognitive functions in old age (DeLuca, Yates, Beale, & Morrow, 2015). BDNF has multifactorial neurological and metabotropic effects, including whole-body energy regulation, skeletal muscle fat oxidation, maintenance, development and repair of the nervous system. Low levels of cerebrospinal fluid and serum BDNF are associated with MS. BDNF is mainly expressed in the hippocampal, cortex cerebra, hypothalamic and cerebral areas of brain. Central BDNF can be released into the bloodstream through the blood-brain barrier and stored in other peripheral tissues. Muscle and adipose peripheral tissues also express BDNF, which does not into circulation. BDNF has an essential and different role in the brain development and plasticity such as differentiation, proliferation, neuronal survival, neurodegeneration, neurogenesis, neuroprotection, learning, memory amplification, cognitive function and hippocampal function. Further, a decrease in BDNF levels leads to hippocampal atrophy and eventually impairs memory (Azoulay D et al., 2008; Sorenson M et al., 2014; Szuhany, Bugatti, & Otto, 2015). Also, the findings of studies have shown that BDNF plays a role in central metabolic pathways and improves cognitive function in the hippocampus. Some studies showed that physical activity and cognitive performance are related to the increase of BDNF and the decrease of kynurenine pathway in the brain (Küster OC et al., 2017). Endurance exercise also increases BDNF protein content in both hippocampus and serum of rodents. Overall, the findings imply that endurance exercise can overexpress tissue BDNF and temporarily increase systemic BDNF concentration, which ultimately induces neuroadaptation in central tissues. The effect of resistance training on increasing BDNF is likely to be similar to short-term intense aerobic exercise because this type of activity leads to transient hormonal response

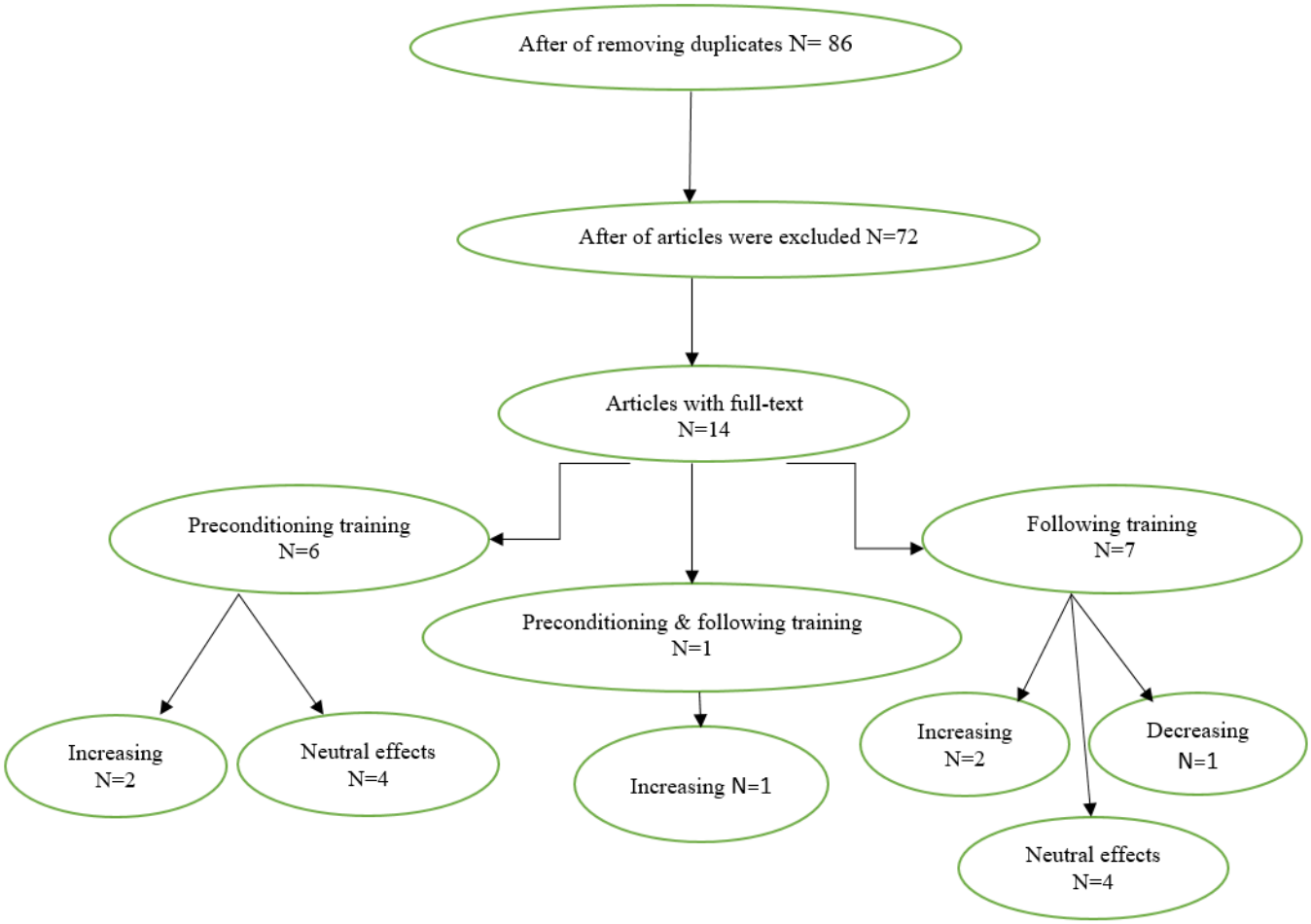

Figure 1. Process of exclusion and inclusion of articles with results.

in skeletal muscle and other tissues (Yarrow, White, McCoy, & Borst, 2010). In examining the effect of regular aerobic training on BDNF levels of rodents, showed BDNF levels increased continuously. But, the acute and chronic effects of resistance training showed no significant change on BDNF levels (Szuhany et al., 2015). According to the present systematic review, the results of the Vatandoust et al. (2018), Kim & Sung (2017), Naghibzadeh et al. (2018), Bernardes et al. (2013) and Xie et al. (2019) studies showed the increasingly effects of exercise on BDNF levels in MS models (Bernardes et al., 2013; Kim & Sung, 2017; Naghibzadeh et al., 2018; Vatandoust M & P., 2018; Xie et al., 2019). These results are in contrast with the findings of Patel et al. (2016). They reported that endurance exercise decrease BDNF in muscular tissue of MS model. . Studies by Wens et al. (2015), Klaren et al. (2016) and Patel & White (2013), Hosseini et al. (2020), Hosseini et al. (2017, 2019) and Zaychik et al. (2020) also reported no significant change in BDNF levels in MS animals following exercise training or preconditioning (Hoseini et al., 2020; SEYED MOJTABA HOSSEINI, FALLAH, & FEIZI, 2017; Sayed Mojtaba Hosseini et al., 2019; Klaren et al., 2016; D. Patel et al., 2016; D. I. Patel & White, 2013; Wens et al., 2015; Zaychik et al., 2020).

The results showed that a tendency of lesser demyelination volume & clinical signs improvement induced by exercise training associated with improvement of inflammatory status and modulation of BDNF levels in MS (Bernardes et al., 2013; Vatandoust, Motamedi, & Rajabi, 2018). In addition, the elevation of BDNF levels in the CNS due to regular exercise has a positive relationship with improvement cognitive function, alleviated memory deficits and motor deficits, in EAE mouse. In addition, improvement cognitive function, alleviated memory deficits and motor deficits are partly as a results of the elevation of BDNF levels in the CNS pre or after regular exercise in EAE mice (Kim & Sung, 2017; Naghibzadeh et al., 2018). From the results of the research, it can be seen that BDNF reduces cognitive disorders. The most effective training variable that helps increase BDNF in the CNS is exercise intensity. So that high intensity versus moderate intensity reduces the progress and pathological symptoms of EAE, so it is a suitable method to reduce chronic inflammation (Naghibzadeh et al., 2018; Xie et al., 2019).

Recent evidence suggests that physical activity may present protective benefits for several animal models of neurological con-

Table 1. Summary of animal studies evaluating the effect of exercise training on BDNF concentration in models of multiple sclerosis.

Author-Date	Animals, Induction of diseases, groups	Experimental- Control Group	Dependent Variable	Results
Naghibzadeh et al. (2018) (Naghibzadeh et al., 2018)	60 mice, 4 weeks old. Groups: 1- interval training, 2- Continuous training, 3- Interval training before cuprizone-induced demyelination (ITCP), 4- Continuous training before cuprizone- induced demyelination (CTCP).	Rodents ran on a treadmill for 4 weeks, 5 days each week Continuous training group: gradually increased the running speed to reach 70% of the maximum training capacity. Interval training group; they performed 2-minute periods with 90% of the maximum training capacity and then 1-minute periods with 50% of the maximum training capacity.	BDNF in hippocampus	Expression of BDNF was increased in the ITCP and CTCP groups compared to the cuprizone group.
Patel et al. (2016) (D. Patel et al., 2016)	40 rats, 8 weeks old. Groups: 1- EAE+Exercise, 2- EAE+Sedentary, 3- Control Exercise 4- Control Sedentary.	The rodents ran on a treadmill for 10 consecutive days. First, the running speed was 15 meters per minute, and finally the speed reached 30 meters per minute. The time at the beginning of the training was 60 minutes and in sessions 3 to 10 it reached 90 minutes.	BDNF in soleus muscle	The concentration of BDNF in the training group was significantly lower compared to the animals in the control group.
Hosseini et al. (2020) (Hoseini et al., 2020)	25 mice, 6 weeks old. Groups: 1- healthy control, 2- MS control, 3- Healthy+swimming, 4- MS+ swimming, 5- Sham.	The rats swam for 6 weeks and 5 days each week. The time at the beginning of training was 30 minutes and in the second week it reached 60 minutes. Each training session was increased by 5 minutes.	BDNF in brain	No significant change in BDNF protein expression in EAE rats in compared to the control group.
Hosseini et al. (2018) (Sayed Mojtaba Hosseini et al., 2018)	25 rats, 6 weeks old. Groups: 1- Healthy +control, 2- MS +control, 3- interval +MS healthy +interval, 4- Sham.	Treadmill, 6 weeks, 5 days per week, each session including 10 repetitions of 1 minute.	BDNF in brain	Not significantly change the BDNF levels of active group compared to inactive group.
Wens et al.(2015) (Wens et al., 2015)	80 rats, 6-7 weeks old. Groups: 1- Sedentary control, 2- exercising control, 3- Sedentary +EAE, 4- Exercising+ EAE	They exercised on a treadmill for 10 days and the duration of exercise was 1 hour and the speed of running on the treadmill was 18 meters per minute and the incline of the treadmill was 25 degrees.	BDNF in Serum	No significant changes were observed in BDNF.
Klaren et al. (2016)(Klaren et al., 2016)	47 mice, 6-8 weeks old. Groups: 1-sedentary, 2-voluntary wheel running, 3-forced treadmill exercise.	Running on a motorized treadmill, 5 days per week, at a 5% grade, 14 m/min, for 30 min. - without training	BDNF in hippocampus	Concentrations of BDNF did not differ among conditions.

Table 1. (continue).

Patel & White. (2013) (D. I. Patel & White, 2013)	40 rats, 8 weeks old. Groups: 1- EAE +exercise, 2- EAE +sedentary, 3- control +exercise, 4- Control+ sedentary.	The rodents ran on a treadmill for 10 consecutive days at a speed of 15 to 30 meters per minute and for a period of 60 to 90 minutes per day.	BDNF in brain	No significant changes were observed in BDNF.
Hosseini et al. (2019)(Sayed Mojtaba Hosseini et al., 2019)	40 rats, 6 weeks old. Groups: 1- control + healthy, 2- control +MS, 3- control +MS+ vitamin D, 4- exercise +MS +vitamin D, 5- exercise +healthy +vitamin D, 6- vehicle (V), 7- exercise +MS 8- Exercise +healthy.	rats swam 5 days a week for 6 weeks The swimming training program was 30 minutes in the first week and 60 minutes in the second week (every day 5 minutes were added to the training time). The principle of exercise overload was applied by increasing the water flow rate. EAE was induced at the end of the sixth week of training. In the week before induction of EAE model, vitamin D2 was injected every two days	BDNF in brain	No significant changes were observed in BDNF.
Hosseini et al. (2017) (HOSSEINI SM et al., 2017)	20 rats, 6 weeks old. Groups: 1-healthy, 2- EXE-healthy, 3- EAE, 4-EXE- EAE.	The interval training program in the second week and during 6 weeks of training in each session included 10 repetitions of 1 minute. The ratio of work to rest was 1 to 2 and the total running time was 30 minutes. During this period, the training intensity gradually increased from 25 meters per minute to 70 meters per minute. Without training	BDNF in brain	No significant changes were observed in BDNF.
Xie et al.(2019)(Xie et al., 2019)	36 mice, 6–8 weeks old. Groups : 1- Control, 2- moderate-intensity swimming exercise (ME), 3- high intensity swimming exercise (HE).	Swimming, 6 weeks, 5 day per week. 50 min per day, ME group; 0% body weight. HE group; 4% body weight. _were kept in their cages without exercise.	BDNF in brain & spinal cord	BDNF concentration was significantly higher in the high-intensity swimming training group compared to the moderate-intensity swimming group and the no-training group.
Bernardes et al.(2013) (Bernardes et al., 2013)	67 mice, 6–8 weeks old. Groups: exercised and unexercised	Swimming, 6 weeks, 5 days per week. 30 min per day. _ Without training	BDNF in brain and spinal cord	The BDNF concentration in the training groups was significantly higher than the non-training group.
Kim & Sung et al. (2017)(Kim & Sung, 2017)	45 mice, 10 weeks old. Induction by intraperitoneal injection of MOG33-55. Groups: Sham, EAE and EAE +exercise.	The training was done on a treadmill and lasted for 4 weeks, and they trained 5 days a week for 30 minutes each day. The training intensity was between 2-5 meters per minute.	BDNF in the Hippocampus	The expression of BDNF in the hippocampus of the EAE+EX group was significantly increased compared to the EAE group.

Table 1. (continue).

Vatandoust et al. (2018)(Vatandoust et al., 2018)	80 mice, 10-12 weeks old, Induction by intraperitoneal injection of MOG33-55. Group: 1- swimming, 2- MS, 3- MS+swimming, 4- MS+interferon beta, 5- MS+interferon 6- beta+swimming 7- MS+solvent, 8- MS+solvent + swimming.	Swimming, 4 weeks, 5 sessions per week, 30 minutes each session. - Without training	BDNF in serum	Physical exercise significantly increased BDNF factor compared to interferon beta-1 treatment.
Zaychik et al.(2020) (Zaychik et al., 2020)	20 Female SJL/JCrHsd mice, 6–7 weeks old. Induction of lymph node - derived T cell encephalitogenicit. Group: Sedentary and HICT.	6 weeks of training were designed, first they warmed up for 5 minutes and then the main training of the first 3 weeks was followed at a speed of 23 cm per minute on the treadmill, but the duration of the training in the first, second and third week was 10, 20 and 30 minutes, respectively. The training intensity in the second three weeks was incremental and 30 centimeters per minute and the duration was 23 minutes	BDNF in CD11b+ microglia cells	HICT did not affect mRNA levels BDNF.

-ditions, including MS (S. Rossi et al., 2009). Additionally, when rodents have been placed in stimulating environments, including running wheels and activity stimulators, benefits in various neurological conditions have been shown (Stam et al., 2008). In many of these conditions, a potential mechanism of this protective influence is thought to be conferred via up-regulation of neurotrophins such as BDNF. BDNF has been implicated as playing a role in CNS neurogenesis (C. Rossi et al., 2006), neuroregeneration of the CNS after injury (Xu, Guénard, Kleitman, Aebischer, & Bunge, 1995), neuroprotection (Schäbitz et al., 2007), learning and memory (Mizuno et al., 2000), cell survival (Yan, Elliott, & Snider, 1992), and synaptic plasticity (Lu, 2003). In MS, BDNF may protect axons from demyelination and may also facilitate remyelination after injury (Xu et al., 1995). Previous studies did not observe an exercise effect on soleus BDNF concentrations in EAE-Ex exercised rats (D. Patel et al., 2016). One hypothesis for decreased BDNF concentrations in activated muscle is the possibility that neuromuscular activity might increase retrograde transport of BDNF from the muscle (Gómez-Pinilla, Ying, Roy, Molteni, & Edgerton, 2002) or possibly translocate into circulation. Secondly, stress response through elevated cortisol has been reported to impact BDNF concentrations (Jacobsen & Mørk, 2006). Previous reports in which high intensity types of exercise decreased concentrations of BDNF (Murakami, Imbe, Morikawa, Kubo, & Senba, 2005) and BDNFmRNA (Pang, Stam, Nithianantharajah, Howard, & Hannan, 2006) in brain tissue, which may have negatively affect-ed multiple neural systems (Vaynman & Gomez-Pinilla, 2005). One of the limitations of this research was the study of articles that were conducted just on animals. This study was conducted on animal models due to the lack of access to the internal body tissues of MS patients, including the brain and muscles.

Although the study of animals provides us with useful information, the generalization of information from animals to humans should be done with caution. The lack of a sufficient number of included articles and, consequently the entry of articles with a 7-8 scores based on the PEDro scale. Also, since the researches reviewed in this study were not similar in terms of the type of interventions and the volume, intensity and frequency of exercises, it was impossible to analyze the exercise method. In addition, more studies are needed on the effect of different exercises on central BDNF in different stages of MS recovery, such as acute, subacute and chronic stages. In this study, no time limit was used to search the databases, and this can be one of the strengths of this research.

Conclusion

The results of the current review show that aerobic exercise can increase the changes in central BDNF concentration in MS animal models, while BDNF responses following non-aerobic exercises, such as resistance training or a combination of resistance and aerobic training, are still controversial. According

to the literature, considering the prevalence of cognition disorders in MS patients and also the increased rate of mortality of MS patients compared to healthy subjects, it seems essential to inquire the effects of exercise training on cognitive indicators, in addition to neurotrophic factors in these patients.

What is already known on this subject?

The results of various researches are conflicting and despite the known positive effects of exercise on BDNF in people with MS, the best exercise protocol is still under discussion.

What this study adds?

Aerobic exercise can increase the changes in central BDNF concentration in MS animal models, while BDNF responses following non-aerobic exercises, such as resistance training or a combination of resistance and aerobic training, are still controversial.

Acknowledgements

None.

Funding

None.

Compliance with ethical standards

Conflict of interest The author declare that she has no conflict of interest.

Ethical approval Not applicable.

Informed consent Not applicable.

Author contributions

Conceptualization: S.E.; Methodology: S.E.; Software: Z.H.F.; Validation: Z.H.F.; Formal analysis: M.D.; Investigation: .M.D.; Resources: Z.H.F.; Data curation: S.E.; Writing - original draft: S.E, Z.H.F, M.D.; Writing - review & editing: S.E, Z.H.F, M.D.; Visualization: S.E, Z.H.F, M.D.; Supervision: Z.H.F.; Project administration: S.E.; Funding acquisition: S.E

References

Azoulay D, Urshansky N, & A., K. (2008). Low and dysregulated BDNF secretion from immune cells of MS patients is related to reduced neuroprotection. j.Neuroimmunol, 195, 186-193. https://doi.org/10.1016/j.jneuroim.2008.01.010

Berchtold NC, Chinn G, Chou M, Kesslak JP, & CW, C. (2005). Exercise primes a molecular memory for brain-derived neurotrophic factor protein induction in the rat hippocampus. Neuroscience, 133(3), 835-861. https://doi.org/10.1016/j.neuroscience.2005.03.026

Bernardes, D., Oliveira-Lima, O. C., da Silva, T. V., Faraco, C. C. F., Leite, H. R., Juliano, M. A., . . . Orian, J. M. (2013). Differential brain and spinal cord cytokine and BDNF levels in experimental autoimmune encephalomyelitis are modulated by prior and regular exercise. Journal of neuroimmunology, 264(1-2), 24-34. https://doi.org/10.1016/j.jneuroim.2013.08.014

Castellano V, & LJ., W. (2008). Serum brain-derived neurotrophic factor response to aerobic exercise in multiple sclerosis. J Neurol Sci, 269(1-2), 85-91. DOI: https://doi.org/10.1016/j.jns.2007.12.030

Chao, M. V., Rajagopal, R., & Lee, F. S. (2006). Neurotrophin signalling in health and disease. Clinical science, 110(2), 167-173. https://doi.org/10.1042/CS20050163

DeLuca, G. C., Yates, R. L., Beale, H., & Morrow, S. A. (2015). Cognitive impairment in multiple sclerosis: clinical, radiologic and pathologic insights. Brain Pathology, 25(1), 79-98. DOI: https://doi.org/10.1111/bpa.12220

Filippi, M., Bar-Or, A., Piehl, F., Preziosa, P., Solari, A., Vukusic, S., & Rocca, M. A. (2018). Multiple sclerosis. Nat. Rev. Dis. Primers, 4(43). DOI: https://doi.org/10.1007/978-3-030-38621-4_1

Fortune J, Norris M, Stennett A, Kilbride C, Lavelle G, Hendrie W, . . . JM., R. (2020). 'I can do this': a qualitative exploration of acceptability and experiences of a physical activity behaviour change intervention in people with multiple sclerosis in the UK. BMJ Open, 6(10), 3. Doi: https://doi.org/10.1136/bmjopen-2019-029831

Halabchi F, Alizadeh Z, Sahraian MA, & M., A. (2017). Exercise prescription for patients with multiple sclerosis; potential benefits and practical recommendations. BMC neurology, 17(1):185. doi: https://doi.org/10.1186/s12883-017-0960-9.

Hoseini, S. M., Falahmohammadi, Z., & Talebi, V. (2020). Preventive effect six weeks of swimming training on the levels of cytokines and brain-derived neurotrophic rat model of EAE. Journal of Sport Biosciences, 12(1), 53-65. https://doi.org/10.22059/jsb.2019.246687.1223

Hosseini SM, Fallah MZ, & F., F. (2017). The effect of high-intensity resistance exercise period on the levels of interleukin-10 (il-10), tumor necrosis factor-alpha (tnf-α), and brain-derived neurotrophic factor (bdnf) in the brain of lewis rats with experimental autoimmune encephalomyelitis. J Isfahan Med Sch, 35(422),270-277. http://eprints.mubabol.ac.ir/id/eprint/474

Hosseini SM, Fallah mohammadi Z, & V., T. (2018). The effect of regular interval training on histochemical symptoms and cytokine and neurotrophic levels of brain tissue of the Lewis rats in experimental model of multiple sclerosis. Feyz Journal of Kashan University of Medical Sciences, 22(5), 450-457. URL: http://feyz.kaums.ac.ir/article-1-3597-fa.html

Hosseini, S. M., Fallahmohammadi, Z., Talebi, V., Mohammadi, H. F., & Patel, D. I. (2019). Pretreatment Effect of a 6-week Swimming Training protocol along with Vitamin D administration on the brain levels of BDNF, TNF-α and IL-10 in Rats Model of EAE. International Journal of Applied Exercise Physiology, 8(1), 51-58. DOI: https://doi.org/10.30472/ijaep.v8i1.359

Huang EJ, & Reichardt LF. (2001). Neurotrophins: roles in neuronal development and function. Annu Rev Neurosci, 24(1), 677. doi: https://doi.org/10.1146/annurev.neuro.24.1.677

Johnson RA, Rhodes JS, Jeffrey SL, Garland T Jr, & GS., M. (2003). Hippocampal brain-derived neurotrophic factor but not neurotrophin-3 increases more in mice selected for increased voluntary wheel running. Neuroscience, 121(1), 1-7. DOI: https://doi.org/10.1016/s0306-4522(03)00422-6

Kalinowska-Lyszczarz, A., & Losy, J. (2012). The role of neurotrophins in multiple sclerosis—pathological and clinical implications. International journal of molecular sciences, 13(10), 13713-13725. doi: https://doi.org/10.3390/ijms131013713

Kim T-W, & Y-H., S. (2017). Regular exercise promotes memory function and enhances hippocampal neuroplasticity in experimental autoimmune encephalomyelitis mice. Neuroscience, 364, 173-181. DOI: https://doi.org/10.1016/j.neuroscience.2017.01.016

Kim, Y., Lai, B., Mehta, T., Thirumalai, M., Padalabalanarayanan, S., Rimmer, J. H., & Motl, R. W. (2019). Exercise training guidelines for multiple sclerosis, stroke, and Parkinson's disease: Rapid review and synthesis. American journal of physical medicine & rehabilitation, 98(7), 613. DOI: https://doi.org/10.1097/PHM.0000000000001174

Klaren, R. E., Stasula, U., Steelman, A. J., Hernandez, J., Pence, B. D., Woods, J. A., & Motl, R. W. (2016). Effects of exercise in a relapsing‐remitting model of experimental autoimmune encephalomyelitis. Journal of neuroscience research, 94(10), 907-914. DOI: https://doi.org/10.1002/jnr.23783

Küster OC, Laptinskaya D, Fissler P, Schnack c, Zügel M, Nold V, & A., v. A. C. (2017). Novel blood-based biomarkers of cognition, stress, and physical or cognitive training in older adults at risk of dementia: preliminary evidence for a role of BDNF, irisin, and the kynurenine pathway. Alzheimer's Disease, 59(3) :1097-1111. doi: https://doi.org/10.3233/JAD-170447.

Latimer-Cheung AE, Pilutti LA, Hicks AL, Ginis KAM, Fenuta AM., MacKibbon KA, & RW., M. (2013). Effects of exercise training on fitness, mobility, fatigue, and health-related quality of life among adults with multiple sclerosis: a systematic review to inform guideline development. Archives of physical medicine and rehabilitation, 94(9), 1800-1828. doi: https://doi.org/10.1016/j.apmr.2013.04.020.

Mizuno, M., Yamada, K., Olariu, A., Nawa, H., & Nabeshima, T. (2000). Involvement of brain-derived neurotrophic factor in spatial memory formation and maintenance in a radial arm maze test in rats. Journal of Neuroscience, 20(18), 7116-7121. DOI: https://doi.org/10.1523/JNEUROSCI.20-18-07116.2000

Motl, R. W., Learmonth, Y. C., Pilutti, L. A., Gappmaier, E., & Coote, S. (2015). Top 10 research questions related to physical activity and multiple sclerosis. Research quarterly for exercise and sport, 86(2), 117-129. DOI: https://doi.org/10.1080/02701367.2015.1023099

Nagahara AH, & MH., T. (2011). Potential therapeutic uses of BDNF in neurological and psychiatric disorders. Nat Rev Drug Discov, 10(3), 209-219. DOI: https://doi.org/10.1038/nrd3366

Naghibzadeh, M., Ranjbar, R., Tabandeh, M. R., & Habibi, A. (2018). Effects of two training programs on transcriptional levels of neurotrophins and glial cells population in hippocampus of experimental multiple sclerosis. International journal of sports medicine, 39(08), 604-612. DOI: https://doi.org/10.1055/a-0608-4635

Patel, D., White, L., Lira, V., & Criswell, D. (2016). Forced exercise increases muscle mass in eae despite early onset of disability. Physiological research, 65(6), 1013. DOI: https://doi.org/10.33549/physiolres.933096

Patel, D. I., & White, L. J. (2013). Effect of 10-day forced treadmill training on neurotrophic factors in experimental autoimmune encephalomyelitis. Applied Physiology, Nutrition, and Metabolism, 38(2), 194-199. DOI: https://doi.org/10.1139/apnm-2012-0303

Prokopova, B., Hlavacova, N., Vlcek, M., Penesova, A., Grunnerova, L., Garafova, A., . . . Jezova, D. (2017). Early cognitive impairment along with decreased stress-induced BDNF in male and female patients with newly diagnosed multiple sclerosis. Journal of neuroimmunology, 302, 34-40. DOI: https://doi.org/10.1016/j.jneuroim.2016.11.007

Robinson, A. P., Harp, C. T., Noronha, A., & Miller, S. D. (2014). The experimental autoimmune encephalomyelitis (EAE) model of MS: utility for understanding disease pathophysiology and treatment. Handbook of clinical neurology, 122, 173-189. DOI: https://doi.org/10.1016/B978-0-444-52001-2.00008-X

Rossi, C., Angelucci, A., Costantin, L., Braschi, C., Mazzantini, M., Babbini, F., . . . Berardi, N. (2006). Brain‐derived neurotrophic factor (BDNF) is required for the enhancement of hippocampal neurogenesis following environmental enrichment. European Journal of Neuroscience, 24(7), 1850-1856. DOI: https://doi.org/10.1111/j.1460-9568.2006.05059.x

Rumrill Jr, P. D. (2009). Multiple sclerosis: Medical and psychosocial aspects, etiology, incidence, and prevalence. Journal of Vocational Rehabilitation, 31(2), 75-82. DOI: https://doi.org/10.3233/JVR-2009-0476

Schäbitz W. R, Steigleder T, Cooper-Kuhn C. M, Schwab S, Sommer C, Schneider A, & G., K. H. (2007). Intravenous brain-derived neurotrophic factor enhances poststroke sensorimotor recovery and stimulates neurogenesis. Stroke, 38(7), 2165-2172. DOI: https://doi.org/10.1161/STROKEAHA.106.477331

Sorenson M, Jason L, Peterson J, Herrington J, & H., M. (2014). Brain derived neurotrophic factor is decreased in chronic fatigue syndrome and multiple sclerosis. Neurology & Neurophysiology, 1-6. DOI: https://doi.org/10.4172/2155-9562.S12-013

Sparaco, M., Lavorgna, L., Conforti, R., Tedeschi, G., & Bonavita, S. (2018). The role of wearable devices in multiple sclerosis. Multiple sclerosis international, 2018. https://doi.org/10.1155/2018/7627643

Szuhany, K. L., Bugatti, M., & Otto, M. W. (2015). A meta-analytic review of the effects of exercise on brain-derived neurotrophic factor. Journal of psychiatric research, 60, 56-64. DOI: https://doi.org/10.1016/j.jpsychires.2014.10.003

Vatandoust M, & P., M. (2018). The effect of 4 weeks of aerobic activity on the ratio of Serum levels of tumor necrosis factor alpha, interleukin-10 and brain-derived neurotrophic factor in C57 rat brain tissue by induction of experimental autoimmune encephalomyelitis (EAE). SSU_Journals., 26(7), 624-645. DOI: https://doi.org/10.18502/ssu.v26i7.213

Vatandoust, M., Motamedi, P., & Rajabi, H. (2018). The effect of 4 weeks of aerobic activity on the ratio of Serum levels of tumor necrosis factor alpha, interleukin-10 and brain-derived neurotrophic factor in C57 rat brain tissue by induction of experimental autoimmune encephalomyelitis (EAE). SSU_Journals, 26(7), 624-645. DOI: https://doi.org/10.18502/ssu.v26i7.213

Wens, I., Dalgas, U., Verboven, K., Kosten, L., Stevens, A., Hens, N., & Eijnde, B. (2015). Impact of high intensity exercise on muscle morphology in EAE rats. Physiological research, 64(6), 907-23. doi: https://doi.org/10.33549/physiolres.932824.

Wens, I., Keytsman, C., Deckx, N., Cools, N., Dalgas, U., & Eijnde, B. (2016). Brain derived neurotrophic factor in multiple sclerosis: effect of 24 weeks endurance and resistance training. European journal of neurology, 23(6), 1028-1035. DOI: https://doi.org/10.1111/ene.12976

Xie, Y., Li, Z., Wang, Y., Xue, X., Ma, W., Zhang, Y., & Wang, J. (2019). Effects of moderate-versus high-intensity swimming training on inflammatory and CD4+ T cell subset profiles in experimental autoimmune encephalomyelitis mice. Journal of neuroimmunology, 328, 60-67. DOI: https://doi.org/10.1016/j.jneuroim.2018.12.005

Xu XM, Guénard V, Kleitman N, & Aebischer P. (1995). A combination of BDNF and NT-3 promotes supraspinal axonal regeneration into Schwann cell grafts in adult rat thoracic spinal cord. Bunge MB. Exp Neurol, 134(2), 261-272. DOI: https://doi.org/10.1006/exnr.1995.1056

Yarrow, J. F., White, L. J., McCoy, S. C., & Borst, S. E. (2010). Training augments resistance exercise induced elevation of circulating brain derived neurotrophic factor (BDNF). Neuroscience letters, 479(2), 161-165. DOI: https://doi.org/10.1016/j.neulet.2010.05.058

Zaychik, Y., Fainstein, N., Touloumi, O., Goldberg, Y., Hamdi, L., Segal, S., . . . Katz, A. (2020). High-Intensity Exercise Training Protects The Brain Against Autoimmune Neuroinflammation: Regulation of Microglial Redox and Pro-Inflammatory Functions. Front Cell Neurosci, ; 15: 640724. https://doi.org/10.3389/fncel.2021.640724