



Molecular Mechanisms of the Effects of Aerobic Exercise on Cerebellar Brain-Derived Neurotrophic Factor

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Abstract

Context: Aerobic exercise (AE) is a nonpharmacological strategy that may support nervous system function. AE increases the expression of neurotrophins, particularly brain-derived neurotrophic factor (BDNF), in the circulation and several brain regions. BDNF is highly expressed in the hippocampus and cerebellum and is among the most extensively studied neurotrophins in relation to physical activity. Given the importance of AE in maintaining and promoting cerebellar function, this review evaluated the effects of AE on cerebellar BDNF and the molecular mechanisms that may underlie these effects.

Evidence Acquisition: This narrative review searched PubMed for studies examining the effects of AE on BDNF and cerebellar neurogenesis. The literature search was conducted between November and December 2024 and included publications from 2000 to 2024.

Results: Based on the inclusion and exclusion criteria, 19 PubMed articles examining the effects of AE on BDNF expression were identified. These studies were published between 2002 and 2022; no eligible articles were identified in 2000, 2001, 2023, or 2024. Thirteen studies used rats, 5 used mice, and 1 involved BALB/c mice. Eight studies investigated treadmill running, 7 used wheel running, 2 used swimming training, 1 used gait training, and 1 examined running on a flat track. Overall, 3 studies reported no significant effect of AE on BDNF expression in cerebellar tissue, whereas the remaining 16 studies reported increased BDNF expression and improved cerebellar function in healthy rodents and in models of menopause, lactation, depression, ataxia, early-onset cerebellar degeneration, and spinocerebellar ataxia type 6.

Conclusions: Based on the available evidence, AE may represent a promising strategy for improving cerebellar function, potentially by increasing BDNF expression and activity.

Keywords: Aerobic Exercise, Brain-derived Neurotrophic Factor, Cerebellum

1. Context

Aerobic exercise (AE) has important physiological effects on the cardiovascular, respiratory, musculoskeletal, and nervous systems (1). AE increases myelin regeneration, axonal regeneration, brain angiogenesis, myelin sheath thickness, Schwann cell core area, and neurogenesis. These effects may improve sensory and motor function, enhance the survival and differentiation of transplanted stem cells, relieve pain, and improve cognitive function (2-4). With

population aging and the increasing number of patients with Alzheimer disease, several studies have investigated the effects of AE on neurogenesis, particularly in the hippocampus. AE can increase neurogenesis and improve cognitive function, especially memory (5-7). Evidence also indicates that neurogenesis occurs in brain regions other than the hippocampus (8-10), including the cerebellum (11).

Brain-derived neurotrophic factor (BDNF) is highly expressed in the hippocampus and cerebellum, regions in

which substantial neurogenesis has been reported (12). The cerebellum contributes to movement coordination as well as cognitive, emotional, and reward-related processes (13). Consistent with its role in cognitive function, cerebellar involvement has also been described in nonmotor disorders, including autism spectrum disorder and attention-deficit/hyperactivity disorder (14). Neurogenesis is one mechanism through which AE may affect brain function, and AE is an important stimulus for neurogenesis (15, 16). Aerobic training can promote neurogenesis by increasing the gene and protein expression of neurotrophic factors, particularly BDNF (17, 18). BDNF is among the primary neurodevelopmental factors investigated in relation to physical activity (PA) (18). Exercise-related changes have been reported in BDNF expression in the rodent hippocampus (19, 20), in circulating BDNF levels, and in hippocampal volume (21, 22).

BDNF promotes neurogenesis, neuronal plasticity, neuronal and microglial growth and survival, signal transmission, and the induction and maintenance of synaptic potentiation (23). Its neurotrophic effects may improve cognitive and emotional processes and may reduce the risk of mood disorders, depression, and cognitive impairment (24, 25). Although the effects of AE on hippocampal BDNF and neurogenesis have been widely examined, the cerebellum is also an important target. Therefore, this review focuses on the effects of AE on cerebellar BDNF and the molecular mechanisms that may mediate these effects.

2. Evidence Acquisition

A comprehensive PubMed search was conducted to identify studies examining the effects of AE on BDNF and cerebellar neurogenesis. The literature search was performed between November and December 2024 and included publications from 2000 through 2024. Only original experimental studies conducted in rats or mice and published in English were included; letters and reviews were excluded. Studies that did not evaluate the effects of AE or aerobic training on BDNF gene or protein expression, or on cerebellar neurogenesis, were excluded. Search terms included aerobic exercise, aerobic training, endurance exercise, endurance training, cerebellum, the cerebellum, neurogenesis, brain-derived neurotrophic factor, and BDNF.

3. Results

According to the inclusion and exclusion criteria, 19 PubMed articles investigated the effects of AE on BDNF and neurogenesis. These articles were published between 2002

and 2022. Thirteen studies used rats, 5 used mice, and 1 used BALB/c mice. Eight studies investigated treadmill running, 7 investigated wheel running, 2 used swimming training, 1 used gait training, and 1 examined running on a flat track. No articles meeting the inclusion criteria were published in 2000, 2001, 2023, or 2024.

3.1. Effects of Aerobic Exercise on Cerebellar BDNF

Aerobic exercise alters brain morphology, biochemistry, and behavior (17). Neurogenesis is among the most prominent changes associated with AE and is largely related to increased gene and protein expression of neurotrophic factors, particularly BDNF (26). Most studies reviewed here reported increased cerebellar BDNF after AE; however, findings were not uniform.

Risedal et al. (27) reported no change in cerebellar BDNF expression after wheel running, exposure to an enriched environment, or social housing in rats with cortical infarction, although behavioral performance improved across groups independently of BDNF expression. Johnson et al. (28) reported increased hippocampal BDNF protein expression after voluntary wheel running, but no increase in the spinal cord or cerebellum. In aged rats exposed to D-galactose, light- and moderate-intensity AE for 4 weeks did not change IGF-1 or BDNF levels (29). In a model of incomplete spinal cord injury, AE improved motor function and increased synaptophysin, MAP-2, and BDNF levels in the motor cortex, but not in the cerebellum or spinal cord (30).

Given the role of the cerebellum in movement control, Klintsova et al. (31) assessed the effects of 1 to 14 days of acrobatic training and moderate AE on BDNF and TrkB expression. Both interventions increased expression, and training duration influenced the magnitude of the changes. The effects persisted longer after acrobatic training than after moderate-intensity AE, suggesting that complex motor learning and moderate PA with lower learning demands may have different effects on BDNF and TrkB expression.

Because inflammation and oxidative stress can negatively affect neurogenesis, Toldy et al. (32) examined the combined effects of swimming training and *Urtica dioica* leaf supplementation, which contains antioxidant and anti-inflammatory compounds, on oxidative stress markers and neurotrophic factors in the cerebellum and frontal lobe. *Urtica dioica* reduced free-radical production, whereas swimming had no significant effect on oxidative damage. Neither swimming nor *Urtica dioica* significantly affected NGF or BDNF. Swimming and *Urtica dioica* increased nuclear factor kappa B DNA-binding activity, whereas activator protein-1 DNA-binding activity increased more markedly. C-Jun levels decreased with swimming.

These findings suggest that the antioxidant effects of *Urtica dioica* may occur independently of neurogenesis and that swimming may contribute to antiapoptotic processes (32).

Consistent with these findings, treadmill running for 20 minutes per day for 2 weeks did not significantly change BDNF content in the hippocampus, cortex, striatum, or cerebellum (33). Because this exercise protocol had neuroprotective effects, BDNF may not be directly involved in all neuroprotective mechanisms induced by AE after ischemia. In rats fed a high-fat diet, combining AE with melatonin inhibited the reduction in cerebellar BDNF and TrkB expression and reduced inflammatory cytokines, whereas training alone and melatonin alone had no significant effect (34).

Intermittent individual housing affects behavior and neurotrophin levels. Zhu et al. (35) studied wheel running in BALB/c mice under different housing conditions and found that intermittent individual housing altered behavior and brain neurotrophin levels; some of these changes were modified by AE. In adolescent rats, voluntary wheel running increased global histone 3 acetylation and BDNF expression in the hippocampus and cerebellum, whereas the expression of DNA methyltransferases and histone deacetylases decreased (36), indicating an epigenetic contribution to exercise-related effects.

In rats exposed to vanadium during lactation, impaired motor coordination and reduced plasma and cerebellar BDNF levels were reported. Five weeks of treadmill running during childhood and adolescence normalized plasma and cerebellar BDNF levels and increased cerebellar TrkB phosphorylation, thereby preventing motor coordination impairment (37). Moderate-intensity AE also reduced Purkinje cell degeneration, delayed motor dysfunction, and increased lifespan in spastic Han Wistar rats, a model of ataxia, in association with increased BDNF and TrkB expression (38).

Chalimoniuk et al. (39) reported that moderate-intensity endurance running increased spontaneous locomotor activity and BDNF and TrkB mRNA in the hippocampus, midbrain, and striatum, but not in the cerebellum or cerebral cortex. In contrast, components of the nitric oxide/soluble guanylyl cyclase/cyclic guanosine monophosphate pathway were altered in several brain regions, including the cerebellum (39). Inoue et al. (40) reported that treadmill exercise 5 days per week increased BDNF protein in the motor cortex and improved motor coordination. The study also reported increased cerebellar BDNF expression, whereas long-term inhibition of GABA receptors reduced BDNF mRNA expression and impaired coordination, suggesting that the duration of GABA receptor inhibition should be considered in clinical studies (40).

BDNF expression is reduced in the dentate gyrus, medial prefrontal cortex, and cerebellum in depression models, and voluntary running increased BDNF expression in these regions (41). In ovariectomized rats, 6 weeks of moderate-intensity interval training increased the number of cerebellar Purkinje cells and downregulated Bax expression. Improvements in motor function were correlated with Bcl-2, Bax, BDNF, synaptophysin, and Pgc-1 α mRNA expression and with the number of cerebellar Purkinje cells, suggesting enhanced neurotrophic and neuroprotective signaling (42). Maternal PA increased neurotrophin expression in the cerebellum, cortex, and placenta and was associated with changes related to neural plasticity and cognitive function (43). Forced AE improved motor learning and increased BDNF in a mouse model of early-onset cerebellar degeneration (44). AE also improved ataxia and deficits in cerebellar Purkinje cell firing in mice with spinocerebellar ataxia type 6 after 1 month, supporting a neuroprotective role for exercise in this model (45). Table 1 summarizes the studies examining AE and BDNF in cerebellar tissue.

3.2. Molecular Mechanisms of BDNF Increase Following Aerobic Exercise

Aerobic exercise increases BDNF synthesis in the brain through several molecular mechanisms. In addition to stimulating brain BDNF, AE also affects circulating BDNF (46). High-intensity interval training and moderate-intensity AE can produce transient increases in circulating BDNF (47, 48). Proposed mechanisms include lactate-mediated activation of sirtuin 1 deacetylase, fibronectin type III domain-containing protein 5 (FNDC5), beta-hydroxybutyrate production, and pro-BDNF cleavage by tissue plasminogen activator, all of which may contribute to BDNF synthesis and release after AE (49-52).

Evidence suggests that BDNF can cross the blood-brain barrier (BBB) bidirectionally, such that circulating BDNF levels may reflect brain BDNF levels (53). Proteins and metabolic derivatives released by active skeletal muscle, including cathepsin B, lactate, and FNDC5/irisin, can cross the BBB during AE and stimulate BDNF expression in different brain regions (54). Increased intracellular Ca²⁺ in neurons and activation of the MAPK/ERK signaling pathway may also contribute. Ca²⁺/calmodulin-dependent protein kinase phosphorylates cAMP response element-binding protein, which activates BDNF gene transcription (55). When the ATP/ADP ratio increases, AMP kinase is activated, triggering the PGC-1 α /FNDC5/irisin pathway and stimulating BDNF secretion in the brain (56).

The intensity, duration, and training period of AE affect BDNF expression and neurogenesis. Schmolesky et al. (57) reported that high-intensity AE at 80% of heart rate reserve

Table 1. Summary of Studies Investigating the Effects of Aerobic Exercise on Cerebellar Tissue BDNF ^a

Studies	Exercise Protocol	Subjects	Sample	Biomarkers	Findings
Risedal et al. (2002) (27)	4 weeks running on the running wheel	cortical infarct rats	contralateral cortex, thalamus, hippocampus and cerebellum	BDNF gene expression	↔ BDNF gene expression
Johnson et al. (2003) (28)	7 days running on the running wheel	Mice	hippocampal Spinal and cerebellar	BDNF level	↑ hippocampal BDNF level and ↔ spinal and cerebellar BDNF
Partadiredja et al. (2019) (29)	Four weeks, four sessions per week of light- (45% VO2max) and moderate- (55% VO2max) intensity exercise, by running on a treadmill.	Aged rats with D-galactose	cerebellar and serum	BDNF expression	↔ cerebellar and serum BDNF
Ilha et al. (2019) (30)	4-week overground gait training program	Spinal cord injury rat model	Motor cortex, cerebellum and spinal cord	BDNF expression	↑ motor cortex and ↔ cerebellum and spinal cord
Klintsova et al. (2004) (31)	Fourteen days of moderately paced running on flat track	Rat	Cerebellar molecular layer and upper motor cortical layers	BDNF and TrkB expression	↑ BDNF and TrkB expression in cerebellar molecular layer; ↑ BDNF and ↔ TrkB in upper motor cortical layers
Toldy et al. (2005) (32)	1.5 h of swimming per day, 5 times/week, for 6 weeks, with <i>Urtica dioica</i> supplementation	Rat	cerebellum	protein BDNF	↔ cerebellar BDNF protein
Cechetti et al. (2008) (33)	2 weeks of 20 min/day of treadmill training	Rat	Hippocampus, cortex, striatum, and the cerebellum	BDNF levels	↔ BDNF levels in hippocampus, cortex, striatum, and cerebellum
Sugiyama et al. (2020) (34)	9 weeks of treadmill running, 5 sessions per week	high-fat diet-fed rat	cerebellum	BDNF and TrkB expression	↑ cerebellar BDNF and TrkB expression with combined aerobic training and melatonin
Zhu et al. (2006) (35)	6 weeks running on a running wheel	BALB/c mice	hippocampus, amygdala and cerebellum	BDNF and NGF levels	Regulating BDNF and NGF levels in hippocampus, amygdala and cerebellum
Abel et al. (2013) (36)	1 week running on a running wheel	Mice (male, female)	Hippocampus cerebellum	BDNF expression	↑ hippocampal and cerebellar BDNF expression
Wang et al. (2015) (37)	5 weeks running on the treadmill	Rat	cerebellar and serum	BDNF level	Normalization of plasma and cerebellar BDNF levels
Van Kummer et al. (2015) (38)	4 weeks of treadmill running (30 min/day, 5 days/week)	spastic Han Wistar rat	cerebellum Purkinje cell	BDNF and TrkB level	↑ cerebellar Purkinje cell BDNF and TrkB
Chalimoniuk et al. (2015) (39)	6-week endurance training (running) of moderate intensity on a treadmill	Rat	hippocampus, midbrain, striatum, cerebellum, and cerebral cortex	BDNF and TrkB expression	↑ BDNF and TrkB mRNA in hippocampus, midbrain, and striatum; ↔ in cerebellum and cerebral cortex
Inoue et al. (2018) (40)	Running on a treadmill 5 days/week for 4 weeks	Mice	cerebellum	mRNA expression of BDNF	↑ cerebellar BDNF mRNA expression
Algaidi et al. (2019) (41)	Voluntary running for 3 weeks on a running wheel	Depressed rat	Dentate gyrus, medial prefrontal cortex and cerebellum	BDNF expression	↑ dentate gyrus, medial prefrontal cortex, and cerebellum
Rauf et al. (2020) (42)	5 days a week running on a treadmill for 6 weeks	Ovariectomized rats	cerebellum	mRNA expressions of BDNF	↑ cerebellar BDNF mRNA expression
Fragoso et al. (2020) (43)	voluntary PA cages, containing a running wheel, for 4 weeks	Rat	cerebellum hypothalamus, hippocampus and cortex	mRNA expressions of BDNF	↔ cerebellar, hypothalamic, hippocampal, and cortical BDNF
Salomova et al. (2021) (44)	6 weeks of running on running wheels (voluntary running) or a treadmill (forced PA)	Lurcher mice	cerebellum	BDNF level	↑ cerebellar BDNF level
Cook et al. (2022) (45)	6 weeks of running on running wheels or a treadmill (20 minutes at an increasing speed)	Spinocerebellar ataxia type 6 mice	cerebellar	BDNF expression	↑ cerebellar BDNF expression

^a ↑ denotes an increase; ↔ denotes no change. Abbreviations: BDNF, brain-derived neurotrophic factor; PA, physical activity.

and a longer duration of 40 minutes increased BDNF expression. BDNF expression also increased with exercise duration (57). A meta-analysis showed that high-intensity AE increased BDNF expression (58), and other studies have reported that moderate- to high-intensity AE increases BDNF (59).

4. Conclusions

Overall, the available evidence indicates that AE increases BDNF expression in rodents. This effect may be mediated by the release of myokines and metabolites from skeletal muscle, including cathepsin B, lactate, and FNDC5/irisin, into the circulation. These factors can cross

the blood–brain barrier and stimulate BDNF expression in the brain. Increased cerebellar BDNF has been reported in healthy rodents, vanadium-exposed lactating rodents, and models of depression, ataxia, menopause, early-onset cerebellar degeneration, and spinocerebellar ataxia type 6. In these studies, AE-induced increases in BDNF were associated with improved brain function. Given the important role of the cerebellum in the central nervous system, increasing BDNF in this region may improve cerebellar function and reduce associated functional impairments. Therefore, AE may be considered a nonpharmacological strategy to support cerebellar function and may have potential as an intervention for disorders associated with cerebellar dysfunction.

Footnotes

AI Use Disclosure: The authors declare that no generative AI tools were used in the creation of this article.

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