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OBM Neurobiology

Review

The Effects of Exercise on Long-Term Potentiation: A Candidate Mechanism of the Exercise-Memory Relationship

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Academic Editor: Bart Ellenbroek

OBM Neurobiology
2019, volume 3, issue 2
doi:10.21926/obm.neurobiol.1902026

Received: March 30, 2019
Accepted: May 08, 2019
Published: May 10, 2019

Abstract

***Objective*:** The objective of this paper was to evaluate the extent to which exercise may influence long-term potentiation (LTP), a key cellular correlate of episodic memory function.

Methods: Studies were identified using electronic databases, including PubMed, PsychInfo, Sports Discus and Google Scholar.

Results: The computerized searches revealed 20 articles meeting the study criteria. Among these 20 evaluated articles, 17 were conducted in an animal model and 3 among humans. All 17 of these studies, with the exception of one, provided evidence that exercise enhances LTP. Each of the three human studies demonstrated evidence that exercise was favorably associated with LTP or LTP-like mechanisms. In animal models, exercise reliability increases LTP and lowers the threshold for LTP induction.

Conclusion: Chronic exercise appears to robustly enhance LTP. The mechanisms of this effect are multifold and include, for example, exercise modulation of the structure and function of NMDA receptors.

Keywords

Encoding; consolidation; NMDA

1. Introduction

Long-term potentiation (LTP) [1] is considered a cellular correlate of episodic memory function [2-4], involving an enhanced functional connectivity among neurons, characteristically shown by sustained excitatory post-synaptic potentiation (EPSP). Two factors that induce LTP are the frequency and intensity of the stimulation. The intensity of the stimulation increases the amplitude of the EPSP, whereas the frequency of the stimulation facilitates an additive effect on EPSP. In animal models, LTP is often induced via a three-step process, including 1) stimulating the axon (e.g., Schaffer collaterals) and then recording the post-synaptic EPSP, with the baseline period of axon stimulation occurring approximately once every 10-seconds, 2) a conditioning stimulus at a higher intensity to induce plasticity, and 3) re-stimulation of the axon followed by post-synaptic EPSP recording. If the post-conditioning EPSP in step 3 is greater than that recorded in step 1, then evidence of LTP is present. As noted below, LTP is largely dependent on kinase activation and protein synthesis.

In brief, LTP consists of an early (E-LTP) and late (L-LTP) phase, including non-protein synthesis and protein synthesis mechanisms, respectively. LTP-related mechanisms likely occur at both the pre- and post-synaptic neuron [5]. On the pre-synaptic neuron, related mechanisms may include, for example, increased neurotransmitter release, increase number of neurotransmitters in the vesicle, and increased probability of vesicle fusion. In E-LTP, pre-synaptic action potential increases Ca^{2+} (calcium) influx, facilitating vesicle docking. A neurotransmitter (e.g., glutamate) binds to an AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor, facilitating Na^{+} (sodium) influx and K^{+} (potassium) efflux, inducing cell depolarization. Ca^{2+} enters through NMDA (N-methyl-D-aspartate) via electrostatic repulsion, which phosphorylates AMPA receptors via protein kinases. Further, NMDA activation can facilitate membrane insertion of new AMPA receptors [6]. In L-LTP, cAMP (cyclic adenosine monophosphate)-dependent protein kinase and mitogen-activated protein kinase (MAPK) are activated, which upregulate transcription factors (e.g., CREB; cAMP response element binding protein) to facilitate synaptic plasticity by necessary synaptic proteins.

Recent work demonstrates that acute and chronic exercise may subserve episodic memory function [7-16]. Regarding acute exercise, the timing of the bout of exercise plays a critical role in influencing episodic memory performance [17]. Generally, when the acute bout of exercise occurs shortly before memory encoding or during memory consolidation, episodic memory is enhanced, whereas when it occurs during memory encoding, episodic memory is impaired. However, as detailed elsewhere, the intensity of exercise and the memory type may moderate these effects [18]. The potential mechanisms of this acute exercise effect are multifold [2, 19, 20], including, for example, exercise-induced LTP, via muscle spindle and vagus nerve activation, inducing hippocampal neuronal excitability. Chronic exercise, however, is likely to influence long-term memory function via structural and functional changes that are influenced by molecular and cellular mechanisms. For example, chronic exercise-induced molecular changes (e.g., increased brain-derived neurotrophic factor, vascular endothelial growth factor, and insulin-like growth factor) may alter cellular adaptations (e.g., gliogenesis, neurogenesis, synaptogenesis, and angiogenesis), which may influence episodic memory via structural and functional outcomes (e.g.,

increased white and grey matter, increased receptor and neural activity) [21]. These acute and chronic exercise-induced alterations may influence LTP, and in turn, enhance episodic memory function.

However, no reviews have specifically focused on the acute and chronic effects of exercise on LTP. Thus, the purpose of this brief review was to evaluate the extent to which exercise may induce LTP. This will provide insights on the potential underlying mechanisms through which exercise may influence episodic memory function. As stated, narrative reviews have suggested that LTP may mediate the effects of exercise on episodic memory, but to date, no systematic review has evaluated this possibility.

2. Methods

Studies were identified using electronic databases, including PubMed, PsychInfo, Sports Discus and Google Scholar. Computerized searches were conducted from inception to February, 2019. The search terms included: exercise, physical activity, running, LTP, and long-term potentiation (and their combinations). For example, "exercise AND LTP", "physical activity AND LTP", "running AND LTP", and "exercise AND long-term potentiation."

To be eligible for inclusion in this review, studies had to:

- Be published in English.
- Include a measure of exercise as the independent variable.
- Directly measure LTP or LTP-like mechanisms (e.g., measured EPSP or a stimulus-induced event-related potential).

3. Results

The computerized searches revealed 252 unique articles. The title and abstract of each of these articles were reviewed. Among these 252 articles, 25 appeared to meet the study criteria. The full-text of these 25 articles were retrieved and read in full. Among these, 20 articles met the study criteria listed above. Among these 20 evaluated articles, 17 were conducted in an animal model and 3 among humans.

Table 1 displays the results for the 17 animal studies. The animal experiments included varied exercise protocols, ranging from an acute bout of walking to up to 4-months of voluntary running. The LTP induction protocol also varied, including, for example, low-frequency stimulation protocols, single high-frequency stimulations, and multiple high-frequency stimulations. All 17 of these studies, with the exception of one [22], provided some evidence that exercise enhanced LTP.

Table 2 displays the results for the 3 human studies. All 3 studies employed young adult samples. One study employed an exhaustive bout of acute exercise [23]; another employed a high-intensity 20-minute cycling session [24]; and another stratified participants into being active or inactive based on self-report [25]. Two of these studies employed a paired associate stimulation protocol [23, 24], with the other utilizing a visual stimuli to induce visual cortex LTP [25]. Each of these three studies demonstrated evidence to suggest that exercise was favorably associated with LTP-like mechanisms.

Table 1 Extraction table of the evaluated studies among animals.

Study	Subjects	Exercise Protocol	LTP Induction	Did Exercise Increase LTP?	Other Notable Findings
Praag (1999)[26]	C57Bl6 mice	Up to 4-months of voluntary wheel running	A burst of 50 pulses at 100 Hz; bursts were repeated four times at 30-sec intervals	Yes, voluntary wheel running selectively increased LTP in the dentate gyrus	NMDA blocking completely blocked the LTP effects in the running mice.
Leung (2003)[27]	Male hooded rats	An acute bout of walking	A high-frequency train of 200 Hz of 0.5-1 sec	Yes	LTP was increased when the high-frequency train was employed when rats were walking. The increased cholinergic activity during walking may be responsible for the enhancement of LTP. Postulated mechanisms through which cholinergic activity may increase LTP is through blockage of K+ mediated conductances, disinhibition of CA1 pyramidal cells, and enhancement of NMDA receptor currents.
Farmer (2004)[28]	Sprague-Dawley rats	1-month voluntary wheel running	Weak and strong stimulation. Weak stimulation involved 10 bursts of 5 pulses at 100 Hz, with 200 ms interburst interval. Strong stimulation involved 10 pulses at 400 Hz, with 200 ms interburst interval	Yes	The threshold for LTP induction is lower in runners. LTP induction was NMDA dependent. Exercise increase mRNA levels of NR2B. Exercise also increased BDNF and glutamate receptor 5 mRNA (GluR5). Thus, alterations in BDNF and GluR5 may reduce the threshold for LTP.
Ahmed (2006)[29]	Wistar rats	An acute swim protocol (ranging from 15 min to 4 hr)	3-10 bursts (200 Hz with 0.1 ms duration and 10 sec interpulse intervals)	Yes	Acute exercise also increased various markers of L-LTP. Mineralocorticoid receptors (MR) were rapidly upregulated, whereas glucocorticoid receptors (GR) were elevated with a 3-hr delay. Further, MAPK2, p38 MAPK, and CAMKII stayed elevated for 24 hours post exercise.
O'Callaghan (2007)[30]	Wistar rats	7 days of treadmill running, 60 min/day	3 trains of stimuli; 250 Hz in 50 ms; 30 s inter-train interval.	Yes	

Vasuta (2007)[31]	C57Bl6 mice	7-10 days of voluntary wheel running	High-frequency stimulation (4 bursts of 50 pulses at 100 Hz, 30-sec between burst	Yes	LTP in the DG was completed blocked by NR2B antagonists in control animals, but not in the running animals. The short running period suggests that increases in LTP were likely due to alterations in synaptic structure rather than due to the increase in neurogenesis.
Patten (2013)[32]	Sprague-Dawley rats	Voluntary running for 28-56 days	10 bursts of five pulses at 100 Hz, with inter-burst interval of 200 ms	No for 28 days of running, but when ran for 56 days, LTP increased.	
Yu (2013)[33]	Wistar rats	4-weeks of training, 30 min/day, 2 times/day, 6 days per week. Training included drum-type reticular training, balance training, and mesh barrier training	LTP recording in vivo, single square wave pulse	Yes	Exercise reduced peak latency after the Y-maze discrimination learning. Exercise training improved NMDA opening conductance level.
Miladi-Gorji (2014)[34]	Wistar rats	10 days of voluntary wheel running	10 pulses at 100 Hz.	Yes	Exercise significantly increased the mean baseline EPSP and population spike amplitude.
Dao (2016)[35]	Wistar rats	Treadmill running, 5 days/wk, 4-weeks, up to 15 min/session	8 trains (400 Hz), every 10 sec, for 30 sec	Yes	Aβ impaired CREB phosphorylation, and this impairment was prevented by regular exercise. Exercise also relieved the AD-induced suppression of BDNF.
Radahmadi (2016)[36]	Wistar rats	6 days of running, 1 hr/day	High frequency stimulation; 400 Hz, 10 bursts of 20 stimuli, 0.2 ms stimulus duration, 10 s inter-burst interval	Yes	Exercise increased the neuronal excitability of granule cells at lower stimulus intensities (i.e., induced LTP at a lower intensity threshold). Exercise also increased EPSP to a higher degree after stimulation. Exercise withdrawal (21 days later) reversed the exercise-LTP beneficial effects.

Zheng (2016)[37]	C57Bl6 mice	Voluntary wheel running for 1-month	Either a single high-frequency stimulation (100 Hz, 1 sec) or two stimulations (100 Hz, 1 sec, 1-min interval)	In adenylyl cyclase knockout mice, exercise attenuated the impaired LTP.	Exercise and exogenous BDNF application overcame defective Ca^{2+} stimulated cAMP signaling.
D'Arcangelo (2017)[38]	BALB/c mice	6-weeks of running, either in a continuous running fashion or using interval methods (high-intensity and low-intensity phases). Also, the volume of running was different.	100 Hz, 1 sec	Dependent on the volume and pattern of exercise. Only the group that engaged in 50% volume, with interval-type exercise had increased LTP	The high-volume exercise groups may have induced a high content of metabolites or corticosteroid hormones, particularly cortisol, which may have prevented LTP due to the stressful nature of the protocol. Further, inflammatory cytokines, such as IL-6 and TNFα may inhibit the induction of LTP.
Cheng (2018)[39]	Wistar-Kyoto rats	6-weeks of swimming, 6 days per week, building up to 60 min/day	Tetanic stimulation, 10 trains, each containing 20 pulses at 200 Hz, 2-sec interval	Exercise attenuated diet-induced (low soybean oil) suppression of LTP.	These effects occurred through the up-regulation of BDNF and NMDA expression.
Ma (2018)[22]	C57Bl6 mice	Fatiguing exercise protocol: 7 consecutive days of intense exercise, including running at 85% of max until exhaustion.	High-frequency stimulation of 100 Hz for 3 sec, three trains, 20 sec inter-train interval	LTP was only induced in the control animals, not in the animals engaging in exhaustive exercise	Exhaustive exercise may prevent LTP by reducing NMDA/AMPA ratio, which may lead to less Ca2+ influx, which is insufficient to induce LTP
Miller (2018)[40]	C57Bl6 mice	Voluntary exercise for at least 4-weeks	Theta burst stimulation, 2 bursts with each burst consisting of 10 sets of 5 pulses, each pulse applied at 100 Hz with 200 ms between each set; 20 sec delay between the two bursts.	Exercise alone increased LTP when compared to controls.	If exercise and stress occur concurrently, exercise is able to combat the stress so that the dorsal hippocampus can experience normal levels of LTP. The BDNF pathway is a likely mechanism elucidating this effect.
Tsai (2018)[41]	C57Bl6 mice	6-weeks of running, 20-60 min/day, 5 days/week	One high-frequency train (100 Hz, 1 sec)	Yes	Exercise increased LTP across young, middle-age, and old mice. Exercise also increased dendritic complexity in all age groups.

Table 2 Extraction table of the evaluated studies among humans.

Study	Subjects	Exercise Protocol	LTP Induction	Did Exercise Increase LTP?	Other Notable Findings
Mang (2014)[23]	16 young adults	An exhaustive maximal exercise test on a cycle	Paired associate stimulation (PAS) via transcranial magnetic stimulation (TMS)	Yes, exercise prior to the TMS showed greater PAS when compared to non-exercise prior to TMS.	These findings suggest that exhaustive aerobic exercise can prime LTP-like neuroplasticity and promote implicit motor learning.
Singh (2015)[24]	11 young adults	20-min cycling session	Paired associate stimulation (PAS)	Yes	PAS induced increases in motor cortical excitability were enhanced when exercise occurred before the stimulation.
Smallwood (2015)[25]	21 young adults	Stratified into high-active and low-active groups based on self-reported physical activity	Visual stimuli was presented to induce visual cortex LTP	Yes	Both groups (active vs. inactive) demonstrated early LTP; however, high-active group demonstrated late LTP (30-min after induction). Thus, this study suggests that chronic exercise can influence LTP-like changes in the human visual cortex. The visual cortex represents the same underlying processes as hippocampal LTP.

4. Discussion

4.1 Overall Summary

Emerging research suggests that exercise (both acute and chronic) can subserve memory function [2, 5]. Long-term potentiation (LTP) is considered a cellular correlate of episodic memory function [42]. No reviews, to date, have evaluated the extent to which exercise may enhance LTP. All of this served as the motivation for the present review, which was to evaluate the extent to which exercise is associated with LTP. The main finding from this brief review was that there is consistent evidence in animal models demonstrating that chronic exercise may enhance LTP, with some evidence, among humans, to suggest that acute exercise may enhance LTP. Notably, the exercise protocol for these chronic training studies varied considerably (e.g., 6 days to 6-weeks of exercise; walking, running, and swimming protocols). Despite the variability in the exercise paradigm, there were consistent findings, demonstrating a robust effect of exercise on LTP in animal models. The human findings also support these results, but additional work in this area among humans is needed. Specifically, additional work in humans is needed to evaluate whether exercise duration (e.g., acute vs. chronic) has a differential effect on LTP. In totality, despite the variation in exercise protocols in the animal studies (e.g., 6 days to 6-weeks of exercise; walking, running, and swimming protocols) and human studies (e.g., acute bout of exercise, or using habitual exercise patterns to classify individuals as active or inactive), across both populations, there was consistent evidence of an exercise-induced LTP effect. This, ultimately, suggests that exercise robustly influences LTP. The narrative that follows will highlight key observations from the evaluated studies, for both the animal and human studies, as well as discuss candidate mechanisms through which exercise may enhance LTP.

4.2 Non-Human Studies

A key observation of the evaluated animal studies was that exercise, either before or during LTP induction, enhanced LTP. A likely mechanism explaining this observation is through exercise-induced alterations in NMDA structure and function. Dietrich et al. [43] reported that the level of phosphorylation of NR1 and NR2 subunits of the rat cerebral cortex NMDA receptor was increased with voluntary wheel running for one month. Further, the NMDA receptor channel open rate was increased with running. Molteni et al. [44] also showed that voluntary wheel running increased the expression of NR1, NR2A, and NR2B mRNA in the rat hippocampus after 3 and 7 days of running. Importantly, exercise-induced NMDA receptor expression increases not only in the hippocampus, but in the prefrontal cortex as well [45], which is an important brain structure involved in memory function [46].

Exercise has been shown to increase BDNF levels [20] and BNDF (brain-derived neurotrophic factor) may help upregulate the expression and function of the NMDA receptor [47-49]. BDNF also buffers against depotentiation [50]. Downstream of the BDNF/TrkB (Tropomyosin receptor kinase B) signaling pathway, PI3K-AKT activation is thought to contribute to the maintenance of LTP via NMDAR activity [51]. That is, substrates of AKT (e.g., girdin; actin-binding protein) may interact with kinases and NMDA subunits, leading to phosphorylation of NMDA receptors. Importantly, physical exercise has been shown to alter the kinetics of TrkB phosphorylation induced by

exogenous BDNF, with sustained TrkB signaling acting as a key mechanism underlying the synergistic effects of neuronal activity and BDNF [52]. Neurogenesis may also be a mechanism through which chronic exercise may increase LTP, as newly generated neurons can be more easily activated and more readily to produce LTP [53]. Relatedly, exercise-related, BDNF-induced neurogenesis influences synaptic development, and in turn, likely plays an important role in LTP production. Other candidate mechanisms include exercise-related alterations in cholinergic activity [27], mineralocorticoid/glucocorticoid receptor expression [29], cAMP signaling [37], and inflammatory cytokines [38].

In addition to exercise subserving LTP via NMDA-related mechanisms, exercise may maintain this beneficial effect even in the presence of a neuronal insult. For example, from various determinants, such as epilepsy or sleep deprivation, exercise has been shown to revert the reduced CA1 (Cornu Ammonis-1) LTP [54, 55]. Similarly, when exercise and stress occurs concurrently, exercise is able to combat the stress so that the dorsal hippocampus can experience normal levels of LTP [40]. Additionally, in Alzheimer's disease (AD) models, Aβ impairs CREB phosphorylation, and this impairment is prevented by regular exercise, which also relieves the AD-induced suppression of BDNF [35]. Relatedly, exercise has been shown to increase LTP across the entire lifespan, including aging populations [41].

Although the current evidence suggests that acute and chronic exercise can enhance LTP, exercise withdrawal may reverse the exercise-LTP beneficial effects [36]. Further, extremely high levels of exercise or exhaustive exercise has not been shown to enhance LTP among mice, which is thought to occur from the reduction of NMDA/AMPA levels, which may lead to less Ca^{2+} influx [22]. However, this finding has not been replicated in humans, as in young adult humans, a maximal bout of acute exercise has been shown to enhance LTP-like neuroplasticity and promote implicit motor learning [23].

4.3 Human Studies

Three human studies evaluated the effects of exercise on LTP [23-25], two of which employed an acute bout of exercise, whereas one study evaluated whether LTP was different among active and inactive individuals [25]. Mang et al. [23] employed an exhaustive exercise test on a cycle ergometer and induced LTP via transcranial magnetic stimulation (TMS). Exercise prior to the TMS showed greater paired associate stimulation (PAS) when compared to a non-exercise stimulus. Relatedly, in a similar young adult population, Singh et al. [24] showed that PAS-induced increases in motor cortical excitability were enhanced when a 20-min cycle session occurred before the stimulation. Lastly, Smallwood et al. [25] showed that, among young adults, visually-evoked (later phase) LTP-like responses in the occipital cortex where higher in habitually active individuals when compared to their less active counterparts. Specifically, the active group demonstrated a greater increase in the amplitude of the N1b following tetanus.

4.4 Limitations

Limitations of this review include the use of a single author to screen and retrieve articles for this review. Thus, not all aspects of a systematic review were able to be adhered to. Further, given the heterogeneity in the study designs, I did not employ a meta-analysis. Such limitations should

be considered when interpreting the findings from this review as well as inform future reviews on this topic.

5. Conclusion

In conclusion, this brief review demonstrates that, in animal models, exercise reliability increases LTP and lowers the threshold for LTP induction. The mechanisms of this effect are multifold and include, for example, exercise modulation of the function of NMDA receptors. Additional creative work in humans is needed to continue to evaluate the extent to which exercise may subserve LTP in adults. Such work should continue to investigate both acute and chronic exercise paradigms. Acute exercise studies should evaluate whether there is an exercise intensity-dependent effect on LTP and whether certain molecular proteins (e.g., BDNF) mediate this effect.

Acknowledgments

I declare no conflicts of interest and no funding was used to prepare this manuscript.

Author Contributions

The author did all the research work of this study.

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