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THE EFFECTS OF EXERCISE ON DENDRITIC SPINE DENSITY: IMPLICATIONS FOR EXERCISE-INDUCED MEMORY ENHANCEMENT

EGZERSİZİN DENDRİTİK DİKENLERİN YOĞUNLUĞU ÜZERİNE ETKİLERİ: EGZERSİZE BAĞLI BELLEK GELİŞTİRME UYGULAMALARI

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Abstract

The purpose of this brief review was to highlight the potential mediational role of dendritic spine morphology on the exercise-memory interaction. I first start out delineating the role of dendritic spine density on episodic memory function and then discuss mechanisms involved in spine density alteration. Following this, I discuss the effects that exercise has on dendritic spine density, including its underlying mechanisms. Ultimately, this discussion will provide us with greater insights on the mediating mechanisms through which exercise may influence episodic memory function.

Keywords: BDNF; cognition; long-term potentiation; synapse

Özet

Bu kısa derlemenin amacı, dendritik dikenlerin morfolojisinin egzersiz--bellek etkileşimi üzerine etkisini incelemektir. Bu bağlamda, öncelikle dendritik dikenlerin yoğunluğunun epizodik bellek üzerine etkisinin altı çizilecek, ardından dikenlerin yoğunluğundaki değişiklikler mekanizması ile ilgili tartışılacaktır. Bundan sonrasında, egzersizin altta yatan mekanizmaları ile birlikte dendritik dikenlerin yoğunluğu üzerindeki etkisi tartışılacaktır. Son olarak, tartışma egzersizin epizodik bellek kapasitesi üzerindeki aracı rolü hakkındaki bilgilerimizi arttırmamıza imkan sağlayacaktır.

Anahtar Kelimeler: *BDNF; biliş; uzun dönemli potansiyasyon; sinaps*

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1. Introduction

Both acute and chronic exercise have been shown to enhance episodic memory (Frith, Sng, & Loprinzi, 2017; Haynes Iv, Frith, Sng, & Loprinzi, 2018; Loprinzi, Scott, Ikuta, Addoh, & Tucker, 2018; Sng, Frith, & Loprinzi, 2018), which is the retrieval of retrospective information from a spatio-temporal context (Tulving, 1983). We have previously discussed various mechanisms through which both acute and chronic exercise may subserve episodic memory (Loprinzi, 2018; Loprinzi, Edwards, & Frith, 2017; Loprinzi & Frith, 2018; Loprinzi, Ponce, & Frith, 2018). These include, for example, exercise-induced alterations in neurotrophic factors, hormones, and long-term potentiation. The present review extends this body of work by highlighting the role of exercise on synaptic plasticity, and specifically, dendritic spine density. This is of critical importance, as the brain's ability to retain information depends on the strength of existing synapses and on the appearance or elimination of dendritic spines (Fregozo & Vega, 2012; Kasai, Fukuda, Watanabe, Hayashi-Takagi, & Noguchi, 2010).

I first start out delineating the role of dendritic spine density on episodic memory function and then discuss mechanisms involved in spine density alteration. Following this, I discuss the effects that exercise has on dendritic spine density, including its underlying mechanisms. Ultimately, this discussion will provide us with greater insights on the mediating mechanisms through which exercise may influence episodic memory function.

2. Dendritic Spines and Memory Function

As illustrated elsewhere (Poo et al., 2016), structural and molecular mediators of memory are complex, and unlikely attributed to a single structure or protein. Of interest to this paper, however, is the role of dendritic spines and how they are formed and modified during learning. A spine consists of three basic components, including a base structure joined to the dendrite, a neck, and a head which may connect with an axon. Normal dendritic spine density ranges from 0.2 to 3.5 spines per 1 μm of dendrite (Benavides-Piccione, Fernaud-Espinosa, Robles, Yuste, & DeFelipe, 2013). Further, spines are often classified into three morphological groups, including, thin, stubby, and mushroom types. Spines may become stable for days to years (Zuo, Lin, Chang, & Gan, 2005), and the amount of stable spines correlates with memory performance (Yang, Pan, & Gan, 2009). Notably, however, the actin filaments that supports the spine turns over in minutes to hours, with 80% of F-actin in spines turning over every minute (Star, Kwiatkowski, & Murthy, 2002).

Dendritic spines exist in certain types of neurons, such as pyramidal neurons in the cortex, hippocampal neurons and Purkinje cells in the cerebellum (Kasai, Fukuda, Watanabe, Hayashi-Takagi, & Noguchi, 2010). Each neuron may include over 10,000 spines, each representing a point of synaptic contact (Kasai, Fukuda, Watanabe, Hayashi-Takagi, & Noguchi, 2010). Relatedly, dendritic spines are sites for synaptic communication, and thus, alterations of the spine (via LTP and LTD (Trommald, Hulleberg, & Andersen, 1996)) play an important role in synaptic plasticity, and ultimately, memory function. Notably, spines with large postsynaptic densities have more AMPA receptors (Noguchi et al., 2011), which may facilitate LTP. Further, spine neck size may also influence NMDA-dependent Ca2+ signaling (Noguchi, Matsuzaki, Ellis-Davies, & Kasai, 2005).

In addition to increasing the surface area for synaptic contact, the majority of dendritic spines have an excitatory synapse, with Ca2+ concentrated in the spine, as well as voltage-gated Na channels in the spine (Rose, Kovalchuk, Eilers, & Konnerth, 1999), suggesting that dendritic spines play a critical role in the formation and plasticity of functional neural networks involved in memory function (Yuste, 2011). Thus, structural changes in dendrites may be an important mechanism of long-term information storage. This has been demonstrated in empirical work showing that spine loss among networks that were active during learning impairs long-term memory function (Sanders, Cowansage, Baumgartel, & Mayford, 2012). Further, stress-induction has been shown to impair memory and reduce the density of CA3 dendritic spines, and blocking this stress-induced effect prevents spine loss and restores memory function (Chen et al., 2010). Other work also demonstrates that genetic manipulation of spine turnover influences storage capacity and memory function (Frank et al., 2018). Certain neuropsychiatric conditions, such as depression (decreased number of spines), fragile X syndrome (elongated, tortuous spines), and Down syndrome (fewer spines, some with large heads), have spine- and memory-related impairments (McCann & Ross, 2017).

3. Mechanisms Involved in Dendritic Spine Density

Several key reviews have provided mechanistic insight on the regulation of dendritic spines (Basu & Lamprecht, 2018; Borovac, Bosch, & Okamoto, 2018; Cornelia Koeberle et al., 2017; Ebrahimi & Okabe, 2014; Fregozo & Vega, 2012; Hotulainen et al., 2009; Kumar et al., 2016; Merriam et al., 2013; Penzes & Rafalovich, 2012; Sala & Segal, 2014; Spence & Soderling, 2015; Sutton & Schuman, 2006). Remodeling of the actin cytoskeleton is a likely candidate behind the structural alterations of dendritic spines, and plays a fundamental role in the formation, elimination, motility, stability, size, and shape of the spine (Penzes & Rafalovich, 2012).

In neurons, actin consists of soluble monomeric G-actin and polymerized F-actin filaments. Polymerization of free G-actin is regulated by various pathways, activated by select surface receptors, such as NMDA receptors (Cingolani & Goda, 2008). Upon activation of this NMDA receptor, the dendritic spine undergoes a temporary increase in Ca2+ (Sobczyk & Svoboda, 2007), which then activates calcium-sensing calmodulin, ultimately activating various kinases (e.g., CamKI, CamKII, and CamKIV) (Hook & Means, 2001). These kinases then proceed on to phosphorylate targets involved in spine

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structural plasticity (e.g., Kalirin-7) (Penzes & Rafalovich, 2012).

More specifically, this process can be conceptualized as a 4-step process, including an initial basal state, F-actin disassembly, F-actin assembly, and F-actin stabilization (Borovac, Bosch, & Okamoto, 2018). During the basal state, bundled F-actin maintains a stable spine structure. During the F-actin disassembly stage, kinases (e.g., CamKII) are activated and become detached from F-actin and then unbundle the filaments. Cofilin/ADF then enters the spine and severs the filaments. Drebrin and α-actinin reduce the concentration of filaments in the spine. Aip1 and Arp2/3 enter the spine and branch F-actin together, resulting in enlargement of spine size. Following this enlargement, stabilizing proteins, such as Drebrin, α-actinin, and inactivated CamKII return to their basal state, bind to F-actin, re-bundle and cross-link the reorganized filaments, ultimately stabilizing the enlarged dendritic spine (Borovac, Bosch, & Okamoto, 2018).

Activation of 5-HT2A receptors in pyramidal neurons has been shown to increase spine size via Kalirin-7-Rac1-PAK-dependent mechanisms (Jones et al., 2009). Data also supports the role of dopamine (Solis, Limon, Flores-Hernandez, & Flores, 2007; Wang & Deutch, 2008) and the cholinergic system (Sherren & Pappas, 2005) in regulating spine morphology. Relatedly, numerous studies have reported BDNF-induced changes in spine morphology (Lu, Christian, & Lu, 2008), with TrkB-deficient mice having fewer dendritic spines in the CA1 hippocampal neurons (Luikart & Parada, 2006).

4. Effects of Exercise on Dendritic Spine Density

Treadmill exercise (two weeks of daily exercise) in mice has been shown to attenuate stress-induced dendritic spine elimination (Chen et al., 2017). This stress-induced memory impairment is attenuated with exercise, mediated via neurogenesis and dendritic remodeling (Yau et al., 2011). Similarly, exercise has been shown to attenuate diabetes-induced dendritic spine elimination, likely through BDNF augmentation (Stranahan et al., 2009). Other work also supports this exercise-induced attenuation of spine elimination in Parkinson's disease (Toy et al., 2014) and multiple sclerosis (Rossi et al., 2009).

5. Mechanisms through which Exercise Influences Dendritic Spine Density

Dendritic spines may respond morphologically to a large variety of physiological stimuli, including acute and chronic exercise. As we thoroughly discussed elsewhere (Loprinzi, Ponce, & Frith, 2018), skeletal muscle contraction, via exercise, may activate peripheral afferent muscle spindle fibers, which have direct projections to the brainstem, and ultimately, the hippocampus. Similarly, exercise-induced lung expansion and heart rate increases will activate afferent vagus nerve fibers, which also have projections to the hippocampus. Such exercise-induced neuronal excitability may increase various neurotransmitters (e.g., glutamate) to initiate dendritic spine morphology. As discussed above, key proteins, such as BDNF, and surface receptors, such as NMDA, play an important role in spine alterations.

Previous research by Dietrich et al. (Dietrich et al., 2005) demonstrated that the level of phosphorylation of NR1 and NR2 subunits of the rat cerebral cortex NMDA receptor was upregulated with exercise. Further, the NMDA receptor channel open rate also increased with exercise. Molteni et al. (Molteni, Ying, & Gomez-Pinilla, 2002) also demonstrated that exercise increased the expression of NR1, NR2A, and NR2B mRNA in the rat hippocampus after 3 and 7 days of exercise. Exercise has also been shown to increase BDNF levels (Loprinzi & Frith, 2018) and BNDF may help upregulate the function of the NMDA receptor (Caldeira et al., 2007; Clarke & Johnson, 2008; Kim et al., 2012).

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