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Review article

Physical exercise as an epigenetic modulator of brain plasticity and cognition

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ABSTRACT

A large amount of evidence has demonstrated the power of exercise to support cognitive function, the effects of which can last for considerable time. An emerging line of scientific evidence indicates that the effects of exercise are longer lasting than previously thought up to the point to affect future generations. The action of exercise on epigenetic regulation of gene expression seem central to building an "epigenetic memory" to influence long-term brain function and behavior. In this review article, we discuss new developments in the epigenetic field connecting exercise with changes in cognitive function, including DNA methylation, histone modifications and microRNAs (miRNAs). The understanding of how exercise promotes long-term cognitive effects is crucial for directing the power of exercise to reduce the burden of neurological and psychiatric disorders.

1. Introduction

Exercise is perceived as an indispensable aspect of our daily routine to maintain overall health of body and brain. In particular, abundant evidence supports the action of exercise in sharpening cognitive abilities throughout lifespan such that the lack of exercise is considered a risk for the incidence of several neurological disorders (Gomez-Pinilla and Hillman, 2013; Cotman et al., 2007; Lista and Sorrentino, 2010). New studies indicate that the effects of exercise on brain function go beyond those previously thought, and indeed, the brain has the potential to save the effects of exercise for considerable time. There has been tremendous progress in the last decade about the molecular mechanisms through which exercise and other environmental challenges modify the program of genes with functional consequences. The action of epigenetics has come to play as it refers to alterations in chromatin that modify the transcription of genes which are saved as "an epigenetic memory" that influences long-term brain plasticity and function. An increasing body of research indicates that epigenetic modifications elicited by exercise seem to confer individuals throughout lifespan and even their progeny with the capacity to resist diseases (Denham et al., 2015; Laker et al., 2014; McPherson et al., 2015). Here we discuss recent research revealing main epigenetic mechanisms by which exercise affects brain function, particularly focusing on cognitive abilities.

1.1. Effects of exercise on cognitive abilities

The positive actions of exercise on learning and memory in humans and animals have received abundant support (Lista and Sorrentino, 2010; Erickson et al., 2011; van Praag et al., 1999a; Gomez-Pinilla and Hillman, 2013). In older adults, exercise has been shown to improve cognitive performance (Colcombe et al., 2004; Cassilhas et al., 2007) and to counteract the mental decline associated with ageing (Yaffe et al., 2009; Heyn et al., 2008), and these effects have been associated with modifications in hippocampal size (Erickson et al., 2011). In schoolchildren, exercise has been found to be associated with cognitive performance: children who engaged in greater amounts of aerobic exercise generally performed better on verbal, perceptual, and mathematical tests (Sibley and Etnier, 2003). Recently, a meta-analysis study reported that a single bout of moderate aerobic exercise improves inhibitory control, cognitive flexibility, and working memory in preadolescent children and older adults (Ludyga et al., 2016), indicating that beyond the well know effects of long-term exercise on the brain, acute exercise also can be used as a tool for situations demanding a high executive control. Interestingly, we and others have found that a single bout of both aerobic (Siette et al., 2014) and resistance (Fernandes et al., 2016) exercise is able to enhance memory consolidation in rats.

Exercise is also perceived as one of the most effective therapies to reduce depression (Rethorst and Trivedi, 2013; Kvam et al., 2016) and to improve several aspects of other brain-related diseases such as

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Parkinson and Alzheimer's, Epilepsy, anxiety and traumatic brain injury (Grealy et al., 1999; Chin et al., 2015; Intlekofer and Cotman, 2013; Matura et al., 2016; de Almeida et al., 2017; Peixinho-Pena et al., 2012; Shu et al., 2014; Reynolds et al., 2016; Jayakody et al., 2014). Concerning to depression, a randomized controlled trial showed a dose-response relationship between exercise and depression score (reduction of 47% of high-dose aerobic exercise and 30% in the low-dose exercise) evaluated by Hamilton Rating Scale for Depression (HAM-D) (Dunn et al., 2005). Furthermore, Blumenthal et al. (1999) reported that aerobic exercise by itself or in combination with sertraline (a selective serotonin reuptake inhibitor) lowered depressive score and relapse rate at 6-month of follow-up.

In rodents, the memory improvements induced by physical exercise are accompanied by increases in cell proliferation, neurogenesis, dendritic complexity and spine density (Lista and Sorrentino, 2010; van Praag et al., 1999b). Moreover, these studies showed that the positive effects of exercise on learning and memory are rooted to molecular regulatory mechanisms involved in neurotransmission, metabolism and synaptic plasticity (Vaynman et al., 2004; Cotman et al., 2007; Lista and Sorrentino, 2010). As discussed below, exercise activates the transcriptional machinery inside the nucleus to modulate the expression of genes associated with regulation of synaptic plasticity, learning and memory using epigenetic mechanisms.

2. Epigenetics mechanisms and brain

It is well accepted that adaptations to an ever-changing environment involve long-lasting physiological modifications that cannot be explained by mutations. This belief has led to the search of alternative mechanisms to account for how environmental influences can be saved in the genome. Conrad Hal Waddington coined the term “epigenetics” based on a conceptual model to account for how genes might interact with their surroundings to produce the phenotype (Waddington, 1939). Nowadays, epigenetics refers to changes in gene expression through modulation of chromatin without alterations in the DNA sequence (Jaenisch and Bird, 2003; Goldberg et al., 2007). These concepts also opened up to the possibility that epigenetic modifications could be inherited and provide a source for individual variability.

The epigenetic research has been centered on the analysis of changes on top of the genome that do not involve alterations in the nucleotide sequence. The two most studied epigenetic mechanisms are covalent modifications of DNA (methylation) or of histone proteins (i.e. acetylation and methylation), and their resulting effects on altering gene expression (Fig. 1). These changes in gene expression are generally associated with the intermediate action of proteins that act as transcription activators or repressors by binding to regulatory regions of the DNA (Jaenisch and Bird, 2003; Goldberg et al., 2007). Original studies showed that exercise regulates the transcription of *brain-derived neurotrophic factor* (*Bdnf*) gene by engaging changes in histone acetylation and DNA methylation (Gomez-Pinilla et al., 2011; Ieraci et al., 2015; Sleiman et al., 2016). Thereafter, an increasing number of studies indicate the involvement of epigenetic mechanisms on the action of exercise on the brain (Table 1). It appears that exercise-induced changes in acetylation and methylation are instrumental to regulate synaptic plasticity and learning and memory (Abel and Rissman, 2013; Gomez-Pinilla et al., 2011; Intlekofer et al., 2013; Ieraci et al., 2015). Indeed, a growing body of evidence indicates that physical exercise activates signaling cascades that trigger a wave of phosphorylation and other post-translational modifications that reach the nucleus, and engage epigenetic mechanisms to alter chromatin conformation and gene expression. As discussed below, a group of small non-coding RNAs, particularly microRNAs (miRNAs), have emerged as potent epigenetic regulators of brain plasticity and memory function (Saab and Mansuy, 2014; Konopka et al., 2011; Wang et al., 2012), and this information has paved the road to a better understanding of the epigenetic mechanism underlying the action of exercise on the brain.

2.1. DNA methylation

DNA methylation is a post-replication modification in which a methyl group is covalently added to the 5-carbon of cytosine bases (Guo et al., 2011a) located in cytosine-phosphate-guanine (CpG) dinucleotides. The CpG notation is used to distinguish a cytosine followed by a guanine in one strand from a cytosine base paired to a guanine in double-stranded sequences. Although underrepresented throughout the mammalian genome, these sites are occasionally clustered in CpG islands located close to, and in, approximately 40% of gene promoters (Jaenisch and Bird, 2003; Goldberg et al., 2007). Interestingly, DNA methylation of CpG islands is usually associated with silencing of genes with dramatic importance for cell function under homeostatic and disease conditions (Goll and Bestor, 2005). DNA methylation is catalyzed by two groups of enzymes called DNA methyltransferases (DNMTs), which transfer methyl groups from *S*-adenosyl-L-methionine (SAM) to the cytosine residue (Bird, 1992). As discussed below, much of what is known about the heritability of methylation depends on the action of DNMTs. While de novo DNMTs (DNMT3a and DNMT3b) target unmethylated cytosines on both DNA strands (Okano et al., 1999), the maintenance DNMT1 recognizes hemimethylated DNA and transfers a methyl group to the complementary cytosine base (Okano et al., 1999; Pradhan et al., 1999).

The methylated DNA can repress transcription by interfering with the binding of transcription factors and by assembling the transcriptional machinery to regulatory sites of genes (Takizawa et al., 2001). Moreover, the methylation of CpG dinucleotides alters gene transcription by serving as a docking site for proteins containing the methyl-binding domain (MBD) (Nan et al., 1998). The methyl-CpG-binding protein 2 (MeCP2) is the best characterized member of MDB proteins in the central nervous system (CNS), and plays a role in the neurodevelopmental disorder Rett syndrome, synaptic plasticity, and memory formation (Amir et al., 1999; Chao et al., 2007; Moretti et al., 2006). Mechanistically, MeCP2 modulates gene expression by promoting a closed chromatin, via the recruitment of transcriptional repressors (i.e. HDACs and mSin3) (Drewell et al., 2002; Fuks et al., 2003), or by activating transcription through interaction with the transcriptional activator cAMP responsive element binding protein 1 (CREB1) (Chahrour et al., 2008).

Evidence shows that DNA methylation is dynamically modulated by activity-dependent events (Kangaspeska et al., 2008; Métivier et al., 2008; Guo et al., 2011b,a). The growing interest in this area of research has contributed to discover putative mechanisms regulating DNA demethylation. One of these mechanisms is represented by the action of ten-eleven translocation (TET) proteins on converting the 5-methylcytosine (5mC) into 5-hydroxymethylcytosine (5hmC), which involves base excision repair by thymine DNA glycosylase (TDG) (Guo et al., 2011b; Kohli and Zhang, 2013). Alternatively, it has been suggested that growth arrest and DNA damage 45 (Gadd45) proteins can promote DNA demethylation through recruitment of nucleotide and/or base excision repair machinery (Niehrs and Schäfer, 2012). Métivier et al. (2008) have shown that DNMTs are implicated in DNA demethylation through deamination of 5mCs, which served to demonstrate the dual role of these enzymes in maintaining the cyclical changes in the methylation status of promoter CpGs.

2.1.1. Exercise, DNA methylation, and memory

Over the last decade, several studies have been conducted to understand the role of DNA methylation on neuronal function and long-term memory (LTM). Miller and Sweatt (2007) reported the participation of de novo DNMTs in the consolidation of LTM. In this study, the authors found increased hippocampal levels of DNMT3a and DNMT3b after the acquisition of contextual fear memory (CFM), with concomitant increased DNA methylation at the promoter of *protein phosphatase 1* (*PP1*; a memory-suppressor gene) and decreased methylation at the promoter of reelin (a plasticity-associated gene) (Miller and