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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.

Keywords

Exercise; Memory; Epigenetics; Brain; DNA methylation; Histones; miRNAs

1. Introduction

Exercise is perceived as a 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 and Berchtold, 2002, Cotman et al., 2007, Intlekofer and Cotman, 2013, Lista and Sorrentino, 2010). New studies indicate that the effects of exercise on brain function go

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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, Cotman and Berchtold, 2002, 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 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 (Blumenthal et al., 1999).

In rodents, the memory improvements induced by physical exercise are accompanied by increases in cell proliferation, neurogenesis, dendritic complexity and spine density (van

Praag, 2008, 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, van Praag, 2008, 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 (Figure 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 byactivity-dependent events (Kangaspeska et al., 2008,Métivier et al., 2008, Guo et al., 2011b, Guo et al., 2011a). 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 Sweatt, 2007). Additional studies showed that learning induces changes in CpG methylation at promoters of genes with essential roles in synaptic plasticity and memory formation such as *Bdnf*, *arc*, and *calcineurin* (Lubin et al., 2008, Miller et al., 2010, Penner et al., 2011).For example, the effects of CFM on increasing the expression of *Bdnf* was shown to be accompanied by a significant demethylation of its promoter region (Lubin et al., 2008); these changes were reversed by intrahippocampal infusions of DNMT inhibitors, drugs recognized as negative regulators of memory formation.

Unlike *Bdnf*, CFM triggers hypermethylation and subsequent decrease in mRNA levels of the memory suppressor gene *calcineurin* in the prefrontal cortex (Miller et al., 2010). Importantly, this pattern of methylation can persist for at least 30 days following the acquisition of CFM and can be abolished by anterior cingulate cortex infusions of DNMTs inhibitors, which also prevent memory retrieval. Beyond memory deficits and deregulation of plasticity-related genes, pharmacological and transgenic inhibition of DNMTs in hippocampal and forebrain neurons promotes defects in dendritic branching, action potential and long-term potentiation (LTP) (Golshani et al., 2005, Levenson et al., 2006, Feng et al., 2010). Taken together, these findings suggest the existence of an intricate balance between DNA methylation and demethylation that is necessary for proper neuronal function underlying memory processing. In this case scenario, DNA methylation relieves the repressive effects of memory-suppressor genes to favor the expression of plasticity-promoting genes and memory consolidation.

In agreement with its well-described role in cognition, physical exercise can coordinate the action of genes involved in synaptic plasticity with resulting effects on memory preservation. For example, while exercise enhances the expression of genes (i.e. *Bdnf*, *igf-1* and *creb*) that positively regulate memory consolidation (Ding et al., 2006a, Vaynman et al., 2004, Molteni et al., 2002), it downregulates genes (i.e.*PP1* and *calcineurin*) with a repressive role in these events (Chen et al., 2007, Dao et al., 2015, Zagaar et al., 2012). Evidence shows that DNA methylation is an important mechanism by which exercise affects gene expression. It is known that exercise differentially modulates the methylation pattern of specific CpG islands located at *Bdnf* gene (Zajac et al., 2010), decreases hippocampal expression of DNMTs (DNMT1, DNMT3a and DNMT3b) (Abel and Rissman, 2013, Elsner et al., 2013, Kashimoto et al., 2016), attenuates the global methylation changes induced by stress (Rodrigues et al., 2015, Kashimoto et al., 2016), and increases *Bdnf* transcription through demethylation of its promoter IV (Gomez-Pinilla et al., 2011).

Similarly to *Bdnf*, it has been recently demonstrated that 2 weeks of physical exercise increases the hippocampal expression of *Tet1* while promotes demethylation of CpG islands

located at the gene promoter of *VegfA* (Sølvsten et al., 2016), a growth factor involved in the beneficial effects of physical exercise on the brain (Jin et al., 2002, Zacchigna et al., 2008, Fabel et al., 2003, Kiuchi et al., 2012). Interestingly, a previous study showed that aged mice exposed to environmental enrichment - a procedure known to elicit positive brain changes based on its physical activity component - had an improvement in learning and memory as well as a reduction in 5hmC abundance in the hippocampus (Irier et al., 2014). Altogether, these findings indicate that an enhancement of physical activity levels can reprogram the brain's methylation pattern to modulate the transcription of genes necessary for the maintenance of brain health and cognitive function.

2.2. Chromatin and histone modifications

Nucleosome is the basic repeat element of chromatin and consists of 147bp of DNA wrapped around an octamer of four core histone proteins (two pairs of H2A, H2B, H3 and H4) compacted by association with the linker histone H1. The histone proteins are structurally characterized by a globular core domain and their N-terminal tails which are susceptible to a wide range of post-translational modifications, including acetylation, methylation, phosphorylation, ubiquitination, sumoylation, ADP-ribosylation, deamination and proline isomerization (Bernstein et al., 2007). A substantial progress has been made in understanding the role of acetylation and methylation in determining the chromatin conformation and accessibility to transcriptional machinery (Kouzarides, 2007). Whereas acetylation of lysine residues on histone tails is thought to activate transcription, lysine methylation can have an activating or inactivating effect depending on the target residue and the state of methylation (i.e., mono-, di- or trimethylated). For example, while the methylation of histone (H) 3 lysine (K) 4 (H3K4) and H3K36 is related with a transcriptionally active chromatin (euchromatin), the methylation of H3K9, H3K27, and H4K20 is commonly associated with a silent state of chromatin (heterochromatin) and transcriptional repression (Kouzarides, 2007, Bernstein et al., 2007).

The histone modifications are bidirectionally regulated by a specific group of enzymes (Strahl and Allis, 2000). Histone acetyltransferases (HATs) catalyze the transfer of acetyl groups from Acetyl-Coenzyme A to the lysine residue of histones, whereas histone deacetylases (HDACs) act by removing the acetyl groups. The phosphorylation pattern of histone tails, which is tightly associated with histone acetylation, is regulated by nuclear kinases and protein phosphatases (Brami-Cherrier et al., 2009, Koshibu et al., 2009). In a similar fashion, histone methylation is catalyzed by histone methyltransferases (HMTs) such as G9a and SUV39H2, whereas demethylation of specific histone residues is dependent on histone demethylases (HDMs) such as lysine-specific demethylase 1A (LSD1) and jumonji domain-containing protein 2A (JMJD2) (Shin and Janknecht, 2007, Benevento et al., 2015). This array of histone modifications gives enormous potential for epigenetic responses, especially when considering that each of these changes can impact each other and may also interact with DNA methylation through recruitment of chromatin remodeling complexes.

There are two ways by which histone modifications can alter the chromatin organization and gene expression. While the first is related to the acetylation-induced neutralization of the charge interaction between the histones and DNA, the second requires the binding of larger

multi-molecular complexes containing enzymatic activities (i.e., remodeling ATPases) to specific histone modifications marks. Acetylated histone residues are recognized by bromodomains within chromatin remodeling complexes, whereas methylation and phosphorylation are recognized by chromodomain and 14-3-3 domain containing proteins, respectively (Kouzarides, 2007, Bernstein et al., 2007, Campos and Reinberg, 2009). CHD1 (chromo-ATPase/helicase-DNA binding domain 1), a component of the SAGA chromatin-remodeling complex, recognizes di- and trimethyl H3K4 (H3K4me2 and H3K4me3) via one of its two chromodomains to establish an epigenetic environment favoring gene transcription (Pray-Grant et al., 2005, Sims et al., 2005). Conversely, chromatin condensation can be mediated through the binding of HP1 (Heterochromatin protein 1) and Polycomb proteins to methylated H3K9 and H3K27, respectively (Margueron et al., 2005). This pattern of recognition is complex and depends on the methylation state of lysine residues. For instance, while HP1 shows similar affinities for H3K9me2 and H3K9me3, Polycomb proteins bind preferentially to H3K27m3 (Fischle et al., 2003). These modifications altogether raise the possibility that histone proteins act as platforms for convergence and integration of upstream signaling pathways to direct the chromatin configuration to an open or a closed state.

2.2.1. Exercise, histone modifications and memory—It has been shown that the acetylation of histone proteins is a requisite for LTM (Day and Sweatt, 2011, Levenson et al., 2004, Guan et al., 2015, Vecsey et al., 2007, Barrett and Wood, 2008). For example, intrahippocampal injection of global HDAC inhibitors (HDACis) such as sodium butyrate (NaB) and trichostatin A (TSA) enhances LTP at Schaffer collaterals in CA1 area of the hippocampus, and results in improved consolidation of CFM (Vecsey et al., 2007, Levenson et al., 2004). The pro-cognitive function of HDACis is partially attributed to their ability to increase histone acetylation and consequently the establishment of an open chromatin state. Interestingly, a previous study has shown that, like HDACis, physical exercise has the ability to transform a learning event that does not normally lead to a stable memory trace into a long-lasting form of memory (Interfolker *et al.*, 2013). Additionally, it was found that physical exercise increases histone acetylation and reduces HDAC expression (HDAC2, HDAC3, HDAC5, HDAC7 and HDAC8) and neural activity in the hippocampus (Gomez-Pinilla et al., 2011, Sleiman et al., 2016, Abel and Rissman, 2013, Elsner et al., 2011, Intlekofer et al., 2013).

Physical exercise (Zhong et al., 2016) and the acquisition of CFM (Peleg et al., 2010) increases the acetylation of histones H3 and H4 at multiple sites including H3K9, H3K14, H4K5, H4K8, and H4K12. With regard to the role of histone H4 on cognitive function, it was demonstrated that deregulation of H4K12 acetylation is associated with memory impairments induced by aging (Peleg et al., 2010) and by neonatal exposure to isoflurane (Zhong et al., 2016) in rodents. Notably, restoration of H4K12 acetylation levels promoted by a HDACi (Peleg et al., 2010) or by physical exercise (Zhong et al., 2016) attenuated the cognitive deficits observed in these animals. Moreover, 2 weeks of treadmill exercise improved memory performance in the inhibitory avoidance task and increased hippocampal H4K12ac levels in young adult and aged rats (de Meireles et al., 2016). Using the same exercise paradigm, this research group also demonstrated the ability of physical exercise to increase the histone H4 acetylation in the prefrontal cortex of aged rats (Cechinel et al.,

2016), and to restore the aversive memory-induced reduction in H3K14ac levels in the hippocampus of adult rats (de Meireles et al., 2014).

Global HAT activity has been found to be increased in the cortex (Spindler et al., 2014) and hippocampus (Elsner et al., 2011) of rodents subjected to treadmill exercise. Moreover, in a recent study, Zhong et al (2016) observed that exercise-induced memory improvements was associated with enhanced expression of cAMP response element-binding protein (CREB)-binding protein (CBP) in the hippocampus. Acting more than just a molecular scaffold for recruiting components of the transcription machinery, CBP serves this capacity by inducing chromatin remodeling via its HAT activity, which is likely necessary for activity-dependent gene expression in LTP and long-term memory formation (Day and Sweatt, 2011, Barrett and Wood, 2008).Mechanistically, the recruitment of CBP triggers histone acetylation and the formation of a transcriptional complex at the promoters of many CREB-target genes to activate transcription. Mutations in the CBP gene are responsible for the mental retardation syndrome Rubinstein–Taybi (Petrij et al., 1995) and CBP mutant mice exhibit profound deficits in synaptic plasticity and LTM (Alarcón et al., 2004, Korzus et al., 2004, Vecsey et al., 2007). Altogether, the aforementioned findings raise the idea that physical exercise promotes synaptic plasticity and memory improvements by altering the balance of HAT/HDAC enzymatic activity to favor a permissive state of chromatin, leading to the transcriptional activation of a myriad of genes with preponderant roles in cognition.

The phosphorylation and methylation of histones are also tightly associated with regulation of learning and memory. It has been demonstrated that CFM increases histone H3 phosphorylation at residue serine (S) 10 (H3S10) in the hippocampus (Chwang et al., 2006). Importantly, inhibition of histone dephosphorylation, using a transgenic mouse model in which *PP1* was selectively inhibited, increased H3S10 levels and enhanced LTP and LTM in the hippocampus and amygdala (Koshibu et al., 2009, Koshibu et al., 2011). It seems that PP1 promotes chromatin condensation by dephosphorylating histone proteins and by negatively regulating the histone acetylation and methylation through association with HDACs and HDMs (Koshibu et al., 2009). Histone phosphorylation can be one of the ways by which physical exercise can enhance neurocognitive functions, i.e., increasing histone H3 phosphoacetylation (Collins et al., 2009) and reducing PP1 expression (Chen et al., 2007) in the hippocampus.

As discussed earlier, histones can be mono-, di-, or trimethylated, and depending on the residue of modification, they can repress or activate transcription. While dimethylation or trimethylation of H3K4 are associated with a transcriptionally permissive chromatin state, dimethylation at H3K9 is associated with transcriptional repression (Kouzarides, 2007). The global levels of H3K4 trimethylation and H3K9 dimethylation are transiently increased in hippocampal CA1 area 1 h after the acquisition of CFM (Gupta et al., 2010, Gupta-Agarwal et al., 2012). Indeed, mutant mice deficient in the H3K4-specific histone methyltransferase, Mll (Mixed-lineage leukemia), have shown an impairment in the consolidation of CFM (Gupta et al., 2010). Surprisingly, hippocampal inhibition of G9a/G9a-like protein (GLP) lysine complex, which control H3K9 dimethylation, has been shown to disrupt LTP at the Schaffer collateral-CA1 synapses and LTM (Gupta-Agarwal et al., 2012). These data, in conjunction with gene expression and chromatin immunoprecipitation analysis suggest that

the consolidation of LTM are modulated, at least partially, by dynamic regulation of histone methylation in regulatory regions of genes with opposite roles in memory formation. While H3K4me3 induces the expression of memory-related genes, H3K9me2 suppresses the expression of memory-repressive genes (Gupta et al., 2010, Gupta-Agarwal et al., 2012). Interestingly, recent studies have demonstrated that physical exercise counteracts the aging-induced decreases in the global methylation of H3K9 in the hippocampus (Elsner et al., 2013) and reverts the stress-induced downregulation of G9a and H3K9me2 in the amygdala (Kim et al., 2016). These results suggest the capability of exercise to work at various stages of epigenetic regulation to alter brain plasticity and cognition.

2.3. The epigenetic regulatory role of miRNAs

MicroRNAs (miRNAs) are small (17 to 25 nucleotides) single stranded RNA that belong to the class of non-coding RNAs. miRNAs act as powerful silencers of gene expression by inducing translational repression and/or degradation of target transcript through partial base-pairing to its 3' untranslated region (3'-UTR) (Ambros, 2004, Bartel, 2004). Beyond the 3′ UTRs, evidence indicates that miRNAs can also bind to other sites such as 5′ UTRs and coding regions (Tay et al., 2008, Lytle et al., 2007, Eiring et al., 2010). The miRNA genes can be located in introns or exons of protein coding genes, or intergenic regions (Rodriguez et al., 2004). The number of known miRNAs has increased markedly in recent years, and it is estimated that there are more than 2500 different miRNAs in human cells. Interestingly, each miRNA has the ability to interact with a large number of mRNA (approximately 200–500 mRNA for each miRNA), suggesting that the majority of the protein-coding genes may be regulated by miRNAs (Friedman et al., 2009). Therefore, it is not surprising that miRNAs are widely expressed in the brain, and that they can participate in epigenetic mechanisms.

This group of non-coding RNAs arises from long primary microRNA (pri-miRNAs) precursors that can be transcribed by RNA polymerase II or III. Inside the nucleus, the pri-miRNA is processed by a complex consisting of the ribonuclease (RNase) III Drosha and its cofactor DGCR8 (DiGeorge syndrome critical region 8) to give rise to the precursor miRNA (pre-miRNA). Pre-miRNA has approximately 70 nucleotides (Lee et al., 2003, Han et al., 2004), and is subsequently transported to the cytoplasm by exportin-5, in a guanosine triphosphate (GTP)-dependent manner. Pre-miRNA is further cleaved by the RNase enzyme Dicer into a double-stranded molecule representative of the mature miRNA, named guide strand or 5p, and its complementary sequence miRNA*, referred as passenger strand or 3p (Chendrimada et al., 2005, Bartel, 2004). Thereafter, the miRNA:miRNA* duplex are separated by helicases, and the mature strand is incorporated into the RNA-induced silencing complex (RISC) whereas the miRNA* strand is usually degraded. Once bound to the RISC, the mature miRNA guide this complex to the target mRNA to inhibit its translation or degrade it (Ambros, 2004, Bartel, 2004) (Figure 2).

2.3.1. Exercise, miRNAs and memory—Over the past decade, miRNAs have emerged as potential regulators of numerous biological processes within the brain, ranging from cell proliferation, differentiation, apoptosis, synaptic plasticity and memory formation (Saab and Mansuy, 2014). Brain miRNAs are susceptible to regulation by neuronal activity acting at the synapto-dendritic compartment resulting in control mRNA translation of several synaptic

transcripts (Kye et al., 2007, McNeill and Van Vactor, 2012, Schratt, 2009). A large number of miRNAs have been identified in brain regions responsible for specific forms of memory such as hippocampus, amygdala and cortex (Schratt et al., 2006, Griggs et al., 2013, Gao et al., 2010, Konopka et al., 2010, Kye et al., 2011, Lin et al., 2011). Some miRNAs regulate memory by targeting CREB-BDNF signaling, a well know pathway activated by exercise. MicroRNA-132 (miR-132) is a CREB-regulated miRNA that is induced by neuronal activity and BDNF, and exerts a critical role in regulation of neuronal structure and excitability (Cheng et al., 2007, Wayman et al., 2008). The action of miR-132 on learning and memory is very dependent on its levels, such that very low (Wang et al., 2013) or high (Hansen et al., 2010, Scott et al., 2012) levels of miR-132 may be detrimental for memory while moderate levels can improve it (Hansen et al., 2013).In turn, the miR-134 has been shown to reduce hippocampal CREB levels and impairs LTM and LTP in CA1 hippocampal area (Gao et al., 2010).

Microarray analysis revealed that 32 miRNAs are differently expressed in the hippocampus of healthy mice subjected to physical exercise, from which 20 of them were upregulated and 12 were downregulated (Bao et al., 2014). In addition, it has been shown that exercise can mitigate the detrimental effects of traumatic brain injury and aging on cognitive function by regulating the hippocampal expression of miR-21 (Hu et al., 2015) and miR-34a (Kou et al., 2017). Physical exercise has also been shown to alter the expression of seven miRNAs (upregulated: miR-28a-5p, miR-98a-5p, miR-148b-3p, miR-7a-5p and miR-15b-5p; downregulated: miR-105, and miR-133b-3p) in the hippocampus of senescence-accelerated SAMP8 mice (Cosín-Tomás et al., 2014). Finally, physical exercise has been shown to attenuate the effects of stress-related increase in miR-124 - a miRNA known for its role in neurogenesis and memory formation (Pan-Vazquez et al., 2015).

3. Exercise and circulating miRNAs (c-miRNAs): The link between periphery and the brain

During the course of evolution, the eukaryotes have developed an elegant cell-to-cell communication system to allow efficient coordination among different cell types and tissues. Eukaryotic cells can communicate directly with each other through cell-cell contact or at distance by secreting soluble factors such as hormones, growth factors, cytokines and chemokines. In 2007, Valadi and collaborators extended this concept by showing that both RNA and miRNAs can be functionally transferred from a donor to a recipient cell via membrane-derived vesicles called exosomes. Interestingly, similarly to hormones, miRNAs are released into the circulation (Mitchell et al., 2008, Chim et al., 2008) to affect cells throughout the organism (Figure 2). The c-miRNAs are transported by exosomes (Valadi et al., 2007), high-/low-density lipoproteins (Vickers et al., 2011), apoptotic bodies (Zernecke et al., 2009), and RNA-binding proteins (Arroyo et al., 2011, Turchinovich and Burwinkel, 2012); these molecules confer c-miRNAs with stability and protection against plasma RNases. Once inside the recipient cells, the miRNAs use cellular machinery to reduce the expression of target mRNAs and to alter the cellular phenotype of the host (Cortez et al., 2011).

A growing body of evidence in human and animal has shown that exercise alters blood levels of several miRNAs (Gomes et al., 2015, Xu et al., 2015, Flowers et al., 2015), and indicates that exercise can use these epigenetic modulators to regulate communication between the brain and peripheral organs. It has been described that a single bout of acute intermittent exercise rapidly elevates circulating levels of miR-132 (Radom-Aizik et al., 2012) in young healthy men. As discussed above, miR-132 is linked to multiple functions in the brain, including neuronal development (Tognini and Pizzorusso, 2012), synaptic plasticity (Wayman et al., 2008, Impey et al., 2010) and memory formation (Wang et al., 2013, Hansen et al., 2013, Scott et al., 2012). It has been shown that miR-132 alters dendritic morphogenesis by activating the Rac1-PAK pathway (Impey et al., 2010, Wayman et al., 2008) and by regulating MeCP2 expression (Klein et al., 2007, Hansen et al., 2010). More recently, it has been shown that conditional knockout of miR-132/212 gene cluster impairs memory and promotes gross alterations in hippocampal transcriptional profile in mice (Hansen et al., 2016).

A bout of exercise reduces miR-146a levels and increases miR-223 levels in the circulation in young healthy men (Nielsen et al., 2014). The miR-146a is a NF-κB-sensitive miRNA whose enhanced expression has been associated with the proinflammatory state in neurodegenerative disorders, including Alzheimer's disease, age-related macular degeneration, and prion disease (Su et al., 2016). This miRNA is a putative biomarker for Alzheimer's disease and targets key inflammatory mediators such as the complement factor H (CFH), the membrane spanning beta-amyloid precursor protein (bAPP)-associated TSPAN12, and interleukin receptor-associated kinase IRAK-1 (Cui et al., 2010). It has been shown that miR-223 regulates neuronal differentiation (Jovičić et al., 2013), and can protect the brain from transient global ischemia and excitotoxic injury by targeting GluR2 and NR2B subunits of the glutamate receptor (Harraz et al., 2012). In turn, the lack of miR-223 leads to hippocampal-dependent memory deficits and neuronal cell death (Harraz et al., 2012).

Long-term physical exercise can also affect basal levels of c-miRNAs. Nielsen et al. (2014) performed global miRNA screening in young healthy men before and after 12 weeks of endurance exercise and found decreased plasma levels of miR-21, in apparent discrepancy to increased c-miR-21 levels in competitive athletes after 90 days of endurance training (Baggish et al., 2011). Given the heterogeneity of subjects involved in these studies (athletes vs non-athletes) and differences in the exercise protocols employed, it is likely that miRNAs, like hormones and others molecules, are differentially modulated by the type and intensity of physical exercise. Several studies have shown that miR-21 is one of the most commonly and dramatically up-regulated miRNA after TBI (Redell et al., 2011, Lei et al., 2009, Ge et al., 2014). This miRNA has been implicated in the control of cellular survival and apoptosis by targeting genes encoding the phosphatase and tensin homolog (PTEN), programmed cell death 4 (PDCD4), reversion-inducing-cysteine-rich protein with kazal motifs (RECK), and tissue inhibitor of metalloproteinases-3 (TIMP3) (Sayed et al., 2010, Chen et al., 2008, Gabriely et al., 2008). It has been shown that miR-21 inhibits apoptosis and improves the neurological outcome in TBI animal models by post-transcriptionally repressing PTEN expression, and by activating Akt (a downstream mediator of survival pathway) signaling in

the brain (Ge et al., 2014). The overall information indicates that c-miRNAs are important conveyors of the salutary action of exercise across several tissues.

4. Can the beneficial effects of physical exercise be transmitted across generations?

The transmission of epigenetic alterations in response to environment that control gene expression and phenotypes across generations is becoming a realistic possibility (Szyf, 2015, Heard and Martienssen, 2014). Of note, it is important to differentiate parental (or intergenerational) effects, which occurs due to the exposure of embryo (F1) and its germline (F2) to an environmental factor, from truly transgenerational effects which are observed in generations not directly exposed to the environmental stimuli. Thus, transgenerational epigenetic evidence requires transmission of the epigenetic traits for at least three generations for maternal exposure and two generations for paternal exposure (Szyf, 2015, Heard and Martienssen, 2014).

Epigenetic inheritance can be triggered in response to a wide range of stimuli, including stress, infection, drugs, diet and exercise (Franklin and Mansuy, 2010, Barrès and Zierath, 2016). For example, prenatal administration of the viral mimetic poly(I:C), an experimental model for neurodevelopmental disorders, has been shown to induce significant behavioral abnormalities. Behavioral changes are accompanied by global hypoacetylation of H3K9K14 and H4K8, increased DNA methylation and MeCP2 binding in the gene promoters of glutamate decarboxylase (*Gad*) 1 and *Gad2* in the cortex of mice offspring (Tang et al., 2013). In addition, depressive-like behavior induced by chronic and unpredictable maternal separation in F1 mice can be passed on to the F2 and F3 generations. The increased DNA methylation observed in the MeCP2 promoter of F1 sperm cells can be also found in F2 sperm and brain, suggesting that the changes in DNA methylation triggered by maternal separation survived epigenetic reprogramming during embryogenesis (Franklin et al., 2010).

Although not well explored in the CNS, current studies have provided some insights regarding the epigenetic inheritance induced by physical exercise. Denham et al. (2015) reported that 3 months of physical exercise altered global and genome wide sperm DNA methylation in young healthy men. Importantly, the authors observed that exercise increased DNA methylation at promoters of several genes associated with brain pathologies such as schizophrenia and Parkinson disease (Denham et al., 2015). Recently, it has been reported that physical exercise alters the expression of miRNAs in paternal sperm, whereas suppresses the reinstatement of fear memory and reduces anxiety in male mice offspring (Short et al., 2017).

In obese male mice, 8 wk of physical exercise restored insulin sensitivity and normalized the expression profile of X-linked sperm miRNAs that target genes playing important roles in pathways related to early embryogenesis, cell cycle and apoptosis (McPherson et al., 2015). Interestingly, paternal exercise has also been shown to restore insulin sensitivity, to reduce adiposity and to improve metabolic health in F1 female offspring. In another study, maternal exercise prevented the prenatal high-fat diet induced hypermethylation of peroxisome proliferator-activated receptor γ co-activator-1 α (PGC-1α; a transcriptional co-activator

critical for mitochondrial biogenesis and oxidative metabolism) in the skeletal muscle of neonatal and 12-month-old offspring (Laker et al., 2014). Altogether, these findings provide compelling evidence suggesting that environmental stimuli can promote epigenetic modifications in germline and somatic cells to allow the transfer of parental experiences to the following generations.

Although there is a lack of experimental evidence for the existence of epigenetic alterations in the offspring brain of exercised parents, indirect studies indicate this possibility. Clinical evidence indicates that maternal exercise during pregnancy promotes a healthy intrauterine milieu for the fetus and enhances cognitive function in childhood (Clapp, 1996, Wolfe et al., 1994, Weissgerber et al., 2006). Clapp (1996) assessed the neurodevelopmental characteristics of offspring (5 years old) from mothers who exercised regularly throughout pregnancy, and found that their children had better performance on tests of general intelligence and oral language skills. Moreover, it has been shown that male offspring from physically active mothers had higher scores in academic performance (i.e. math and language) than boys from sedentary mothers (Esteban-Cornejo et al., 2016).

Rodent studies show that prenatal exercise enhances several features in the offspring's brain such as memory (Lee et al., 2006, Akhavan et al., 2008, Robinson and Bucci, 2014), antioxidant defenses (Marcelino et al., 2013), hippocampal neurogenesis (Bick-Sander et al., 2006, Lee et al., 2006), expression of neurotrophic factors (Aksu et al., 2012, Gomes da Silva et al., 2016), while prenatal exercise reduces anxiety (Aksu et al., 2012). In a recent study, we showed that maternal exercise during pregnancy enhances cognitive function (habituation behavior and spatial learning) and increases BDNF levels and cells numbers (neuronal and non-neuronal) in the hippocampus of rat offspring (Gomes da Silva et al., 2016). Furthermore, prenatal exercise was able to attenuate the progression of Alzheimer's disease-like pathology in the TgCRND8 mice (Herring et al., 2012). In this study, pups born from mothers that ran during their pregnancy time exhibited a reduction in β-amyloid (Aβ) plaque burden and amyloid precursor protein (APP), decreased expression of proinflammatory mediators, and an increased expression of genes involved in synaptic plasticity and memory formation. In addition to the positive effects of maternal exercise on the progeny, pups from physically active fathers are also privileged in terms of cognitive function (Yin et al., 2013). As demonstrated by Yin et al. (2013), 6 wk of paternal exercise enhanced the spatial learning and memory of F1 mice offspring, with a concomitant increase in hippocampal BDNF and reelin expression. Yet, it has been recently shown that paternal exercise transgenerationally alters the affective behavior and the endocrinological response to stress (Yeshurun et al., 2017). Therefore, it is reasonable to assume that physical exercise may use epigenetic mechanisms to affect future generations.

5. Exercise influences cognition engaging epigenetic mechanisms: Central action of *Bdnf* Transcription

It is getting recognition that exercise and BDNF can reduce depression and improve cognitive function, and that epigenetic regulation of the *Bdnf* gene is a biological mechanism by which exercise promote mental health and build resistance to neurological

disorders (Gomez-Pinilla et al., 2011, Intlekofer et al., 2013, Sleiman et al., 2016). For example, BDNF is essential for hippocampal-dependent spatial learning (Linnarsson et al., 1997, Mizuno et al., 2000) such that elevations in hippocampal BDNF improve learning in animals (Nagahara et al., 2009, Moguel-González et al., 2008). In addition, peripheral levels of BDNF have been associated with cognitive function and hippocampal size in human subjects (Erickson et al., 2011). Data from rodent studies suggest that proteins up-regulated by exercise in the hippocampus are associated with energy metabolism and neurocognitive plasticity, in a process in which BDNF has a preponderant role (Ding et al., 2006b, Ding et al., 2006a, Vaynman et al., 2004, Gomez-Pinilla et al., 2008).

The *Bdnf* gene consists of nine 5' non-coding exons and one 3' coding exon (Aid et al., 2007). In each of these promotor regions, the methylation status of CpG islands and post-translational modifications of histones (i.e.acetylation, phosphorylation, methylation) are thought to regulate *Bdnf* transcription in an activity dependent manner (Martinowich et al., 2003, Lubin et al., 2008, Guo et al., 2011b). We and others have shown that exercise impacts *Bdnf* expression by engaging epigenetic modifications such as acetylation and methylation (Gomez-Pinilla et al., 2011, Intlekofer et al., 2013, Sleiman et al., 2016), and these mechanisms are likely associated with synaptic plasticity, and learning and memory. Exercise enhances BDNF expression and facilitates LTP through activation of N-methyl-D-aspartate receptors (NMDA-Rs) (Vaynman et al., 2003, Farmer et al., 2004). Upon activation, NMDA-Rs allow the influx of Ca2+ in the postsynaptic neuron to initiates a cascade of molecular events leading to the activation of Ca2+/Calmodulin-dependent kinase (CaMK) and mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) signaling pathways, which in turn phosphorylates the nuclear transcription factor CREB at serine 133 (S133) (Nguyen and Woo, 2003, Xia and Storm, 2012). Exercise increases the active form of CaMKII, ERK1/2 and CREB (pCaMKII, pERK1/2 and pCREB) in the hippocampus (Gomez-Pinilla et al., 2011, Muller et al., 2008), which are part of the intracellular signaling cascades through which exercise induces BDNF-mediated synaptic plasticity and cognition (Vaynman et al., 2004, Vaynman et al., 2003) (Figure 3). Blocking the function of CaMKII and MAPK in the hippocampus reduces *CREB* and *Bdnf* mRNAs and abrogates the cognitive enhancement induced by exercise (Vaynman et al., 2003, Vaynman et al., 2007).

The efficacy of CREB to regulate gene transcription, including *Bdnf*, is dependent on the activation of various transcriptional coactivators such as CBP (Vecsey et al., 2007), and various HATs (McManus and Hendzel, 2001, Perissi et al., 1999). The phosphorylation of CREB at serine-133 is a requisite to recruit CBP and to initiate subsequent transcription (Chrivia et al., 1993). It has been demonstrated that CBP acetylates lysines on histones H2B, H3, and H4, in vivo, and that although neurons lacking CBP maintain pCREB levels, fail to activate CREB/CBP-mediated gene expression. Moreover, the CBP homolog p300 is unable to compensate for the loss of CBP activity, indicating some level of specificity for CBP in hippocampal neurocognitive processes (Barrett et al., 2011). Interestingly, recent studies have shown that physical exercise increases CBP expression in the hippocampus and promotes acetylation of histones H4K8 and H3 at different *Bdnf* promoters (Gomez-Pinilla et al., 2011, Intlekofer et al., 2013, Ieraci et al., 2015). While acetylation of H4K8ac is

enriched at *Bdnf* exon I and IV (Intlekofer et al., 2013), H3 acetylation is increased at exons I, II, III, IV, VI and VII (Ieraci et al., 2015).

The acetylation of histones associated with DNA can promote a permissive/active chromatin form necessary for the transcription of select genes such as *Bdnf*. Experience-dependent plasticity promotes acetylation of lysine amino acid residues in histones H3 and H4 in unbound, transcriptionally active chromatin (Barrett and Wood, 2008, Day and Sweatt, 2011). Neuronal activity has been shown to regulate *Bdnf* transcription involving epigenetic mechanisms important for regulation of synaptic plasticity, and learning and memory (Martinowich et al., 2003, Lubin et al., 2008, Levenson et al., 2006, Feng et al., 2007). Acquisition of CFM increases acetylation of histones H3 and H4 at *Bdnf* promoter IV (Lubin et al., 2008), while inhibition of HDACs has been shown to increase *Bdnf* mRNA levels in hippocampal neurons (Tian et al., 2010), LTP and LTM formation (Levenson et al., 2004). In the prefrontal cortex, the extinction of conditioned fear memory involves the acetylation of histone H4 on the *Bdnf* promotor region (Bredy et al., 2007). Moreover, high-frequency stimulation in the medial prefrontal cortex increases acetylation of H3 and H4 in the *Bdnf* gene, and local administration of an HDAC inhibitor increases LTP and LTM (Sui et al., 2012).

Beyond the acetylation, histone proteins are subjected to other post-translational modifications that impact chromatin structure, and their interplay provide an additional level of functional regulation (Latham and Dent, 2007). For example, phosphorylation of histone H3S10 is coupled to acetylation of H3K14 in the hippocampus (Crosio et al., 2003). During the acquisition of CFM, the activation of NMDA-R stimulates the MAPK/ERK pathway that, via kinase 1 (MSK1) contributes to histone H3 acetylation and phosphorylation (Levenson et al., 2004, Chwang et al., 2006, Chwang et al., 2007). Lubin et al. (2008) reported that learning-induced *Bdnf* transcription increases H3 phosphoacetylation at promoter IV. Recently, it has been shown that NMDA increases transcriptional activation of *Bdnf* through demethylation of H3K27Me3 (via JMJD3) and phosphorylation of H3K27me3 at Serine 28 (via MAPK/MSK1/2 pathway). These modifications lead to dissociation of the enzyme enhancer of zeste homologue 2 (EZH2), the catalytic subunit of polycomb repressor complex 2, allowing transcription of *Bdnf* (Palomer et al., 2016). Additionally, NMDA stimulation increases H3K4me3 (activation marker) levels and triggers H3K27 acetylation by recruiting the CREB/CBP complex to *Bdnf* promoters.

As previously discussed, physical exercise influences synaptic plasticity and memory consolidation involving alterations of histones related to transcription of the *Bdnf* gene. In aged rats, the effects of the environment on memory have been associated with increased levels of hippocampal H3K4me3 at *Bdnf* promoter IV (Morse et al., 2015), HAT activity, *Pcaf* (*P300/CBP-associated factor*) expression, and histone H3 acetylation in the *Bdnf* promoter I (Neidl et al., 2016). Sleiman et al. (2016) observed reduced levels of HDAC2 in the hippocampus of mice subjected to voluntary exercise, which was accompanied by decreased binding of HDAC2 to *Bdnf* promoter I and increased *Bdnf* expression. Interestingly, BDNF induces nitrosylation of HDAC2 at cysteines 262 and 274 leading to the displacement of this HDAC from chromatin, which results in increased level of histone acetylation in BDNF target genes, including *Bdnf* itself (Nott et al., 2008). Therefore, it can

be proposed that exercise and experience-driven memory formation engage a positive feedback loop triggered by histone modifications at *Bdnf* promoters. This, in turn, would induce *Bdnf* expression that could self-sustain a transcriptional program underlying synaptic plasticity and LTM formation.

5.1. MeCP2 and SIRT1 act as transcriptional regulators of *Bdnf*

MeCP2 belongs to the family of methylcytosine-binding proteins that are abundantly expressed in the central nervous system and are notably recognized for their contribution to the gene silencing effect of DNA methylation (Lewis et al., 1992, Nan et al., 1998, Fuks et al., 2003). MeCP2 phosphorylation seems to be requisite for activity-dependent gene expression, dendritic patterning, spine morphogenesis, LTP and LTM (Zhou et al., 2006, Li et al., 2011). In the absence of stimulation, MeCP2 binds to methylated CpG on the *Bdnf* promoter IV (referred to at the time as promoter III) to silence its expression through the recruitment of a transcriptional repressor complex containing mSin3A and HDACs (Martinowich et al., 2003). The calcium influx triggered by neuronal depolarization induces phosphorylation of MeCP2 at serine 421 and, consequently, its dissociation from the *Bdnf* promoter IV (Chen et al., 2003, Zhou et al., 2006). This effect is mediated by a CaMKII-dependent mechanism and occurs in parallel with demethylation of promoter IV to allow *Bdnf* transcription.

Gomez-Pinilla et al. (2011) reported that the exercise-induced *Bdnf* expression was linked to reductions in promoter IV methylation and an enhancement in the levels of phospho-CaMKII and phospho-MeCP2 in the hippocampus. Importantly, blockade of CaMKII signaling in this region attenuated the increases in *Bdnf* expression and the cognitive improvement elicited by exercise (Vaynman et al., 2003, Vaynman et al., 2007). Furthermore, studies conducted in *Mecp2* mutant mice, a mouse model of Rett syndrome, have shown that environmental enrichment restores BDNF levels (Kondo et al., 2008, Lonetti et al., 2010, Kondo et al., 2016), attenuates LTP deficits (Lonetti et al., 2010) and ameliorates several behavioral abnormalities including memory deficits, affective dysfunction, anxiety, and impairments in motor function (Lonetti et al., 2010, Kondo et al., 2008, Kondo et al., 2016, Nag et al., 2009).

It has been recently reported that *Bdnf* transcription can be regulated by sirtuin 1 (SIRT1)-dependent deacetylation of MeCP2 (Zocchi and Sassone-Corsi, 2012). SIRT1 is a highly conserved nicotinamide-adenine dinucleotide (NAD+)-dependent Class III HDAC (Thiagalingam et al., 2003) that, beyond its role on processes related to ageing, stress tolerance, and energy metabolism (Schwer and Verdin, 2008, Haigis and Sinclair, 2010), has emerged as a key regulator of synaptic plasticity and memory formation (Gao et al., 2010). SIRT1-dependent deacetylation of MeCP2 precedes its detachment from *Bdnf* promoter IV in neuronal culture and $SIRT1^{dex4}$ mutant mice exhibit increased binding of MeCP2 to the *Bdnf* promoter IV and reduced *Bdnf* expression (Zocchi and Sassone-Corsi, 2012). In accordance with the positive effects of exercise on *Bdnf* expression and memory formation, evidence shows that physical exercise alters SIRT1 dynamics in the brain. It was demonstrated that exercise increases SIRT1 activity in the hippocampus (Marton et al., 2016), and elevates its expression in various brain regions including cortex, hippocampus

and hypothalamus (Steiner et al., 2011). Furthermore, in a recent study of the effects of physical exercise on the pathophysiology of Alzheimer's disease, the downregulation of SIRT1 in the cerebral cortex of 3xTgAD mice was attenuated by exercise treatment (Revilla et al., 2014).

The mechanisms connecting SIRT1 activity to BDNF were first explored through SIRT1 loss-of-function experiments, using SIRT1Δ mutant mice lacking SIRT1 catalytic activity. SIRT1 loss-of-function results in higher levels of miR-134, the brain specific miRNA that acts as a translational block of CREB. Concomitantly, BDNF (mRNA and protein) and CREB (protein) are down regulated in the hippocampus, and LTP and memory formation are impaired (Gao et al., 2010). Notably, SIRT1 loss-of-function also abolishes the learning-related increases in *Bdnf* promoter (I and IV) binding by CREB (Gao et al., 2010). Mechanistically, SIRT1 normally functions in cooperation with Ying Yang 1 (YY1), a ubiquitous and highly conserved transcription factor that can act as a transcriptional repressor or activator (Shi et al., 1997). SIRT1 is recruited as a co-repressor by YY1 to inhibit the expression of the miR-134 gene, which in turn decreases the probability that miR-134 will act as a translational block of CREB and consequently facilitates *Bdnf* transcription via *Bdnf* promoter binding by phospho-CREB (Gao et al., 2010). The coordination of SIRT1/YY1 in transcriptional repression with complementary activity-dependent mechanisms may regulate *Bdnf* transcription in the hippocampus during exercise.

6. Concluding remarks

Exercise has played a crucial action on shaping the modern brain through thousands of years of evolution. Nowadays, the adaptive force of exercise is vitally instrumental for controlling susceptibility to a wide range of neurological and metabolic disorders with the potential to be inheritable. Accumulating scientific evidence in the last few years portray the capacity of exercise to promote profound alterations in the program of genes and their protein products in the form of epigenomic manifestations. The remarkable capacity of epigenetic mechanisms to regulate synaptic and cognitive plasticity has a fundamental value for the control of neurological and psychological disturbances. As more studies continue to reveal the details by which exercise influences a varied assortment of gene regulatory mechanisms, it is becoming clear that gene reprogramming is instrumental for transducing the effects of exercise on brain structure and function. Recent developments in the epigenetic field are leading to a paradigm shift in basic and clinical neuroscience to account for how environmental factors can impact long-term brain function with profound implications for public health of current and future generations.

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Highlights

- Exercise regulates DNA methylation and histone acetylation in the hippocampus
- Exercise enhances *bdnf* expression by engaging epigenetic mechanisms.
- Exercise modulates the expression of memory-related miRNAs.
- The beneficial effects of exercise are epigenetically inherited.

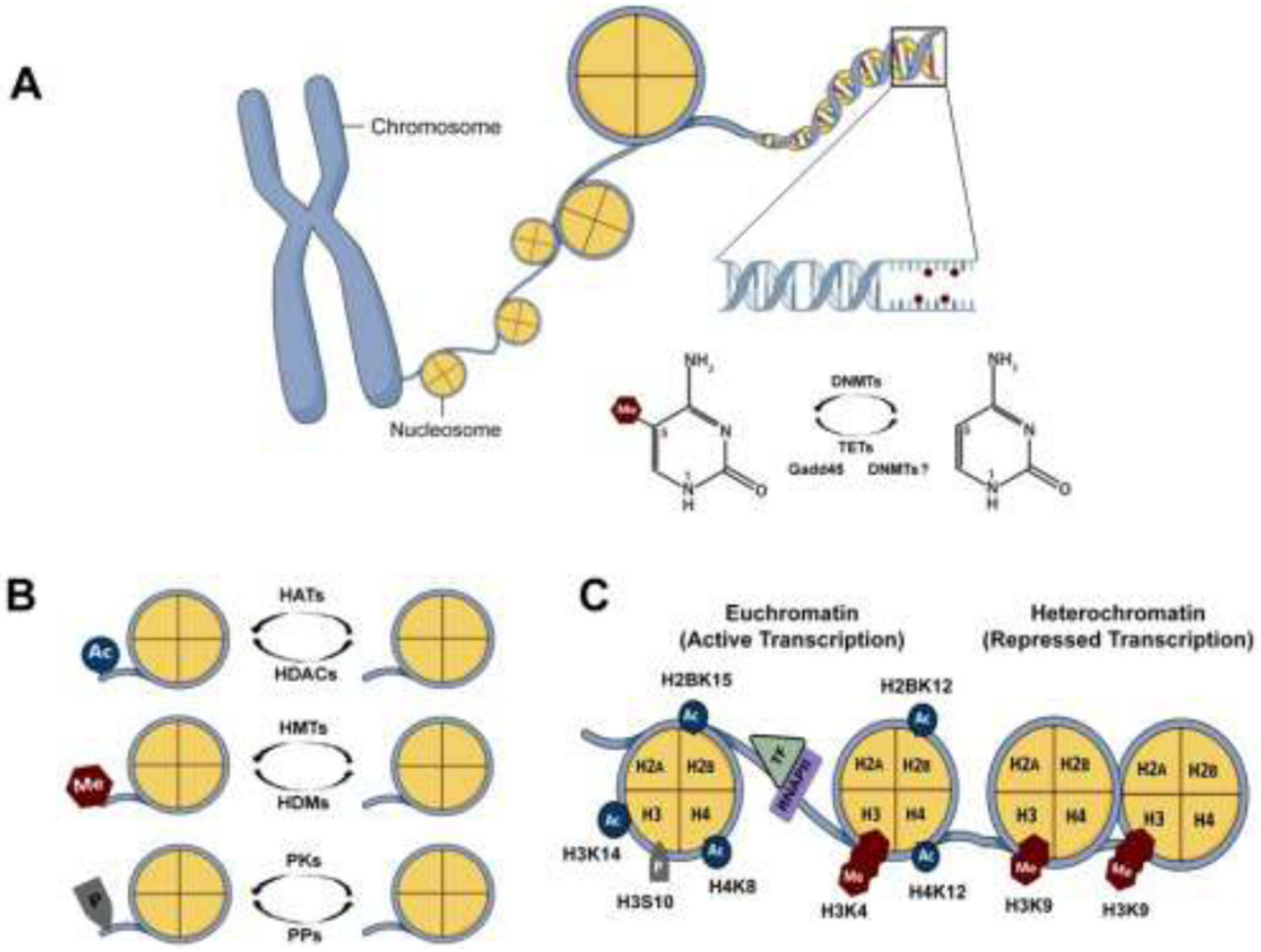

Figure 1.

Dynamic regulation of DNA methylation and histone modifications. (A) Nucleosome, the basic repeat element of chromatin, consists of 147bp of DNA wrapped around an octamer of four core histone proteins (H2A, H2B, H3 and H4) compacted by a linker histone. DNA methylation is related to repressed transcription and involves the covalent addition of a methyl group to the 5-carbon of cytosine bases [5-methylcytosine (5mC)] located in CpG dinucleotides by DNMTs. Conversely, active DNA demethylation can occur through mechanisms involving enzymes from Gadd45, TET and even DNMT families. (B) Chromatin-modifying enzymes regulate the addition and removal of histone modifications to establish an open or a silent transcriptional state. While HATs catalyze the addition of acetyl group, HDACs catalyze its removal. The histone tail is methylated by HMTs and demethylated by HDMs. PKs and PPs are responsible for the addition and removal of phosphate groups. (C) Chromatin can be found at an open (euchromatin) or a closed (heterochromatin) state according to the pattern of histone modifications. In general, euchromatin is characterized by hyperacetylated, hyperphosphorylated and specific histone methylation patterns related to active transcription whereas heterochromatin is featured by opposite post-translational modifications. Ac, acetyl group; CpG, cytosine-phosphate-guanine dinucleotides; DNMTs, DNA methyltransferases; Gadd45, growth arrest and DNA

damage 45 proteins; HATs, histone acetyltransferases; HDACs, histone deacetylases; HDMs, histone demethylases; HMTs, histone methyltransferases; Me, methyl group; P, phosphate group; PKs, protein kinases; PPs, protein phosphatases; RNAPII, RNA polymerase II; TET, ten-eleven translocation proteins; TF, transcription factor.

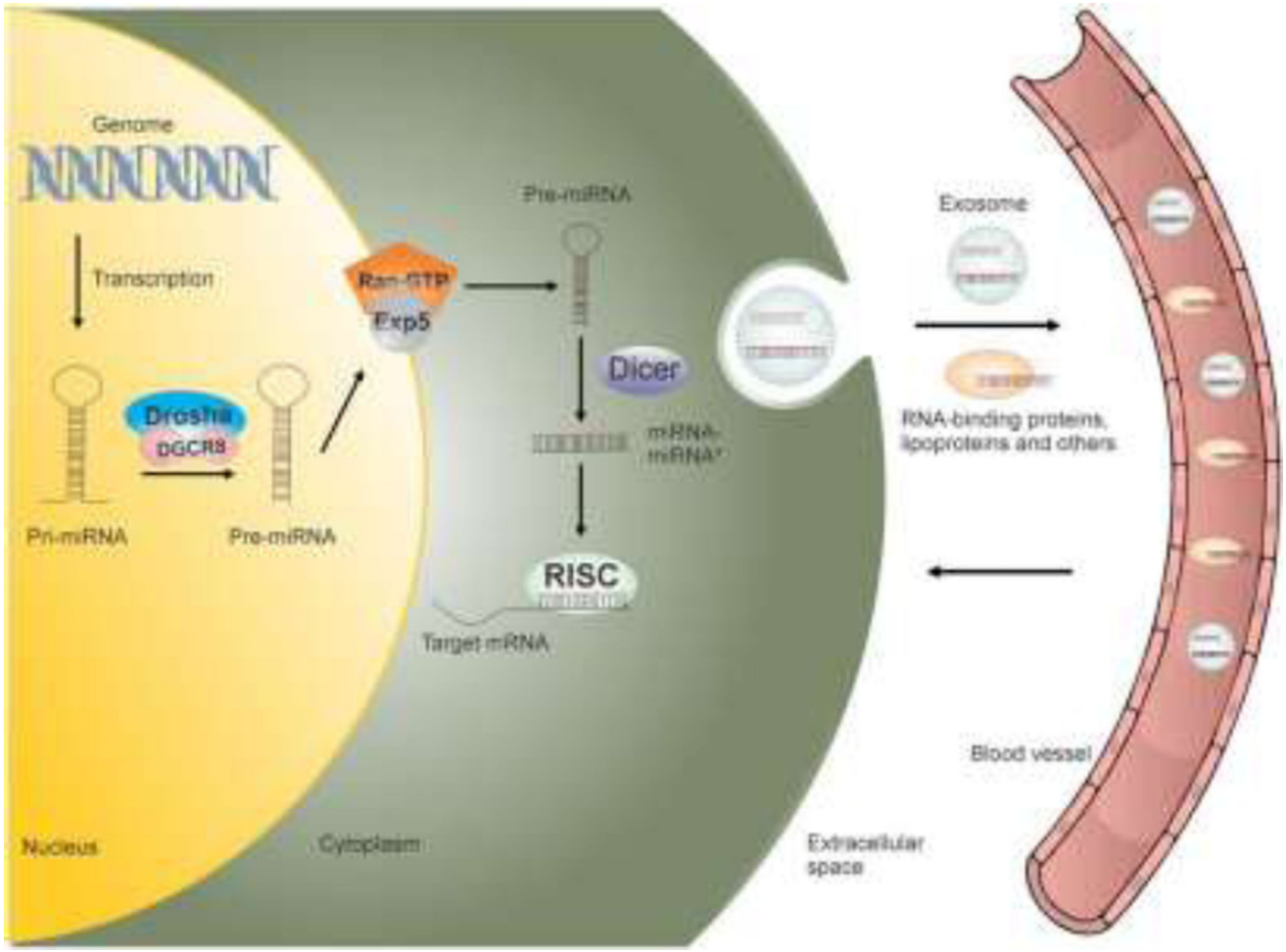

Figure 2.

miRNA biogenesis. miRNAs are initially transcribed into primary miRNA (pri-miRNA) that undergo processing by a microprocessor complex composed of Drosha and DiGeorge syndrome critical region 8 (DGCR8). The resulting precursor miRNAs (pre-miRNAs) are transported from the nucleus to the cytoplasm by exportin 5 (Exp5), in a guanosine triphosphate (GTP)-dependent manner, and further processed into its mature form by Dicer. The mature miRNA is then loaded into the RNA-induced silencing complex (RISC) to degrade or inhibit the translation of target mRNA. The miRNAs can be released in the blood inside exosomes or in association with RNA-binding proteins and lipoproteins to spread signals to cells located in the vicinity or in other parts of the organism.

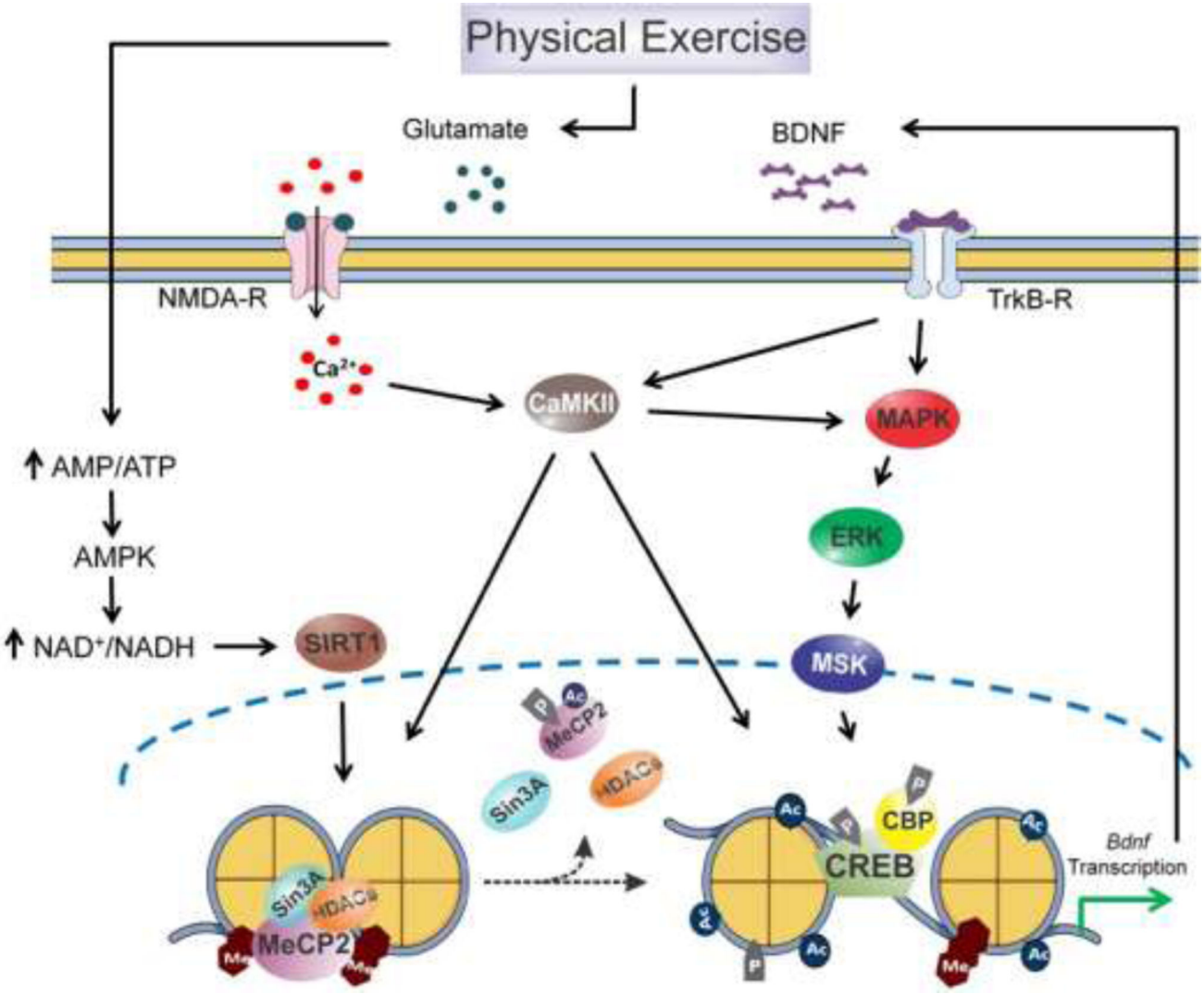

Figure 3.

Potential epigenetic mechanism through which exercise-induced *Bdnf* expression may enhance synaptic plasticity and cognition. Exercise-induced glutamate release stimulates NMDA-R and, consequently, the influx of Ca2+ in the postsynaptic neurons. Increases in Ca2+ levels trigger a wave of molecular events leading to the activation of CaMKII and MAPK/ERK/MSK signaling. CaMKII phosphorylates MeCP2 inducing its dissociation, along with other co-repressors (Sin3A and HDACs), from the promoter region of *Bdnf* gene. The effects of exercise on MeCP2 dissociation from *Bdnf* promoter may also involve the SIRT1-dependent deacetylation of MeCP2, given that the metabolic changes underlying SIRT1 activity and expression are directly modulated by exercise. Besides the phosphorylation of the transcription factor CREB, the activation of CAMKII and MAPK/ERK/MSK signaling induced by exercise phosphorylates some histone proteins and promotes the recruitment and activation of CBP, a HAT. Altogether, these alterations changes the configuration of chromatin to an open state allowing the transcription of *Bdnf* which, after translated, can bind to its receptor TrkB to engage a positive feedback loop underlying the positive effects of exercise on synaptic plasticity and cognitive abilities. Ac,

acetyl group; AMP, adenosine monophosphate; AMPK, AMP-activated protein kinase; ATP, adenosine triphosphate; *Bdnf*, brain-derived neurotrophic factor; CaMKII, Ca2+/Calmodulin-dependent kinase II; CBP, CREB-binding protein; MAPK/ERK, mitogen-activated protein kinase/extracellular signal-regulated kinase; Me, methyl group; MeCP2, methyl-CpG-binding protein 2; NAD+, nicotinamide adenine dinucleotide (oxidized); NADH, nicotinamide adenine dinucleotide (reduced); NMDA-R, N-methyl-D-aspartate receptor; P, phosphate group; Sin3a, paired amphipathic helix protein Sin3a; HDACs, histone deacetylases; SIRT1, sirtuin 1.

Table 1

Summary of studies on brain epigenetic changes induced by physical exercise.

Study (year)	Species	Exercise model	Brain region	Epigenetic changes
Collins *et al.* (2009)	Rats	Running wheel	Dentate gyrus	↑ histone H3 phospho-acetylation
Elsner *et al.* (2011)	Rats	Treadmill exercise	Hippocampus	↓ HDAC activity; ↑ HAT activity; ↑ HAT/HDAC balance
Gomez-Pinilla *et al.* (2011)	Rats	Running wheel	Hippocampus	↓ DNA demethylation at *Bdnf* promoter IV; ↑ pMeCP2 levels; ↑ histone H3 acetylation; ↓ HDAC5 expression
Elsner *et al.* (2013)	Rats	Treadmill exercise	Hippocampus	Adult rats: ↓ DNMT1 and DNMT3b; ↓ H3K9 methylation Aged rats: ↑ H3K9 methylation
Intlekofer *et al.* (2013)	Mice	Running wheel	Hippocampus	↑ histone H4K8 acetylation at *Bdnf* promoters I and IV
Abel *et al.* (2013)	Mice	Running wheel	Hippocampus and cerebellum	↑ histone H3 acetylation in both regions; Cerebellum: ↑ HDAC2 and ↓ MeCP2, HDAC8 and DNMT1; Hippocampus: ↓ HDAC5, HDAC7, HDAC 8, DNMT1, DNMT3a, DNMT3b
Lovatel *et al.* (2013)	Rats	Treadmill exercise	Hippocampus	↑ histone H4 acetylation in aged rats
Patki *et al.* (2014)	Rats	Treadmill exercise	Hippocampus	Exercise normalized stress-induced changes in histone H3 acetylation, HDAC5 and MeCP2
Spindler *et al.* (2014)	Rats	Treadmill exercise	Frontal cortex	↑ HAT activity; ↓ HDAC activity.
Cosín-Tomás *et al.* (2014)	Mice	Running wheel	Hippocampus	↑ miR-28a-5p, miR-98a-5p, miR-148b-3p, miR-7a-5p and miR-15b-5p; ↓ miR-105, and miR-133b-3p
Bao *et al.* (2014)	Mice	Running wheel	Hippocampus	↑ 20 miRNAs and ↓ 12 miRNAs
Hu *et al.* (2015)	Mice	Running wheel	Hippocampus	Exercise restored traumatic brain injury (TBI)-induced changes in miR-21
Pan-Vazquez *et al.* (2015)	Mice	Running wheel	Hippocampus	Exercise attenuated the increased expression of miR-124 in a stress model
Ieraci *et al.* (2015)	Mice	Running wheel	Hippocampus	↑ histone H3 acetylation at *Bdnf* promoters I, II, III, IV, VI and VII; ↓ HDAC5 expression in stressed mice
Zhong *et al.* (2016)	Mice	Swimming exercise	Hippocampus	↑ H3K9, H3K14, H4K5, H4K8 and H4K12 acetylation; ↑ CBP expression
Kim *et al.* (2016)	Mice	Running wheel	Basolateral amygdala	Exercise prevented the reduction in G9a histone methyltransferase expression induced by chronic stress; ↑ histone H3K9 dimethylation at oxytocin and vasopressin gene promoters

Study (year)	Species	Exercise model	Brain region	Epigenetic changes
Sleiman *et al.* (2016)	Mice	Running wheel	Hippocampus	↓ HDAC2 and HDAC3 expression; ↓ HDAC2 and HDAC3 occupancy at *Bdnf* promoters