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REVIEW PAPER

Biological Mechanisms of Physical Activity in Preventing Cognitive Decline

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Abstract In order to guarantee better conditions for competition, the nervous system has developed not only mechanisms controlling muscle effectors, but also retrograde systems that, starting from peripheral structures, may influence brain functions. Under such perspective, physical activity could play an important role in influencing cognitive brain functions including learning and memory. The results of epidemiological studies (cross-sectional, prospective and retrospective) support a positive relationship between cognition and physical activities. Recent meta-analysis confirmed a significant effect of exercise on cognitive functions. However, the biological mechanisms that underlie such beneficial effects are still to be completely elucidated. They include supramolecular mechanisms (e.g. neurogenesis, synaptogenesis, and angiogenesis) which, in turn, are controlled by molecular mechanisms, such as BDNF, IGF-1, hormone and second messengers.

Keywords Physical activity · Exercise · Cognitive decline · Prevention · Neurogenesis · Synaptogenesis · Angiogenesis · BDNF · Alzheimer's disease

Introduction

The complex functions of the central nervous system (CNS) of all animals include the ability to elaborate differentiated motor responses, ranging from the very simple ones such as the movement of cilia to the extremely intricate ones such as human speech. All these kinds of motor activities are aimed at reaching better conditions in the competition for survival, keeping in mind that in humans, competition does not only mean to obtain food, but also to elaborate multifaceted behavioural responses in order to guarantee adaptability to very complex social interactions for which cognitive functions are important components. In order to provide such an important function, it is possible that the nervous system has developed not only mechanisms controlling muscle function, but also feedback systems that influence brain activity through signaling systems starting from peripheral structures such as muscles or joints. Based on this proposal, it is possible that behaviours such as physical activity (PA) may have developed simultaneously and interdependently during evolution to ultimately influence brain functions, including cognition, learning and memory (Vaynman and Gomez-Pinilla 2006).

In the last two decades both epidemiological and experimental studies have accumulated showing that PA may act as primary prevention for cognitive decline in elderly. The results of cross-sectional, prospective and retrospective epidemiological studies generally support a positive relationship between the cognitive activity of older adults and PA (Friedland et al. 2001; Weuve et al. 2004; Taaffe et al. 2008). However, several authors failed to observe such a relationship (Tsutsumi et al. 1997; Verghese et al. 2003; Sturman et al. 2005). There are many reasons that can explain such scattered exceptions including the use of self-report versus more objectively measured PA; the difficulties to evaluate the relative contribution of social, intellectual and physical factors to different everyday activities; the failure to distinguish between different PA

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training protocols (aerobic versus non-aerobic, exercise versus fitness); the difficulty of eliminating subjects with subclinical signs of dementia; and finally the role played by genetic factors.

Recently, Hamer and Chida (2009) conducted a very large meta-analysis of 16 prospective studies which included 163,797 non-demented subjects at baseline with 3,219 cases at follow-up. The authors concluded that PA is inversely associated with risk of dementia. Over the past years several clinical trials and cohort studies have been conducted reporting significant effect in preserving cognition in older adults (Blumenthal and Maden 1988; Kramer et al. 1999; Williamson et al. 2009) and preventing dementia (Verghese et al. 2009; Middleton et al. 2008; Lautenschlager et al. 2008). In order to determine whether the positive effect of PA on the cognitive functions across the literature is reliable, several meta-analyses have been conducted. Colcombe and Kramer (2003) observed a significant effect of aerobic exercise training in those studies with a randomized design of an aerobic fitness training group and a control group. Moreover, the effects were greatest for those tasks involving executive control processes. Further studies, also recently, largely confirmed these results (Heyn et al. 2004; Angevaren et al. 2008; van Uffelen et al. 2008).

Although the ability of PA in reducing the risk of cognitive decline is generally accepted, the biological mechanisms that result in such effect are only poorly understood. The purpose of the present work is to provide an up-to-date overview on the biological mechanisms which lie behind the benefits of PA on cognitive functions. We will first address the controversial topic of the experimental paradigms used to study the effect of environment on nervous system and the biological relationship between periphery and CNS. We will then report the experimental studies focused to understand the cellular (supramolecular) and molecular mechanisms responsible for exercise effects on cognitive functions. Finally, we will critically discuss the topic focusing on future directions for the research.

Experimental Paradigms to Study the Effect of Environment on CNS

Many of the animal studies addressed to understand the relationship between environment and CNS have used as experimental paradigm the so-called environmental enrichment (EE). EE is an experimental paradigm which includes a variety of objects (toys, tunnel, running wheels) that generally need an increased PA to be used. Although it is not easy to discriminate between the effects of PA *per se* and those related to cognitive stimulation, many observations suggest that these two manipulations affect CNS through ways only apparently equivalent. Behavioural manipulations such as housing the animals in an EE or allowing them to engage in voluntary exercise (i.e. animals with access to a running wheel for voluntary activity) have shown that cognitive stimulation and PA may influence structures and functions of CNS differently. In the by now classical experiments of van Praag et al. (1999a, b), the authors showed that EE produced increased neurogenesis, but when the single components of EE were removed, only the exercise wheel continued to be associated with enhanced neurogenesis. During these and the following studies it became evident that EE and PA affect CNS differently, whereas PA seems to act prevalently on proliferating precursor cells inducing neurogenesis, EE promotes synaptogenesis. Also at molecular level the two experimental paradigms act differently. While EE increases the expression of two proteins found in the mature synapse such as synaptophysin (Lambert et al. 2005) and Postsynaptic-Density-95 (PSD-95 or SAP-90) (Nithianantharajah et al. 2004), several genes important for synaptic plasticity (e.g. GluR5, NR2A, NR2B and EAAC1) have been found to be increased after PA (Molteni et al. 2002). Furthermore, PA is also associated with both increased long-term potentiation (LTP) in the dentate gyrus (DG) and enhanced performance of hippocampal-dependent learning and memory tasks (van Praag et al. 1999a; Naylor et al. 2005), while EE exposure actually reverses already established LTP (Abraham et al. 2002).

Molecular Crosstalk Between Muscle and CNS

The functional relationship between CNS and its periphery has been traditionally regarded as an unidirectional downstream flow of information controlling muscle function, ultimately the contraction. Considering the crucial role of movement in the adaptability of the animal organisms to the environment, it is plausible to assume the presence of a retrograde, or upstream, flow of information to the CNS, possibly with feedback functions. This possibility is supported by many observations, including that in rats the discharge frequency of hippocampal CA1 pyramidal cells and interneurons result increased as the running velocity increased (Czurko et al. 1999).

The molecular details of the signaling system between periphery and CNS are still incompletely understood. Experimental observations suggest two fundamental mechanisms. Evidence indicates that events associated with energy balance can play a role in nervous functions. Brain metabolic responses to acute PA seem to extend beyond the regions specifically associated with skeletal motor, sensory, and cardiovascular autonomic control (Ide and Secher 2000). In contrast, McCloskey et al. (2001) reported that oxidative capacity after chronic voluntary activity wheel running is only increased in the striatum and limb representations in the

motor cortex and not in the hippocampus of rats. Lactate taken up from skeletal muscle seems to act as an intercellular energy shuttle within the brain during high-intensity exercise (Dalsgaard et al. 2004). Exercise increases pyruvate dehydrogenase kinase-4 (PDK-4) transcription in skeletal muscle, thus limiting the use of glucose by the muscle to assure sufficient amounts for the increased brain metabolic needs (Pilegaard et al. 2000).

However, there is also clear evidence for effects of PA on nervous functions that are only indirectly dependent, or independent on energy metabolism. It was found that in the hippocampus, exercise significantly increases the levels of the uncoupling protein 2 (UCP2), a mitochondrial protein which uncouples substrate oxidation from ATP synthesis. Vaynman et al. (2006) proposed a model in which the presence of UCP2 at the pre-synaptic and post-synaptic membranes could allow neuronal mitochondria to limit oxidative stress, increase ATP production and modulate calcium levels. These modulations would subsequently influence vesicular release and transcription, by acting on vesicular release proteins, such as synapsin I, and signal transduction molecules, such as cAMP response element binding (CREB) protein, respectively. These results suggest the presence of fundamental mechanisms through which exercise affects key elements of energy metabolism that modulate substrates of synaptic plasticity underlying learning and memory. Finally, UCP2 could represent a mechanism linking the energy metabolism to the production of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF). Indeed, UCP2 seems to modulate the synthesis of BDNF and its downstream molecular effectors such as CREB and calcium/calmodulin protein kinase II (CAMK-II) (Vaynman et al. 2003).

A possible candidate for the role of reciprocal signaling systems between muscle and CNS may be interleukin-6 (IL-6), a cytokine with primarily immunomodulatory effects. It was demonstrated that the level of circulating IL-6 increases dramatically in response to exercise. Data from marathon runners suggest that there is a correlation between the intensity of exercise and the increase in plasma IL-6 level (Ostrowski et al. 2001). Muscle biopsies obtained before and after exercise in humans (Starkie et al. 2001; Steensberg et al. 2001) and in rats (Jonsdottir et al. 2000) revealed very little IL-6 mRNA in resting muscle, but up to a 100-fold increase in exercising skeletal muscle. Recently, Chennaoui et al. (2008) showed in rats that a training program induced a decrease of IL-6 concentration in the cerebellum, suggesting that this effect could contribute to the positive consequences of PA on the CNS.

The mechanisms responsible for IL-6 production in the contracting skeletal muscle are still not fully understood. It was proposed that IL-6 increase may be linked to glycogen depletion. Steensberg et al. (2001) found that situations in which muscle glycogen concentrations were low, such as exercise, increased the IL-6 mRNA, the transcription rate and the protein release. There is evidence suggesting that IL-6 may be linked to the regulation of glucose homeostasis during exercise and/or that IL-6 may work as a sensor of carbohydrate availability. Steensberg et al. (2001) observed that the increased expression of IL-6 was associated with increased glucose uptake during exercise. Additionally, Helge et al. (2003) demonstrated that the IL-6 release from working skeletal muscle is positively related to work intensity, glucose uptake and plasma adrenaline concentration. This might suggest that IL-6 may be involved, at least in part, in mediating glucose uptake.

Neurobiological Bases

The biological mechanisms responsible for the beneficial effects of PA on cognition are still debated. PA was demonstrated to affect angiogenesis, neurogenesis and synaptogenesis through different molecular mechanisms (Fig. 1).

Supramolecular Mechanisms

Angiogenesis

The brain vascular system is highly plastic throughout life. Any manipulation that increases brain vascularisation, and hence blood flow, might prove to be an effective strategy to minimize or delay the cognitive decline associated with aging. A large body of evidence suggests that angiogenesis can be induced by PA (Black et al. 1991; Isaacs et al. 1992). Increasing evidence supports the observation that manipulating blood flow to the brain alters behavioural performance. For example, administration of erythropoietin has been shown to enhance cognitive performance in rodents (Sadamoto et al. 1998) and humans (Ajmani et al. 2000). Numerous studies have documented transient increases in cerebral blood flow both in animals (Sokoloff et al. 1997) and humans (Fox and Raichle 1986), during the performance of motor tasks as well as for a brief period following the cessation of PA. In addition to these studies that have revealed an increased blood flow, subsequent studies in rats and primates have shown that fitness training can also enhance vascularisation in other regions of the brain than the motor cortex. Churchill et al. (2002) proposed the hypothesis that angiogenesis is likely to occur in any area of the adult brain that is activated and lacks sufficient vascularisation to support chronic levels of elevated neuronal activity requiring increased oxygen. Black et al. (1990) compared the effects of aerobic fitness training to motor skill learning and showed that these two different

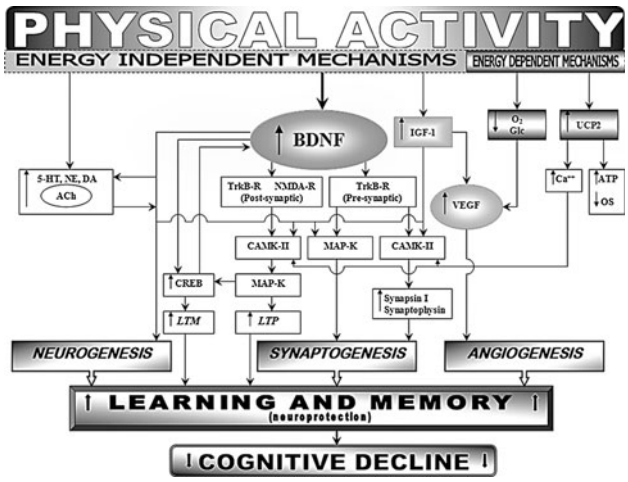

Fig. 1 Potential mechanisms through which physical activity may counteracts cognitive decline. BDNF is a critical modulator of the energy independent effects of physical activity on neurogenesis and synaptogenesis. BDNF increases neurogenesis (directly or through neurotransmitters, especially ACh) and activates a complex presynaptic and postsynaptic molecular cascades that induce synaptogenesis. In this process, CAMK-II and MAP-K pathways seem to be fairly important acting on both LTP and LTM, the latter through the regulation of CREB level. Physical activity also activates IGF-1 production that may lead both to synaptogenesis and angiogenesis. IGF-1 acts on synaptogenesis through a downstream signaling cascade that at presynaptic level includes CAMK-II and MAP-K whereas postsynaptically involves CAMK-II. Angiogenesis is increased by VEGF that is regulated by IGF-1 and several energy-dependent mechanisms such as cellular hypoxia and glucose deficit. Details are given in the text. *BDNF* brain-derived neurotrophic factor, *IGF-1* insulin-like growth factor, *VEGF* vascular endothelial growth factor, *UCP2* uncoupling protein 2, *TrKB-R* tyrosine kinase receptor B, *CAMK-II* Ca/calmodulin protein kinase II, *MAPK* mitogen-activated protein kinase, *CREB* cAMP response element-binding, *LTP* long-term potentiation, *LTM* long-term memory

forms of training had effects on the vasculature and synaptic connectivity of the brain respectively.

The molecular mechanisms for angiogenesis are only partially known. Vascular endothelial growth factor (VEGF) seems to play an important role in this process. Many philological and pathological conditions may affect VEGF production. For example, cellular hypoxia (Ladoux and Frelin 1993) or glucose deficits (Satake et al. 1998) have been reported to increase the production of VEGF in cell cultures.

Neurogenesis

It is now accepted that in the adult brain of various species (i.e. rodents, non-human primates and humans), neurogenesis occurs at least in selected regions, such as the subgranular zone and granule cell layer of the DG in the hippocampus and the subventricular zone of the lateral ventricle (Ming and Song 2005), in response to specific conditions including stroke (Arvidsson et al. 2002), ischemia (Liu et al. 1998), seizures (Parent et al. 1997; Steiner et al. 2008) or injuries (Gould and Tanapat 1997). The focus of neurogenesis investigations has been directed to identify stimuli that can modulate the proliferation and/or survival rate of the newly formed neurons. Many substances, including hormones, growth factors, drugs and neurotransmitters (Ming and Song 2005) affect hippocampal neurogenesis. Behavioural stimuli such as PA (Uda et al. 2006) or EE (Brown et al. 2003) are also able to affect neurogenesis. Research on animals demonstrated that exercise-induced hippocampal cell proliferation and cell survival can occur at many stages of development, including pups (Kim et al. 2007), juvenile (Lou et al. 2008), young adulthood (van Praag et al. 1999b) and old age (van Praag et al. 2005).

Although the functional significance of such constitutive neurogenesis was initially unclear (Eriksson et al. 1998), there is growing evidence that newly formed neurons can be integrated into neural networks and become functionally active (Lledo et al. 2006). Experiments in animal models showed that stimulation of hippocampal neurogenesis by aerobic exercise is accompanied by facilitated induction and maintenance of LTP (van Praag et al. 1999a) and by enhancement of short-term memory in the DG (Kim et al. 2007; Hillman et al. 2008). Regarding the relationship between the effects of PA and EE on neurogenesis, Olson et al. (2006) suggested that the two conditions act differently: PA could increase cell proliferation, and thus more cells are generated that might become neurons, while EE could increase neurogenesis without affecting cell proliferation.

Synaptogenesis

The specific role on synaptogenesis of PA compared to EE is more controversial. Whereas the role of PA on neurogenesis is well established, synaptogenesis seems to be prevalently induced by cognitive stimuli such as those present in the experimental paradigm of EE (Kempermann 2008). Nevertheless, a direct effect of PA on synaptogenesis has been reported. Eadie et al. (2005) showed in rats that spine density on dendrites in DG increased following voluntary exercise which suggests profound changes in synaptic molecules. Using high-density oligonucleotide microarrays, a large number of gene transcripts (synaptotagmin 5, clathrin-associated protein 17, beta prime COP, kinesin light chain C, Vesl) associated with synaptic structure and function has been showed in the hippocampus of rats voluntary running for 3 weeks (Tong et al. 2001). The ability of PA to affect the composition of pre- and postsynaptic compartment was further confirmed (Molteni et al. 2002; Farmer et al. 2004) also very recently (Hu et al. 2009). The mechanisms that underlie the exercise-induced synaptic modifications are still unclear. Recently, it has been suggested that a mitochondrial mechanism related to

UCP2 function is essential to induce synaptogenesis in response to PA (Dietrich et al. 2008). Along with the structural changes, there is evidence for modifications in synaptic plasticity following PA. In particular, LTP amplitude appeared enhanced in the DG in running mice as compared to controls (van Praag et al. 1999a). These findings have also been replicated since the initial report (Farmer et al. 2004).

Experimental evidence also suggests that PA might possess therapeutic efficacy for some of pathologies characterized by synaptic loss. Jankowsky et al. (2005) showed that learning and memory deficits observed in a transgenic mouse model of Alzheimer's disease (AD) can be ameliorated by EE. They conclude that environmental factors can strongly modulate the pathological and behavioural progression of AD in a mouse model. Lazarov et al. (2005) reported that exposure of the AD model-transgenic mice to EE caused a reduction in cerebral Aβ levels and its deposition as compared to controls in standard housing. However, other studies with AD transgenic mouse models, whereby EE and PA were compared, suggested that EE seems to be more beneficial for cognition than PA alone (Wolf et al. 2006; Cracchiolo et al. 2007).

Molecular Mechanisms

Brain-Derived Neurotrophic Factor

For the past few years there have been an increasing number of investigations focused on the molecular bases of PA benefits. A crucial role seems to be played by growth factors such as BDNF (Ang et al. 2003; Neeper et al. 1995). BDNF is involved in neuroplasticity, neuroprotection, growth and differentiation, during development and in adult brain (Lindvall et al. 1994; Xuan et al. 2008). Direct administration of BDNF increases cell proliferation in the hippocampus and blocking BDNF reduces cell proliferation (Vaynman et al. 2004). Besides its traditional trophic function, BDNF has emerged as a critical modulator of many other neuronal functions such as neurotransmitter release (Bolton et al. 2000) and synaptic plasticity (Lo 1995). BDNF has been shown to regulate neurotransmitters, including dopaminergic and cholinergic systems playing an important role in the exercise-induced effects on neurotransmitters. A large number of observations suggest that BDNF plays a crucial role in LTP. For example, BDNF gene deletion or inhibition (Figurov et al. 1996) impairs LTP. Ma et al. (1998) showed that blocking endogenous BDNF reduced LTP. Moreover, replenishing the factor-depleted hippocampus with exogenous BDNF restored the ability to induce LTP (Patterson et al. 1996). Learning increases BDNF gene expression, suggesting that mechanisms inducing BDNF gene expression may enhance learning (Tokuyama et al. 2000). Clinical studies also support the importance of BDNF in learning and memory in humans. A study conducted by Hariri et al. (2003) reported that individuals expressing a specific polymorphism in the BDNF gene exhibit learning impairments.

Neeper et al. (1995) first observed that PA affects BDNF production in the brain. Surprisingly, the authors showed that the greatest effects of exercise on BDNF mRNA occurred in regions not directly related to the motor system but associated with cognitive function such as the hippocampus and caudal cortex. Voluntary exercise in rodents increases both mRNA and protein levels of BDNF in the hippocampus, cerebellum and frontal cortex. Blocking the binding of BDNF to its tyrosine kinase B receptor (TrkB-R) abolishes the exercise-induced performances benefits (Vaynman et al. 2004). Other trophic factors, including NGF (Neeper et al. 1995) and fibroblast growth factor 2 (FGF-2) (Gomez-Pinilla et al. 1997), were also induced in the hippocampus in response to exercise, but their upregulation was transient and less robust than that of BDNF, suggesting that BDNF is a better candidate for mediating the long-term benefits of exercise on the brain.

These findings suggest that PA through the regulation of BDNF synthesis might be neuroprotective and prevent the development of cognitive symptoms associated with neurodegenerative diseases such as AD. BDNF shows large deficit in AD brain (Connor et al. 1997). In AD transgenic mice model (APPswe X PS1ΔE9), it was reported that transcripts encoding BDNF are significantly upregulated in brain of mice exposed to EE and PA (Adlard et al. 2005; Farmer et al. 2004). In contrast, Wolf et al. (2006) in a different AD transgenic mice model (APP23) observed an increased hippocampal production of BDNF in animals expounded to EE. Surprisingly, in animals expounded to PA alone a down-regulation of BDNF was observed. The reasons of such conflicting results might be in both the different animal models used and the not comparable type of PA.

The mechanisms that underlie the exercise-driven increase in the level of BDNF are varied. They include neurotransmitters with their receptors (Blomstrand et al. 1989; Fordyce et al. 1991; MacRae et al. 1987; Poutlton and Muir 2005) and peripheral factors such as estrogen, corticosterone (Berchtold et al. 2001) and possibly insulin-like growth factor 1 (IGF-1) (Carro et al. 2000; Trejo et al. 2001). Finally, it is now well accepted that the PA effects on BDNF modulate the function of intracellular signaling systems.

Insulin-Like Growth Factor-1

Exercise enhances hippocampal neurogenesis most likely by stimulating the systemic production of IGF-1 (Carro

et al. 2000). Trejo et al. (2001) reported that blocking the entrance of IGF-1 into the brain repressed exercise-induced neuron proliferation in the DG. Peripheral IGF-1 appears to participate in the neuroprotective effect of exercise, as peripheral infusion of IGF-1 blocking antibodies before a CNS injury reduced the protective effect (Carro et al. 2001).

IGF-1 is also crucial for exercise-induced angiogenesis in the brain. It has been shown that the systemic injection of IGF-1 stimulates angiogenesis and its inhibition reduces the phenomenon. IGF-1 might induce new blood vessel formation indirectly through the synthesis of VEGF, a molecule that plays a pivotal role in blood vessel growth. Lopez-Lopez et al. (2004) reported that blocking IGF-1 abolished the secretion of VEGF, which resulted in a significant reduction in the appearance of new capillaries. Furthermore, it was reported that IGF-1 and VEGF are upregulated following aerobic exercise, leading to the formation of new blood vessels and that this event occurs both in childhood and in the elderly (Ding et al. 2004). Finally, IGF-1 might mediate the effects of BDNF, being an upstream mediator of its gene regulation (Carro et al. 2001; Trejo et al. 2001). Indeed, peripheral administration of IGF-1 induces BDNF mRNA in the brain (Carro et al. 2000).

Neurotransmitters

The neurotransmitter systems are also affected by exercise. Serotonin levels are increased throughout the brain in exercising rats (Blomstrand et al. 1989). Chronic wheel running increased basal levels of serotonin (Dishman et al. 1997), attenuated stress-induced c-Fos induction in the serotoninergic neurons (Greenwood et al. 2005) and increased levels of $5HT_{1A}$ inhibitory autoreceptor mRNA (Greenwood et al. 2003) in the dorsal rafhe nucleus. Furthermore, serotonin has been shown to enhance neuron proliferation (Brezun and Daszuta 2000), whereas its depletion decreases neuron proliferation (Brezun and Daszuta 1999).

Exercise may also act through noradrenergic system. Wheel running increased basal levels of noradrenalin (Dishman et al. 1997) and mRNA for the noradrenalin modulator, galanin (O'Neal et al. 2001) in the locus coeruleus. The same type of exercise blunted the release of noradrenalin in the frontal cortex (Soares et al. 1999) and its depletion in the locus coeruleus, hippocampus, hypothalamus, and amygdala (Dishman et al. 2000) in response to stress.

It was shown that exercise can reverse age-related cognitive declines through an increased dopamine receptor density in the striatum (MacRae et al. 1987). Animal studies (Poutlton and Muir 2005) suggested that exercise may be a potential intervention for reduction of the onset rate or incidence of Parkinson disease, based on the observation that treadmill running resulted in an attenuation of dopamine depletion in the striatum of hemi-Parkinsonian rats.

Acetylcholine level and muscarinic receptor density are increased in the hippocampus of adult exercising rats (Fordyce et al. 1991). Along with a direct effect of PA on ACh, a large body of evidence supports the idea that an ACh-mediated mechanism regulates BDNF gene expression in the hippocampus (Knipper et al. 1994; Berchtold et al. 2002). Furthemore, Knusel et al. (1991), in a study in culture, have shown that rhBDNF (recombinant human BDNF) stimulates development of basal forebrain cholinergic neurons and increases dopamine uptake in mesencephalic cultures.

Intracellular Pathways

The effect of exercise on signal transduction mechanisms has not been extensively explored. The most important signal transduction mechanisms for mediating exercise effects on hippocampal synaptic plasticity are mitogen-activated protein kinase (MAP-K), CAMK-II, and the *N*-methyl-D-aspartate receptor (NMDA-R). MAP-K, CAMK-II, and the NMDA-R were found to influence downstream effectors of BDNF action on gene expression and synaptic transmission, such as CREB and synapsin I (Vaynman et al. 2003).

CREB, a well-known stimulus-induced transcriptional regulator, was described as a switch for the activation of transcription of molecules essential for long-term memory (LTM) (Yin et al. 1995) and involved in activity-dependent long-term neuronal plasticity (Tully 1997). In addition, CREB seems to be important in the BDNF-mediated mechanism responsible for the potentiating effects of exercise on learning and memory (Vaynman et al. 2004). With exercise, CREB mRNA and BDNF levels were significantly and positively associated with each other as well as with performance on memory recall in animals. CREB may provide a self-perpetuating loop for BDNF action, since it has been found to regulate BDNF transcription (Tao et al. 1998) and is regulated itself by BDNF (Finkbeiner et al. 1997; Tully 1997). Both MAP-K and CAMK-II have been repeatedly described as conserved signaling pathways that lead to CREB mediated gene transcription (Finkbeiner et al. 1997; Ying et al. 2002). MAP-K targets synaptic potentiation (English and Sweatt 1996), nuclear signaling (Adams et al. 2000), LTP (English and Sweatt 1997), and seems to be especially necessary for learning and memory (Blum et al. 1999; Sweatt 2001). It was suggested that the capacity of MAP-K to induce synaptic plasticity was to be attributed to its ability to regulate (Finkbeiner et al. 1997) and prolong the

transcriptionally active state of CREB (Hardingham et al. 2001). Like MAP-K, CAMK-II is believed to be important for mechanisms underlying learning and memory (Yin and Tully 1996). Mice with gene deletions of a CAMK-II isoform show an impaired performance on spatial learning tasks (Silva et al. 1992). Finally, NMDA-R is one more factor able to mediate the effects of exercise on hippocampal synaptic plasticity. BDNF can enhance synaptic transmission through the NMDA-R (Song et al. 1998), providing an alternative pathway to CAMK-II and MAP-K mediated changes. The NMDA-R is critical for modulating LTP (Bliss and Collingridge 1993) and for learning and memory processes (Cammarota et al. 2000). Vaynman et al. (2003) showed that blocking the NMDA-R abolished the exercise-induced increases in BDNF, TrkB-R, CREB and synapsin I mRNAs.

Modulation of the transmission properties at the synapse has been proposed for the beneficial effects of exercise on brain function. It has been shown that BDNF regulates synapsin I and synaptophysin. BDNF gene deletion in mice results in a reduction in synaptic proteins, sparsely docked vesicles, impaired neurotransmitter release, and decreased synapsin I levels (Pozzo-Miller et al. 1999). An important function of synapsin I is to modulate vesicular release by tethering synaptic vesicles to the actin cytoskeleton of the cell (Greengard et al. 1993). Synaptophysin, a major integral protein on synaptic vesicles, may be a key protein in the biogenesis of synaptic vesicles from cholesterol which promotes membrane curvature facilitating vesicular budding and membrane retrieval (Thiele et al. 2000). During exercise, MAP-K and CAMK-II were shown to contribute to the BDNF regulation of synapsin I expression (Vaynman et al. 2003). Exercise may augment the effects of BDNF on synaptic-plasticity, through a positive feedback loop in which it concurrently increases the mRNA levels of both itself and its TrkB-R (Vaynman et al. 2003).

BDNF-mediated regulation of synapsin I may influence synaptic plasticity in additional alternative ways. Besides modulating transmitter release, synapsin I is involved in the formation and maintenance of the presynaptic structure (Melloni et al. 1994) and in axonal elongation (Akagi et al. 1996). An adequate vesicular release pool and adequate and sustainable transmitter release provided by functional levels of synapsin I may provide the level of synaptic communication necessary for learning. Evaluation of an array of genes activated by exercise has corroborated the involvement of these molecules in exercise-induced synaptic plasticity. In the rat hippocampus, 3 weeks of exercise led to changes, both increases (e.g. synaptotagmin, Vesl and AP17) and decreases (e.g. synaptopotin, thrombomodulin precursor gene, cytosolyc sorting protein PACS-1b) in the expression of a number of genes, indicating a direct effect of exercise on synaptic function (Tong et al. 2001).

Conclusions and Critical Topics

A growing body of animal and human studies suggests that PA strongly influences brain functions, including cognition, learning and memory and their pathological counterpart, such as cognitive decline in aging. In recent years, there has also been increased acknowledgement of the biological mechanisms that underlie the beneficial effects of the movement on brain health. Nevertheless, many critical topics remain to be clarified. From a practical point of view, we know little about the optimal amount and kind of PA for sustaining this beneficial effect. We are also largely ignorant of the possible interaction between exercise and other lifestyle factors. Finally, data about the ability of fitness to reduce the ruinous effects of neurodegenerative process are still insufficient.

The challenge lies in understanding the relationships between systemic, cellular, and molecular mechanisms by which PA influences brain functions such as cognition, learning and memory and to possibly recognize the relative contribute of each of them. In order to reach this goal, it will be mandatory to understand not only the single mechanisms but also to put together the single pieces of the puzzle made by the complex interactions between different levels. Several of such interactions are those between different systems (e.g. nervous, cardiovascular, endocrinological etc), between molecular and cellular mechanisms and, finally, between different molecules. For example, are the effects of exercise mediated by the reduction of internal pathologies (e.g. cardiovascular diseases, diabetes, hypertension) or is PA able to act directly on brain function? If a cooperative contribute between these two levels is the most likely hypothesis, recognizing the specific contribute of both mechanisms on each single function could open new pharmacological perspective in preventing cognitive decline. Still, are there molecular mechanisms (e.g. BDNF, IGF-1, IL-6) specifically involved in mediating the neurotrophic effects of PA, as several observations seem to suggest or, on the contrary, PA shares the same mechanisms with other kind of environmental stimulations. Finally, we ignore other aspects that in the future might open exiting scenarios such as the relationship between exercise and genetic polymorphisms. In conclusion, although future research still has many aspects to clarify, PA may represent a simple and inexpensive approach to maintain brain health.

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