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The combined effects of exercise and foods in preventing neurological and cognitive disorders

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ABSTRACT

Objective. Exercise and select diets have important influences on health and plasticity of the nervous system, and the molecular mechanisms involved with these actions are starting to be elucidated. New evidence indicates that exercise, in combination with dietary factors, exerts its effects by affecting molecular events related to the management of energy metabolism and synaptic plasticity.

Methods. Published studies in animals and humans describing the effects of exercise and diets in brain plasticity and cognitive abilities are discussed.

Results. New evidence indicates that exercise and select diets exert their effects by affecting molecular events related to the management of energy metabolism and synaptic plasticity. An important instigator in the molecular machinery stimulated by exercise is brain-derived neurotrophic factor (BDNF), which acts at the interface of metabolism and plasticity.

Conclusions. Recent studies show that selected dietary factors share similar mechanisms with exercise, and in some cases they can complement the action of exercise. Therefore, exercise and dietary management appear as a non-invasive and effective strategy to counteract neurological and cognitive disorders.

Introduction

It is becoming well accepted that the type of environment and lifestyle of individuals have a strong influence on the health of the body and mind, and exert an influence on the pathology of several modern diseases. In particular, insufficient levels of exercise and poor dietary practices, typical of our modern society, are considered risk factors for various neurodegenerative diseases such as Alzheimer's, as well as psychiatric disorders such as depression. Evidence accumulated in the last decade indicates that the etiology of various neurological disorders is multifactorial. In particular, we know now that inflammatory, metabolic, and genetic events can compromise fundamental aspects of neuronal signaling that are required for cognitive function. Exercise has a benevolent action on brain function affecting fundamental and broad aspects of brain plasticity. Similarly, new information indicates that dietary factors have a broad and positive action on a range of molecular systems supporting neuronal function and plasticity. For example, the omega-3 fatty acid docosohexaenoic acid (DHA) provides building material to the brain, which is fundamental for supporting intercellular signaling events. In addition to this, omega-3 fatty acids positively influence molecular systems that serve synaptic function. Conversely, diets rich in saturated fats and sugar, or high in calories are considered deleterious for neural function, as they act to elevate levels of oxidative stress and to reduce synaptic plasticity and cognitive functions. Interestingly, exercise has been shown to interact with both dietary interventions — boosting the positive effects of DHA and attenuating the unhealthy effects of the high fat diet. The overall evidence seems to indicate that combined strategies based on exercise and dietary management can derive maximal benefit for neural health promotion.

Adequate levels of exercise and healthy dietary practices have the advantage of being non-invasive, highly efficacious, and borne with a broad spectrum of action, and with strong translational potential. Development of clinical applications to reduce the hardship of several neurodegenerative disorders is a highly desirable objective in view of the poor efficacy of pharmaceutical compounds. Notably, the type of broad protection elicited by exercise and dietary factors can be advantageous for the treatment of neurological disorders characterized by a diffused pathology. Interestingly, the results of new research indicate that the actions of exercise and diet share similar features, and in many cases their effects can be complementary. This implies that combined therapies using the power of diet and exercise can stimulate the level of brain plasticity capable to counteract neurological disorders. Accordingly, in this review, we discuss the mechanisms by which exercise and diet influence brain health and plasticity, and the conditions by which their combined application can derive additional benefits. The discussion of nutrients has been restricted to those types with described interaction with exercise according to recent studies.

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Traumatic brain injury (TBI) as a model to study the effects of exercise and foods on cognition

Concussive brain injury is a prevalent cause of disability in domestic, work-related, and military environments. Although patients suffering mild to moderate human concussion often experience persistent cognitive dysfunction that can last for years (Klonoff et al., 1977; Levin et al., 1982, 1988), their brain scans show modest structural pathology. The most prevalent types of cognitive impairments include disturbances in attention and learning and memory function (Arciniegas et al., 1999; Borgaro et al., 2003). Patients exhibit a loss of selective and sustained attention (Arciniegas et al., 1999) required for recognizing and processing stimuli. Several of these features make TBI remarkably similar to other types of neurological disorders with a diffuse pathology such as mild cognitive impairment of unknown etiology. Neurological deficit in the absence of neuronal degeneration is suggestive that altered neuronal signaling and synaptic transmission may underlie functional deficits (Dash et al., 2002; Wu et al., 2003). Concussive injury appears to disrupt hippocampal function, which plays an important role in attention, and learning and memory (Dixon et al., 1994; Gorman et al., 1996).

Brain metabolic dysfunction is a common stage in the pathology after TBI as well as a part of the sequel of various neurological disorders. Studies in humans (Bergsneider et al., 2000; Vagnozzi et al., 2008) and animal models of TBI (Dietrich et al., 1994; Hovda et al., 1991; Moore et al., 2000) show that dysfunctional energy homeostasis seems to impose a toll on the ability of the brain to maintain normal function and plasticity. Fluid percussion injury (FPI), is a suitable animal model with which to evaluate the effects of concussion or other brain challenges, associated with marked cognitive impairment in spite of a relative paucity of histological damage (Hovda et al., 1995). Following FPI in the rat, the brain cells are unable to respond to physiological levels of stimulation, resulting in difficulty supporting functional recovery (Colle et al., 1986; Hovda et al., 1987). Importantly, as a consequence of the energy dysfunction, therapeutic approaches that rely on activity such as exercise become less effective. As discussed below, exercise has been shown to counteract some of the effects of FPI on synaptic plasticity and cognitive function (Chytrova et al., 2008). However, the timing of application of exercise after the onset of the injury seems critical, and dependent on the metabolic stage of the brain (Griesbach et al., 2007). Given the capacity of selected dietary factors to promote metabolic homeostasis, we discussed below the advantage of using a combined approach of diet and exercise to counteract neurological disorders.

Metabolic dysfunction also increases oxidative stress and subsequent cellular membrane damage (Merenda et al., 2008). The brain is particularly vulnerable to oxidative membrane damage based on its high contents of polyunsaturated fatty acids (PUFA), high consumption of oxygen, and relatively low antioxidant defenses compared to other organs. Beyond the initial damage to membranes, reaction of free radicals with double bonds of phospholipids produces peroxides that give rise to α,ß-unsaturated aldehydes such as 4-hydroxynonenal (4-HNE) (Sharma et al., 2010). Metabolic dysfunction, membrane damage, and subsequent synaptic dysfunction are not exclusive features of TBI, and indeed, these are common features in most neurological disorders. As discussed below, selected dietary interventions can have the capacity to reduce energy dysfunction in the brain, and contribute to enhance the effects of exercise.

The function of BDNF in energy metabolism and synaptic plasticity is crucial for understanding the effects of exercise and foods on the brain

Exercise and selected dietary factors have the ability to impact molecules related to cellular energy control and neural repair such as brain-derived neurotrophic factor (BDNF), and are important for the function and maintenance of neuronal circuits. The action of BDNF is crucial for supporting cognitive abilities. For example, proper BDNF function is necessary for maintaining learning and memory capacities in humans (Egan et al., 2003; Hariri et al., 2003), as individuals expressing a specific polymorphism in the *Bdnf* gene exhibit learning impairments. Dysfunction in the processing of BDNF or reductions in BDNF levels have been proposed to be part of the pathobiology of various neurological disorders such as Alzheimer, Parkinson's, bipolar, schizophrenia, etc. FPI has been found to reduce BDNF levels in the hippocampus, but its effects are counteracted by exercise and omega-3 fatty acid supplementation (Wu et al., 2008).

A new line of investigation reveals that the action of BDNF on synaptic plasticity is intimately related to the regulation of energy metabolism such that BDNF is considered a "metabotrophin". It is known that BDNF influences synaptic plasticity by acting on molecular systems important for the regulation of energy homeostasis in the hippocampus (Gomez-Pinilla et al., 2008; Vaynman et al., 2006). These actions of BDNF seem to have profound consequences for the neural control of body metabolism as animals with genetic deletion of the *Bdnf* gene are hyperphagic and develop obesity (Lyons et al., 1999), while infusion of BDNF has been found to reduce body weight, to normalize glucose levels, and to increase insulin sensitivity (Tsuchida et al., 2002). The recently discovered interactions between energy metabolism and synaptic plasticity have opened new avenues to understand the mechanism of action of exercise and dietary factors in the brain.

BDNF plays a central role on the effects of exercise on synaptic plasticity

Multiple genes analysis using microarray technology has been instrumental in determining the pathways stimulated by exercise in the brain. These studies have shown that voluntary exercise elevated the expression of a subgroup of genes that are associated with the actions of BDNF and insulin-like growth factor (IGF) systems on synaptic plasticity (Molteni et al., 2002a,b). In the neurotransmitter category, exercise up-regulated genes related to the *N*-methyl-D-aspartate receptor (NMDA-R) and down-regulated genes related to the GABAergic system — these findings are significant given that the GABAergic system generally opposes to the action of glutamate. The majority of the up-regulated genes are members of synaptic trafficking machinery (synapsin I and II, synaptotagmin, and syntaxin); part of signaling transduction pathways calcium/calmodulin protein kinase II (CaM-KII); mitogen-activated protein kinase (MAP-K/ERK, I and II); protein kinase C (PKC-δ); or transcription factor cAMP response element binding protein (CREB). These results indicate that exercise may orchestrate its effects via activation of the intracellular signal pathways MAP-K/ERK and CaM-K.

BDNF function blocking experiments have been crucial to elucidate the contribution of BDNF-related pathways to the effects of exercise on hippocampal synaptic plasticity (Vaynman et al., 2003; Molteni et al., 2004). The results of these studies showed that MAPK, CAMKII, and the NMDA-R, and their actions on CREB and synapsin I are downstream effectors of BDNF (Vaynman et al., 2003). Synapsin I is a phospho-protein localized to the pre-synaptic membrane, and synaptophysin is a major integral protein on synaptic vesicles (Ding et al., 2006a,b). CREB is critical for long-term neuronal plasticity and requisite for the formation of long-term memory (Bourtchuladze et al., 1994; Dash et al., 1990; Gómez-Pinilla et al., 1995). BDNF can potentiate synaptic transmission through the NMDA-R (Song et al., 1998), providing an alternative path to CAMKII and MAPK mediated changes. NMDA-R is critical for modulating long-term potentiation and mediating learning and memory processes (Cammarota et al., 2000). Blocking BDNF signaling abolished the effects of exercise on learning and memory (Vaynman et al., 2004). An association between BDNF and learning and memory was found when measuring the performance of rats on the Morris water maze task (Molteni et al.,

2002a,b), suggesting that levels of BDNF are directly related to learning efficiency and memory stability. In turn, blocking IGF-1 signaling receptors also reduces the cognitive enhancing effects of exercise (Ding et al., 2006a,b). This research points to the possibility that the concerting actions between IGF-1 and BDNF can support cellular processes important for learning and memory.

Exercise modulates BDNF using epigenetic mechanisms

New studies show that exercise can regulate BDNF production using epigenetic mechanisms through the methylation and acetylation of DNA. Epigenetic mechanisms allow for lasting modifications in the genome, and they are emerging as important mediators for the effects of the environment on cognitive functions and emotions (Nestler, 2009; Sweatt, 2009), in a process in which the *Bdnf* gene may be involved. It has recently been reported that an exercise regimen known for its capacity to enhance learning and memory through a BDNF-related mechanism, promotes remodeling of chromatin containing the *Bdnf* gene (Gomez-Pinilla et al., 2011). These studies indicate that exercise influences histone acetylation and DNA methylation localized to the promoter IV region of the *Bdnf* gene. Transcription involving promoter IV (formerly promoter III) can mediate synapse plasticity and learning and memory (Feng et al., 2007), and can be suppressed by methyl-CpG-binding protein (MeCP2). MeCP2 contributes to the gene silencing effect of DNA methylation (Chao and Zoghbi, 2009). Interestingly, the effects of exercise on *Bdnf* gene transcription regulation seem to involve MeCP2. These studies have also shown that exercise elevated the levels of p-CaMKII and p-CREB — molecules intimately involved in the pathways by which neural activity engage mechanisms of epigenetic regulation to stimulate *Bdnf* transcription.

Results are consistent with the notion that exercise influences epigenetic mechanisms to promote stable elevations in *Bdnf* gene expression, which may have important implications for regulation of synaptic plasticity and behavior. It has been shown that depression-like behavior in mice results in methylation of histone H3 and long-lasting suppression of *Bdnf* transcription (Tsankova et al., 2006). In turn, exercise and BDNF have been associated with reducing depression and promoting cognitive enhancement. Therefore, it is possible that exercise can influence the epigenome to reduce depression and enhance cognitive abilities, and this can open new avenues in the wage against neurological and psychiatric disorders. The original concept of epigenetics implies the idea that modifications in DNA expression and function can contribute to inheritance of information (Waddington, 1942). Although this principle has not been fully demonstrated in mammals, exercise remains as a crucial candidate for promoting stable heritable biological adaptations.

Neurological priorities vs healing capacity of broad spectrum interventions

Most of the pharmacological strategies to intervene in neurodegenerative disorders have had limited success, and this seems to reside on the multifactorial nature of the etiology involved, i.e., wide variety of neuronal types and factors such as inflammation, metabolism, and genetics. Therefore, the narrow mode of action of most pharmaceutical agents may exclude important aspects of the pathology. The fact that exercise and selected dietary factors support a wide range of molecular mechanisms important for neuronal function and repair strongly support their potential to promote neural health and plasticity. As discussed below, the action of selected nutrients has been studied in animal models of neurological disorder with promising results. For example, recent animal studies have shown the efficacy of dietary interventions in reducing important aspects of the pathobiology involved in TBI, including attenuation of cognitive and emotional distress. These findings have strong translational potential considering the strong safety profile of natural nutrients.

Diet and exercise collaborate to preserve neuronal plasticity and function

Much like a healthy diet, physical activity is thought to benefit neuronal function. According to recent studies, the combination of diet and exercise can deliver more beneficial effects than intervention alone. The main types of foods studied for their interactions with exercise are: omega-3 fatty acids, polyphenols, and saturated fats.

Omega-3 fatty acids

The omega-3 is a large family of fatty acids in which DHA is one of the most relevant forms for brain function. DHA is a key component of neuronal membranes at sites of signal transduction at the synapse, such that its action is vital for the maintenance of neuronal structure and function (Gomez-Pinilla, 2008). Because of the inefficiency of mammals in producing DHA, supplementation of DHA in the diet is important for proper function of neurons throughout the lifespan. In addition to reducing oxidative stress and inflammation, DHA serves to improve neuronal function by supporting synaptic membrane fluidity (Suzuki et al., 1998), and regulating gene expression and cell signaling (Salem et al., 2001). This implies that insufficient DHA in the brain can compromise neuronal function with subsequent effects on a broad range of neurological and behavioral faculties.

DHA has shown great potential to protect the brain against incurred damage, such that DHA dietary supplementation for a few weeks reduces the effects of subsequent brain trauma (Wu et al., 2007, 2004a,b, c). For example, brain injured animals receiving DHA supplementation showed nearby normal performance in learning and memory tasks and nearly normal levels of BDNF-related synaptic markers in the hippocampus (Wu et al., 2007, 2008). The action of DHA is also effective to counteract the effects of the injury when supplemented in the diet of animals after the injury onset, acting on the brain (Mills et al., 2011; Wu et al., 2004a, 2007) and spinal cord (Huang et al., 2007; Mills et al., 2011). As discussed in a later section, the concurrent application of exercise to animals fed on a DHA diet has been shown to have additional beneficial effects on synaptic plasticity and cognition (Wu et al., 2008).

Dietary polyphenols

Polyphenols are found in plants and are characterized by the presence of one or more phenol groups. Curcuminoids and flavonoids are the main polyphenol subtypes with demonstrated actions on the brain. Dietary flavonoid consumption has been associated with the reduction of stroke in a 15 year longitudinal study in a cohort of 552 men aged 50–69 years (Keli et al., 1996). Several studies have been performed in animals to evaluate the effects of select polyphenols on a large variety of conditions. Dietary supplementation of blueberry extract for 8 weeks can reverse cognitive deficits in spatial learning ability in aged rats (Andres-Lacueva et al., 2005). Blueberry extracts in the diet have also shown to reduce plaque formation in an AD animal model (Joseph et al., 2003).

Curcumin

Curcumin is a major chemical component of the turmeric plant (*Curcuma longa*), which has been widely used as a spice and food preservative in India for several generations. Curcumin has shown excellent efficacy in counteracting neuronal dysfunction in several models of neurodegenerative diseases such as AD and focal cerebral ischemia (Gomez-Pinilla, 2008). Curcumin has also been shown to protect the hippocampus and to counteract learning impairment resulting from experimental TBI, in a process involving the action of the BDNF system (Wu et al., 2006). There is substantial evidence indicating that curcumin has strong antioxidant capacity exerted by increasing free radical scavengers and reducing lipid peroxidation (Wei

et al., 2006). Recent studies in rodents have shown that curcumin may counteract some of the pathology involved in TBI by restoring events important for energy homeostasis (Sharma et al., 2009).

The insidious effects of saturated fats and sugars

While certain foods can contribute positively to enhance neuronal health, diets that are rich in saturated fats and sugar can do the opposite. Molteni and colleagues have shown that rats fed on a diet high in saturated fats and refined sugars (similar in content to "junk food") for a period of 1–2 months performed significantly worse on the spatial learning mater maze test (Molteni et al., 2002a,b). The increased levels of oxidative stress induced by this diet resulted in decreased levels of hippocampal BDNF; however, this was counteracted by antioxidant treatment with vitamin E (Wu et al., 2004a,b,c). Even more alarming is the fact that consumption of this high fat diet for a period of three weeks made the effects of experimental TBI worse by reducing levels of BDNF-related synaptic plasticity, which protracted learning and memory ability (Wu et al., 2003). Interestingly, the application of voluntary exercise concurrent to the consumption of the diet reduced the deleterious effects of the diet on cognition and synaptic plasticity (Molteni et al., 2004).

How do exercise and diet collaborate?

The mechanisms for the complementary influence of diet and exercise on the brain revolve around the control of energy homeostasis and synaptic plasticity (Gomez-Pinilla et al., 2008). DHA dietary supplementation and exercise influence hippocampal plasticity and cognitive function by activating similar molecular systems, and the DHA effects are enhanced by the concurrent application of exercise (Chytrova et al., 2010; Wu et al., 2008). According to these studies, exercise seems to act on mechanisms that preserve DHA on the plasma membrane. This has important implications for neuronal signaling, as it is a well-known fact that the plasma membrane provides the substrate for the transmission of action potentials along nerves. In addition, the concurrent effects of the DHA diet and exercise involve BDNF-mediated synaptic plasticity (Wu et al., 2008). The results of these studies suggest that the inherent capacity of the brain to benefit from the effects of DHA dietary supplementation and exercise.

Studies dissecting the mechanisms for the interaction of diet and exercise (Gomez-Pinilla and Ying, 2010) have shown that DHA dietary supplementation and exercise exerted differential effects on molecular systems controlling important aspects of brain homeostasis associated with food intake, energy metabolism, and stress; all with the capacity to influence cognition. In agreement with the involvement of the hypothalamus and the hippocampus on energy homeostasis and behavior, these two regions showed distinct susceptibilities to the actions of diet and exercise. On another front, the combination of a flavonoid-enriched diet and exercise has been shown to increase the expression of genes that have a positive effect on neuronal plasticity while decreasing genes involved with deleterious processes, such as inflammation and cell death (van Praag, 2009). As discussed above, exercise has also proven to be effective in reducing the deleterious effects of unhealthy diets, i.e., the concurrent exposure to exercise compensated for the effects of this diet on reducing the levels of BDNF-related synaptic plasticity and cognitive function (Molteni et al., 2004). More recently it has been found that particular combinations of dietary factors such as curcumin and DHA can derive a larger outcome than their separate use (Agrawal et al., 2010). The overall information seems to support the possibility that combinatory strategies using exercise and select dietary factors can maximize the efficacy of mechanisms of neural repair.

Control of cell energy metabolism appears as a common denominator for the effects of diet and exercise on the brain, as several of the processes outlined above subside on the management of cellular energy. There is a direct association between pathways associated with metabolism and synaptic plasticity, and that this association can determine important aspects of behavioral plasticity such as learning and memory (Vaynman et al., 2006). Studies of multiple proteins using proteomic technology have revealed the effects of voluntary exercise on the expression pattern and post-translational modification of protein classes in the hippocampus associated with energy metabolism and synaptic plasticity (Ding et al., 2006a,b). In particular, exercise modulates molecular systems in the brain associated with energy balance and energy transduction that have the capacity to affect learning and memory, i.e., AMPK, ghrelin, ubiquitous mitochondrial creatine kinase (uMtCK), uncoupling protein 2 (UCP2), and insulin-like growth factor-I (IGF-I), and ghrelin (Gomez-Pinilla et al., 2008). The overall evidence supports the idea that diet and exercise can influence synaptic plasticity, neuronal signaling, and cognitive function by acting on critical mediators of energy metabolism. This information has functional consequences to use the power of diet to boost the positive effects of exercise. For example, as discussed above, exercise applied after experimental traumatic brain injury has beneficial effects, but the metabolic dysfunction during the acute period of TBI seems to attenuate the effects of exercise (Griesbach et al., 2007). Because certain diets have the potential to restore energy homeostasis, dietary management can be regarded as an intervention to increase the efficacy of exercise after TBI. Therefore, an important aspect of dietary therapy is to restore energy homeostasis, thereby increasing the capacity of the brain for plasticity.

Obesity and mental illness

Although feeding and locomotion have been integral requirements for survival and successful adaptation of the human species to the environment for thousands of years, the biological meaning of diet and exercise has been distorted for the last few decades. The sudden increase in industrialization and pace of life, particularly in Western Societies, has played a toll on the brain. The change in traditional dietary habits has evolved gradually with the rise of restaurant specialized in "junk food" and reductions in the amount of physical activity. In particular, traditional dietary habits based on consumption of vegetables, fruits, lean meat, fish, and whole grains has been progressively replaced by processed or fried foods, fatty meat, refined grains, and sugary products. Recent studies in humans have shown a strong association between the western diet and the risk for depression and anxiety (Jacka et al., 2010). In addition to the harmful effects on the function of the cardiovascular and nervous systems, the high calorie contents of the modern diet are a major promoter of overweight in the population. As discussed earlier, reductions in the levels of exercise can potentiate the negative effects of unhealthy diets, i.e., undermining the substrates for neuronal plasticity and function, and increasing the risk for neurological disorders.

Conclusions and research priorities

The multifactorial aspect of various neurological disorders has proven to be a diffuse target for many pharmacological strategies. In turn, the broad effective mode of action of dietary factors and exercise makes them particularly advantageous. Specific diet and exercise routines have been shown in animal studies to influence select molecular systems, which can make the brain more resistant to damage, facilitate synaptic transmission, and improve cognitive abilities. New evidence shows that dietary supplementation of DHA and curcumin has important actions on the mechanisms that maintain membrane physiology and neuronal signaling. Emerging studies indicate that exercise is capable of boosting the healthy effects of certain diets such as omega-3 fatty acids. In turn, select dietary factors such as curcumin may have the capacity to restore energy management after brain trauma, and to contribute to the effects of exercise. It

has also been observed that exercise can counteract some of the deleterious effects of a saturated-fat diet on synaptic plasticity and cognitive function of rats. Therapies based on DHA, curcumin, and exercise can benefit the brain, and have long-term consequences on molecular systems responsible for maintaining synaptic function, underlying higher order operations such as learning and memory, and emotions. The overall evidence indicates that the broad neuroprotection provided by diet and exercise could be implemented to support fundamental and broad aspects of neuronal signaling that are required for mental operation. Although there is still much to be understood in the scientific front, there is sufficient information that can be applied to solve practical problems in the human population. A practical and feasible strategy in the short-term would be to use current information to implement exercise programs, and dietary policies in schools, hospitals, and other institutions, and the community as a whole.

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