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The Influence of Dietary Factors in Central Nervous System Plasticity and Injury Recovery

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Abstract

Although feeding is an essential component of life, it is only recently that the actions of foods on brain plasticity and function have been scrutinized. There is evidence that select dietary factors are important modifiers of brain plasticity and can have an impact on central nervous system health and disease. Results of new research indicate that dietary factors exert their effects by affecting molecular events related to the management of energy metabolism and synaptic plasticity. Recent study results show that select dietary factors have mechanisms similar to those of exercise, and that, in some cases, dietary factors can complement the action of exercise. Abundant research findings in animal models of central nervous system injury support the idea that nutrients can be taken in through whole foods and dietary supplements to reduce the consequences of neural damage. Therefore, exercise and dietary management appear as a noninvasive and effective strategy to help counteract neurologic and cognitive disorders.

INTRODUCTION

Despite the limited efficacy of current therapeutic approaches to diminish the consequences of brain injury, the brain proves to have an incredible capability for plasticity. Numerous clinical trials have tested the action of pharmacologic compounds toward minimizing the burden of neurologic disorders, such as those resulting from brain and spinal cord injuries (SCI), but the results of many of these trials have been unsuccessful. In addition, the result of these failures reflects a disconnect between actual patient outcome and predicted prognosis, such that questions arise as to what unaccounted-for environmental factors can play major roles for the final expression of brain plasticity and repair [1].

Considerable efforts are being devoted to understanding how environmental conditions and lifestyle can influence the brain and body. Research results show that noninvasive approaches such as diet and exercise can have profound consequences for increasing resilience of the central nervous system (CNS) to injuries and for maintaining cognitive abilities. Diet and exercise, as 2 very important parts of lifestyle and daily routine, each can influence the capability of the brain to fight disease and to react to challenges [2]. Healthy

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diets, such as those high in omega-3 fatty acids and curcumin, contained in foods such as salmon and the plant turmeric, respectively, can stimulate molecular systems that serve neuronal function and plasticity in the brain and spinal cord. Conversely, unhealthy diets that consist of high amounts of saturated fats and sugars, as prevalent in "junk food," do the opposite. Exercise, similar to consumption of healthy foods, augments healing effects of the brain, such as helping to reverse the mental decline associated with age and providing benefits underlying rehabilitative strategies after brain injuries and SCIs, especially when implemented together with a healthy diet. Although more research is needed to fully integrate these approaches as treatment for specific neurologic disorders, results accumulated so far are substantial enough to provide a general framework to guide therapeutic applications.

Most of the published research with regard to the effects of foods in human neurologic function has been related to the use of whole foods. A growing body of evidence exists that shows the effects of select nutrients or food derivatives in several animal models of neurologic disorders. This information is conforming the concept that dietary factors can be used as biologics-based therapies. The capacity of nutrients to influence the CNS may be incorporated through management of whole foods or food-derivative supplements in the diet.

BASIC PRINCIPLES OF HOW DIET CAN AFFECT THE BRAIN AND SPINAL CORD

Healthy diets, such as those rich in omega-3 fatty acids and curcumin, have been shown to elevate levels of molecules important for daily brain function, for example, brain-derived neurotrophic factor (BDNF). BDNF is a neurotrophin considered generally beneficial for maintaining neuronal function and for promoting recovery after neurologic insult. BDNF is profuse in the hippocampus and cerebral cortex, and is found in lesser amounts in the hypothalamus and spinal cord. In addition to regulating the survival, growth, and differentiation of neurons during development, BDNF stimulates synaptic and cognitive plasticity in the adult brain [3,4]. BDNF has been shown to stimulate the efficacy of synaptic transmission in animal studies and to support learning and memory in animals and human beings. Recent findings that BDNF is associated with energy homeostasis are offering new possibilities for understanding the interaction of diet and exercise on the brain, because these are intimately related to energy metabolism. Dietary supplementation with nutrients such as omega-3 fatty acids and those of the herb curcumin can exert their influences on repair and maintenance of neural circuits important for learning and memory and for locomotion. It is also important to note that new research results indicate that the effects of exercise on BDNF are largely achieved by controlling cellular energy metabolism and synaptic plasticity, which are fundamental for modulating important behaviors [5].

DIETARY INTERVENTION FOR IMPROVEMENT OF COGNITIVE ABILITIES

Omega-3 Fatty Acids

Omega-3 fatty acids, found in great abundance in certain fish (particularly wild-caught salmon), have provided some of the strongest evidence for the profound effects that dietary factors can have on the brain. An increasing number of studies have described the health benefits of the essential fatty acid docosahexaenoic acid (DHA), which is one of the most important members of the omega-3 fatty acid family. DHA is a key component of neuronal membranes at sites of signal transduction at the synapse, which suggests that its action is vital for brain function [6]. Formation of new membrane is an essential step for the repair of damaged neural circuits after brain injury and SCI. Accordingly, omega-3 fatty acids have been shown to counteract some of the deterioration consequent to brain injury [7] and spinal

cord traumatic injury [8]. In these processes, DHA can contribute to support synaptic membrane fluidity, to elevate levels of BDNF, to reduce oxidative stress [9], and to regulate cell signaling [10]. In particular, omega-3 fatty acids have shown the capability to help reverse the effects of traumatic brain injury by stabilizing levels of molecular systems important for promoting energy homeostasis [9] and reducing oxidative stress. Study results show that 3 weeks on a fish oil–supplemented diet were sufficient to overcome the effects of concussive injury in rodents in terms of brain plasticity and cognitive function. Because of the human body's inefficiency in producing the essential fatty acid DHA, DHA dietary supplementation can be extremely important for the success of rehabilitative strategies after CNS injury. In general, omega-3 fatty acids offer great neuroprotective potential to help counteract the effects of neurologic injuries [1].

Dietary Polyphenols

Polyphenols are a large group of chemical substances found in plants characterized by the presence of multiple phenol groups. Polyphenols have powerful antioxidant properties, and some of the major groups described for their effects on the CNS are curcuminoids and flavonoids. Curcumin is the principal curcuminoid found in the Indian plant turmeric, which has gotten a reputation for its strong medicinal capacity. Flavonoids are found in many fruits and vegetables or their subproducts, such as berries (eg, blueberries, strawberries), tea, and red wine. Flavonoids can have positive effects on cognition for the treatment of brain diseases and brain injury [11]. The mechanisms by which flavonoids exert their actions in neural repair are diverse, for example, by promoting neuronal signaling and by increasing production of anti-oxidant and anti-inflammatory agents. Similar to higher dietary intake of omega-3 fatty acids, increased consumption of berry fruit shows a positive impact on reducing cognitive decay in aged rodents [12].

Curcumin—This polyphenol is most commonly known for its traditional culinary and medicinal use in India. Curcumin comes from the rhizome, or root, of the turmeric plant and is used frequently in Indian dishes (producing the familiar yellow color of curry). Curcumin has been shown to benefit the brain by providing protection, through multiple mechanisms, against neurologic disorders. As an antioxidant, anti-inflammatory, and antiamyloidal agent, curcumin can improve cognitive function in patients with Alzheimer disease (AD). For example, in a population of elderly Asians, assessment of cognitive function with a mental examination test revealed that those who consumed curry frequently performed significantly better in comparison with those who almost never or rarely consumed curry [13], which suggests a strong capacity for curcumin to affect brain function. Interestingly, the frequent use of turmeric in India has been proposed as one of the main explanations for the low percentage of clinical cases of AD in India [14]. In addition, the supplementation of curcumin to the diets for 3 weeks before [15] or after [16] experimental traumatic brain injury, using the fluid percussion injury model, was associated with a lessening of the consequences of the injury on synaptic plasticity markers and cognitive function tasks. In these studies, several markers of synaptic plasticity, such as BDNF and CREB, were measured in the hippocampus; the main cognitive test used was the Morris water maze. Results of other studies indicate the potential of curcumin for helping to counteract the deleterious effects of SCI as evidenced by increasing neuronal survival and attenuating astrocyte reactivation [17]. Finally, in a rat model, curcumin has been shown to assist recovery after cerebral ischemia/reperfusion injury by preventing blood– brain barrier damage [18].

Green Tea—Green tea is rich in flavonoids, particularly catechins such as epigallocatechin-gallate, epigallocatechin, epicatechin, and epicatechin-3-gallate. Green tea is commonly consumed in China and throughout Asia, and its consumption is perceived as

beneficial for the general heath of the organism. Scientific studies in rodents have related green tea consumption to reductions in cognitive deterioration in aging. Long-term exposure to green tea also has shown the potential to reverse some of the degenerative effects of aging in the hippocampus of rats [19]. Daily doses of the compound GT-catechin, an antioxidant found in green tea, has been shown to help prevent memory loss and DNA oxidative damage [20]. In addition, green tea consumption has been associated with the preservation of cholinergic function, as evidenced by a decline in acetylcholinesterase activity in the brain of old and young rats treated with the green tea extracts [21]. Results of other studies show that green tea polyphenols also can protect the blood– brain barrier permeability after cerebral ischemia, an action apparently related to the reduced expression of caveolin-1 [22]. Similar to the case in India, a lower prevalence of dementia is found in Japan, where green tea is consumed daily [23]. The overall evidence seems to indicate that higher consumption of green tea is associated with a lower prevalence of cognitive impairment in human beings.

Resveratrol—Resveratrol is a nonflavonoid polyphenol with 2 isomeric forms: the biologically inactive *cis*-resveratrol, and the biologically active *trans*-resveratrol (*trans*-3,4, 5-trihydroxystilbene), most commonly found in berries, grapes, and red wine. Results of animal studies have shown that resveratrol treatment 30 minutes before injury onset has protective effects, such as reducing oxidative stress, in the spinal cord after an ischemia-reperfusion injury [24]. Resveratrol has several positive effects on body physiology, such as protecting cells in the heart, brain, and kidney; increasing apoptosis; and reducing tumor growth [25]. In addition, resveratrol has been observed to have a strong “anti-aging capacity” as observed in several studies that showed an inverse correlation between wine consumption and protection against AD [26]. Interestingly, resveratrol’s neuroprotective mechanisms appear to result from its effective ability to promote caloric homeostasis by acting on the mitochondria, which results in low oxidative stress and more efficient neuronal function [27].

Caloric Intake

The amount of calories consumed per meal and the frequency of food consumption have been shown to influence cognitive function and plasticity of the brain. Fasting every other day has been observed to protect neurons in the hippocampus against excitotoxicity-induced death [28]. In this study, rats that were placed on an every-other-day fasting diet for 2–4 months had hippocampal neurons that were much more resistant to degeneration induced by kainic acid, and the animals showed greater preserved memory than rats fed ad libitum. The effects of caloric restriction also have been described in animal models of SCI. In these studies, every-other-day fasting has been shown to improve functional recovery after a partial cervical spinal cord lesion [29]. The fact that restriction of calories can increase levels of brain BDNF reinforces the idea that BDNF is a mediator for the influences of metabolic agents on brain plasticity [5]. Although caloric restriction has been shown to have positive effects in animal studies, its application to the treatment of human neurologic disorders is controversial. It is important to consider that all successful experimental approaches have used, as a base, a complete diet in terms of vitamins, minerals, essential amino acids, and fatty acids. In addition, brain injuries and SCIs involve catabolic states over the longer term that often require patients to increase food intake to maintain a healthy protein and fatty acid status.

Food Types to Avoid

Although certain foods contribute positively to neuronal health, diets that are rich in saturated fats and sugar decrease levels of BDNF in the brain and lead to poorer neuronal performance. Results of a study have shown that rats fed on a diet high in saturated fats and refined sugars (similar in content to the “junk food” that has become popular in Western

societies) for a period of 1–2 months performed significantly worse on the spatial learning water maze test than rats fed a healthier diet that was low in fat and that contained complex carbohydrates [30]. Even more alarming is that the high-fat diet consumption exacerbated the effects of experimental brain injury [31]. In these studies, exposure to a diet high in saturated fats and sucrose for 3 weeks worsened the effects of subsequent brain trauma in terms of increasing the cognitive dysfunction and reducing molecular markers of synaptic plasticity. The effects of this high-caloric diet seem to be related to elevated levels of oxidative stress and reduced synaptic plasticity, which can be reversed by antioxidant treatment [32] or exercise [33]. High caloric intake also is perceived as a risk factor for AD, in which saturated fat consumption has been observed to promote AD type β-amyloidosis in mice, whereas this is prevented by dietary restriction based on reduced carbohydrates (see [34] for review).

EXERCISE CAN COMPLEMENT THE EFFECTS OF DIET

Similar to a good diet, physical activity can benefit neuronal function and plasticity by enhancing synaptic plasticity and reducing oxidative stress. As elaborated below, the actions of exercise are complementary, which is not surprising, given that diet and exercise have been integral aspects of animal survival for thousands of years of evolution. As discussed in detail in other articles in this supplement, physical exercise can have direct effects on the brain [35] and spinal cord [36] by supporting the maintenance of the synaptic structure [37], axonal elongation [38], and neurogenesis in the adult brain [39]. Exercise has the capacity to enhance learning and memory under a variety of conditions, from helping to counteract the mental decline that comes with age [40] to facilitating functional recovery after brain injury and disease [41]. Results of several studies indicate that exercise is an important strategy to attenuate the degenerative effects of aging and to provide protection against mental disorders [40]. In turn, exercise has a demonstrated aptitude to promote plasticity in the normal spinal cord and to reduce the effects of SCI [42]. In these studies, the application of exercise after spinal cord hemisection in rodents has been shown to enhance locomotor recovery and to attenuate the reduction of markers of synaptic plasticity below the injury site.

Combined Effects of Diet and Exercise

Results of emerging studies show that exercise seems to enact its effects via molecular systems that have an intrinsic dependence on activity and energy metabolism, primarily affecting BDNF. BDNF is a recognized mediator of metabolic homeostasis, eating behavior, synaptic plasticity, and learning and memory. Given the ability of exercise to affect energy metabolism and synaptic plasticity involving BDNF, exercise may be an effective adjuvant therapy to balance the effects of dietary choices. In particular, it has been found in rats that exercise counteracts the decrease in hippocampal BDNF, synaptic plasticity, and cognitive function that are due to the consumption of a diet high in saturated fat and sucrose [33]. In turn, the effects of the combination of a healthy diet and exercise can augment the beneficial effects on brain healing and plasticity when compared with either option alone. For example, exercise is capable of boosting the healthy effects of omega-3 fatty acids on synaptic plasticity and cognition [43]. Such a synergistic combination of exercise and various types of nutrients is a common aspect of our daily living. It is remarkable that new advances in molecular biology indicate that nutrients and experiences share common mechanisms that seem to have complementary effects on brain function. The challenge is how to take advantage of this capacity to boost brain health and plasticity, as well as to counteract the effects of neurologic disorders and disease. Strong evidence also suggests that, after acute brain injuries, exercise assists neurocognitive recovery [44], but the timing for the application of exercise after the onset of the injury is still controversial [45]. In this regard,

there is an increasing demand for information on how combined dietary therapies can boost the effects of exercise after CNS injury.

Poor Dietary Management, Sedentary Lifestyle, and the Rise of Obesity

Obesity has dramatically risen in the past few decades as a consequence of inadequate diet and exercise. The sudden increase in industrialization and pace of life, particularly in Western societies, has imposed a challenge on the brain. When considering our biological dependency on physical activity and that the levels of physical activity have been decreasing proportional to the level of modernization of our society, the prevalence of inactivity in the United States has reached extremely unhealthy levels. Increasingly sedentary lifestyle and changes in dietary habits seem to be driving factors responsible for about one-third of deaths due to coronary heart disease, colon cancer, and type 2 diabetes [46]. This is in addition to reducing the resilience of the CNS to diseases and trauma. In particular, a traditional diet 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. Results of a recent study in human subjects has shown a strong association between the Western diet and the risk for depression and anxiety [47]. In addition to the harmful effects on the function of the cardiovascular and nervous systems, the high caloric contents of the modern diet are a major promoter of excessive weight in the population. As discussed earlier, reductions in the levels of exercise can potentiate the negative effects of unhealthy diets, that is, undermine the substrates for neuronal plasticity and function, and increase the risk for neurologic and psychiatric disorders.

Brain imaging studies that used tensor-based morphometry to examine gray matter and white matter volume differences in 94 elderly subjects strongly linked high body mass index, fasting plasma insulin levels, and type 2 diabetes with atrophy in frontal, temporal, and subcortical brain regions [48]. Regarding diabetes, insulin is also important for the control of synaptic plasticity and cognitive function. Although depression is not directly linked to diabetes, it is becoming well recognized that diabetes imposes a high risk for depression and mental illness. Approximately 21 million Americans have diabetes, according to the U.S. Centers for Disease Control and Prevention.

The overall evidence seems to indicate the necessity to control food intake to maintain optimal brain function and cognitive ability. Because food has been generally scarce during evolution, organisms have adapted to eat whenever food becomes available. This implies that brain circuits that control food intake are generally plastic and easily influenced by many stimuli modalities, and often leads to an exacerbation of their biological function. Indeed, many studies point to the possibility that eating disorders can follow similar mechanisms found in common types of addictive behaviors. This also implies that the capacity of exercise to interact with the dietary signal [49] can be used to control “food addictive behaviors.”

CONCLUSION

The brain’s ability to fight neurologic disorders and recover from injury is largely dependent upon lifestyle choices such as diet and exercise. Select factors, such as increasing dietary intake of omega-3 fatty acids and curcumin, as well as exercising regularly, can make the brain more resistant to damage. These healthy dietary choices can facilitate synaptic transmission, improve cognitive ability, and create a positive brain environment for overall health by involving molecules that act on metabolism and synaptic plasticity. An important instigator in the molecular machinery stimulated by exercise is BDNF, which acts at the interface of metabolism and plasticity. Implementing diet and exercise as powerful non-invasive approaches to assist in recovery from brain trauma and to facilitate regeneration of

neurons and plasticity could provide strong positive results for the progress of standard rehabilitative treatment. In particular, new information that shows that combined diet and exercise strategies provide added benefits may have a crucial impact on the design of strategies to promote neural repair after brain and SCIs or other neurologic disorders.

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