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The Influences of Diet and Exercise on Mental Health Through Hormesis

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Abstract

It is likely that the capacity of the brain to remain healthy during ageing depends upon its ability to adapt and nurture in response to environmental challenges. In these terms, main principles involved in hormesis can be also applied to understand relationships at a higher level of complexity such as those existing between the CNS and the environment. This review emphasizes the ability of diet, exercise, and other lifestyle adaptations to modulate brain function. Exercise and diet are discussed in relationship to their aptitude to impact systems that sustain synaptic plasticity and mental health, and are therefore important for combating the effects of aging. Mechanisms that interface energy metabolism and synaptic plasticity are discussed, as these are the frameworks for the actions of cellular stress on cognitive function. In particular, neurotrophins are emerging as main factors in the equation that may connect lifestyle factors and mental health.

Introduction

We interact with a transforming environment that continuously shapes our biological functions including mental health. The brain is a plastic system that derives its functional organization from interaction with environmental factors. In these terms, hormesis defined as the capacity of low doses of a potentially harmful stimulus to promote beneficial changes in adaptive plasticity, takes action. The same principles that apply at the molecular and cellular levels seem to apply at the levels of whole organism physiology. Here, I discuss the mechanisms by which lifestyle factors mold the efficacy of neuronal connections and synaptic plasticity. The ability of specific aspects of lifestyle such as diet, exercise and other challenges to modulate mental function is becoming increasingly recognized. New evidence suggests that the supporting role of brain-derived neurotrophic factor (BDNF) on synaptic plasticity and learning and memory may be achieved by interfacing with mechanisms that modulate cell energy metabolism (Fig. 1). New provocative evidence suggests that the involvement of BDNF with synaptic plasticity and energy metabolisms, may underlie even more profound biological processes such as those related to the epigenetic inheritance of cognitive traits.

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The Influence of Oxidative Metabolism on Synaptic Plasticity and Mental Capacity

Reactive oxygen species (ROS) are generated during cellular respiration, and their levels are greatly increased as a result of abnormal cell metabolism. Cells normally have buffering mechanisms to defend against damage induced by ROS. However, when ROS production exceeds the buffering capacity, cell function and viability are at risk (Gilgun-Sherki et al., 2002). Increase in ROS production has been identified as an important mechanism by which neuronal plasticity is compromised during aging (Gilgun-Sherki et al., 2002). A crucial principle involved with hormesis is that the re-establishment of disrupted homeostasis can result in an adaptive condition that is more beneficial than the prior stage. As discussed below, in this fashion, diet and exercise can affect synaptic plasticity and cognition by involving mechanisms proper of energy balance. New research indicates that oxidative stress (OS) and synaptic plasticity are interrelated events such that an imbalance in free radical formation influences synaptic plasticity and cognitive function. Neuronal and cognitive processes rely on an energy supply to maintain neuronal excitability and synaptic function (Mattson et al., 2004). Emerging evidence indicates that a disruption in energy balance can impact synaptic and cognitive function (Wu et al., 2004b, Vaynman et al., 2006). Recent studies show that molecules typically implicated in serving synaptic plasticity such as BDNF, are affected by cellular energy metabolism. New findings indicate that the interaction between OS and BDNF can be a fundamental mechanism by which aging threaten neuronal plasticity (Cheng and Mattson, 1994, Connor et al., 1997). These studies indicate that elevated ROS decreases BDNF-mediated synaptic plasticity (Wu et al., 2004b). The impact that energy metabolism has on BDNF can be seen by examining disorders of energy balance. Obesity and hyperglycemia in mice are associated with reduced BDNF levels (Lyons et al., 1999, Kernie et al.). Moreover, mitochondrial activity and BDNF are strongly interconnected (El Idrissi and Trenkner, 1999), such that by-products of mitochondrial metabolism as ROS, can limit BDNF protein expression (Wu et al., 2004b). It has also been shown that the BDNF receptor TrKB, mediates signaling mechanisms coupled with the melanocortin-4 receptor (MC4R), a critical hypothalamic element involved in energy balance. MC4R has been shown to regulate the expression of BDNF in the ventral medial hypothalamus (Xu et al., 2003)

Dietary Effects on Brain Plasticity

The effects of oxidative metabolism on cellular physiology can be clearly perceived by observing the mechanisms by which food consumption modulates levels of oxidative stress. From animal studies, it is known that the amount of calories per meal or the frequency of meals affect mental health. This is not surprising considering the feeding habits of our ancestors that have likely imprinted our genome. The early man life was cycled by times of feast and famine, such that those individuals who would convert more of their caloric intake into fat during times of food abundance would be more proficient to survive the times of famine (Booth et al., 2002).

Rodent studies indicate that a caloric restricted (CR) diet or alternating feeding with periods of fasting reduces deficits in motor and cognitive function associated with aging (Ingram et al., 1987, Means et al., 1993). Rodents maintained on an intermittent diet regimen for 2–4 months have shown hippocampal neurons that were much more resistant to degeneration and the degree of neuronal resistance, and this correlated with learning and memory on a water maze task (Bruce-Keller et al., 1999). CR and intermittent feeding increase the production of molecules involved in promoting cell survival, such as the stress proteins heat-shock protein 70 and glucose-regulated protein 78 (Heydari et al., 1996, Duan and Mattson, 1999, Yu and Mattson, 1999). It is also known that CR elevates levels of BDNF (Lee et al.,

2002, Duan et al., 2003), and that BDNF may mediate the effect of CR on increasing hippocampal neurogenesis (Lee et al., 2002). In general, it seems that CR can act by reducing the amount of oxidative stress that cells are exposed to, as evidenced by a reduction in oxidative damage to cellular proteins, lipids, and nucleic acids (McCay et al., 1989).

Besides caloric intake per se, the composition of the diet has a strong influence on the molecular substrate for plasticity, and this may involve aspects of oxidative metabolism. Rats exposure to a diet high in saturated fat and sucrose (HFS), similar in composition to "junk food" consumed in fast food restaurants, show decreased BDNF levels in the hippocampus and deficiency in learning and memory tasks (Molteni et al., 2002a). These studies have also shown high contents of OS in the hippocampus of animals exposed to the HFS diet. The fact that antioxidant therapy reduces the effects of this diet on synaptic plasticity and cognition has prompted to the idea that OS is an intermediate factor for the effects of this diet on the brain (Wu et al., 2004a). BDNF has a critical role in maintaining neural function by affecting neuronal excitability, synaptic transmission, and protecting neurons against insult. Our new studies showing that OS may affect BDNF-mediated synaptic plasticity, suggest that proper balance between OS and BDNF is important to maintain brain function.

An increasing number of studies have shown that anti-oxidant rich foods such as blueberries increase multiple parameters of hippocampal synaptic plasticity, and these parameters correlated with improvements in spatial memory (Casadesus et al., 2004). In contrast, decreasing serum levels of vitamin E were found to be associated with poor memory performance in older people (Perkins et al., 1999). Moreover, a recent study found that vitamin E improves lifespan, mitochondrial function, and tests of neurological performance in aging mice (Navarro et al., 2005). Another line of research has shown that curcumin, the yellow curry spice associated with Indian food, may be neuroprotective. Curcumin has been found to inhibit the formation of amyloid beta oligomers and fibrils, bind plaques, and reduce amyloid in an animal model of Alzheimer's disease (Yang et al., 2005). We have recently found that the curry spice curcumin, when supplemented to the diet, counteracts cognitive dysfunction resulting from elevated ROS after brain trauma (Wu et al., 2004b).

Conversely to the effects of a HFS diet, omega-3 fatty acids -- primary constituents of fish oils -- have been found to increase hippocampal BDNF and enhance cognitive function while reducing oxidative stress under challenging conditions (Wu et al., 2004a). This is consistent with a prospective study in which high fish consumption was inversely associated with cognitive impairment (Kalmijn et al., 1997). Omega-3 fatty acids belong to the family of polyunsaturated fatty acids (PUFAs) that are essential for normal brain function. A diet low in omega-3 content results in decreased learning and memory (Bourre et al., 1989, Moriguchi et al., 2000) and is associated with mental disorders such as attention deficit, dyslexia, dementia, depression, bipolar disorder, and schizophrenia (Hibbeln and Salem, 1995, Adams et al., 1996, Peet et al., 1996, Birch et al., 1998, Hibbeln, 1998, Horrobin, 1998, Fernstrom, 1999, Hoffman et al., 1999). PUFAs are prominent components of neuronal membranes at sites of high signal conduction activity (Crawford and Sinclair, 1972). In this capacity, omega-3 fatty acids, ecosapentaenoic (EPA) and docosahexaenoic acid (DHA) control the function of cells by influencing receptor and intracellular pathways. As omega-3 fatty acids are also components of mitochondrial membranes, they may modulate mitochondrial function. Omega-3 can alter neuronal function by increasing glucose metabolism (Pifferi et al., 2005) such that a deficiency in omega-3 fatty acids reduces brain glucose utilization and transport (Pifferi et al., 2005). As glucose utilization is tightly coupled with neuronal activity (Ip et al., 2003), the ability of omega-3 fatty acids to affect cognitive function may be associated with their capacity to modulate energy

metabolism. In addition to increasing glucose metabolism, omega-3 fatty acids may stimulate cellular metabolism by modulating mitochondrial genes and biogenesis (Flachs et al., 2005) and reduce the by-products of dysfunctional metabolism by limiting oxidative stress (Wu et al., 2004a).

Exercise Benefits Mental Health

Studies in humans (Suominen-Troyer et al., 1986, Kramer et al., 1999) and in rodents (Fordyce and Farrar, 1991, van Praag et al., 1999a) have demonstrated the beneficial effects of exercise on cognitive function. These studies have shown that exercise has the capacity to enhance learning and memory (Suominen-Troyer et al., 1986, Rogers et al., 1990, van Praag et al., 1999b) under a variety of conditions, from counteracting the mental decline associated with aging (Kramer et al., 1999) to facilitating functional recovery in patients suffering from brain injury or disease (Lindvall et al., 1992, Bohannon, 1993, Grealy et al., 1999). An analysis of 18 longitudinal fitness-training studies revealed that cardiovascular fitness training improves overall cognitive function regardless of task type (Colcombe and Kramer, 2003). The finding that exercise increases BDNF levels in the hippocampus --an area vital for learning and memory formation-- has provided insight about the molecular mechanisms responsible for the effects of exercise on cognition (Neeper et al., 1996, Gomez-Pinilla et al., 2002, Vaynman et al., 2003). Blocking BDNF action using specific immuno adhesive chimeres abolished the ability of exercise to augment learning and memory in the rat (Vaynman et al., 2004), in conjunction with abolishing the capacity of exercise to elevate BDNF-mediated synaptic plasticity.

Recent findings illustrate the interdependency of metabolic processes with synaptic plasticity during exercise (Fig. 2). Proteomic studies were conducted to evaluate the effect of voluntary exercise on the expression pattern and post-translational modification of multiple protein classes in the rat hippocampus (Ding et al., 2006b). A mass spectrometry analysis of 80 protein spots of relative high abundance on two-dimensional gels revealed that approximately 90% of the proteins identified were associated with energy metabolism and synaptic plasticity. The fact that most of the proteins that were found up-regulated have been implicated in cognitive function, supports a mechanism by which exercise uses processes of energy metabolism and synaptic plasticity to promote brain health.

Separate studies (Vaynman et al., 2006) have found that in the hippocampus, voluntary exercise decreases oxidative stress and increases the levels of cytochrome c oxidase-II, a specific component of the mitochondrial machinery. Infusion of 1,25-dihydroxyvitamin D3 -- a modulator of energy metabolism -- directly into the hippocampus during voluntary wheel running decreased exercise-induced BDNF and abolished the effects of exercise on end-products of BDNF action (i.e. cyclic AMP response element-binding protein and synapsin I) and modulated phosphorylated calmodulin protein kinase II, a signal transduction cascade downstream to BDNF action that is important for learning and memory. Exercise also significantly increased the expression of the mitochondrial uncoupling protein 2 (UCP2) -- an energy-balancing factor concerned with ATP production and free radical management (Kramer et al., 1999, Laurin et al., 2001) -- to suggest that mitochondrial cellular energy metabolism interacts with the BDNF-mediated system (Ding et al., 2006b). It has been suggested that the aptitude of UCP2 to decrease OS, generate ATP, and buffer calcium may contribute to the ability of the mitochondria to modulate synaptic release and gene expression.

The physiological events involved with the actions of exercise and diet integrate molecular mechanisms of proper energy metabolism to influence brain function. Inherently, exercise and diet are associated with the metabolism of energy throughout the body. The nervous

system possesses the capacity to integrate signals with the periphery that modulate energy metabolism (i.e., feeding behaviors, food breakdown, energy acquisition, expenditure, utilization, storage, and transformation). The autonomic nervous system informs the brain about various aspects of digestion such as motility, secretion, and blood flow. Vagal afferents are both sensitive to chemicals released in to blood as well as visceral distension and pain. Interestingly, it has been found that vagus stimulation enhances memory in animal and human subjects (Clark et al., 1995, Clark et al., 1999). Thus, behaviors such as exercise and feeding can affect the CNS through via neural connections from the visceral, in addition to their ability to alter energy metabolism. Recent findings show that neurotrophic factors may comprise key molecular components of a system that engages brain cellular and whole body energy metabolism to impact gene expression and interface with learning and memory mechanisms.

Mind and Body Interaction, and Hormesis

While the brain influences the body, the opposite scenario also occurs (Fig. 3). Ancient and medieval anatomists and philosophers recognized the importance of the autonomic or visceral nervous system to maintain the harmony between internal organs and the brain. Interestingly, the early observation that the gut plays an important role on emotions has not been completely overridden in the modern age. In fact, the influence of the viscera on emotions, feelings, and sorrows is emphasized in current psychiatry. The possibility to dissect the molecular mechanisms involved with the effects of diet and exercise on the CNS provides a new window to interpret the contribution of the gut to emotions and cognition in the context of modern neuroscience. Several proteins that modulate brain function such as serotonin, dopamine, glutamate, norepinephrine, and nitric oxide have been found in the viscera.

Insulin-like growth factor I (IGF-I) plays a major role in general body metabolism such as regulating plasma lipid concentration (Zenobi et al., 1993)and insulin action (Cusi et al., 1995). Transgenic mice with reduced IGF-I signaling are hyperglycemic and insulin resistant (Murphy and Nolan, 2000). Infusion of insulin IGF-I into the brain results in decreased plasma insulin levels and increased insulin sensitivity (Foster et al., 1991). The IGF-I receptor is expressed in the hippocampus (Islam et al., 1998) and seems to be involved in modulation of synaptic plasticity and cognitive function (Ding et al., 2006a). A decrease of IGF-I may substantially contribute to neurodegenerative diseases as reduced IGF-I levels have been found to exacerbate age-related increases in Aβ accumulations (Carro et al., 2002). IGF-I can also protect the brain from ischemic, oxidative, and amyloid β–peptide insults (Cheng and Mattson, 1992, Carro et al., 2002, Guan et al., 2003). Interestingly, IGF-I has been shown to entrain similar downstream pathways to BDNF action (Roudabush et al., 2000). Moreover, other conditions that intrinsically deal with energy expenditure, such as exercise, stimulate the uptake of blood born IGF-I into the brain, especially into the hippocampus (Trejo et al., 2001). Recent evidence from our own lab revealed that IGF-I is important hippocampal dependent learning and memory and that it may interact with BDNF by modulating the precursor to BDNF during exercise (Ding et al., 2006a).

Ghrelin is another peripheral metabolic protein that has a profound influence on hippocampal architecture and cognitive function (Diano et al., 2006). Ghrelin is defined as an adipogenic hormone that is secreted from the stomach when the stomach is empty (van der Lely et al., 2004), but can also be produced centrally (Cowley et al., 2003). It has been described that peripheral and central ghrelin administration increases food consumption (Wren et al., 2001, Faulconbridge et al., 2003). Ghrelin affects cognitive functions, in addition to its involvement in endocrine and metabolic regulation. This is notably demonstrated by the finding that injections of ghrelin into the hippocampus increase

memory retention in rats (Carlini et al., 2004) and is consistent with the earlier finding that the receptors for ghrelin are present in the hippocampus (Guan et al., 1997). Indeed, a recent study shows that ghrelin may have a profound action on hippocampal synaptic plasticity, altering morphology and electrophysiological parameters such as long-term potentiation, and hippocampal-dependent behavioral functions, enhancing learning and memory (Diano et al., 2006). Aging is associated with decreased ghrelin levels (Rigamonti et al., 2002). Ghrelin may be one of a set of factors that serve as molecular interfaces between energy metabolism and neuronal and cognitive function.

Dietary constraints have been shown to enhance learning and memory. For example, either reducing the amount of calories per meal (CR) or every-other-day-fasting (EODF) demonstrated an effect on mental health. Maintaining rodents on a caloric restricted diet or EODF arrested or delayed the deficits in motor and cognitive function associated with ageing (Ingram et al., 1987, Means et al., 1993). Both of these forms of dietary restriction models seem to protect hippocampal and basal cholinergic neurons against excitotoxicity-induced death (Bruce-Keller et al., 1999, Contestabile and Ciani, 2004). In addition, EODF rats exhibited a greater preserved memory than rats fed ad lib and their degree of hippocampal neuronal resistance correlated with learning and memory on a water maze task (Bruce-Keller et al., 1999). Excessive energy intake is associated with an enhanced risk for Alzheimer's and Parkinson's disease. A cohort study showed that people who ate a low-calorie or low-fat diet had a significantly lower risk for acquiring these neurodegenerative diseases than those who maintained a high-caloric intake. It is interesting to note that this increased risk factor was more strongly correlated with caloric intake than with weight or body mass index (Logroscino et al., 1996, Luchsinger et al., 2002). These findings support the contention that proper energy balance is related to healthiness in the brain machinery that maintains cognitive abilities.

Energy Expenditure, Metabolism, and BDNF

BDNF provides an excellent example of a signaling mechanism, which is both intimately connected with cognitive function and energy metabolism. BDNF is a recognized arbitrator of metabolic efficiency, eating behavior, synaptic plasticity, and learning and memory. In the mature CNS, the BDNF protein is most abundant in brain areas associated with cognitive and neuroendocrine regulation -- the hippocampus and hypothalamus, respectively (Nawa et al., 1995). BDNF function has been shown to regulate obesity (Nawa et al., 1995, Lyons et al., 1999, Kernie et al., 2000), insulin sensitivity (Pelleymounter et al., 1995, Nakagawa et al., 2002), glucose (Tonra, 1999) and lipid metabolism (Tsuchida et al., 2002), and oxidative stress (OS) levels, the harmful by-products of metabolism (Lindvall et al., 1992, Lee et al., 2002, Wu et al., 2004b). A prime example is the effect of BDNF on multiple parameters of energy metabolism in a rodent model of diabetes. Central administration of BDNF to diabetic mice lowered blood glucose levels and simultaneously increased insulin levels, enhanced thermogenesis, and upregulated the mRNA expression of the uncoupling protein 1(UCP-1) in brown adipose tissue (Nonomura et al., 2001).

Studies of transgenic mice heterozygous for BDNF, show that BDNF insufficiency results in hyperphagia, obesity, and hyperinsulinemia (Lyons et al., 1999, Kernie et al., 2000). The peripheral or central administration of BDNF reduces body weight, normalizes glucose levels (Tonra, 1999), ameliorates lipid metabolism in diabetic rodents (Tsuchida et al., 2002), and increases insulin sensitivity (Pelleymounter et al., 1995, Nakagawa et al., 2002). Hyperphagia and high oxidative stress (OS) levels, the harmful by-products of energy metabolism, decrease BDNF levels, while hypoglycemia and intermittent fasting both increase BDNF levels (Lindvall et al., 1992, Lee et al., 2002, Wu et al., 2004b). In humans, a de novo mutation affecting TrkB, the consort receptor to BDNF, is linked with both

hyperphagia and obesity and developmental delays and other defects in higher order neurological functions (Yeo et al., 2004).

The Energy Metabolism - Mind Connection

It has been postulated that as a result of environmental pressures of 'feast and famine' in man's early evolution, mechanisms that modulate cellular energy metabolism have evolved to maximize survival rates during challenging situations (Holliday, 1999). Basically, individuals who were successful in managing food resources became the fittest and this involved adaptations in hypothalamic neuro-metabolic mechanisms. Indeed, new research shows that metabolic signals interface with the hippocampus, to affect the mechanisms of synaptic plasticity underlying cognitive function (Vaynman et al., 2006). Learning and memory are central to the ability of animals to acquire energy sources and ultimately to survive. The discordance between our genes and the environment manifests on the level of diseases related to higher order cognitive function. Numerous studies have found that there may be a link between abnormal glucose metabolism, particularly an increased risk for diabetes type II and psychiatric disorders. Psychiatric disorders such as depression, bipolar, and schizophrenia are associated with cognitive deficits and in many instances in severe cognitive impairment (O'Brien, 2005). Similar findings have been reported for other psychiatric illnesses, such as manic depression. A study of 203 inpatient manic-depressive subjects, (Lilliker, 1980) reported a three fold increased rate of diabetes as compared to other psychiatric inpatients and the general US population. Schizophrenia shows the same increasing rates of diabetes as compared to controls (Tabata et al., 1987, Mukherjee et al., 1996, Dixon et al., 2000). Controlling for the confounding factor of psychotropic medication, many of which are associated with disturbances in glucose metabolism and the onset of diabetes, it has been reported (Regenold et al., 2002) that there is an intrinsic relationship between abnormal glucose metabolism and bipolar disorder type I as well as schizoaffective disorders. Interestingly, the association between metabolic dysfunction and psychiatric disorders, especially type 2 diabetes, may be related to a decrease in BDNF expression (Krabbe et al., 2007). Illustrating the relationship between metabolism and genetics, it has been found that a BDNF polymorphism contributes to a genetic vulnerability to the development of eating disorders such as bulimia nervosa and binge eating disorder (Monteleone et al., 2006).

A specific BDNF genotype polymorphism has been identified in the etiology of psychiatric disorders. The Val66Met BDNF polymorphism is a common single nucleotide missense change (G196A) that produces a non-conservative amino acid substitution of valine to methionine at codon coding exon of the BDNF-gene at position 66 (Val66Met). The Val66Met BDNF gene polymorphism has recently been linked with cognitive impairment and brain morphometric correlates in schizophrenia (Ho et al., 2006). This study found that schizophrenic subjects exhibited impairment in medial temporal lobe-related memory performances, which were associated with the specific BDNF genotype effects on gray matter volumes. Specifically, Met allele carriers exhibited smaller temporal and occipital lobar gray matter volumes (Ho et al., 2006). The Val66Met BDNF gene polymorphism has also been linked with geriatric depression and cognitive performance (Hwang et al., 2006). From the standpoint of affective disorders, BDNF has been identified as the most important neurotrophin contributing to the pathogenesis of the depressive disorders. Preclinical and clinical studies demonstrate altered BDNF expression during chronic stress and increased BDNF activity during antidepressant treatment (Filus and Rybakowski, 2005). Stress models of depression have proposed that stress-induced BDNF downregulation is a result of a repression in the transcription of the BDNF gene promoter by the activated corticosteroid receptor in the hippocampus (Schaaf et al., 2000).

Neurotrophins and Cognitive Function

Neuronal activity enhances the expression, secretion, and actions of BDNF at the synapse to result in the modification of synaptic transmission and connectivity. Sensory stimulation regulates BDNF with visual input in the visual cortex (Castren et al., 1993), and whisker stimulation in the barrel cortex (Rocamora et al., 1996). Additionally, physiological levels of activity such as exercise (Neeper et al., 1996, Vaynman et al., 2003), learning (Kesslak et al., 1998) and sleep and circadian rhythm (Bova et al., 1998, Liang et al., 1998) modulate BDNF levels. Transfection experiments employing BDNF-GFP (green fluorescent protein) fusion constructs have enabled the actual visualization of BDNF in hippocampal and cortical neurons. Accordingly, these studies have revealed that BDNF is packaged in secretory vesicles (Haubensak et al., 1998, Kojima et al., 2001). Colocalization of BDNF with specific markers -- the presynaptic secretory protein synapsin I and the postsynaptic scaffolding protein PSD95 -- revealed that the BDNF-GFP fluorescence was found to be concentrated at synaptic junctions (Haubensak et al., 1998, Kojima et al., 2001). The BDNF-GFP fluorescence spots were found to quickly disappear when depolarization or high frequency stimulation was applied, therefore suggesting that BDNF was secreted from these synaptically localized secretory vesicles (Haubensak et al., 1998, Kojima et al., 2001). Chen et al. have reported an interesting finding revealing aspects of the mechanism involved in the regulation of BDNF gene by activity (Chen et al., 2003). Using a chromatin immunoprecipitation technique, they found that the transcriptional repressor Mecp2 is bound to the rat BDNF promoter III in resting cortical neurons. However, upon the application of activity (i.e., membrane depolarization and subsequent calcium influx) BDNF transcription occurs concurrent with the dissociation of Mecp2 repression from the BDNF promoter.

Numerous studies have documented the role of BDNF in supporting learning and memory, from findings that the hippocampal BDNF expression is increased during learning tasks (Kesslak et al., 1998, Hall et al., 2000) to studies showing that genetic deletion of the BDNF gene impairs memory formation (Linnarsson et al., 1997, Ma et al., 1998, Mizuno et al., 2000). It has also been shown that hippocampal BDNF mediates the ability of exercise to enhance learning and memory (Vaynman et al., 2004). BDNF expression is higher in the hippocampi of rats that underwent hippocampal-dependent learning paradigms such as the Morris water maze task or contextual fear conditioning (Kesslak et al., 1998, Hall et al., 2000). BDNF mRNA levels have been found to be significantly increased in the CA1 region of the hippocampus during contextual fear conditioning, another hippocampal dependent learning paradigm (Hall et al., 2000). An association between hippocampal BDNF levels and learning and memory was found to exist when measuring the performance of rats on a learning and memory task (Molteni et al., 2002b). The results of this study suggest that hippocampal levels of BDNF may be directly related to learning efficiency and memory stability. Clinical studies reveal that the val66met BDNF genotype polymorphism seems implicated in abnormal hippocampal functioning and memory processing (Egan et al., 2003, Hariri et al., 2003). Egan et al. (Egan et al., 2003) found that this BDNF polymorphism seems to be linked with specific deficits in episodic memory and that this may subside with abnormal intracellular trafficking and secretion of BDNF in neuronal cells (Chen et al., 2004).

Downstream BDNF Systems Supporting Learning and Memory

Blocking experiments have identified some of the pathways that contribute to the elevation of BDNF during exercise involving molecules related to gene transcription and synaptic transmission, such as cAMP response element binding protein (CREB) and synapsin I, respectively (Vaynman et al., 2003). Evaluation of the pathways activated downstream to BDNF induction provide further insight into how exercise is capable of orchestrating its

beneficial effects on brain health and learning and memory. The two main intracellular signaling cascades found to be activated by BDNF -- CAMKII and MAPKII -- have important roles in neuronal and behavioral plasticity. TrkB receptor activation has been shown to lead to the launching of the MAPK cascade (Stephens et al., 1994), which serves as an intracellular signaling mechanism that integrates multiple signals (Sweatt, 2001) and leads to the activation of CREB mediated transcription, protein synthesis, and voltage/ion gated channels. Exercise-induced BDNF seems also to activate CAMKII (Blanquet and Lamour, 1997), which has been shown to converge on the MAPK cascade (Blanquet et al., 2003).

The Inheritable Potential for the Effects of Lifestyle on the Brain

Given the importance of lifestyle factors to modulate the health of body and mind, it is likely that the effects of lifestyle can be transmitted across generations as epigenetic phenomena. Indeed, novel findings indicate that exercise in a pregnant mother can also have a positive effect on the brain and spatial learning ability of the offspring. (Parnpiansil et al., 2003). It has been reported that the pups of pregnant rats who run on a treadmill regimen had elevated hippocampal BDNF mRNA and showed better performance on spatial learning tests than pups from sedentary mothers. Although the mechanism by which exercise in the pregnant mother benefits the newborn remains elusive, it is known that maternally derived neurotrophic factors may cross the placenta to influence the health and development of the fetus (Uchida et al., 2000, Parnpiansil et al., 2003). A more recent study on the effect of exercise during pregnancy on the offspring has found that maternal swimming exercise increases neurogenesis in the offspring (Lee et al., 2006). As hippocampal neurogenesis is very well correlated with learning and memory abilities (Kempermann et al., 1998, Gould et al., 1999, Shors et al., 2001), it may well play a significant role in the exercise-induced enhancement of cognitive function in the offspring. Exercise is already known for its ability to induce neurogenesis in the active animal (van Praag et al., 1999a). It is also possible that exercise may influence the new generation by exerting changes at the epigenetic level.

The epigenetic platform integrates with BDNF–mediated plasticity, being methyl-CpG-binding protein (MeCP2) the strongest connection to date. MeCP2 belongs to the family of methylcytosine-binding proteins that are abundantly expressed in the central nervous system and contribute to the gene silencing effect of DNA methylation (Lewis et al., 1992, Ng and Bird, 1999). The dynamic regulation of DNA methylation and MeCP2 modification contribute to the activity driven regulation of the BDNF gene. Findings indicate that MeCP2 occupies a site on the BDNF promoter in the absence of stimulation (Martinowich et al., 2003). When membrane depolarization is applied, MeCP2 dissociates from the BDNF exon IV promoter and methylation of several cysteine residues within the core promoter that results in the transcriptional repression of BDNF (Chen et al., 2003). MeCP2 extends the importance of BDNF to neural and cognitive plasticity. Mutations in the MeCP2 gene have been linked to a neuro-developmental disorder, Rett syndrome (Amir et al., 1999). Multiple studies demonstrating that MeCP2 deficiency in mice results in Rett syndrome–like abnormalities substantiate the role of MeCP2 in neuronal function (Amir et al., 1999, Chen et al., 2001, Guy et al., 2001). New findings point out that the activity dependent BDNF transcription is also regulated by the phosphorylation of MePC2 at serine 421 (S421) (Zhou et al., 2006). Neuronal activity and subsequent calcium influx was found to selectively induce a CAMKII dependent mechanism of MeCP2 phosphorylation at S421 in the brain that was required for dendritic patterning, spine morphogenesis, and activity-dependent gene expression. As MeCP2 functions as a BDNF transcriptional repressor, MeCP2 S421 phosphorylation relieves its transcriptional repressor function on the BDNF promoter IV (Zhou et al., 2006).

Conclusions

The influences of environmental factors on the brain are manifested by their abilities to promote adaptive changes using principles in common with hormesis. The novelty associated with many environmental stimuli represents a physiological challenge for affected individuals. The sustained pressure of these environmental factors results in the activation of adaptive mechanisms that can become beneficial for neuronal health and plasticity. A crucial factor for determining the ultimate biological significance of the challenge is related to the genetic disposition of affected individuals for the type of stimulus. If there is strong discordance between the challenge and the genome, the homeostasis is lost and the brain becomes vulnerable to diseases. Indeed, it is likely that many modern diseases that affect our society subside in incongruence between our genome and the environment. For example, the Western population has experienced an increase in the incidence of metabolic disorders ((Flegal et al., 1998, Sothern et al., 1999, Mokdad et al., 2001, Ogden et al., 2002). In the United States alone, 65% of adults over the age of 20 are overweight or obese (Hedley et al., 2004). The necessity for physical activity imprinted in our genome, in addition to contributing to the prevalence of obesity in modern industrialized societies (Wendorf and Goldfine, 1991, Booth et al., 2002), also imposes a risk factor for metabolic dysfunctions such as type II diabetes, hypertension, and cardiovascular disease (Jung, 1997, Must et al., 1999, Booth et al., 2002). Recent findings illustrate the interdependency of energy metabolic processes and synaptic plasticity, and this may provide a mechanism to explain how metabolic disturbances can affect mental health. Indeed, there are various psychiatric disorders that have a strong association with abnormal metabolism.

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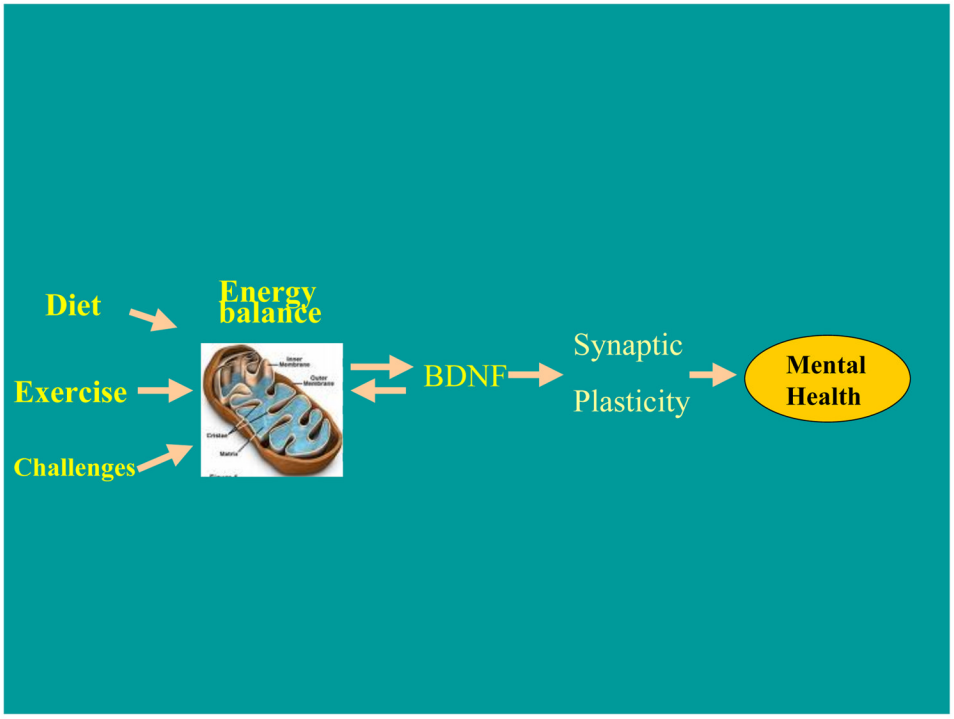

Fig. 1.

Diagram illustrating a general mechanism by which diet, exercise, and other environmental challenges can affect mental health. It is postulated that control of cellular energy balance is a confluent point for the effects of environmental factors. Energy balance via interactions with BDNF, in conjunction with other factors, can modulate synaptic plasticity underlying cognitive processes.

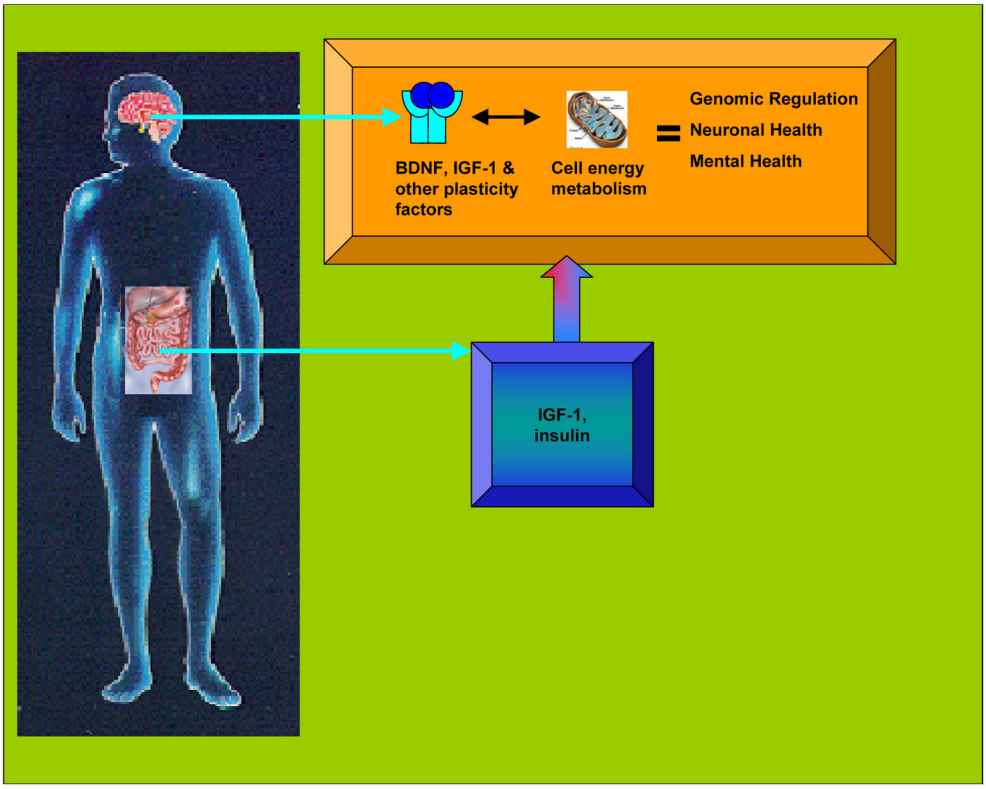

Fig. 2.

Proteomic analysis of hippocampal proteins influenced by exercise. Two-dimensional gel electrophoresis maps of the hippocampus from sedentary (A, C) and exercised (B, D) rats showing the location of protein spots. C and D are high magnifications of A and B, respectively. (E) Mass spectrometry analysis was used to identify specific protein spots, and revealed that a total of approximately 90% of the proteins identified are associated with energy metabolism or synaptic plasticity (Ding et al., Eur. J. Neurosci., 24 (2006) 1265.

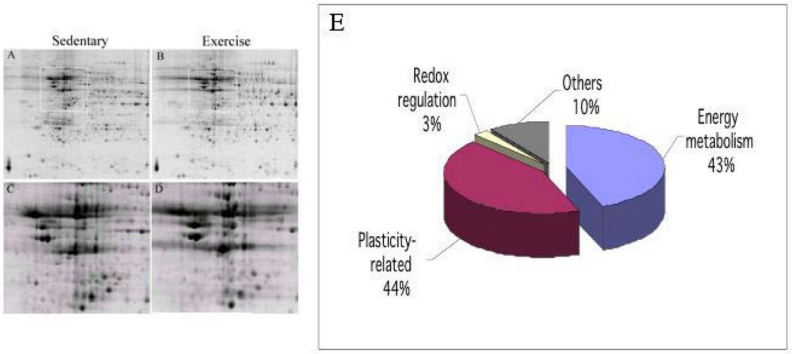

Fig. 3.

Diagram exemplifying the interaction between the gut and the brain on mental health. It is postulated that this interaction is accomplished by involving molecular and cellular mechanisms associated with energy metabolism. As discussed in the text, many molecular mechanisms attributed exclusively to the gut have been found to occur in the brain. For example, IGF-1 and insulin that are produced in the periphery can enter the CNS and modify brain function.