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*Review*

# Revenge of the "Sit": How Lifestyle Impacts Neuronal and Cognitive Health Through Molecular Systems That Interface Energy Metabolism With Neuronal Plasticity

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Exercise, a behavior that is inherently associated with energy metabolism, impacts the molecular systems important for synaptic plasticity and learning and memory. This implies that a close association must exist between these systems to ensure proper neuronal function. This review emphasizes the ability of exercise and other lifestyle implementations that modulate energy metabolism, such as diet, to impact brain function. Mechanisms believed to interface metabolism and cognition seem to play a critical role with the brain derived neurotrophic factor (BDNF) system. Behaviors concerned with activity and metabolism may have developed simultaneously and interdependently during evolution to determine the influence of exercise and diet on cognition. A look into our evolutionary past indicates that our genome remains unchanged from the times of our hunter-gatherer ancestors, whose active lifestyle predominated throughout almost 100% of humankind's existence. Consequently, the sedentary lifestyle and eating behaviors enabled by the comforts of technologic progress may be reaping "revenge" on the health of both our bodies and brains. In the 21st century we are confronted by the ever-increasing incidence of metabolic disorders in both the adult and child population. The ability of exercise and diet to impact systems that promote cell survival and plasticity may be applicable for combating the deleterious effects of disease and ageing on brain health and cognition. 

Lifestyle, befittingly what our ancestors called 'modus vivendi,' (meaning both a method of living and also an accommodation between two seemingly disparate entities), involves our conscious choice to engage in behaviors that can remarkably influence the fitness level of our body and brain. No longer dominated by the Decartian argument for the separation of mind and body, science of the 21st century recognizes that changes occurring in the body may well influence and direct the plasticity of the brain. This review explores the ability of lifestyle implementations to impact the brain, especially molecular systems sub-serving cognitive function. Main emphasis is given to exercise, however extensions into other lifestyle regulatory behaviors such as diet are discussed. Specifically, we will explore how energy metabolism may influence learning and memory processes. This link is prominently illustrated by the ability of behaviors, which involve energy consumption and expenditure, such as exercise and diet, to impact cognitive function. The influence of energy metabolism on neuronal function involves signaling molecules that control various neuronal and neuroendocrine pathways involved in the spectrum of energy metabolism, comprising feeding behaviors, food breakdown, and energy transformation (Mattson et al., 2004). Additionally, this area of biomedical research looks into the regulation of energy metabolism within neurons themselves that can facilitate specific cellular processes to impact neuronal plasticity (Horvath et al., 2003).

The gains reaped by exercise on cognitive function are documented by studies showing that exercise improves learning and memory (Suominen-Troyer et al., 1986; Rogers et al., 1990; van Praag et al., 1999), counteracts the mental decline that comes with age (Kramer et al., 1999; Laurin et al., 2001), and facilitates functional recovery from brain injury, disease (Lindvall et al., 1992; Bohannon et al., 1993; Grealy et al., 1999), and depression (Siuciak et al., 1996; Shirayama et al., 2002). Equally

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impressive, diet has been shown to influence brain function. The consumption of a diet high in saturated fats decreases learning and memory and increases metabolic distress, whereas a diet supplemented with omega 3 fatty acids or vitamin E benefits cognitive function (Molteni et al., 2002; Wu et al., 2003, 2004a). Given that exercise and diet inherently impact elements of energy expenditure and consumption, a central question is how alterations in energy metabolism interface with mechanisms of synaptic plasticity integral to cognitive function.

Possible clues into how cellular energy metabolism influences specific aspects of brain function may be gained by looking into the nature of certain molecular systems, which are central to the mechanisms of the two processes. One such suitable candidate is brain derived neurotrophic factor (BDNF). In fact, a characteristic finding for the effects of exercise on brain cognitive function is an elevation in the levels of BDNF in the hippocampus, a critical area for learning and memory processes (Neeper et al., 1996). BDNF has also been found to be important in regulating energy homeostasis, especially as demarcated by the finding that disorders of energy metabolism such as obesity, hyperglycemia, and insulin insensitivity are associated with diminished BDNF levels (Lyons et al., 1999; Kernie et al., 2000; Rios et al., 2001). Moreover, BDNF and its cognate TrkB receptor have been implicated in regulating eating behavior and energy balance. Particularly, it has been shown that mice lacking one copy of the BDNF gene, which encodes for BDNF, or have a conditional tissue-specific deletion of the BDNF gene develop in the postnatal brain, increase their food intake and develop obesity (Rios et al., 2001).

## HISTORY OF BDNF: SYNAPTIC PLASTICITY, LEARNING AND MEMORY, AND BDNF

Brain derived neurotrophic factor is a neurotrophin whose status as a regulator of the survival, growth, and differentiation of neurons during development (Barde et al., 1994; Wang et al., 1995) has matured to include the adult nervous system. Indeed, it is now known that BDNF functions to translate activity into synaptic and cognitive plasticity in the adult animal. BDNF is able to modulate the efficacy of neurotransmitter release (Kang and Schuman, 1995; Bolton et al., 2000), stimulate the synthesis of vesicle-associated proteins (Lu and Chow, 1999; Schinder and Poo, 2000), and regulate transcriptional factors (Finkbeiner et al., 1997; Tully, 1997). In the hippocampus, BDNF is capable of inducing a rapid potentiation of glutamate-mediated synaptic transmission (Lessmann and Heumann, 1998) and a long-lasting potentiation of perforant path-dentate gyrus connections in vivo (Messaoudi et al., 1998).

Learning and memory (Falkenberg et al., 1992) and long-term potentiation (LTP), considered an electrophysiologic correlate of learning and memory (Patterson et al., 1992, 2001), selectively increase BDNF mRNA levels in the hippocampus. Transgenic animals with diminished BDNF expression lose their ability to induce LTP (Patterson et al., 1996) and are impaired in learning a spatial memory task (Linnarsson et al., 1997). Quenching endogenous BDNF with function-blocking anti-BDNF antibodies, has been shown to impair learning and memory in rats on both the water maze and on an inhibitory avoidance task (Ma et al., 1998; Mu et al., 1999). Similarly, blocking endogenous BDNF was able to significantly reduce LTP (Ma et al., 1998). Moreover, replenishing the depleted hippocampus with exogenous BDNF seems to ameliorate these deficits. Exogenous BDNF application (Patterson et al., 1996) or transfection of hippocampal slices with a BDNF expressing adenovirus (Korte et al., 1995) has been shown to restore the ability to induce LTP. BDNF, but not NGF or NT-3, seems to play a role in consolidating short-term memories into long-term memories (Johnston and Rose, 2001). Clinical studies support the importance of BDNF in learning and memory in humans (Egan et al., 2003; Hariri et al., 2003). A study conducted by Egan et al. (2003) has found that individuals expressing a specific polymorphism in the BDNF gene exhibit learning impairments.

## THE RUNNING MAN: AN EVOLUTIONARY PREDISPOSITION FOR EXERCISE

The influence of the body over the workings of the mind may have its origin in the evolutionary history of mankind. Ironically, in a world that recognizes the benefits of exercise, physical inactivity characterizes most industrialized societies of our modern age. This is likely due to the benefits reaped by technological advances, which have obviated many of the necessities for physical labor. Yet, before the advent of the industrial revolution, occurring a little more than 100 years ago, the tenants of society were prodigiously more active than today. Our early ancestors predominately consisted of hunter-gatherer types (Eaton and Konner, 1985), thereby ensuring that "the running man" dominated the standard for fitness levels, as survival necessitated physical activity in their hunting and gathering excursions. According to Darwinian evolution, one can stipulate that the selection of a phenotype that would support physical activity would be advantageous for survival. The ability to acquire food and transform it into an efficient and usable source of energy was a major force in the evolution of humankind that likely soldered together cooperative molecular mechanisms underlying activity, cognition, and metabolism. Individuals who could outrun and outplan their peers in the hunt for food and then utilize gained food resources more efficiently would survive to advance this "cooperative nervous system" into the genome. Thus, physical activity may be an evolutionarily programmed necessity in our genes.

The importance of activity to brain cognitive functions may be rooted in even earlier evolutionary gains. The brain of early mobile organisms may have developed in complexity, incorporating perception and prediction as learning aspects, to maximize motor operations that increased the chances for obtaining food and therefore

the probability of survival. The need to generate physical movements to gain and compete for energy resources for survival, or what is referred to as "motricity," may have provided the impetus for mental activity: "That which we call thinking is the evolutionary internalization of movement," (Llinás, 2001). An example of this principle in "motion" is that hippocampal discharge frequencies of pyramidal neurons and interneurons are correlated with the locomotion of a rat running on a wheel, such that the discharge frequencies of these cells are found to intensify with increases in running velocity (Czurko et al., 1999). Thus, the hippocampus, a structure that has a fundamental role in memory processing has a functional dependence on physical activity.

In the 21st century, we cannot escape the fact that we are still the progeny of a human genome our ancestors acquired when they adapted an active lifestyle through out almost 100% of humankind's existence (Astrand, 1986; Cordain et al., 1998). Shockingly, the amount of physical activity we get in today's day and age has been surmised to be way below the level of physical exertion that we are genetically predispositioned to sustain (Cordain et al., 1998). Given that most of our current genome remains unchanged from the times of our hunter–gatherer ancestors (Cordain et al., 1998), the prevalence of inactivity in United States society is abnormal for a body whose genome adheres to the laws of "the running man." It has been estimated that at least 70% of the United States population gets <30 min of moderate-intensity physical activity a day (United States Department of Health and Human Services, 1996). However much the comforts of technology unburden us from taxing our bodies with unnecessary physical exertion, the consequences of a sedentary existence are evident by the ever-increasing incidence of metabolic disorders in both the adult and child population (Pinhas-Hamiel et al., 1996; Flegal et al., 1998; Libman and Arslanian, 1999; Sothern et al., 1999; Center for Disease Control and Prevention, 2001; Mokdad et al., 2001; Ogden et al., 2002). The lack of physical activity and our genetics may therefore contribute to the prevalence of obesity in modern industrialized societies (Wendorf and Goldfine, 1991; United States Department of Health and Human Services, 1996; Booth et al., 2002) and derived metabolic dysfunctions such as Type II diabetes, hypertension, and cardiovascular disease (American Diabetes Association, 1996; Jung, 1997; American Heart Association, 1999; Must et al., 1999; Booth et al., 2002). A sedentary lifestyle, or the lack of physical activity, seems to be the primary causal factor responsible for about one-third of deaths due to coronary heart disease, colon, cancer, and Type II diabetes (Powell and Blair, 1994; Allison et al., 1999). Thus, as our genes have been molded by an active lifestyle in our evolutionary past, ironically, in the modern world, the comforts of a sedentary lifestyle may be reaping "revenge" on the health of our bodies and brains.

Given that our genome is essentially that of our active ancestors, it is important to consider the losses "gained" by our present sedentary culture and the contribution of exercise to regulate systems that are critical for synaptic and cognitive plasticity. Particularly, exercise seems to employ systems that have an intrinsic dependence on activity regulation, principally impacting the neurotrophin BDNF, a recognized arbitrator of metabolic efficiency, eating behavior, synaptic plasticity, and learning and memory.

## CONSEQUENCES OF A SEDENTARY LIFESTYLE ON THE BRAIN

The damage imposed by diseases of metabolic function characteristic of today's industrialized societies may have, in addition to their impact on the body, detrimental effects on the brain. The characteristic example is BDNF, which as it is both intimately connected with cognitive function and energy homeostasis, has the capacity to be modulated by behaviors impacting energy metabolism. In fact, it has been found that a high fat diet, whose composition was formulated to closely parallel "the all American diet," decreases BDNF levels in the hippocampus and impairs learning and memory (Molteni et al., 2002).

## EXERCISE ENHANCES LEARNING AND MEMORY

In the last two decades, the benefits of exercise on cognitive function have been commended by many studies conducted on both humans and animals. 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., 1999) under a variety of conditions, from counteracting the mental decline that comes with age (Kramer et al., 1999; Laurin et al., 2001) to facilitating functional recovery after brain injury and disease (Lindvall et al., 1992; Bohannon et al., 1993; Grealy et al., 1999). A metaanalysis of the human literature conducted by Colcombe and Kramer (2003) has provided reproducible findings that exercise has a positive effect on cognitive function in humans. An analysis of 18 longitudinal fitness-training studies showed that cardiovascular fitness training improved overall cognitive function regardless of task type. Additionally, the effects that exercise seems to have on ameliorating the cognitive decline in ageing animals also extends to human senescence (Kramer et al., 1999; Colcombe and Kramer, 2003; Colcombe et al., 2004).

Only recently have studies begun to unravel the mechanisms underlying the ability of exercise to enhance cognition. Exercise seems to activate the neural circuitry involved in learning and memory, as exemplified by its action on BDNF. It has been shown that quenching the action of endogenous BDNF activated during exercise with TrkB-IgGs can fully block the exercise-induced enhancement of both learning and memory on the Morris water maze (MWM) task (Vaynman et al., 2004) (Fig. 1). Measuring the performance of rats on the MWM task has enabled us to dissect a strong relationship between BDNF and learning and memory (Molteni et al., 2002).

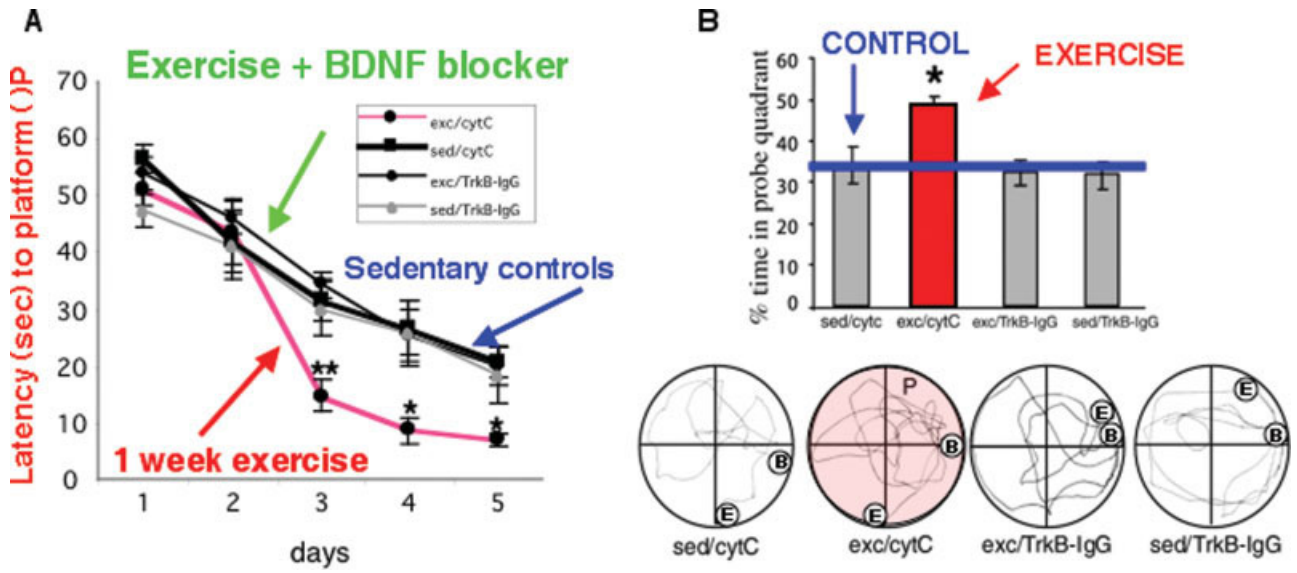


Fig. 1. Effect of exercise and blocking BDNF action during the exercise period on learning and memory as illustrated by the performance of animals on the MWM task. **A:** Exercise improved learning ability, as depicted by the enhanced aptitude of exercised animals to locate the platform in a significantly shorter time frame (shorter escape latencies in the exc/cytC group). Blocking BDNF action during exercise abolished the exercise-induced enhancement in learning ability. Exercised animals given the BDNF blocker had escape latencies comparable to sedentary control animals (exc/TrkB-IgG vs. sed /cytC). Data are expressed as mean ± SEM (ANOVA, Fischer test, Scheffe *F*-test, $^{\star}P < 0.05$, $^{\star\star},^{\ddagger\ddagger}P < 0.01$; $^{\star}$ represents comparison between groups, $^{\ddagger\ddagger}$ represents comparison within groups). **B:** Exercise increased the memory retention on the MWM task as indicated by the performance of exercised animals who spent significantly more time in quadrant P than sedentary controls (exc/cytC vs. sed/cytC). Blocking BDNF action during exercise abolished this exercise-induced preference for the P quadrant (exc/TrkB-IgG vs. exc/cytC) to sedentary control levels (exc/TrkB-IgG vs. sed/cytC), but did not have an effect on the preference of sedentary animals for the P quadrant (sed/TrkB-IgG vs. sed/cytC). Representative samples of trials traveled during the probe test (B, begin, E, end, P, quadrant that previously housed the platform) illustrate the marked preference of the exc/ctyC group for the P quadrant as compared to all other groups. Each value represents the mean ± SEM (ANOVA, Fischer test, $^{\star}P < 0.05$). [Figure can be viewed in color online via www.interscience.wiley.com].

Both learning acquisition (latency to find the platform) and memory recall (the distance swam in the platform quadrant after the platform was removed) were correlated with levels of BDNF for individual animals. The results of this study suggest that hippocampal BDNF levels seem be related to learning efficiency.

## ENTRAINING THE PATHWAYS DOWNSTREAM TO NEUROTROPHIN INDUCTION

Evaluating the pathways activated downstream to BDNF induction provide further insight into how exercise is capable of orchestrating its stimulatory effects on brain health. Especially, mechanisms through which exercise affects synaptic plasticity may underlie hippocampal dependent learning, given the observation that molecules identified as comprising these pathways downstream to BDNF action, are important for both synaptic plasticity and learning and memory (Fig. 2). The use of a novel microbead injection method for drug-mediated blocking experiments has elucidated the contribution of different pathways that may be responsible for mediating the exercise-induced changes in hippocampal synaptic plasticity (Vaynman et al., 2003). Accordingly, it was determined that exercise employs several different conduits of signal transduction, such as mitogen-activated protein kinase (MAPK), calcium/calmodulin protein kinase II (CAMKII), and the *N*-methyl-D-aspartate receptor (NMDA-R), to mediate its effects on hippocampal synaptic plasticity. Importantly, MAPK, CAMKII, and the NMDA-R were found to impact downstream effectors of BDNF action on gene expression and synaptic transmission, i.e., cAMP response element binding protein (CREB) and synapsin I, respectively (Vaynman et al., 2003).

CREB is critical for activity-dependent long-term neuronal plasticity and is believed to be an evolutionarily conserved molecule requisite for the formation of long-term memory (LTM) (Dash et al., 1990; Bourtchouladze et al., 1994; Yin et al., 1995). Specifically, CREB has been described as a molecular switch for the activation of transcription necessary for LTM (Yin et al., 1995). Disrupting CREB function with a dominant negative CREB protein impairs odor memory in Drosophila (Yin et al., 1994). Similarly, a targeted disruption of CREB isoforms results in LTM deficiency in mice (Bourtchouladze et al., 1994). Particularly, CREB seems to be an important piece in the BDNF-mediated machinery responsible for the potentiating effects of exercise on learning and memory. Blocking BDNF action during exercise was sufficient to abrogate the exercise-induced enhance-

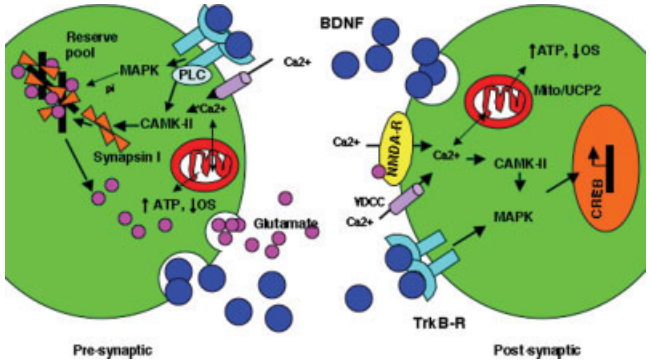


Fig. 2. Potential mechanism through which elements central to energy metabolism at the cellular level, such as mitochondria and UCP2, may interact with the substrates for synaptic plasticity in the hippocampus under the action of exercise. BDNF activates signal transduction cascades (MAP kinase and CAMKII) that in turn activate CREB and synapsin I mediated plasticity. UCP2, the uncoupling protein prominent in the brain and situated within the mitochondria, contributes to calcium homeostasis, ATP production, and oxidative stress (OS) balance. The mitochondria and UCP2 may comprise one of possible mechanisms that can interact with these signal transduction cascades, especially CAMKII, to modulate the capacity of BDNF to regulate CREB and synapsin I during exercise. The mitochondria is placed both near synaptic vesicles on the presynaptic membrane and near the NMDA-R on the postsynaptic membrane where it can serve as a calcium buffer during high calcium influxes. The presence of UCP2 at the edge of pre- and post-synaptic membranes may allow neuronal mitochondria to limit OS, increase ATP production, and modulate calcium levels, subsequently influencing vesicular release, by acting on vesicular release proteins such as synapsin I, and transcription, by impacting signal transduction cascades to activate transcriptional regulators such as CREB.

ment in learning and memory and prevent the exercise-induced increase in CREB mRNA levels and the active form of CREB (p-CREB) (Vaynman et al., 2004). With exercise, BDNF and CREB mRNA levels were significantly and positively associated with each other as well as with performance on the probe trial, illustrating that animals with the highest BDNF expression also had the highest CREB expression and the best memory recall. CREB may provide a self-perpetuating loop for BDNF action, since it has been found to regulate BDNF transcription (Tao et al., 1998) and is in turn itself regulated by BDNF (Finkbeiner et al., 1997; Tully, 1997).

Exercise has been found to employ both MAPK and CAMKII to regulate CREB expression (Vaynman et al., 2003). Both MAPK and CAMK have been repeatedly described as conserved signaling pathways that lead to CREB mediated gene transcription (Finkbeiner et al., 1997; Ying et al., 2002). The MAP kinase cascade integrates multiple intracellular signals (Sweatt, 2001). BDNF has been shown to activate CAMKII (Blanquet and Lamour, 1997), which subsequently converges on the MAP kinase cascade (Blanquet et al., 2003). MAPK targets synaptic potentiation (English and Sweatt, 1996), nuclear signaling (Adams et al., 2000), LTP (English and Sweatt, 1996, 1997), and seems to be especially necessary for learning and memory (Atkins et al., 1998; Blum et al., 1999; Impey et al., 1999; Sweat, 2001). It has been suggested that the adeptness of MAPK to induce synaptic-plasticity is attributed to its ability to regulate (Finkbeiner et al., 1997), and prolong the transcriptionally active state of CREB (Hardingham et al., 2001). Like MAPK, CAMKII is believed to be important for mechanisms underlying learning and memory (Yin and Tully, 1996). Mice with gene deletions of αCAMKII isoforms show an impaired performance on spatial learning tasks (Silva et al., 1992).

An additional player determined to promote the effects of exercise on hippocampal synaptic plasticity is the NMDA-R. 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 activation (Ghosh et al., 1994) can initiate CAMKII (Platenik et al., 2000) to converge on the MAPK cascade (Bading and Greenberg, 1991) (Fig. 2). Like the forerunners described before it, the NMDA-R is critical for modulating LTP (Bliss and Collingridge, 1993) and mediating learning and memory processes (Cammarota et al., 2000).

Other ways that exercise may benefit brain function is by modulating the transmission properties at the synapse. Studies have shown that BDNF regulates synapsin I, a phospho-protein localized to the pre-synaptic membrane, and synaptophysin, a major integral protein on synaptic vesicles (Vaynman et al., 2006a). An important function provided by synapsin I is to modulate vesicular release by tethering synaptic vesicles to the actin cytoskeleton of the cell (Greengard et al., 1993). In fact, inhibiting synapsin I reduces both the synaptic vesicle reserve pool and neurotransmitter release (Hilfiker et al., 1999). BDNF gene deletion in mice results in a reduction in synaptic proteins, sparsely docked vesicles, impaired neurotransmitter release, synaptic fatigue, and decreases synapsin I levels (Pozzo-Miller et al., 1999). Synaptophysin may be a key protein in the biogenesis of synaptic vesicles from cholesterol, whose ability to promote membrane curvature may act to facilitate vesicular budding and membrane retrieval (Thiele et al., 2000). Studies of the giant squid axon have connected synaptophysin with a role in rapid clathrin-independent vesicle endocytosis at the active zone (Daly et al., 2000). The ability to retrieve synaptic vesicle proteins through endocytosis is essential for generating fusion competent vesicles. The ability of behaviors such as exercise to impact vesicular proteins involved in synaptic release recycling, such as synapsin I and synaptophysin, respectively, may provide for rapid neurotransmission.

Findings show that presynaptic neurotransmitter release is coupled with BDNF-mediated synapsin I phosphorylation by way of MAPK induction (Jovanovic et al., 2000). During exercise, CAMKII has been shown to contribute to the BDNF regulation of synapsin I expression (Vaynman et al., 2003). This is illustrated in Figure 2, which shows that exercise induces BDNF to activate CAMKII through phospho-lipase C (PLC) anchored to its TrkB receptor (Blanquet and Lamour, 1997) to regu-

late synapsin I levels. BDNF-mediated regulation of synapsin I may exert synaptic plasticity in additional alternate ways; besides modulating transmitter release (Jovanovic et al., 2000), synapsin I is involved in the formation and maintenance of the presynaptic structure (Melloni et al., 1994; Takei et al., 1995) and in axonal elongation (Akagi et al., 1996). An adequate vesicular release pool and adequate and sustainable transmitter release provided by functional levels of synapsin I may afford the level of synaptic communication necessary for learning. A recent clinical study of familial epilepsy showed that a genetic mutation in the synapsin I gene might be associated with learning difficulties (Garcia et al., 2004).

Evaluation of an array of genes activated by exercise has corroborated the involvement of these molecules in exercise-induced synaptic plasticity. In addition, it showed that although exercise affects the expression of other neurotrophic factors, BDNF is the only neurotrophic factor consistently elevated after a few weeks of continuous exercise (Molteni et al., 2002). In fact, exercise may augment the effects of BDNF on synaptic-plasticity, by employing a positive feedback loop in which it concurrently increases the mRNA levels of both itself and its tyrosine kinase B (TrkB) receptor (Vaynman et al., 2003).

## ENERGY EXPENDITURE, METABOLISM, AND BDNF

Reminiscent of the alliance between physical activity and changes in energy balance (Hill et al., 1983; Nybo et al., 2002; Levin and Dunn-Meynell, 2004), BDNF is intimately connected with energy metabolism. Mice that either lack one copy of the BDNF gene or have a conditioned deletion of BDNF in the postnatal brain are hyperphagic and develop obesity (Rios et al., 2001). Moreover, mice with reduced BDNF levels are both obese and hyperglycemic (Lyons et al., 1999; Kernie et al., 2000). Peripheral or central infusion of BDNF has been found to reduce body weight, normalize glucose levels (Tonra et al., 1999), ameliorate lipid metabolism in diabetic rodents (Tsuchida et al., 2002), and increase insulin sensitivity (Pelleymounter et al., 1995; Nakagawa et al., 2000). Hypoglycemia and intermittent fasting both increase BDNF levels whereas hyperphagia and high oxidative stress (OS) levels, the harmful by-products of energy metabolism, decrease BDNF levels (Lindvall et al., 1992; Lee et al., 2002; Wu et al., 2004a). It is also notable that, in the mature CNS, the BDNF protein is most abundant in brain areas foremost associated with cognitive and neuroendocrine regulation, the hippocampus and hypothalamus, respectively (Nawa et al., 1995). TrB mediated signaling is coupled with the melanocortin-4 receptor (MC4R), a critical receptor involved in energy balance, such that MC4R has been shown to regulate the expression of BDNF in the ventral medial hypothalamus (Xu et al., 2003). Recent evidence from our own lab showed that during exercise, cellular energy metabolism can modulate BDNF-mediated synaptic plasticity in the hippocampus. By infusing 1, 25-dihydroxyvitamin D3 (D3), a modulator of energy metabolism that acts on the mitochondria, directly into the hippocampus during 3 days of voluntary wheel running, we found that BDNF, synapsin I, and CREB where significantly reduced (Vaynman et al., 2006b). Moreover, disrupting energy metabolism in the hippocampus reduced the expression p-CAMKII, the signal transduction cascade downstream to BDNF action. Other findings from the study showed that exercise increases the expression of the uncoupling protein 2 (UCP2), a mitochondrial protein, which uncouples substrate oxidation from ATP synthesis (Bouillaud et al., 1985; Boss et al., 1997; Vidal-Puig et al., 1997; Sanchis et al., 1998; Mao et al., 1999). It has been suggested that the ability 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. Figure 2 illustrates a potential mechanism by which cellular energy metabolism may interface with BDNF-mediated synaptic plasticity in the hippocampus during exercise.

Recently, a study by Yeo et al. (2004) documented a case that may provide clues to evaluate the role of BDNF in metabolism and cognition in human subjects. A human patient with a de novo mutation affecting TrKB, the consort receptor to BDNF, exhibited both hyperphagia and obesity and also suffered developmental delays and other defects in higher order neurologic functions. Thus, metabolism and cognitive function seem to have common signaling pathways.

## WHOLE BODY METABOLISM AND COGNITIVE FUNCTION

To better understand the interaction of synaptic plasticity and learning and memory processes with energy status, it is critical to note that mechanisms intrinsic to food metabolism interface with neuronal plasticity (Fig. 3). For example, the signaling pathways activated by insulin and BDNF regulate food intake, glucose metabolism, and learning and memory (Mattson et al., 2002). An impairment in insulin signaling in humans is an essential mechanism responsible for producing the state referred to as the "metabolic syndrome," a condition characterized by insulin resistance, hypertension, dyslipidemia, and disturbances in energy metabolism and autonomic function (Mattson et al., 2004). Developing a "metabolic syndrome" puts one in a major risk status for suffering cardiovascular disease, diabetes, and premature death (Reaven, 2004). The impaired action of insulin in peripheral tissues may not be solely responsible for the metabolic syndrome. For example, it has been found that intra-cerebroventicularly infusing insulin in sheep results in decreased plasma insulin levels and increased insulin sensitivity, and reduced food intake and body weight (Foster et al., 1991). The hypothalamus is a key site in the brain where insulin binds to its insulin receptor to regulate whole body energy metabolism and food intake. This is best illustrated by the finding that rats with decreased insulin receptors in their hypothalamus are both insulin resistant and hyperphagic

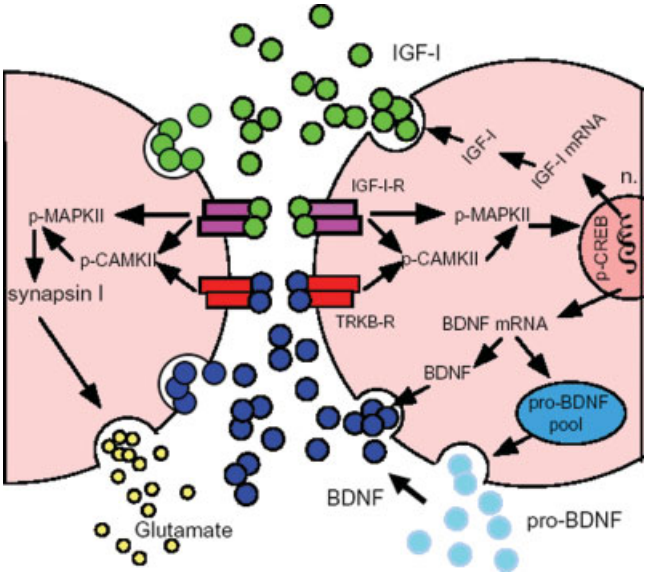


Fig. 3. Potential mechanism through which IGF-1 may interface with BDNF-mediated synaptic plasticity in the hippocampus during exercise. Exercise can induce IGF-1 production in the hippocampus. IGF-1 and BDNF are shown to have similar downstream signaling mechanisms, incorporating both p-CAMKII and p-MAPKII signaling cascades. In turn, these affect the state of vesicular release and gene expression by modulating synapsin I and CREB, respectively. IGF-1 may modulate BDNF possibly at the pro-BDNF level. The regulation of IGF-I and BDNF mRNA expression, BDNF, and pro-BDNF protein is illustrated on the postsynaptic membrane for concise purposes, although this type of regulation likely occurs on the pre-synaptic neuron as well. [Figure can be viewed in color online via www.interscience.wiley.com].

(Obici et al., 2002). However, it is important to recognize that the effect of insulin in the brain extends to structures exigent for learning and memory. Insulin receptors are expressed in high concentrations in areas involved in learning and memory and synaptic plasticity (Zhao et al., 2004). Insulin modulates neurogenesis in developmental and exercise-related paradigms (Anderson et al., 2002). Moreover, insulin resistance seems to be an important factor contributing to age-related diseases (Weindruch and Sohal, 1997) and it is linked with cognitive impairment and an increased risk for Alzheimer's disease (Arvanitakis et al., 2004).

Insulin is not the only factor of energy metabolism that impacts the brain, and in particular structures important for learning and memory. A study by During et al. (2003) found that the glucagon-like peptide 1 (GLP-1), a 37 amino acid peptide recognized as a regulator of energy metabolism, is also involved in learning and memory. Proglucagon produced by intestinal cells is proteolytically cleaved to become GLP-1, which is then released into the blood in response to food ingestion. GLP-1 lies upstream to insulin as it stimulates insulin secretion from pancreatic β-cells (Perry and Grieg, 2003). GLP-1 and its GLP-1 receptor are expressed in other regions of the brain such as the hippocampus (Jin et al., 1988; Alvarez et al., 1996; Merchenthaler et al., 1999), suggesting that GLP-1 acts more than just on the hypothalamus to suppress food intake (Christophe, 1998). According to the During et al. (2003) study, the intracerebroventrical infusion of GLP-1 or the conserved nine-amino acid N-terminal domain of the protein, Ser(2)exendin (1-9) or the intranasal infusion of Ser(2)exedin (1-9), enhanced associative and spatial memory. These effects were blocked by a GLP receptor antagonist. Additionally, hippocampal gene transfer by the overexpression of the GLP-1 receptor using an adeno-associated virus vector improved learning and memory in rats. Moreover, GLP-1 receptor deficient mice exhibit a learning deficit that is relieved after hippocampal Glp1r gene transfer (During et al., 2003). Another interesting finding of the study was that ser(2)exendin (1-9) increased the activity of mitogen activated kinase (MAP) kinase, whereas a MAP kinase inhibitor blocked the memory enhancing effects of intranasal ser(2)exendin (1-9). As discussed previously in detail, the MAP kinase cascade has a documented role in learning and memory (Atkins et al., 1998; Blum et al., 1999; Impey et al., 1999; Patterson et al., 2001; Sweatt, 2001) and seems to mediate the effects of exercise on hippocampal synaptic plasticity through its interactions with BDNF (Vaynman et al., 2003). Moreover, in pancreatic β-cells, activation of the GLP-1 receptor through its coupling to G-binding protein induces cAMP response element binding protein (CREB) activation leading to insulin secretion (Skoglund et al., 2000; Yamada et al., 2002). CREB is an evolutionary conserved molecule believed to be requisite for learning and memory (Dash et al., 1990; Bourtchouladze et al., 1994; Yin et al., 1995) and has been found to interact with BDNF on synaptic plasticity and learning and memory during exercise (Vaynman et al., 2004). Thus, it is conceivable that GLP-1 may have an effect on brain plasticity and cognitive function by interacting with molecular mechanisms associated with the action of BDNF, such as MAP kinase and CREB.

Another example of a metabolic constituent that has an action on learning and memory is the plasma insulin-like growth factor I (IGF-I). IGF-1 plays a major role in different aspects of general body metabolism such as regulating plasma lipid concentration (Zenobi et al., 1993) and insulin action (Cusi and DeFronso, 2000). Transgenic mice with reduced IGF-1 signaling are hyperglycemic and insulin resistant (Murphy, 2000). Infusion of insulin IGF-1 into the brain results in decreased plasma insulin levels and increased insulin sensitivity (Foster et al., 1991). IGF-1 also seems to be involved in synaptic plasticity (Torres-Aleman, 1999), especially as the IGF-1 receptor is expressed in the hippocampus (Islam et al., 1998). IGF-1 function has also been found to support nerve growth and differentiation, neurotransmitter synthesis and release (Anlar et al., 1999), and may contribute to sustaining cognitive function during brain trauma (Saatman et al., 1997; Carro et al., 2001), diabetes (Lupien et al., 2003), and old age (Markowska et al., 1998; Sonntag et al., 2000). A decrease of IGF-1 may substantially contribute to neurodegenerative diseases.

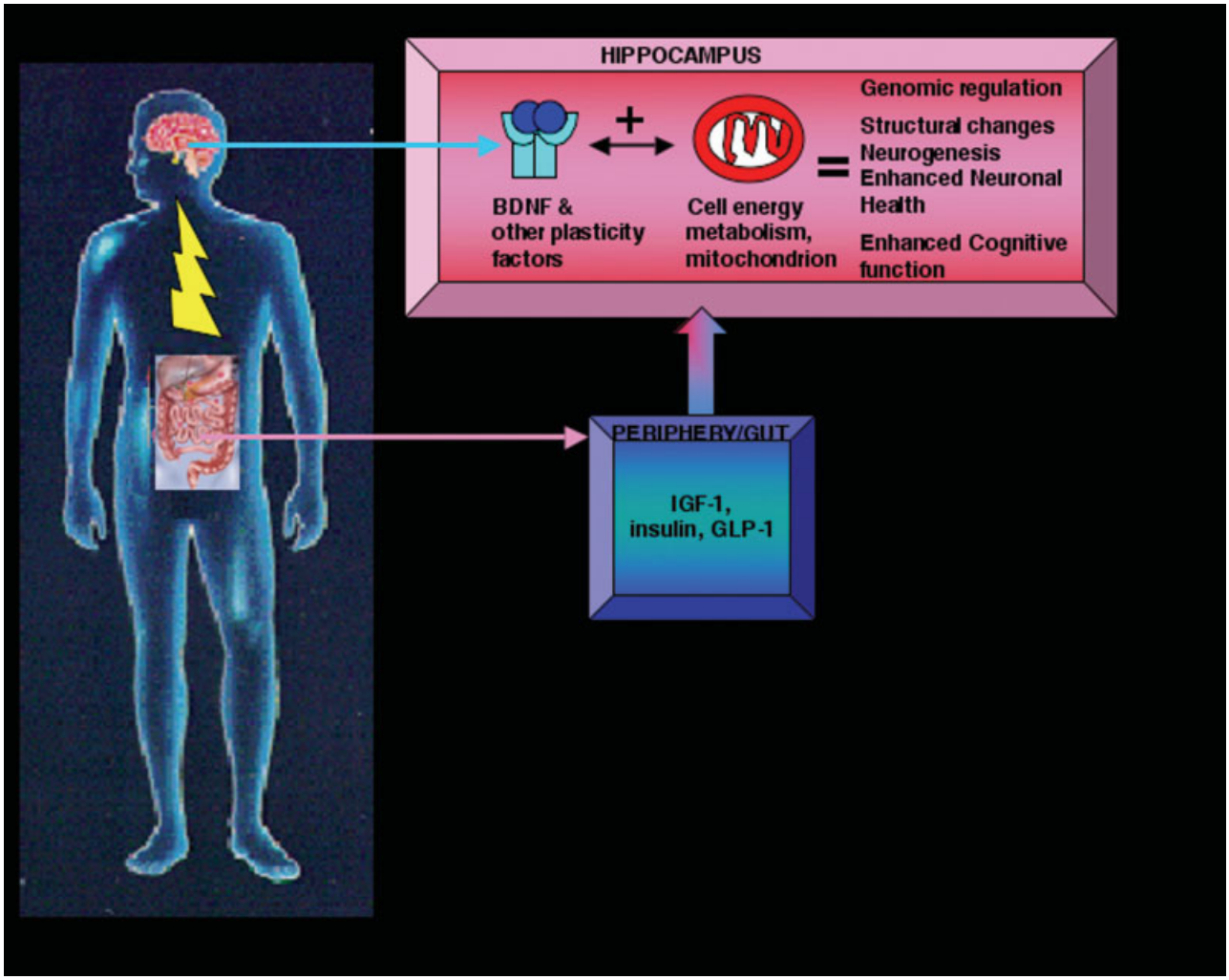


Fig. 4. This illustration summarizes the main idea of the manuscript of how the body and brain work together to influence neuronal and cognitive health. Factors produced in the periphery from the gut such as IGF-1, insulin, and GLP-1, are shown to impact BDNF and cellular energy metabolism in the hippocampus. The addition of whole body metabolism to synaptic plasticity factors and cellular metabolism contributes to induce changes in the brain such as genomic regulation, structural alterations, and neurogenesis, which ultimately promote neuronal health and cognitive function. Symbols for BDNF and the mitochondria are color coded to correspond to the detailed mechanism depicted in Figure 2.

Reduced IGF-1 levels exacerbate age-related increases in Aβ accumulations (Carro et al., 2002), especially as reuced levels of IGF-1 mRNA are found in the hippocampus of aged rats (Lai et al., 2000). This is consistent with the finding that IGF-1 can protect nervous tissue from ischemic, oxidative, and amyloid β-peptide insults (Cheng and Mattson, 1992; Carro et al., 2002; Guan et al., 2003).

The relationship between cognitive function and general body metabolism is best illustrated by the finding by Paolisso et al. (1997). Accordingly, healthy centenarians were found to exhibit plasma IGF-1/IGF-binding protein 3(IGFBP-3) molar concentrations higher than aged subjects that approximated healthy younger adults. Importantly, the IGF-1/IGFBP-3 molar ratio reflects the availability of the biologically active unbound IGF-1 that can go to the brain (Juul et al., 1995). The outstanding finding from this study was that the IGF-1/IGFBP-3 parameter in centenarians was not only positively associated with measures of general body metabolism such as a lowered body fat, reduced plasma triglycerides, free fatty acid, and low density lipoprotein, but also with the state of cognitive function (Paolisso et al., 1997). Thus, it is not surprising that IGF-1 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-1 into the brain, especially into the hippocampus (Trejo et al., 2001). Recent evidence from our own lab showed that IGF-1 is important for hippocampal dependent learning and memory and that it may interact with BDNF by modulating the precursor to BDNF during exercise

(Ding et al., 2006). Figure 3 illustrates how IGF-1 may impact BDNF-mediated synaptic plasticity. Figure 4 gives a more comprehensive view by illustrating how factors from the periphery (gut) such as IGF-1 can impact both cellular energy metabolism and synaptic plasticity related factors in the hippocampus to enhance neuronal health and cognitive function.

## MODULATING ENERGY STATUS THROUGH DIET: WAYS TO ENHANCE COGNITIVE FUNCTION

We have reviewed several elements of general body metabolism that reinforce our understanding that energy status influences our cognitive state. In this section we will look into how certain changes in diet can modulate cognitive function.

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). This study is representative of the current interest in caloric restriction.

## TO EAT OR NOT TO EAT

Dietary restriction is not a novel concept in human dietary guidelines. Back in the 12th century, Moses Malmonides, Jewish philosopher and a physician to the Persian Emperor Salahadin, stressed the importance of restricting food intake for maintaining body and brain health and particularly cautioned against the hazards to health derived from overeating, "One should not eat until one's stomach is full, but one should [only] eat until one's stomach is three-quarters full" (O'levy, 1993). Moreover, dietary restriction customs are maintained today in different religions. A prominent example is the practice of Ramadan in the Muslim faith, where for the entirety of a month, one fasts during the day to eat only after sun fall. Although possibly considered mystical in earlier times, the benefits of such dietary restriction was found to increase several factors indicative of health and disease risk such as increasing high density lipoprotein and decreasing low-density lipoprotein, cholesterol, and platelet aggregation when measured during and after the period of Ramadan (Aybak et al., 1996).

Digging further back into our evolutionary history we come to realize that just as in the case of physical activity, our ancestors had significantly different consummatory practices from the ones we have today. As hunters and gatherers, our ancestors consumed food less frequently, since meal acquisition heavily relied on the success of a hunting or gathering expedition. As food procurement and exercise were inextricably linked (Neel, 1999), early man frequently missed meals and often went for several days without eating (Rollo et al., 2002; Zimmet et al., 2003). Given that prehistoric life was cycled by times of feast and famine, those individuals that could convert more of their caloric intake into fat during times of feasting would be more adept to survive the times of famine (Neel, 1962; Booth et al., 2002). It is argued that 95% of human biology existent to day is believed to have been naturally selected in the time when our ancestors were hunters and gatherers (Trevathen et al., 1999). Thus, the lifestyles we live today in civilized countries are ones that may be maladaptive to those directed by our evolutionary makeup. Particularly, a sedentary lifestyle and a change in dietary habits seem to be prominent contributing factors to many diseases of the body and mind.

Both reducing the amount of calories per meal (CR) and every-other-day-fasting (EODF) have been shown to affect mental health. Maintaining mice or rats on a 30–40% CR or EODF has been shown to arrest or delay deficits in motor and cognitive function associated with ageing (Ingram et al., 1987; Means et al., 1993). Both CR and EODF have been shown to protect hippocampal and basal cholinergic neurons against excitotoxicity induced death (Bruce-Keller et al., 1999; Contestabile et al., 2004). Specifically, rats maintained on a EODF regimen for 2–4 months had hippocampal neurons that were much more resistant to degeneration induced by kainic acid, an amnesic excitotoxin, and greater preserved memory than rats fed ad lib; the degree of neuronal resistance correlated with learning and memory on a water maze task (Bruce-Keller et al., 1999). It should be emphasized that all of the studies so far on CR and EODR have been carried out in animals and therefore the implementation of these types of diets into our lifestyles should await concurrence from clinical trials.

The mechanisms through which DR practices promote their effects on brain function are likely due to the upregulation of proteins involved in neuronal survival and plasticity. It has been suggested that the ability of cells to activate the stress response is enhanced in animals maintained on a CR diet (Heydari et al., 1996; de Cabo et al., 2003). CR and EODF increase the production of multiple proteins 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 of prime interest that BDNF is also increased by the DR paradigm (Lee et al., 2002; Duan et al., 2003). There is evidence that BDNF may mediate the effect of DR on increasing hippocampal neurogenesis (Lee et al., 2002). In general it seems that CR can reduce the amount of oxidative stress that cells are exposed to, as it has been found that it reduces the oxidative damage to cellular proteins, lipids, and nucleic acids (McCay et al., 1989).

## WHAT TO EAT

Changes one can make in his/her dietary habits include altering the nutritional components of the food consumed. For instance, it has been shown that a high fat

diet decreases BDNF levels in the hippocampus and associated learning and memory (Molteni et al., 2002) and increases oxidative stress (Wu et al., 2004a). Conversely, omega-3 fatty acids, the primary constituents of fish oils, have been found to increase BDNF and enhance cognitive function while reducing oxidative stress in the traumatic injury model (Wu et al., 2004b). This is consistent with the prospective study in which high fish consumption was inversely associated with cognitive impairment (Kalmijn et al., 1997). Certain vitamins such as vitamin E may be beneficial for brain health. 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 ageing mice (Navarro et al., 2005). Vitamin E even may have the anti-oxidant capacity to counteract the consumption of a high fat diet, as research shows that Vitamin E has a powerful effect on limiting the amount of oxidative stress imposed by a high fat diet (Wu et al., 2004a). The oxidative capacity of vitamin E has recently been shown to normalize the levels of the silent information regulator 2 (Sir2) in the hippocampus and cerebral cortex after it had been significantly reduced by the consumption of a high fat diet (Wu et al., 2006). Sir2 increases the ability of cells to repair damaged DNA (Guarente, 2000; Kirkwood and Austad, 2000). Moreover, the anti-oxidant capacity of Vitamin E may make its supplementation a particularly accessible dietary means to modulate molecular mechanisms of synaptic plasticity and cognitive function, such as BDNF-mediated synaptic plasticity in the hippocampus (Wu et al., 2004a). Supplementing the diet with anti-oxidant rich foods such as blueberries was recently shown to increase multiple parameters of hippocampal synaptic plasticity, neurogenesis, extracellular receptor kinase activation, and IGF-1 and IGF-1 receptor levels. Moreover, all these parameters correlated with improvements in spatial memory (Casadesus et al., 2004). Another change one can make is to add a little spice to one's diet. Research has shown that curcumin, the yellow curry spice most associated with Indian food, may be good for brain health and in particular, 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).

## AGEING

To live a cell must obtain energy. The predominant part of a cell's energy supply comes from the mitochondria through the process of oxidative phosphorylation. Unfortunately, consequent of this cellular metabolic process, the cell is exposed to the harmful by-products of oxidative respiration known as reactive oxidative species (ROS). Excess ROS production could produce deleterious consequences to cell integrity by oxidative modification of its proteins, nucleic acids, and membrane phospholipids.

Ageing is a process by which the cell's integrity gets weakened over time by the accumulation of ROS, which wreck havoc on cellular mechanisms and machinery. It may be surmised that differences in how we age are really differences in the accumulation of wear and tear experienced by our cells due to the interaction of our genetic constitution with lifestyle choices. These changes in molecular structure transmute to the behavioral level, as ROS accumulation has been implicated in perpetuating the cognitive decline seen with age (Liu et al., 2002; Nagai et al., 2003). The accumulation of oxidative modifications in proteins has been reported to be elevated in older animals as compared to their younger counterparts (Stadtman, 1992; Sohal and Weindruch, 1996) and has been associated with age-related losses in cognitive function and motor skills in mice (Forster et al., 1996). Direct evidence for the involvement of ROS in ageing comes from a study conducted by Carney and Floyd (1991); a 2-week administration of *N*-tert-butyl α-phenylnitrone, a spin trapping compound that is believed to interfere with the oxidative events involved in the formation of oxidized proteins, decreased age-associated increases in the accumulation of reactive carbonyl derivatives (a measure of ROS) in the brain of gerbils while simultaneously improving their short-term memory. This finding was reproduced in the rat model, such that chronic anti-oxidant treatment improved cognitive performance in aged rats (Socci et al., 1995).

A major finding has been that ageing is accompanied with decreased BDNF levels in the brain. As suggested from studies on monkeys, this trend seems to be especially conspicuous in hippocampal pyramidal and dentate granule cells (Hayashi et al., 2001). Moreover, age-related decreases in hippocampal BDNF levels seem to translate to the behavioral level, as they correlate with age-related impairments in learning and memory in rats (Schaaf et al., 2001).

Exercise, which increases BDNF levels, has been shown to counteract the mental decline accompanying senescence (Kramer et al., 1999; Laurin et al., 2001). Studies over the last decade have shown the beneficial effects of exercise on improving or maintaining cognition, especially in aged populations. Human studies, involving a large number of subjects, have shown that the provision of an exercise program reduces the normal decay in cognitive function observed during ageing (Kramer et al., 1999).

The ability of exercise to improve cognitive function by engaging neurotrophic action may also rely on an interface with metabolic processes, which alter the amount of oxidative stress. Studies have shown that a regular exercise regimen retards the accumulation of cell damage and physiologic dysfunction characteristic of the ageing process (Radak et al., 2001; Kirkwood, 2002). A study that exposed rats to a regular exercise regimen (5 days a week over a 9-week period) found that the exercised animals exhibited improved performance on a learning and memory task accompanied by reduced brain levels of membrane lipid peroxidation and oxidative damage to DNA (Radak et al., 2001). Interestingly, the ability of exercise to reduce oxidative stress was especially robust when carried out on older rats (Goto et al., 2004).

Brain derived neurotrophic factor is capable of promoting the survival of various cell types throughout the CNS and PNS both in vitro and in vivo (Nonmura and Hatanaka, 1992; Koliatsos et al., 1993; Lindholm et al., 1993; Abiru et al., 1996). Particularly, BDNF can protect CNS neurons from oxidative stress (Cheng and Mattson, 1994; Kirschner et al., 1996) and may target the source of free radical production as BDNF addition has been shown to impact mitochondrial activity (El Idrissi and Trenker, 1999).

## EXERCISE INDUCES NEUROGENESIS AND POSSIBLY NEW CONDUITS FOR LEARNING AND MEMORY

A characteristic feature of the developing brain is the continual production of neuronal precursor cells (Altman and Bayer, 1990). The proliferative potential of the adult brain was suggested by Altman in 1962 (Altman, 1962). However, it has only been recently substantiated that the adult mammalian brain continues to produce limited pockets of neural stem cells that are capable of undergoing neurogenesis, i.e., dividing and differentiating into neurons. This process of neurogenesis seems to be circumscribed to the subventricular zone, lying adjacent to the lateral ventricle, and the subgranular zone of the hippocampal dentate gyrus (Gage et al., 1998). These inceptive neurons, constantly arising from the precursor cells in the subgranular zone of the dentate gyrus, migrate into the subgranular cell layer and can incorporate into existing synaptic circuitry (Gould et al., 2000). In fact, thousands of new granule cells are produced per day (Cameron and McKay, 2001).

The number of these nascent cells is influenced by environmental conditions, with exercise being a powerful inducer of neurogenesis in the adult dentate gyrus (van Praag et al., 1999). Because hippocampal neurogenesis may play a role in the formation of hippocampal dependent memories (Shors et al., 2001), this exercise-induced neurogenesis may contribute to remodeling hippocampal synaptic circuitry and enhancing cognitive function in the adult brain. Indeed, exercise-induced hippocampal neurogenesis is accompanied by an enhancement in learning and memory and it's electrophysiological correlate, LTP (van Praag et al., 1999). The properties of these new neurons, especially their ability to more readily induce associative LTP, may guide their wiring into neural circuits and thereby facilitate synaptic plasticity processes possibly important for new memory formation (Schmidt-Hieber et al., 2004). Brain derived neurotrophic factor may mediate the effect of exercise on hippocampal neurogenesis as BDNF administration into the dentate gyrus has recently been shown to increase neurogenesis (Scharfman et al., 2005). Moreover, BDNF induction may be provisional for the sustenance of newly formed circuits given its significance to cell survival and communication. BDNF is important for the growth and survival of granule cells in primary culture (Holtzman and Lowenstein, 1995; Patel and McNamara, 1995) and the morphology of adult granule cells (Danzer et al., 2002). BDNF has been shown to increase excitatory transmission, in CA1 (Korte et al., 1995; Figurov et al., 1996; Patterson et al., 1996; Lu, 2003), CA3 (Scharfman, 1997) and the DG (Messaoudi et al., 1998; Asztely et al., 2000). The significance of these findings is that it may be possible to use activators of endogenous BDNF, such as exercise, to increase neuronal cell number after the brain has undergone cell loss as in the case of trauma, disease, and ageing.

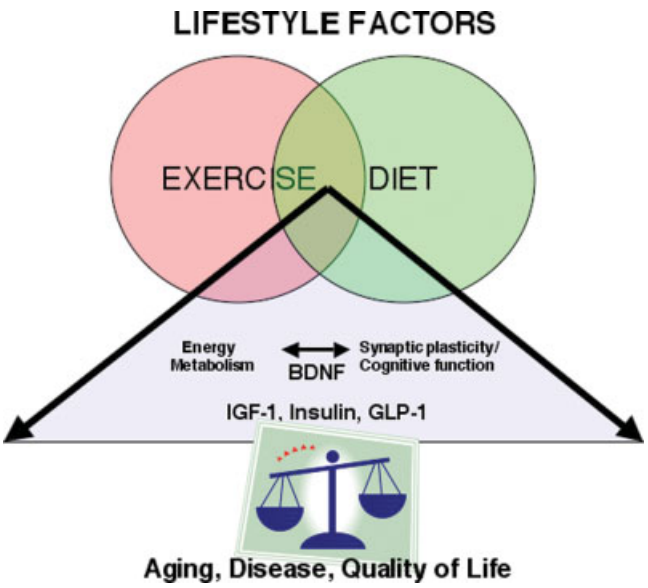


Fig. 5. The influence of lifestyle choices, exercise and diet, on metabolism and neuro-cognitive health. Energy metabolism and aspects of brain function are shown to interface through common factors, BDNF, and possibly IGF-1, insulin, and GLP-1. A lack of exercise as characterized by a sedentary lifestyle, and an unhealthy diet may tip the scales, leading to accelerated ageing, diseases of the body and brain, and an overall decline in the quality of life. [Figure can be viewed in color online via www.interscience.wiley.com].

## CONCLUSIONS

The findings presented in this review stress that lifestyle implementations such as exercise, seem to inherently activate systems concerned with whole body metabolism and brain plasticity (Fig. 5). The ability of behaviors, which rely on managing energy status to interface with molecular mechanisms underlying cognitive function, may have been selected by the active lifestyle and eating patterns of our early ancestors. In a modern world where the ills of the body and brain can be delineated to sedentary lifestyle and bad dietary choices, it is ever more so important to realize the connection that the body holds with the brain. The literature presented suggests that physical activity or what one can call "Motricity" is intimately connected with cognitive function. Behaviors such as exercise, which are concerned with activity and metabolism, may have developed simultaneously and interdependently during evolution to ultimately determine how

lifestyle influences cognitive function. To take the metaphor of the sea squirt, we can visualize an extreme example of this connection between Motricity and mentality. The sea squirt is a marine creature that starts life as a motile larva, equipped with a rudimentary brain-like ganglion of about 300 neurons. After swimming to find its final habitat destination it puts its roots down. Once it becomes a sessile organism, it has no further use for a "brain," and so the cerebral ganglion breaks down. Although not as conspicuous as the sea squirt, the persistence of a strong relationship between activity and brain function in animals engenders the question whether a sedentary lifestyle can be harmful for the brain.

Given the ability of exercise to augment BDNF levels, exercise may be an effective life style implementation that can abate if not combat the effects of stress-related lifestyle choices. In particular, it has been found that exercise can counteract the decrease in hippocampal BDNF levels due to the consumption of a high fat diet (Molteni et al., 2004). It should be emphasized that other complementary lifestyle alterations such as changes in the nutrient content of one's diet (Paolisso et al., 1997; Molteni et al., 2002; Wu et al., 2004a,b) can also be implemented to increase both body and brain health. Moreover, these lifestyle implementations, by activating systems that act on metabolism and plasticity, such as BDNF, can be used to ameliorate the natural accumulations of oxidative stress our bodies and brains accumulate over time and thereby contribute to successful ageing, resistance to disease, and our overall quality of life.

## REFERENCES


Abiru Y, Nishio C, Hatanaka H. 1996. The survival of striatal cholinergic neurons cultured from postnatal 2-week-old rats is promoted by neurotrophins. Brain Res Dev Brain Res 91:260–267.

Adams JP, Roberson ED, English JD, Selcher JC, Sweatt JD. 2000. MAPK regulation of gene expression in the central nervous system. Acta Neurobiol Exp (Warsz) 60:377–394.

Akagi S, Mizoguchi A, Sobue K, Nakamura H, Ide C. 1996. Localization of synapsin I in normal fibers and regenerating axonal sprouts of the rat sciatic nerve. Histochem Cell Biol 105:365–373.

Allison DB, Fontaine KR, Manson JE, Stevens J, VanItallie TB. 1999. Annual deaths attributable to obesity in the United States. JAMA 282: 1530–1538.

Altman J. 1962. Are neurons formed in the brains of adult mammals? Science 135:1127–1128.

Altman J, Bayer SA. 1990. Migration and distribution of two populations of hippocampal granule cell precursors during the perinatal and postnatal periods. J Comp Neurol 301:365–381.

Alvarez E, Roncero I, Chowen JA, Thorens B, Blazquez E. 1996. Expression of the glucagon-like peptide-1 receptor gene in rat brain. J Neurochem 66:920–927.

American Diabetes Association. Diabetes 1996. Vital statistics. Alexandria, VA: American Diabetes Association.

American Heart Association. 1999. Heart and stroke statistical update. Dallas, TX: American Heart Association

Anderson MF, Aberg MA, Nilsson M, Eriksson PS. 2002. Insulin-like growth factor-I and neurogenesis in the adult mammalian brain. Brain Res Dev Brain Res 134:115–122.

Anlar B, Sullivan KA, Feldman EL. 1999. Insulin-like growth factor-I and central nervous system development. Horm Metab Res 31:120–125.

Arvanitakis Z, Wilson RS, Bienias JL, Evans DA, Bennett DA. 2004. Diabetes mellitus and risk of Alzheimer disease and decline in cognitive function. Arch Neurol 61:661–666.

Astrand PO, Rodahl K. 1986. Textbook of work physiology. New York: McGraw Hill. p 1–11.

Asztely F, Kokaia M, Olofsdotter K, Ortegren U, Lindvall O. 2000. Afferent-specific modulation of short-term synaptic plasticity by neurotrophins in dentate gyrus. Eur J Neurosci 12:662–669.

Atkins CM, Selcher JC, Petraitis JJ, Trzaskos JM, Sweatt JD. 1998. The MAPK cascade is required for mammalian associative learning. Nat Neurosci 1:602–609.

Aybak M, Turkoglu A, Sermet A, Denli O. 1996. Effect of Ramadan fasting on platelet aggregation in healthy male subjects. Eur J Appl Physiol Occup Physiol 73:552–556.

Bading H, Greenberg ME. 1991. Stimulation of protein tyrosine phosphorylation by NMDA receptor activation. Science 23:912–914.

Barde YA. 1994. Neurotrophins: a family of proteins supporting the survival of neurons. Prog Clin Biol Res 390:45–56.

Blanquet PR, Mariani J, Derer P. 2003. A calcium/calmodulin kinase pathway connects brain-derived neurotrophic factor to the cyclic AMP-responsive transcription factor in the rat hippocampus. Neuroscience 118: 477–490.

Blanquet PR, Lamour Y. 1997. Brain-derived neurotrophic factor increases Ca2+/calmodulin-dependent protein kinase 2 activity in hippocampus. J Biol Chem 272:24133–24136.

Bliss TVP, Collinridge GL. 1993. A synaptic model of memory: long-term potentiation in the hippocampus. Nature 361:31–39.

Blum S, Moore AN, Adams F, Dash PK. 1999. A mitogen-activated protein kinase cascade in the CA1/CA2 subfield of the dorsal hippocampus is essential for long-term spatial memory. J Neurosci 19:3535–3544.

Bohannon RW. 1993. Physical rehabilitation in neurologic diseases. Curr Opinion Neurol 6:765–772.

Bohannon RW. 1993. Physical rehabilitation in neurologic diseases. Curr Opinion Neurol 6:765–772.

Bolton MM, Pittman AJ, Lo DC. 2000. Brain-derived neurotrophic factor differentially regulates excitatory and inhibitory synaptic transmission in hippocampal cultures. J Neurosci 20:3221–3232.

Booth FW, Chakravarthy MV, Gordon SE, Spangenburg EE. 2002. Waging war on physical inactivity: using modern molecular ammunition against an ancient enemy. J Appl Physiol 93:3–30.

Boss O, Samec S, Dulloo A, Seydoux J, Muzzin P, Giacobino JP. 1997. Tissue-dependent upregulation of rat uncoupling protein-2 expression in response to fasting or cold. FEBS 412:111–114.

Bouillaud F, Ricquier D, Thibault J, Weissenbach J. 1985. Molecular approach to thermogenesis in brown adipose tissue: cDNA cloning of the mitochondrial uncoupling protein. Proc Natl Acad Sci U S A 82: 445–448.

Bourtchouladze R, Frenguelli B, Blendy J, Cioffi D, Schutz G, Silva AJ. 1994. Deficient long-term memory in mice with a targeted mutation of the cAMP-responsive element-binding protein. Cell 79:59–68.

Bruce-Keller AJ, Umberger G, McFall R, Mattson MP. 1999. Food restriction reduces brain damage and improves behavioral outcome following excitotoxic and metabolic insults. Ann Neurol 45:8–15.

Cameron HA, McKay RD. 2001. Adult neurogenesis produces a large pool of new granule cells in the dentate gyrus. J Comp Neurol 435:406–417.

Cammarota M, de Stein ML, Paratcha G, Bevilaqua LR, Izquierdo I, Medina JH. 2000. Rapid and transient learning-associated increase in NMDA NR1 subunit in the rat hippocampus. Neurochem Res 25: 567–572.

Carney JM, Floyd RA. 1991. Protection against oxidative damage to CNS by alpha-phenyl-tert-butyl nitrone (PBN) and other spin-trapping agents: a novel series of nonlipid free radical scavengers. J Mol Neurosci

3:47–57.
Carro E, Trejo JL, Busiguina S, Torres-Aleman I. 2001. Circulating insulin-like growth factor I mediates the protective effects of physical exercise against brain insults of different etiology and anatomy. J Neurosci 21:5678–5684.
Carro E, Trejo JL, Gomez-Isla T, LeRoith D, Torres-Aleman I. 2002. Serum insulin-like growth factor I regulates brain amyloid-beta levels. Nat Med 8:1390–1397.
Casadesus G, Shukitt-Hale B, Stellwagen HM, Zhu X, Lee HG, Smith MA, Joseph JA. 2004. Modulation of hippocampal plasticity and cognitive behavior by short-term blueberry supplementation in aged rats. Nutr Neurosci 7:309–316.
Center for Disease Control and Prevention. 2001. Behavioral risk factor surveillance system survey data. Atlanta, GA: US Department of Health and Human Services, Center for Disease Control and Prevention.
Cheng B, Mattson MP. 1992. IGF-I and IGF-II protect cultured hippocampal and septal neurons against calcium-mediated hypoglycemic damage. J Neurosci 12:1558–1566.
Cheng B, Mattson MP. 1994. NT-3 and BDNF protect CNS neurons against metabolic/excitotoxic insults. Brain Res 640:56–67.
Christophe J. 1998. Is there appetite after GLP-1 and PACAP? Ann NY Acad Sci 865:323–335.
Colcombe S, Kramer AF. 2003. Fitness effects on the cognitive function of older adults: a meta-analytic study. Psychol Sci 14:125–130.
Colcombe SJ, Kramer AF, McAuley E, Erickson KI, Scalf P. 2004. Neurocognitive aging and cardiovascular fitness: recent findings and future directions. J Mol Neurosci 24:9–14.
Contestabile A, Ciani E, Contestabile A. 2004. Dietary restriction differentially protects from neurodegeneration in animal models of excitotoxicity. Brain Res 1002:162–166.
Cordain L, Gotshall RW, Eaton SB, Eaton SB 3rd. 1998. Physical activity, energy expenditure and fitness: an evolutionary perspective. Int J Sports Med 19:328–335.
Cusi K, DeFronzo R. 2000. Recombinant human insulin-like growth factor I treatment for 1 week improves metabolic control in type 2 diabetes by ameliorating hepatic and muscle insulin resistance. J Clin Endocrinol Metab 85:3077–3084.
Czurko A, Hirase H, Csicsvari J, Buzsaki G. 1999. Sustained activation of hippocampal pyramidal cells by 'space clamping' in a running wheel. Eur J Neurosci 11344–11352.
Danzer SC, Crooks KR, Lo DC, McNamara JO. 2002. Increased expression of brain-derived neurotrophic factor induces formation of basal dendrites and axonal branching in dentate granule cells in hippocampal explant cultures. J Neurosci 22:9754–9763.
Daly C, Sugimori M, Moreira JE, Ziff EB, Llinas R. 2000. Synaptophysin regulates clathrin-independent endocytosis of synaptic vesicles. Proc Natl Acad Sci U S A 97:6120–6125.
Dash PK, Hochner B, Kandel ER. 1990. Injection of the cAMP-responsive element into the nucleus of Aplysia sensory neurons blocks long-term facilitation. Nature 345:718–721.
de Cabo R, Furer-Galban S, Anson RM, Gilman C, Gorospe M, Lane MA. 2003. An in vitro model of caloric restriction. Exp Gerontol 38:631–639.
Ding Q, Vaynman S, Akhavan M, Ying Z, Gomez-Pinilla F. 2006. Insulin-like growth factor I interfaces with brain-derived neurotrophic factor-mediated synaptic plasticity to modulate aspects of exercise-induced cognitive function. Neuroscience 140:823–833.
Duan W, Guo Z, Jiang H, Ware M, Li XJ, Mattson MP. 2003. Dietary restriction normalizes glucose metabolism and BDNF levels, slows disease progression, and increases survival in huntingtin mutant mice. Proc Natl Acad Sci U S A 100:2911–2916.
Duan W, Mattson MP. 1999. Dietary restriction and 2-deoxyglucose administration improve behavioral outcome and reduce degeneration of dopaminergic neurons in models of Parkinson's disease. J Neurosci Res 57:195–206.
During MJ, Cao L, Zuzga DS, Francis JS, Fitzsimons HL, Jiao X, Bland RJ, Klugmann M, Banks WA, Drucker DJ, Haile CN. 2003. Glucagon-like peptide-1 receptor is involved in learning and neuroprotection. Nat Med 9:1173–1179.
Eaton SB, Konner M. 1985. Paleolithic nutrition. A consideration of its nature and current implications. N Engl J Med 312:283–289.
Egan MF, Weinberger DR, Lu B. 2003. Schizophrenia, III: brain-derived neurotropic factor and genetic risk. Am J Psychiatry 160:1242.
El Idrissi A, Trenker E. 1999. Growth factors and taurine protect against excitotoxicity by stabilizing calcium homeostasis and energy metabolism. J Neurosci 19:9459–9468.
English JD, Sweatt JD. 1997. A requirement for the mitogen-activated protein kinase cascade in hippocampal long term potentiation. J Biol Chem 272:19103–19106.
English JD, Sweatt JD. 1996. Activation of p42 mitogen-activated protein kinase in hippocampal long-term potentiation. J Biol Chem 271:24329–24332.
Falkenberg T, Mohammed AK, Henriksson B, Persson H, Winblad B, Lindefors N. 1992. Increased expression of brain-derived neurotrophic factor mRNA in rat hippocampus is associated with improved spatial memory and enriched environment. Neurosci Lett 138:153–156.
Figurov A, Pozzo-Miller LD, Olafsson P, Wang T, Lu B. 1996. Regulation of synaptic responses to high-frequency stimulation and LTP by neurotrophins in the hippocampus. Nature 381:706–709.
Finkbeiner S, Tavazoie SF, Maloratsky A, Jacobs KM, Harris KM, Greenberg ME. 1997. CREB: a major mediator of neuronal neurotrophin responses. Neuron 19:1031–1047.
Flegal KM, Carrol MD, Kuczmarski RJ, Johnson CL. 1998. Overweight and obesity in the United States: prevalence and trends, 1960–1994. Int J Obesity 22:39–47.
Forster MJ, Dubey A, Dawson KM, Stutts WA, Lal H, Sohal RS. 1996. Age-related losses of cognitive function and motor skills in mice are associated with oxidative protein damage in the brain. Proc Natl Acad Sci U S A 93:4765–4769.
Foster LA, Ames NK, Emery RS. 1991. Food intake and serum insulin responses to intraventricular infusions of insulin and IGF-I. Physiol Behav 50:745–749.
Gage FH, Kempermann G, Palmer TD, Peterson DA, Ray J. 1998. Multipotent progenitor cells in the adult dentate gyrus. J Neurobiol 36: 249–266
Garcia CC, Blair HJ, Seager M, Coulthard A, Tennant S, Buddles M, Curtis A, Goodship JA. 2004. Identification of a mutation in synapsin I, a synaptic vesicle protein, in a family with epilepsy. J Med Genet 41:183–186.
Ghosh A, Ginty DD, Bading H, Greenberg ME. 1994. Calcium regulation of gene expression in neuronal cells. J Neurobiol 25:294–303.
Goto S, Radak Z, Nyakas C, Chung HY, Naito H, Takahashi R, Nakamoto H, Abea R. 2004. Regular exercise: an effective means to reduce oxidative stress in old rats. Ann NY Acad Sci 1019:471–474.
Gould E, Tanapat P, Rydel T, Hastings N. 2000. Regulation of hippocampal neurogenesis in adulthood. Biol Psychiatry 48:715–720.
Grealy MA, Johnson DA, Rushton SK. 1999. Improving cognitive function after brain injury: the use of exercise and virtual reality. Arch Phys Med Rehabil 80:661–667.
Greengard P, Valtorta F, Czernik AJ, Benfenati F. 1993. Synaptic vesicle phosphoproteins and regulation of synaptic function. Science 259:780–785.
Guan J, Bennet L, Gluckman PD, Gunn AJ. 2003. Insulin-like growth factor-1 and post-ischemic brain injury. Prog Neurobiol 70:443–62.
Guarente L. 2000. Sir2 links chromatin silencing, metabolism, and aging. Genes Dev 14:1021–1026.
Hardingham G, Arnold FJ, Bading H. 2001. Nuclear calcium signaling controls CREB-mediated gene expression triggered by synaptic activity.

Nat Neurosci 4:261–267.

Hariri AR, Goldberg TE, Mattay VS, Kolachana BS, Callicott JH, Egan MF, Weinberger DR. 2003. Brain-derived neurotrophic factor val66met polymorphism affects human memory-related hippocampal activity and predicts memory performance. J Neurosci 23:6690–6694.

Hayashi M, Mistunaga F, Ohira K, Shimizu K. 2001. Changes in BDNF immunoreactive structures in the hippocampal formation of the aged macaque monkey. Brain Res 918:191–196.

Heydari AR, You S, Takahashi R, Gutsmann A, Sarge KD, Richardson A. 1996. Effect of caloric restriction on the expression of heat shock protein 70 and the activation of heat shock transcription factor 1. Dev Genet 18:114–124.

Hilfiker S, Pieribone VA, Czernik AJ, Kao HT, Augustine GJ, Greengard P. 1999. Synapsins as regulators of neurotransmitter release. Philos Trans R Soc Lond B Biol Sci 354:269–279.

Hill JO, Davis JR, Tagliaferro AR. 1983. Effects of diet and exercise training on thermogenesis in adult female rats. Physiol Behav 31:133–135.

Holtzman DM, Lowenstein DH. 1995. Selective inhibition of axon outgrowth by antibodies to NGF in a model of temporal lobe epilepsy. J Neurosci 15:7062–7070.

Horvath TL, Diano S, Barnstable C. 2003. Mitochondrial uncoupling protein 2 in the central nervous system: neuromodulator and neuroprotector. Biochem Pharmacol 65:1917–1921.

Impey S, Obrietan K, Storm DR. 1999. Making new connections: role of ERK/MAP kinase signaling in neuronal plasticity. Neuron 23:11–14.

Ingram DK, Weindruch R, Spangler EL, Freeman JR, Walford RL. 1987. Dietary restriction benefits learning and motor performance of aged mice. J Gerontol 42:78–81.

Islam A, Ayer-LeLievre C, Heigenskold C, Bogdanovic N, Winblad B, Adem A. 1998. Changes in IGF-1 receptors in the hippocampus of adult rats after long-term adrenalectomy: receptor autoradiography and in situ hybridization histochemistry. Brain Res 797:342–346.

Jin SL, Han VK, Simmons JG, Towle AC, Lauder JM, Lund PK. 1988. Distribution of glucagonlike peptide I (GLP-I), glucagon, and glicentin in the rat brain: an immunocytochemical study. J Comp Neurol 271:519–532.

Johnston AN, Rose SP. 2001. Memory consolidation in day-old chicks requires BDNF but not NGF or NT-3; an antisense study. Brain Res Mol Brain Res 88:26–36.

Jovanovic JN, Czernik AJ, Fienberg AA, Greengard P, Sihra TS. 2000. Synapsins as mediators of BDNF-enhanced neurotransmitter release. Nat Neurosci 3:323–329.

Jung RT. 1997. Obesity as a disease. Br Med Bull 53:307–321.

Juul A, Dalgaard P, Blum WF, Bang P, Hall K, Michaelsen KF, Muller J, Skakkebaek NE. 1995. Serum levels of insulin-like growth factor (IGF)-binding protein-3 (IGFBP-3) in healthy infants, children, and adolescents: the relation to IGF-I, IGF-II, IGFBP-1, IGFBP-2, age, sex, body mass index, and pubertal maturation. J Clin Endocrinol Metab 80:2534–2542.

Kalmijn S, Feskens EJ, Launer LJ, Kromhout D. 1997. Polyunsaturated fatty acids, antioxidants, and cognitive function in very old men. Am J Epidemiol 145:33–41.

Kang H, Schuman EM. 1995. Long-lasting neurotrophin-induced enhancement of synaptic transmission in the adult hippocampus. Science 267:1658–1662.

Kernie SG, Liebl DJ, Parada LF. 2000. BDNF regulates eating behavior and locomotor activity in mice. EMBO J 19:1290–1300.

Kirkwood TB. 2002. Molecular gerontology. J Inherit Metab Dis 25: 189–196.

Kirkwood TB, Austad SN. 2000. Why do we age? Nature 408:233–238.

Kirschner PB, Jenkins BG, Schulz JB, Finkelstein SP, Matthews RT, Rosen BR, Beal MF. 1996. NGF, BDNF and NT-5, but not NT-3 protect against MPP+ toxicity and oxidative stress in neonatal animals. Brain Res 713:178–185.

Koliatsos VE, Clatterbuck RE, Winslow JW, Cayouette MH, Price DL. 1993. Evidence that brain-derived neurotrophic factor is a trophic factor for motor neurons in vivo. Neuron 10:359–367.

Korte M, Carroll P, Wolf E, Brem G, Thoenen H, Bonhoeffer T. 1995. Hippocampal long-term potentiation is impaired in mice lacking brain-derived neurotrophic factor. Proc Natl Acad Sci U S A 92:8856–8860.

Kramer AF, Hahn S, Cohen NJ, Banich MT, McAuley E, Harrison CR, Chason J, Vakil E, Bardell L, Boileau RA, Colombe A. 1999. Aging, fitness, and neurocognitive function. Nature 400:418–419.

Lai M, Hibberd CJ, Gluckman PD, Seckl JR. 2000. Reduced expression of insulin-like growth factor 1 messenger RNA in the hippocampus of aged rats. Neurosci Lett 288:66–70.

Laurin D, Verreault R, Lindsay J, MacPherson K, Rockwood K. 2001. Physical activity and risk of cognitive impairment and dementia in elderly persons. Arch Neurol 58:498–504.

Lee J, Duan W, Mattson MP. 2002. Evidence that brain-derived neurotrophic factor is required for basal neurogenesis and mediates, in part, the enhancement of neurogenesis by dietary restriction in the hippocampus of adult mice. J Neurochem 82:1367–1375.

Lessmann V, Heumann R. 1998. Modulation of unitary glutamatergic synapses by neurotrophin-4/5 or brain-derived neurotrophic factor in hippocampal microcultures: presynaptic enhancement depends on pre-established paired-pulse facilitation. Neuroscience 86:399–413.

Levin BE, Dunn-Meynell AA. 2004. Chronic exercise lowers the defended body weight gain and adiposity in diet-induced obese rats. Am J Physiol Regul Integr Comp Physiol 286:R771–R778.

Libman I, Arslanian SA. 1999. Type 2 diabetes mellitus: no longer just adults. Pediatr Ann 28:589–593.

Lindholm D, Dechant G, Heisenberg CP, Thoenen H. 1993. Brain-derived neurotrophic factor is a survival factor for cultured rat cerebellar granule neurons and protects them against glutamate-induced neurotoxicity. Eur J Neurosci 5:1455–1464.

Lindvall O, Ernfors P, Bengzon J, Kokaia Z, Smith ML, Siesjo BK, Persson H. 1992. Differential regulation of mRNAs for nerve growth factor, brain-derived neurotrophic factor, and neurotrophin 3 in the adult rat brain following cerebral ischemia and hypoglycemic coma. Proc Natl Acad Sci U S A 89:648–652.

Linnarsson S, Bjorklund A, Ernfors P. 1997. Learning deficit in BDNF mutant mice. Eur J Neurosci 9:2581–2587.

Liu J, Atamna H, Kuratsune H, Ames BN. 2002. Delaying brain mitochondrial decay and aging with mitochondrial antioxidants and metabolites. Ann NY Acad Sci U S A 959:133–166.

Llinás R. 2001. I of the vortex: from neurons to self. Cambridge, MA: MIT Press. 302 p.

Logroscino G, Marder K, Cote L, Tang MX, Shea S, Mayeux R. 1996. Dietary lipids and antioxidants in Parkinson's disease: a population-based, case-control study. Ann Neurol 39:89–94.

Lu B, Chow A. 1999. Neurotrophins and hippocampal synaptic transmission and plasticity. J Neurosci Res 58:76–87.

Lu B. 2003. BDNF and activity-dependent synaptic modulation. Learn Mem 10:86–98.

Luchsinger JA, Tang MX, Shea S, Mayeux R. 2002. Caloric intake and the risk of Alzheimer disease. Arch Neurol 59:1258–1263.

Lupien SB, Bluhm EJ, Ishii DN. 2003. Systemic insulin-like growth factor-I administration prevents cognitive impairment in diabetic rats, and brain IGF regulates learning/memory in normal adult rats. J Neurosci Res 74:512–523.

Lyons WE, Mamounas LA, Ricaurte GA, Coppola V, Reid SW, Bora SH, Wihler C, Koliatsos VE, Tessarollo L. 1999. Brain-derived neurotrophic factor-deficient mice develop aggressiveness and hyperphagia in conjunction with brain serotonergic abnormalities. Proc Natl Acad Sci U S A 96:15239–15244.

Ma YL, Wang HL, Wu HC, Wei CL, Lee EH. 1998. Brain-derived neurotrophic factor antisense oligonucleotide impairs memory retention and inhibits long-term potentiation in rats. Neuroscience 82:957–

967.
Mao W, Yu XX, Zhong A, Li W, Brush J, Sherwood SW, Adams SH, Pan G. 1999. UCP4, a novel brain-specific mitochondrial protein that reduces membrane potential in mammalian cells. FEBS Lett 443:326–330.
Markowska AL, Mooney M, Sonntag WE. 1998. Insulin-like growth factor-1 ameliorates age-related behavioral deficits. Neuroscience 87:559–569.
Mattson MP, Maudsley S, Martin B. 2004. A neural signaling triumvirate that influences ageing and age-related disease: insulin/IGF-1, BDNF and serotonin. Ageing Res Rev 3:445–464.
Mattson MP. 2002. Brain evolution and lifespan regulation: conservation of signal transduction pathways that regulate energy metabolism. Mech Ageing Dev 123:947–953.
McCay CM, Crowell MF, Maynard LA. 1989. The effect of retarded growth upon the length of life span and upon the ultimate body size. Nutrition 5:155–172.
Means LW, Higgins JL, Fernandez TJ. 1993. Mid-life onset of dietary restriction extends life and prolongs cognitive functioning. Physiol Behav 54:503–508.
Melloni RH Jr, Apostolides PJ, Hamos JE, DeGennaro LJ. 1994. Dynamics of synapsin I gene expression during the establishment and restoration of functional synapses in the rat hippocampus. Neuroscience 58:683–703.
Merchenthaler I, Lane M, Shughrue P. 1999. Distribution of pre-proglucagon and glucagon-like peptide-1 receptor messenger RNAs in the rat central nervous system. J Comp Neurol 403:261–280.
Messaoudi E, Bardsen K, Srebro B, Bramham CR. 1998. Acute intrahippocampal infusion of BDNF induces lasting potentiation of synaptic transmission in the rat dentate gyrus. J Neurophysiol 79:496–499.
Mokdad AH, Bowman BA, Ford ES, Vinicor F, Marks JS, Koplan JP. 2001. The continuing epidemics of obesity and diabetes in the United States. JAMA 286:1195–1200.
Molteni R, Barnard RJ, Ying Z, Roberts CK, Gomez-Pinilla F. 2002. A high-fat, refined sugar diet reduces hippocampal brain-derived neurotrophic factor, neuronal plasticity, and learning. Neuroscience 112: 803–814.
Molteni R, Wu A, Vaynman S, Ying Z, Barnard RJ, Gomez-Pinilla F. 2004. Exercise reverses the effects of consumption of a high-fat diet on synaptic and behavioral plasticity associated to the action of brain-derived neurotrophic factor. Neuroscience 123:429–440.
Mu J, Li W, Yao Z, Zhou X. 1999. Deprivation of endogenous brain-derived neurotrophic factor results in impairment of spatial learning and memory in adult rats. Brain Res 835:259–265.
Murphy LJ. 2000. Overexpression of insulin-like growth factor binding protein-1 in transgenic mice. Pediatr Nephrol 14:567–571.
Must A, Spadano J, Coakley EH, Field AE, Colditz G, Dietz WH. 1999. The disease burden associated with overweight and obesity. JAMA 282:1523–1529.
Nagai T, Yamada K, Kim HC, Kim YS, Noda Y, Imura A, Nabeshima Y, Nabeshima T. 2003. Cognition impairment in the genetic model of aging klotho gene mutant mice: a role of oxidative stress. FASEB J 17: 50–52.
Nakagawa T, Tsuchida A, Itakura Y, Nomonura T, Ono M, Hirota F, Inoue T, Nakayama C, Taiji M, Noguchi H. 2000. Brain-derived neurotrophic factor regulates glucose metabolism by modulating energy balance in diabetic mice. Diabetes 49:436–444.
Navarro A, Gomez C, Sanchez-Pino MJ, Gonzalez H, Bandez MJ, Boveris AD, Boveris A. 2005. Vitamin E at high doses improves survival, neurological performance and brain mitochondrial function in aging male mice. Am J Physiol Regul Integr Comp Physiol 289: R1392–R1399.
Nawa H, Carnahan J, Gall C. 1995. BDNF protein measured by a novel enzyme immunoassay in normal brain and after seizure: partial disagreement with mRNA levels. Eur J Neurosci 7:1527–1535.
Neel JV. 1962. Diabetes mellitus: a "thrifty" genotype rendered detrimental by "progress"? Am J Hum Genet 14:353–362.
Neel JV. 1999. Diabetes mellitus: a "thrifty" genotype rendered detrimental by "progress"? 1962. Bull World Health Organ 77:694–703.
Neeper SA, Gomez-Pinilla F, Choi J, Cotman CW. 1996. Physical activity increases mRNA for brain-derived neurotrophic factor and nerve growth factor in rat brain. Brain Res 726:49–56.
Nonomura T, Hatanaka H. 1992. Neurotrophic effect of brain-derived neurotrophic factor on basal forebrain cholinergic neurons in culture from postnatal rats. Neurosci Res 14:226–233.
Nybo L, Nielsen B, Pedersen BK, Moller K, Secher NH. 2002. Interleukin-6 release from the human brain during prolonged exercise. J Physiol (Lond) 542:991–995.
Obici S, Feng Z, Karkanias G, Baskin DG, Rossetti L. 2002. Decreasing hypothalamic insulin receptors causes hyperphagia and insulin resistance in rats. Nat Neurosci 5:566–572.
Ogden CL, Flegal KM, Carroll MD, Johnson CL. 2002. Prevalence and trends in overweight among US children and adolescents, 1999–2000. JAMA 288:1728–1732.
O'levy I. 1993. The first book of Maimonides' Mishneh Torah, the code of Jewish Law: the Book of Knowledge. http://www.panix.com/~jjbaker/MadaD.html. Sefer Hamada, Halachot Deot 4:1.
Paolisso G, Ammendola S, Del Buono A, Gambardella A, Riondino M, Tagliamonte MR, Rizzo MR, Carella C, Varricchio M. 1997. Serum levels of insulin-like growth factor-I (IGF-I) and IGF-binding protein-3 in healthy centenarians: relationship with plasma leptin and lipid concentrations, insulin action, and cognitive function. J Clin Endocrinol Metab 82:2204–2209.
Patel MN, McNamara JO. 1995. Selective enhancement of axonal branching of cultured dentate gyrus neurons by neurotrophic factors. Neuroscience 69:763–770.
Patterson SL, Abel T, Deuel TA, Martin KC, Rose JC, Kandel ER. 1996. Recombinant BDNF rescues deficits in basal synaptic transmission and hippocampal LTP in BDNF knockout mice. Neuron 16: 1137–1145.
Patterson SL, Grover LM, Schwartzkroin PA, Bothwell M. 1992. Neurotrophin expression in rat hippocampal slices: a stimulus paradigm inducing LTP in CA1 evokes increases in BDNF and NT-3 mRNAs. Neuron 9:1081–1088.
Patterson SL, Pittenger C, Morozov A, Martin KC, Scanlin H, Drake C, Kandel ER. 2001. Some forms of cAMP-mediated long-lasting potentiation are associated with release of BDNF and nuclear translocation of phospho-MAP kinase. Neuron 32:123–140.
Pelleymounter MA, Cullen MJ, Wellman CL 1995. Characteristics of BDNF-induced weight loss. Neurol 131:229–238.
Perkins AJ, Hendrie HC, Callahan CM, Gao S, Unverzagt FW, Xu Y, Hall KS, Hui SL. 1999. Association of antioxidants with memory in a multiethnic elderly sample using the Third National Health and Nutrition Examination Survey. Am J Epidemiol 150:37–44.
Perry T, Greig NH. 2003. The glucagon-like peptides: a double-edged therapeutic sword? Trends Pharmacol Sci 24:377–383.
Pinhas-Hamiel O, Dolan LM, Daniels SR, Standiford D, Khoury PR, Zeitler P. 1996. Increased incidence of non-insulin-dependent diabetes mellitus among adolescents. J Pediatr 128:608–615.
Platenik J, Kuramoto N, Yoneda Y. 2000. Molecular mechanisms associated with long-term consolidation of the NMDA signals. Life Sci 67: 335–364.
Powell KE, Blair SN. 1994. The public health burdens of sedentary living habits: theoretical but realistic estimates. Med Sci Sports Exerc 26:851–856.
Pozzo-Miller LD, Gottschalk W, Zhang L, McDermott K, Du J, Gopalakrishnan R, Oho C, Sheng ZH, Lu B. 1999. Impairments in high frequency transmission, synaptic vesicle docking, and synaptic protein distribution in the hippocampus of BDNF knockout mice. J Neurosci 19:

4972–4983.

Radak Z, Kaneko T, Tahara S, Nakamoto H, Pucsok J, Sasvari M, Nyakas C, Goto S. 2001. Regular exercise improves cognitive function and decreases oxidative damage in rat brain. Neurochem Int 38:17–23.

Reaven P. 2004. Metabolic syndrome. J Insur Med 36:132–142.

Rios M, Fan G, Fekete C, Kelly J, Bates B, Kuehn R, Lechan RM, Jaenisch R. 2001. Conditional deletion of brain-derived neurotrophic factor in the postnatal brain leads to obesity and hyperactivity. Mol Endocrinol 15:1748–1757.

Rogers RL, Meyer JS, Mortel KF. 1990. After reaching retirement age physical activity sustains cerebral perfusion and cognition. J Am Geriatr Soc 38:123–128.

Rollo F, Ubaldi M, Ermini L, Marota I. 2002. Otzi's last meals: DNA analysis of the intestinal content of the Neolithic glacier mummy from the Alps. Proc Natl Acad Sci U S A 99:12594–12599.

Roudabush FL, Pierce KL, Maudsley S, Khan KD, Luttrell LM. 2000. Transactivation of the EGF receptor mediates IGF-1-stimulated Shc phosphorylation and ERK1/2 activation in COS-7 cells. J Biol Chem 275:22583–22589.

Saatman KE, Contreras PC, Smith DH, Raghupathi R, McDermott KL, Fernandez SC, Sanderson KL, Voddi M, McIntosh TK. 1997. Insulin-like growth factor-1 (IGF-1) improves both neurological motor and cognitive outcome following experimental brain injury. Exp Neurol 147:418–427.

Sanchis D, Fleury C, Chomiki N, Goubern M, Huang Q, Neverova M, Gregoire F, Easlick J, Raimbault S, Levi-Meyrueis C, Miroux B, Collins S, Seldin M, Richard D, Warden C, Bouillaud F, Ricquier D. 1998. BMCP1, a novel mitochondrial carrier with high expression in the central nervous system of humans and rodents, and respiration uncoupling activity in recombinant yeast. J Biol Chem 273:34611–34615.

Schaaf MJ, Workel JO, Lesscher HM, Vreugdenhil E, Oitzl MS, de Kloet ER. 2001. Correlation between hippocampal BDNF mRNA expression and memory performance in senescent rats. Brain Res 915: 227–233.

Scharfman H, Goodman J, Macleod A, Phani S, Antonelli C, Croll S. 2005. Increased neurogenesis and the ectopic granule cells after intrahippocampal BDNF infusion in adult rats. Exp Neurol 192:348–356.

Scharfman HE. 1997. Hyperexcitability in combined entorhinal/hippocampal slices of adult rat after exposure to brain-derived neurotrophic factor. J Neurophysiol 78:1082–1095.

Schinder AF, Poo M. 2000. The neurotrophin hypothesis for synaptic plasticity. Trends Neurosci 23:639–645.

Schmidt-Hieber C, Jonas P, Bischofberger J. 2004. Enhanced synaptic plasticity in newly generated granule cells of the adult hippocampus. Nature 429:184–187.

Shirayama Y, Chen ACH, Nakagawa S, Russell DS, Duman RS. 2002. Brain-derived neurotrophic factor produces anti-depressant effects in behavioral models of depression. J Neurosci 22:3251–3261.

Shors TJ, Miesegaes G, Beylin A, Zhao M, Rydel T, Gould E. 2001. Neurogenesis in the adult is involved in the formation of trace memories. Nature 410:372–376.

Silva AJ, Paylor R, Wehner JM, Tonegawa S. 1992. Impaired spatial learning in alpha-calcium-calmodulin kinase II mutant mice. Science 257:206–211.

Siuciak JA, Boylan C, Fritsche M, Altar CA, Lindsay RM. 1996. BDNF increases monoamine activity in the rat brain following intracerebroventricular or intraparenchymal administration. Brain Res 710:11–20.

Skoglund G, Hussain MA, Holz GG. 2000. Glucagon-like peptide 1 stimulates insulin gene promoter activity by protein kinase A-independent activation of the rat insulin I gene cAMP response element. Diabetes 49:1156–1164.

Socci DJ, Crandall BM, Arendash GW. 1995. Chronic antioxidant treatment improves the cognitive performance of aged rats. Brain Res 693:88–94.

Sohal RS, Weindruch R. 1996. Oxidative stress, caloric restriction, and aging. Science 273:59–63.

Song DK, Choe B, Bae JH, Park WK, Han IS, Ho WK, Earm YE. 1998. Brain-derived neurotrophic factor rapidly potentiates synaptic transmission through NMDA, but suppresses it through non-NMDA receptors in rat hippocampal neuron. Brain Res 799:176–179.

Sonntag WE, Lynch C, Thornton P, Khan A, Bennett S, Ingram R. 2000. The effects of growth hormone and IGF-1 deficiency on cerebrovascular and brain ageing. J Anat 4:575–585.

Sothern MS, Hunter S, Suskind RM, Brown R, Udall JN Jr, Blecker U. 1999. Motivating the obese child to move: the role of structured exercise in pediatric weight management. South Med J 92:577–584.

Stadtman ER. 1992. Protein oxidation and aging. Science. 257:1220–1224.

Suominen-Troyer S, Davis KJ, Ismail AH, Salvendy G. 1986. Impact of physical fitness on strategy development in decision-making tasks. Percept Mot Skills 62:71–77.

Sweatt JD. 2001. The neuronal MAP kinase cascade: a biochemical signal integration system subserving synaptic plasticity and memory. J Neurochem 76:1–10.

Takei Y, Harada A, Takeda S, Kobayashi K, Terada S, Noda T, Taka Hirokawa N. 1995. Synapsin I deficiency results in the structural change in the presynaptic terminals in the murine nervous system. J Cell Biol 131:1789–1800.

Tao X, Finkbeiner S, Arnold DB, Shaywitz AJ. 1998. And Greenberg ME. Ca2+ influx regulates BDNF transcription by a CREB family transcription factor-dependent mechanism. Neuron 20:709–726.

Thiele C, Hannah M, Fahrenholz F, Huttner WB. 2000. Cholesterol binds to synaptophysin and is required for biogenesis of synaptic vesicles. Nat Cell Biol 2:42–49.

Tonra JR, Ono M, Liu X, Garcia K, Jackson C, Yancopoulos GD, Wiegand SJ, Wong V. 1999. Brain-derived neurotrophic factor improves blood glucose control and alleviates fasting hyperglycemia in C57BLKSLepr (db)/lepr(db) mice. Diabetes 48:588–594.

Torres-Aleman I. 1999. Insulin-like growth factors as mediators of functional plasticity in the adult brain. Horm Metab Res 31:114–119.

Trejo JL, Carro E, Torres-Aleman I. 2001. Circulating insulin-like growth factor I mediates exercise-induced increases in the number of new neurons in the adult hippocampus. J Neurosci 21:1628–1634.

Trevathen WR, Smith EO, McKenna JJ. 1999. Introduction. In: Trevathan WR, Smith EO, McKenna JJ, eds. Evolutionary medicine. New York: Oxford University Press. p 3–6.

Tsuchida A, Nonomura T, Nakagawa T, Itakura Y, Ono-Kishino M, Yamanaka M, Sugaru E, Taiji M, Noguchi H. 2002. Brain-derived neurotrophic factor ameliorates lipid metabolism in diabetic mice. Diabetes Obes Metab 4:262–269.

Tully T. 1997. Regulation of gene expression and its role in long-term memory and synaptic-plasticity. Proc Natl Acad Sci U S A 94:4239–4241.

United States Department of Health and Human Services. 1996. Physical activity and health: a report of the Surgeon General. Atlanta, GA: US Dept. of Health and Human Services.

van Praag H, Christie BR, Sejnowski TJ, Gage FH. 1999. Running enhances neurogenesis, learning, and long-term potentiation in mice. PNAS 96:13427–13434.

Vaynman S, Ying Z, Gomez-Pinilla F. 2003. Interplay between BDNF and signal transduction modulators in the regulation of the effects of exercise on synaptic-plasticity. Neuroscience 122:647–657.

Vaynman S, Ying Z, Gomez-Pinilla F. 2004. Hippocampal BDNF mediates the efficacy of exercise on synaptic plasticity and cognition. Eur J Neurosci 20:2580–2590.

Vaynman SS, Ying Z, Yin D, Gomez-Pinilla F. 2006a. Exercise differentially regulates synaptic proteins associated to the function of BDNF. Brain Res 1070:124–130.

Vaynman S, Ying Z, Wu A, Gomez-Pinilla F. 2006b. Coupling energy metabolism with a mechanism to support brain-derived neurotrophic

factor-mediated synaptic plasticity. Neuroscience 139:1221–1234.
Vidal-Puig A, Solanes G, Grujic D, Flier JS, Lowell BB. 1997. UCP3: an uncoupling protein homologue expressed preferentially and abundantly in skeletal muscle and brown adipose tissue. Biochem Biophys Res Commun 235:79–82.
Wang T, Xie K, Lu B. 1995. Neurotrophins promote maturation of developing neuromuscular synapses. J Neurosci 15:4796–4805.
Weindruch R, Sohal RS. 1997. Seminars in medicine of the Beth Israel Deaconess Medical Center. Caloric intake and aging. N Engl J Med 337: 986–994.
Wendorf M, Goldfine ID. 1991. Archaeology of NIDDM. Excavation of the "thrifty" genotype. Diabetes 40:161–165.
Wu A, Molteni R, Ying Z, Gomez-Pinilla F. 2003. A saturated-fat diet aggravates the outcome of traumatic brain injury on hippocampal plasticity and cognitive function by reducing brain-derived neurotrophic factor. Neuroscience 119:365–375.
Wu A, Ying Z, Gomez-Pinilla F. 2004a. The interplay between oxidative stress and brain-derived neurotrophic factor modulates the outcome of a saturated fat diet on synaptic plasticity and cognition. Eur J Neuro-Sci 19:1699–1707.
Wu A, Ying Z, Gomez-Pinilla F. 2004b. Dietary omega-3 fatty acids normalize BDNF levels, reduce oxidative damage, and counteract learning disability after traumatic brain injury in rats. J Neurotrauma 21:1457–1467.
Wu A, Ying Z, Gomez-Pinilla F. 2006. Oxidative stress modulates Sir2α in the rat hippocampus and cerebral cortex. Eur J Neurosci 23:2573–2580.
Xu B, Goulding EH, Zang K, Cepoi D, Cone RD, Jones KR, Tecott LH, Reichardt LF. 2003. Brain-derived neurotrophic factor regulates energy balance downstream of melanocortin-4 receptor. Nat Neurosci 6:736–742.
Yamada S, Komatsu M, Sato Y, Yamauchi K, Kojima I, Aizawa T, Hashizume K. 2002. Time-dependent stimulation of insulin exocytosis by 3′, 5′-cyclic adenosine monophosphate in the rat islet beta-cell. Endocrinology 143:4203–4209.
Yang F, Lim GP, Begum AN, Ubeda OJ, Simmons MR, Ambegaokar SS, Chen PP, Kayed R, Glabe CG, Frautschy SA, Cole GM. 2005. Curcumin inhibits formation of amyloid beta oligomers and fibrils, binds plaques, and reduces amyloid in vivo. J Biol Chem 280:58925–58901.
Yeo GS, Connie Hung CC, Rochford J, Keogh J, Gray J, Sivaramakrishnan S, O'Rahilly S, Farooqi IS. 2004. A de novo mutation affecting human TrkB associated with severe obesity and developmental delay. Nat Neurosci 7:1187–1189.
Yin JC, Tully T. 1996. CREB and the formation of long-term memory. Curr Opin Neurobiol 6:264–268.
Yin JC, Wallach JS, Del Vecchio M, Wilder EL, Zhou H, Quinn WG, Tully T. 1994. Induction of a dominant negative CREB transgene specifically blocks long-term memory in Drosophila. Cell 79:49–8.
Yin JC, Del Vecchio M, Zhou H, Tully T. 1995. CREB as a memory modulator: induced expression of a dCREB2 activator isoform enhances long-term memory in Drosophila. Cell 81:107–115.
Ying SW, Futter M, Rosenblum K, Webber MJ, Hunt SP, Bliss TV, Bramham CR. 2002. Brain-derived neurotrophic factor induces long-term potentiation in intact adult hippocampus: requirement for ERK activation coupled to CREB and upregulation of Arc synthesis. J Neurosci 22:1532–1540.
Yu ZF, Mattson MP. 1999. Dietary restriction and 2-deoxyglucose administration reduce focal ischemic brain damage and improve behavioral outcome: evidence for a preconditioning mechanism. J Neurosci Res 57:830–839.
Zenobi PD, Holzmann P, Glatz Y, Riesen WF, Froesch ER. 1993. Improvement of lipid profile in type 2 (non-insulin-dependent) diabetes mellitus by insulin-like growth factor I. Diabetologia 36:465–469.
Zhao WQ, Chen H, Quon MJ, Alkon DL. 2004. Insulin and the insulin receptor in experimental models of learning and memory. Eur J Pharmacol 490:71–81.
Zimmet P, Thomas CR. 2003. Genotype, obesity and cardiovascular disease—has technical and social advancement outstripped evolution? J Intern Med 254:114–125.