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ACTIVITY-DEPENDENT, STRESS-RESPONSIVE BDNF SIGNALING AND THE QUEST FOR OPTIMAL BRAIN HEALTH AND RESILIENCE THROUGHOUT THE LIFESPAN

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Abstract

During development of the nervous system, the formation of connections (synapses) between neurons is dependent upon electrical activity in those neurons, and neurotrophic factors produced by target cells play a pivotal role in such activity-dependent sculpting of the neural networks. A similar interplay between neurotransmitter and neurotrophic factor signaling pathways mediates adaptive responses of neural networks to environmental demands in adult mammals, with the excitatory neurotransmitter glutamate and brain-derived neurotrophic factor (BDNF) being particularly prominent regulators of synaptic plasticity throughout the central nervous system. Optimal brain health throughout the lifespan is promoted by intermittent challenges such as exercise, cognitive stimulation and dietary energy restriction, that subject neurons to activity-related metabolic stress. At the molecular level, such challenges to neurons result in the production of proteins involved in neurogenesis, learning and memory and neuronal survival; examples include proteins that regulate mitochondrial biogenesis, protein quality control, and resistance of cells to oxidative, metabolic and proteotoxic stress. BDNF signaling mediates up-regulation of several such proteins including the protein chaperone GRP-78, antioxidant enzymes, the cell survival protein Bcl-2, and the DNA repair enzyme APE1. Insufficient exposure to such challenges, genetic factors may conspire to impair BDNF production and/or signaling resulting in the vulnerability of the brain to injury and neurodegenerative disorders including Alzheimer's, Parkinson's and Huntington's diseases. Further, BDNF signaling is negatively regulated by glucocorticoids. Glucocorticoids impair synaptic plasticity in the brain by negatively regulating spine density, neurogenesis and long-term potentiation, effects that are potentially linked to glucocorticoid regulation of BDNF. Findings suggest that BDNF signaling in specific brain regions mediates some of the beneficial effects of exercise and energy restriction on peripheral energy metabolism and the cardiovascular system. Collectively, the findings described in this article suggest the possibility of developing prescriptions for optimal brain health based on activity-dependent BDNF signaling.

Keywords

BDNF; caloric restriction; exercise; glucocorticoid; LTP; synaptic plasticity

INTRODUCTION

During the development of the nervous system, more neurons arise from neural progenitor cells than are ultimately retained as nerve cell networks are established and refined (Raff et

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al., 1993). Neurons that are electrically active (i.e., firing action potentials) as they interact with target (postsynaptic) neurons are more likely to survive compared to those neurons that are electrically quiescent (Catsicas et al., 1992). In many cases, such activity-dependent neuronal survival results from the production of a neurotrophic factor(s) by the presumptive target cell (Raff et al., 1993). For example, in the developing hippocampus, as the growth cones of pyramidal neuron axons encounter the dendrites of potential postsynaptic neurons, those that are actively releasing the neurotransmitter glutamate are more likely to establish stable synapses compared to axons not releasing glutamate (Mattson et al., 1988a,b). Neurons that are relatively inactive and/or receive insufficient target-derived neurotrophic support undergo programed cell death (apoptosis). The evidence supporting this concept has been reviewed previously (Mennerick and Zorumski, 2000; Mattson, 2008).

The maintenance and adaptive remodeling of neural circuits in the adult mammalian CNS are mediated, in large part, by the same neurotransmitter and neurotrophic factor signaling pathways that regulate the formation of neural circuits during development. Prominent among such activity-dependent neurotrophic signaling pathways are those involving glutamate, the major excitatory neurotransmitter in the CNS, and brain-derived neurotrophic factor (BDNF) (Fig. 1). Activity in neurons results in the release of glutamate from presynaptic terminals. Synaptic glutamate activates ionotropic receptors on the membrane of dendrites resulting in the influx of Na^+ (via α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors) and Ca^{2+} (via *N*-methyl-D-aspartate (NMDA) receptors and voltage-dependent Ca^{2+} channels). Ca^{2+} activates kinases (e.g., Ca^{2+}-calmodulin-dependent protein kinases and protein kinase C) which, in turn, activate transcription factors including AP-1 (Morgan and Curran, 1988), cyclic AMP response element-binding protein (CREB) (Redmond and Ghosh, 2005) and nuclear factor κB (NF-κB) (Boersma et al., 2011), and translational regulators such as Arc (Bramham et al., 2008) and FMRP (Antar et al., 2004).

Ca^{2+} influx through NMDA receptors in dendrite(s) influences the production of numerous proteins involved in synaptic plasticity and associated behavioral responses including learning and memory, sensory–motor integration, and emotional responses. Among such activity-dependent proteins, BDNF plays particularly important and seemingly widespread roles. At the transcriptional level the *Bdnf* gene is induced by CREB and NF-κB (Marini et al., 2004; Pruunsild et al., 2011). Moreover, BDNF mRNA is transported into dendrites, where local Ca^{2+} influx can stimulate BDNF protein production by mechanisms that likely involve FMRP (Napoli et al., 2008). BDNF exerts its effects on synaptic structure and function (Lu et al., 2008), neurogenesis (Bergami et al., 2008) and neuronal survival and disease resistance (Mattson et al., 2004a; Nagahara and Tuszynski, 2011) by activating a high-affinity membrane receptor tyrosine kinase called trkB. Activation of TrkB engages several downstream signaling cascades including those involving PI3 kinase, Akt and FOXO, and MAP kinases (Reichardt, 2006). In addition, BDNF can activate a low-affinity receptor called p75NTR which is coupled to Jun N-terminal kinases and NF-κB (Reichardt, 2006). In the remainder of this article we: (1) describe the roles of BDNF signaling in the adaptive responses of neural cells to environmental challenges; (2) elucidate the differences between “good” and “bad” stressors on brain health from a BDNF-centric viewpoint; (3) consider if and how perturbations of BDNF signaling contribute to age-related neurodegenerative disorders; and (4) discuss potential ‘prescriptions for brain health’ based on intermittent challenges that up-regulate BDNF signaling throughout the lifespan.

THE ROLE OF BDNF IN ADAPTIVE RESPONSES OF NEURONS TO VOLUNTARY AND INVOLUNTARY CHALLENGES

Examples of voluntary challenges to the nervous system include the brain-friendly trio (BFT) of exercise, engaging in intellectual activities, and dietary energy restriction. We have developed the concept that such behavioral challenges are perceived by nerve cells as mild stresses resulting from increased excitatory activity in the neurons involved in the behavior. A simple (and accurate) analogy of the nature of such cellular stress is the events that occur in skeletal muscle cells in response to vigorous physical exercise. When muscle cells and neurons are active the following 'stressful' events occur: Na^+ and Ca^{2+} influx, increased activity of the mitochondrial electron transport chain, generation of free radicals (superoxide, nitric oxide and others), and oxidative damage to DNA and proteins; muscle cells and neurons respond adaptively to these ionic, oxidative and metabolic stresses (Powers and Jackson, 2008; Steinert et al., 2010; Yang et al., 2010). Among the major intracellular pathways that mediate adaptive responses of muscle cells and neurons to activity-dependent stress are those involving enzymes and transcription factors engaged by Ca^{2+}, redox-sensitive proteins, and cellular energy sensors (Mabuchi et al., 2001; Narkar et al., 2008; Suwa et al., 2008; Dhar et al., 2009). Such adaptive responses to the daily challenges neurons encounter provide a vast potential for the optimization of brain health, a central theme upon which we elaborate in the remainder of this article.

There are numerous targets of transcription factors and translational regulators that are involved in adaptive response of neurons to physiological environmental challenges (Fig. 1). Gene array analyses have elucidated the complexity of the molecular changes that occur in brain cells in response to the BFT (Tong et al., 2001; Cavallaro et al., 2002; Xu et al., 2007; Kohman et al., 2011). Examples of genes induced by these environmental challenges include those encoding proteins involved in synaptic plasticity, cell cycle regulation, cell survival, stress-activated kinases, DNA repair enzymes, ubiquitin-mediated proteolysis, autophagy and mitochondrial biogenesis (Mattson, 2012). In addition, BDNF is prominently up-regulated in several different brain regions (hippocampus, cerebral cortex, striatum and brainstem, among others) in response to the BFT (Kesslak et al., 1998; Oliff et al., 1998; Lee et al., 2002). Accordingly, several proteins up-regulated by the BFT are likely secondary to enhanced BDNF signaling; examples include: glutamate receptor subunits involved in synaptic plasticity (Caldeira et al., 2007b; Fortin et al., 2012), guanine nucleotide exchange factors that control actin polymerization and associated dendritic spine formation (Hale et al., 2011), synaptic vesicle-associated proteins (Luikart et al., 2005), the anti-apoptotic protein Bcl-2 (Almeida et al., 2005), antioxidant enzymes (Mattson et al., 1995), and the DNA repair enzyme APE-1 (Yang et al., 2010).

Examples of involuntary challenges to the nervous system include epileptic seizures, ischemic stroke, and traumatic brain or spinal cord injury. The first evidence that electrical activity in neurons induces BDNF expression came from studies showing that levels of BDNF mRNA are elevated greatly in hippocampal neurons in response to epileptic seizures in rats (Zafra et al., 1990). Subsequent studies have shown that BDNF is also up-regulated in response to traumatic and ischemic injury to the CNS (Yang et al., 1996) and in response to peripheral nerve injury (Funakoshi et al., 1993; Hsu et al., 1993; Hayashi et al., 2000). When initiated prior to the insult, interventions that induce BDNF expression, including exercise, dietary energy restriction and environmental enrichment, can reduce neuronal degeneration and improve functional outcome in one or more animal models of severe epileptic seizures, traumatic CNS injury and stroke (Ohlsson and Johansson, 1995; Bruce-Keller et al., 1999; Young et al., 1999; Yu and Mattson, 1999; Reiss et al., 2009; Rich et al., 2010; Zhang et al., 2011). In many cases, the BFT can also improve functional outcome when initiated after the injury. For example, voluntary exercise elevates BDNF levels in the brain and improves

functional outcome in a rat model of traumatic brain injury (Griesbach et al., 2004). As described in the next section of this article, BDNF can reduce damage to neurons and improve functional outcome in experimental models of both acute and chronic neurodegenerative conditions.

NEUROPROTECTIVE ACTIONS OF BDNF

BDNF has demonstrated the ability to protect neurons against damage caused by oxidative, metabolic and excitotoxic stress in experimental models relevant to aging and disease (Mattson et al., 2004b; Marini et al., 2007). When cultured hippocampal or cortical neurons are treated with BDNF 1–100 ng/ml, they are relatively resistant to being damaged and killed by a range of insults of relevant to acute and/or chronic neurodegenerative conditions including: glutamate and excitotoxins (Cheng and Mattson, 1994; Wu et al., 2004); glucose and oxygen deprivation (Cheng and Mattson, 1994); oxidative stressors (e.g., Fe^{2+} and H_2O_2) (Mattson et al., 1995; Harper et al., 2009); mitochondrial toxins (Markham et al., 2012); and amyloid β-peptide (Counts and Mufson, 2010). BDNF can also protect neurons against insults relevant to the pathogenesis of Huntington's disease (Wu et al., 2009; Jiang et al., 2011). Endogenous BDNF production and signaling protects neurons against the same kind of adverse conditions associated with aging, acute injury and neurodegenerative disorders. For example, selective suppression of BDNF production or trkB-mediated BDNF signaling increases the vulnerability of neurons to excitotoxicity (Jiang et al., 2005) and promotes amyloidogenic APP processing (Matrone et al., 2008). Moreover, when BDNF activity was blocked using a TrkB-Fc fusion protein, brain damage caused by transient global ischemia was enhanced, suggesting a critical role for endogenous BDNF in protecting neurons against cardiac arrest and stroke (Larsson et al., 1999).

Studies of animal models of aging and neurological disorders support a role for BDNF signaling in optimal brain health and resistance to disease (Fig. 1).Several environmental interventions that reduce age-dependent neuropathology and cognitive decline also increase BDNF production implying a role for BDNF in this process. In a study of aged canines, animals receiving both an antioxidant diet and environmental enrichment displayed increased BDNF mRNA compared to untreated animals and BDNF mRNA levels were positively correlated with improved cognitive performance (Fahnestock et al., 2012). Object recognition memory is improved in male rats after exercise and these improvements are correlated with BDNF levels (Hopkins and Bucci, 2010). Administration of exogenous BDNF can protect neurons against dysfunction and degeneration in models of normal aging and neurodegenerative conditions. In aged rodents and primates, BDNF administration improves cognition and reverses neuronal atrophy (Nagahara et al., 2009). Long-term potentiation of synaptic transmission at hippocampal CA1 synapses, believed critical for memory acquisition, is impaired in a chronic intermittent hypoxia mouse model of sleep apnea, and restored to normal by infusion of BDNF into the brain (Xie et al., 2010). In a mouse model of AD, administration of stem cells which naturally secrete BDNF after the onset of the disease reverses synapse loss and improves neuronal signaling cognition demonstrating the powerful neuroprotective effects of this neurotrophic factor (Blurton-Jones et al., 2009). Transplantation of a cell line expressing BDNF into the striatum protected the atrophy of striatal projection neurons in an excitotoxin (quinolinic acid) model of Huntington's disease (Pérez-Navarro et al., 1999). Experimental studies in rodents and non-human primates show that environmental interventions that have beneficial effects on brain function and are neuroprotective, including dietary energy restriction, engaging in cognitively stimulating activities and exercise, also increase BDNF production and signaling (Lee et al., 2002; Maswood et al., 2004; Aguiar et al., 2011; Rosas-Vargas et al., 2011; Marlatt et al., 2012). For reasons elaborated upon in the final section of the present article, the latter 'natural' ways of increasing BDNF signaling in neuronal networks are, in our

opinion, much preferred to invasive procedures such as infusing BDNF into the brain or transplanting cells that produce BDNF into the brain.

One potential mechanism by which BDNF exerts neuroprotective effects is via the modulation of synaptic plasticity by regulating dendritic spines and synaptic density, and the expression of synaptic proteins. Application of BDNF to organotypic hippocampal slices in culture increases the densities of dendritic spines and synapses, and increases the number of neurotransmitter vesicles in presynaptic terminals of excitatory synapses on CA1 neurons (Tyler and Pozzo-Miller, 2001). BDNF increases the expression of synaptic proteins synaptophysin, synaptobrevin, and synaptotagmin in hippocampal slice cultures. and the regulation of these proteins was shown to be via both protein synthesisdependent and independent pathways (Tartaglia et al., 2001). BDNF has also been shown to directly modulate long-term potentiation (LTP), which is thought to be the electrophysiological phenomenon underpinning long-term memory. LTP consists of early and late phases, and the transformation from early-phase to late-phase LTP can be induced by BDNF (Lu et al., 2008). LTP is mediated via AMPA and NMDA receptors (Kang et al., 1997; Lu et al., 2005; Diógenes et al., 2011). BDNF alters the frequency of AMPA receptor-mediated miniature excitatory postsynaptic currents and acutely up-regulates the AMPA receptor subunits GluR1, GluR2 and GluR3 in cultured hippocampal neurons (Caldeira et al., 2007a,b). BDNF also regulates NMDA receptor function and synaptic maturity (Matsumoto et al., 2006; Caldeira et al., 2007a; Kumamaru et al., 2008). Beyond the hippocampus, BDNF in the amygdala mediates LTP by a postsynaptic action (Meis et al., 2012). BDNF alters synaptic plasticity via both protein synthesis-dependent and-independent mechanisms. Using mouse acute brain slices, Mei et al. (2011) demonstrated that inhibition of protein kinase ζ (PKM ζ) reversed the BDNF-dependent form of L-LTP and BDNF increased PKMζ when coupled with a theta burst stimulation, all of which imply that BDNF modulates LTP via PKMζ. Conversely, running-induced increases in BDNF and neurogenesis are not observed in NMDA receptor subunit ε1 knockout mice, implying that increases in BDNF rely on NMDA receptor function (Kitamura et al., 2003).

Finally, another mechanism by which BDNF alters synaptic plasticity is through the control of neurogenesis. Animals subjected to exercise demonstrate increased neurogenesis and acquisition and memory retention, effects that are potentially mediated by increases in BDNF in response to exercise (van Praag et al., 2005; Gomez-Pinilla et al., 2008; Stranahan et al., 2009). Just 1 month of voluntary wheel running increases both neurogenesis and BDNF levels in the hippocampus in old mice (van Praag et al., 2005). Exercise-induced increases in hippocampal BDNF levels are age-dependent; young mice show higher rises in BDNF compared to old (Adlard et al., 2005). Consistent running throughout middle age increases both neurogenesis in the dentate gyrus and BDNF levels in the hippocampus, implying that these effects are maintained during the exercise period and not abolished due to adaptation (Marlatt et al., 2012). Further, that study showed an increase in BDNF levels in aged mice that had completed a long (8 month) course of exercise in contrast to previous work showing that a short period of exercise did not induce increases in BDNF in aged rodents (Adlard et al., 2005). Finally, Lee et al. (2002) showed that neurogenesis was decreased in BDNF(+/−) mice implying an important role for BDNF in promoting adult neurogenesis. Further, that study showed that cell survival of newly generated neurons was improved by dietary energy restriction in normal mice, however this effect was lessened in BDNF(+/−) mice suggesting that BDNF promotes the survival of new neurons in the dentate gyrus and, in this way, mediates increases in neurogenesis following dietary energy restriction (Lee et al., 2002).

CHRONIC INVOLUNTARY STRESS AND GLUCOCORTICOIDS SUPPRESS BDNF PRODUCTION AND SIGNALING

In contrast to up-regulation in response to beneficial stressors, neurotrophic factor expression is suppressed under conditions of chronic adverse stress. Chronic stress induces activation of the hypothalamic–pituitary–adrenal (HPA) axis, which results in the release of circulating glucocorticoids (cortisol in humans and corticosterone in rodents) (Nelson, 1972; Munck and Guyre, 1986). Adverse stressors and aging have been consistently shown to reduce the expression of neurotrophic factors. Administration of glucocorticoids and experimental stressors decrease both BDNF protein and mRNA in the rodent hippocampus (Smith et al., 1995; Schaaf et al., 1998; Hansson et al., 2003, 2006). For example, BDNF levels in the hippocampus are decreased in animals subjected to chronic immobilization stress or chronic unpredictable mild stressors (Smith et al., 1995; Ueyama et al., 1997; Li et al., 2008). Hippocampal BDNF mRNA is negatively correlated with plasma glucocorticoid levels after repeated restraint stress (Murakami et al., 2005). These studies suggest an adverse effect of chronic stress on the ability of neurons to protect themselves against injury and disease potentially due to inhibition of BDNF signaling by glucocorticoids. Further, chronic social stress during adolescence in mice causes reduced hippocampal BDNF levels and cognitive impairment in aged mice, implying that early life adverse stressors endanger the aging brain (Sterlemann et al., 2010).

Pathways by which glucocorticoids exert effects on BDNF production are not entirely known. Several glucocorticoid response elements (GREs) are present on the promoter region of exon IV of the BDNF gene implying direct transcriptional control of BDNF by glucocorticoid signaling. However the presence of the promoter does not directly indicate its activity; it is possible that glucocorticoid regulation of BDNF is indirect, at least one study shows it could be via CREB (Alboni et al., 2011). The control of *Bdnf* gene transcription by these GREs is also affected by adrenalectomy (Funakoshi et al., 1993). Dexamethasone, a synthetic glucocorticoid, decreases BDNF-induced increases in levels of synaptic proteins via a reduction in the activation of the MAPK/ERK pathway implying that this intracellular signaling pathway has an important role in glucocorticoid-induced reductions in BDNF (Kumamaru et al., 2008). Further, dexamethasone also suppresses interactions between Src homology-2 domain-containing phosphatase2 (Shp2) and the TrkB receptor, which binds BDNF, in cortical neurons suggesting that another method of modulation of BDNF function by glucocorticoids is via Shp2 (Kumamaru et al., 2011).

In addition to cases of chronic stress, disease states may elevate glucocorticoids and/or suppress BDNF production and signaling. Studies show a decrease in serum BDNF in Alzheimer's disease (AD) patients as well as a decrease in cortical and hippocampal BDNF mRNA in postmortem analysis of AD brains and a decline in the overall number of BDNF-immunoreactive cell bodies in both the hippocampus and cortex compared to normal tissue (Phillips et al., 1991; Connor et al., 1997; Holsinger et al., 2000; Yasutake et al., 2006). Further, impaired trkB signaling is noted in both clinical and experimental studies of AD (Ginsberg et al., 2006; Kemppainen et al., 2012). Downregulation of trkB is associated with cognitive decline; a reduction in trkB is noted in MCI patients compared to control with a greater reduction in mild to moderate AD (Ginsberg et al., 2006).

THE GLUCOCORTICOID PARADOX OF ENERGY RESTRICTION AND EXERCISE

Glucocorticoids exert their biological effects via two receptors, the higher affinity mineralocorticoid receptor (MR), predominantly expressed in the hippocampus, and the

lower affinity glucocorticoid receptor (GR) most densely expressed in the CA1 region of the hippocampus (Reul and de Kloet, 1985; de Kloet et al., 1999; Nishi et al., 2007; Patel et al., 2008; Romeo et al., 2008). In the unstressed state, glucocorticoid levels are low and only the high-affinity MR receptors are occupied. When glucocorticoid levels rise, as is the case during chronic adverse stress, aging, or in many disease states, GR receptors begin to become activated, suggesting that adverse affects of glucocorticoids are mediated mainly through GR rather than MR (Swaab et al., 1994; Conrad et al., 1999; Pavlides et al., 2002; de Kloet and Derijk, 2004).

It is likely that beneficial and adverse stressors differentially regulate the expression of GR and MR receptors and in this way, also differentially affect how neurons respond to changes in glucocorticoid levels and also BDNF expression. In hippocampal neurons, acute adverse stressors such as psychosocial stress and sleep deprivation decrease the expression of MRs whereas beneficial stressors such as dietary energy restriction decrease the expression of GRs (Lee et al., 2000). The inhibition of BDNF-induced alterations in synaptic proteins and neuronal function by dexamethasone is abolished in the presence of RU486, a GR antagonist, implying that glucocorticoids mediate BDNF function via the GR, but not MR (Kumamaru et al., 2008). However, hippocampal BDNF levels were negatively regulated in adrenalectomized mice by both GR and MR signaling implying that both receptor subtypes mediate the effects of glucocorticoids on BDNF signaling (Hansson et al., 2000).

It is likely that the level of glucocorticoid elevation has a strong role on the balance between protective and detrimental effects of the hormone; glucocorticoids have been shown to demonstrate a U-shaped response curve with very low and very high levels of glucocorticoids exerting adverse effects on cellular function. This could explain why dietary restriction, which is known to increase lifespan and promote neuroprotection, causes chronic rises in circulating corticosterone in rodents (Sabatino et al., 1991; Patel and Finch, 2002) and cortisol in humans (Walford et al., 1995). It is possible that organisms are distinctly sensitive to even small alterations in glucocorticoid levels and that caloric restriction induces the maximal glucocorticoid response for beneficial effect. Further, as discussed above, it is possible that beneficial and adverse stressors, differentially regulate the levels of expression of GR and MR in the brain, thus regulating positive and adverse outcomes of glucocorticoid signaling. For example, energy restriction is associated with rises in BDNF in the brain, which could potentially induce an increase in MR expression and/or a decrease in GR expression whereas adverse stressors exert the opposite effect. Indeed, rats maintained on an alternate day fasting diet for several months exhibited reduced expression of GR in hippocampal and cortical neurons (Lee et al., 2000) and increased levels of BDNF in these same brain regions (Duan et al., 2001). However, the elevation of glucocorticoids resulting from dietary energy restriction, or other beneficial stressors, may, nevertheless, inhibit BDNF expression. Qiu et al. (2012) demonstrated elevations in BDNF in adrenalectomized mice exposed to dietary energy restriction compared to those on DR with intact adrenal glands implying that the loss of corticosterone was related to a rise in BDNF. It is noteworthy that the adrenal gland releases several hormones in addition to glucocorticoids that may interfere with BDNF production including noradrenaline and androgens. Whereas adrenalectomy increases BDNF, treadmill exercise in AD mice also increases BDNF along with a decrease in corticosterone further lending credence to the hypothesis that glucocorticoids regulate BDNF (Um et al., 2011).

In humans, vigorous exercise increases levels of circulating cortisol acutely (Paccotti et al., 2005) and trained endurance athletes exhibit an overall chronic elevation of cortisol levels as indicated by greater amounts of cortisol in samples of their hair (Skoluda et al., 2012). Rats that run regularly exhibit elevated levels of corticosterone in their blood (Gibbs, 1976) and brain (Droste et al., 2009). Compared to sedentary controls, rats that run voluntarily exhibit

no significant differences in levels of GR or MR mRNAs in the frontal cortex or paraventricular nucleus of the hypothalamus, but did exhibit elevated levels of GR mRNA in some hippocampal neurons (Droste et al., 2007). Nevertheless, running (and presumably other types of vigorous exercise), promote optimal brain health by enhancing synaptic plasticity and neurogenesis, and by protecting neurons against injury and disease. Again, there is a seeming paradox in which exercise increases glucocorticoid levels, but enhances BDNF expression. Apparently, any potential negative impact of elevated glucocorticoid levels, is countered/reversed by the activation of adaptive cellular stress response pathways in neurons, such as upregulation of BDNF, as described above.

OPTIMIZATION OF BDNF SIGNALING FOR BRAIN HEALTH AND DISEASE RESISTANCE

The question often arises as to what levels of exercise, energy restriction and cognitive stimulation are most beneficial for brain function and protection against age-related cognitive impairment and AD. The answer is that we do not know, although emerging findings do point to some general guidelines for prescriptions for such behavioral modifications. In this section, we focus on BDNF expression/signaling as a proxy for optimal brain health/neuroplasticity. Exercise, energy restriction and cognitive challenges differ with regard to the magnitude of their effects on BDNF production, and may also differ in the brain regions in which BDNF expression is most greatly affected. Although specific regimens of exercise and energy restriction that result in optimal brain function and disease resistance remain to be established, data suggest that the nature and duration of exercise and energy restriction influence the magnitude of the up-regulation of BDNF expression. Animal studies suggest that voluntary exercise can stimulate BDNF production in some brain regions to a greater extent than does forced exercise. Voluntary exercise was more effective than forced treadmill exercise in up-regulating BDNF expression in the hippocampus and improving functional outcome in a rat stroke model (Ke et al., 2011). In addition to inducing BDNF gene transcription, voluntary exercise can increase the conversion of pro-BDNF to mature (active) BDNF in the hippocampus (Sartori et al., 2011). Voluntary running wheel exercise can protect against depression-like symptoms of chronic stress in mouse and rat models by a mechanism involving increased production of BDNF in the striatum (Duman et al., 2008; Marais et al., 2009).

In the case of energy restriction, intermittent fasting appears more effective in inducing BDNF production compared to daily caloric restriction. Alternate day fasting resulted in elevated levels of BDNF in the hippocampus, piriform cortex and hypothalamus of rats; the elevation of BDNF levels was associated with resistance to pilocarpine-induced seizures (Kumar et al., 2009). Caloric restriction also increased BDNF expression in the cerebral cortex and protected rats against traumatic brain injury, effectively reducing the extent of brain damage and improving functional outcome (Rich et al., 2010). Alternate day fasting can also enhance functional recovery when administered after spinal cord injury in an animal model, demonstrating a potential for energy restriction as a therapeutic intervention for CNS trauma (Plunet et al., 2008). Collectively, the available data suggest that intermittent fasting is more effective in up-regulating BDNF production when compared to daily caloric restriction; apparently, fasting imposes a greater mild stress on nerve cells resulting in the activation of multiple adaptive stress response pathways (Mattson, 2012).

Rodents that live in cognitively challenging enriched environments exhibit increased BDNF expression in several different brain regions, including the hippocampus, cerebral cortex, basal forebrain and hindbrain (Ickes et al., 2000). BDNF signaling may contribute to the neuroprotective effects of environmental enrichment (Young et al., 1999). Increased BDNF levels were associated with improved cognitive function in an animal model of transient

global ischemia (Gobbo and O'Mara, 2004). Enrichment can also rescue, in part, behavioral deficits in mice with BDNF haploinsufficiency (Chourbaji et al., 2008). Huntingtin mutant mice, an animal model of Huntington's disease exhibit reduced levels of BDNF in the hippocampus and striatum, and environmental enrichment normalizes BDNF levels in these brain regions (Spires et al., 2004).

Results from animal studies suggest that the expression of BDNF changes during aging at least in some brain regions. In F344 rats BDNF levels and levels of phosphorylated CREB decline in the hippocampus in mid- and late-life (Hattiangady et al., 2005). In male C57BL/6 mice, BDNF protein levels decline in the cerebral cortex and striatum progressively from 7 to 13 to 20 months of age (Arumugam et al., 2010). The ability of exercise to increase BDNF expression in the hippocampus is significantly attenuated in old animals (Adlard et al., 2005). Caloric restriction did not reverse age-related changes in BDNF levels in the hippocampus (Newton et al., 2005). Whereas alternate day fasting results in an increase in BDNF in young and middle-age mice, it fails to increase BDNF levels in old mice (Arumugam et al., 2010). In rats, daily caloric restriction resulted in an increase in BDNF levels in the hippocampus and amygdala, but not in the prefrontal cortex, in young and middle-aged rats, but not in old rats (Del Arco et al., 2011). Injury-induced up-regulation of BDNF expression in multiple regions of the nervous system is also blunted in old animals. For example, lesion-induced BDNF production is much greater in the striatum of young compared to old rats (Yurek and Fletcher-Turner, 2000). In addition to an age-related decrease in BDNF expression in some brain regions, it was reported that levels of the BDNF receptor trkB decrease more broadly throughout the rat brain during aging (Croll et al., 1998). Levels of mature BDNF and activation of trkB and downstream kinases are decreased in synaptic terminals from aged compared to young rodents (Cortese et al., 2011). Age-related decreases in BDNF expression have been reported to occur in dogs in association with cognitive impairment (Fahnestock et al., 2012). BDNF signaling may also be compromised in one or more brain regions during aging in non-human primates (Hayashi et al., 2001) and humans (Erickson et al., 2012).

POTENTIAL THERAPEUTIC INTERVENTIONS TO SUSTAIN, RESTORE AND ENHANCE BDNF SIGNALING

The evidence that BDNF plays fundamental roles in synaptic plasticity, neuronal survival, neurogenesis and adaptive behaviors, as described above, is conclusive. The evidence that physiological interventions that increase BDNF production and signaling also enhance neuroplasticity and protect the nervous system against injury and disease is also strong. One pharmacologic approach that has been suggested is the activation of TrkB via TrkB agonists. Qian et al. (2006), demonstrated selectivity of several monoclonal TrkB antibodies that do not bind to TrkA, TrkC or p75NTR. These antibodies promote neurite outgrowth and enhance the survival of SH-SY5Y cells implying neuroprotective and neurotrophic potency (Qian et al., 2006). Further, a class of small molecule non-peptide mimetics were shown to have nanomolar neurotrophic properties also specific to the TrkB receptor (Massa et al., 2010). One such molecule, termed LM22A-4, showed efficacy in improving both breathing frequency and levels of TrkB phosphorylation in a mouse model of Rett syndrome (Massa et al., 2010; Schmid et al., 2012). Finally, in a mouse model of AD, a flavonoid TrkB agonist improved memory performance in a y-maze and a similar agonist prevented the impairment of spatial memory caused by immobilization stress in rats (Jang et al., 2010; Andero et al., 2012; Devi and Ohno, 2012).

BFT (exercise, energy restriction and cognitive challenges) has emerged as a potentially effective approach for the optimization of brain health throughout the lifespan. There are several reasons that exercise, energy restriction and cognitive challenges are superior to any

drug with regard to their beneficial effects on brain health. First, the BFT can be implemented throughout life with few or no adverse side effects, whereas all drugs have side effects. Second, the BFT exerts their beneficial actions by engaging adaptive cellular responses in neurons in a highly controlled manner involving activation and potentiation of specific synapses, and local production of BDNF at those synapses. As with most tightly-regulated signaling pathways, excessive uncontrolled activation of BDNF receptors has untoward consequences. For example, we found that endogenous BDNF signaling in the brainstem positively regulates parasympathetic neurons in the brainstem resulting in a reduction in heart rate. In this way, BDNF signaling in the brainstem may mediate some of the beneficial effects of exercise and intermittent energy restriction on the cardiovascular system (Wan et al., 2003; Mager et al., 2006; Griffioen et al., 2012). Acute infusion of BDNF into the brainstem also lowers heart rate, whereas chronic infusion of BDNF elevates heart rate (M. P. Mattson, unpublished data). Third, there are multiple adaptive signaling pathways activated by the BFT, with each pathway making an important contribution to the beneficial effects of the exercise, energy restriction and cognitive stimulation. Fourth, the BFT are interventions for which there is no or minimal cost. Indeed, energy restriction reduces the amount of money spent on food. However, as ‘effort-sparing technologies’ have largely eliminated the need for physical activities in daily life, and energy-dense foods are readily available and heavily promoted by the food industry, far too few people are willing to restrict their food intake or exercise regularly.

Importantly, even though it is well-established and widely known that energy restriction and exercise are critical for maintaining good health, there have been few or no efforts to make this approach to optimal health a mainstay of medical practice. BFT-based prescriptions could and should be developed to accommodate different work schedules and lifestyles. Recent studies have shown that such prescriptions can be adhered to and have striking beneficial effects on the health of overweight subjects. Importantly, it was found in studies using two different intermittent energy restriction diets that after the first 2–3 weeks on the diets the subjects found that their mood improved and that they enjoyed its health and cognitive benefits (Johnson et al., 2007; Harvie et al., 2011). Examples of four prescriptions from which patients could choose are depicted in Fig. 2. A key feature of all four prescriptions is that they incorporate intermittent fasting or major energy restriction. For example, one approach is to consume a very low calorie diet on alternate days, eating *ad libitum* on the intervening days. The latter diet resulted in weight loss, improved asthma symptoms, and reduced inflammation and oxidative stress in overweight asthma patients (Johnson et al., 2007). Another approach is to skip lunch and instead exercise during lunchtime each day. While intermittent energy restriction diets improve multiple health indicators in human subjects, the effects of such diets on the brain in humans remain to be established. It will be of considerable interest to determine how the kinds of BFT prescriptions shown in Fig. 2 affect the brain at the levels of functional status, neuronal network activity and metabolism, and cellular signaling. The data from numerous animal studies reviewed above suggest that it is very likely that such prescriptions will enhance BDNF signaling, improve cognitive performance, and protect the brain against injury and disease.

Finally, efforts to develop pharmacological interventions that increase BDNF production or activate trkB should continue. In this regard, animal studies have demonstrated neuroprotective effects of: (1) infusion of BDNF into the brain (Beck et al., 1994; Novikova et al., 2000; Nomura et al., 2005); (2) viral vector-mediated delivery of the BDNF gene into neurons (Bemelmans et al., 2006; Nosheny et al., 2007; Nagahara et al., 2009); (3) transplantation of cells genetically engineered to overexpress BDNF (Frim et al., 1994; Liu et al., 1999; Nomura et al., 2005); (4) administration of chemicals that stimulate neurons to produce BDNF (Hou et al., 2010; Xu et al., 2011; Fass et al., 2012); and (5) treatment with

chemicals that activate trkB (Lee and Chao, 2001; Massa et al., 2010; Devi and Ohno, 2012; Schmid et al., 2012). Drugs in one class of widely prescribed anti-depressants, the serotonin- and norepinephrine reuptake inhibitors, are believed to exert their clinical benefit by up-regulating BDNF production (Xu et al., 2003, 2006; De Foubert et al., 2004; Russo-Neustadt et al., 2004; Yoshimura et al., 2007). Such antidepressant drugs have also exhibited disease-modifying actions in animal models of Parkinson's disease (Nelson et al., 2007) and Huntington's disease (Duan et al., 2004). There is therefore ample precedence for the clinical potential of drugs that induce BDNF signaling in psychiatric and neurodegenerative disorders, as well as in the treatment of patients suffering from traumatic brain injury and stroke. A combination of an aggressive approach to primary prevention via interventions such as the BFT, and disease-modifying drugs is the way forward.

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Abbreviations

AD	Alzheimer's disease
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid
BDNF	brain-derived neurotrophic factor
BFT	brain-friendly trio
GR	glucocorticoid receptor
GREs	glucocorticoid response elements
MR	mineralocorticoid receptor
NF-κB	nuclear factor κB
NMDA	*N*-methyl-D-aspartate
PKMζ	protein kinase ζ

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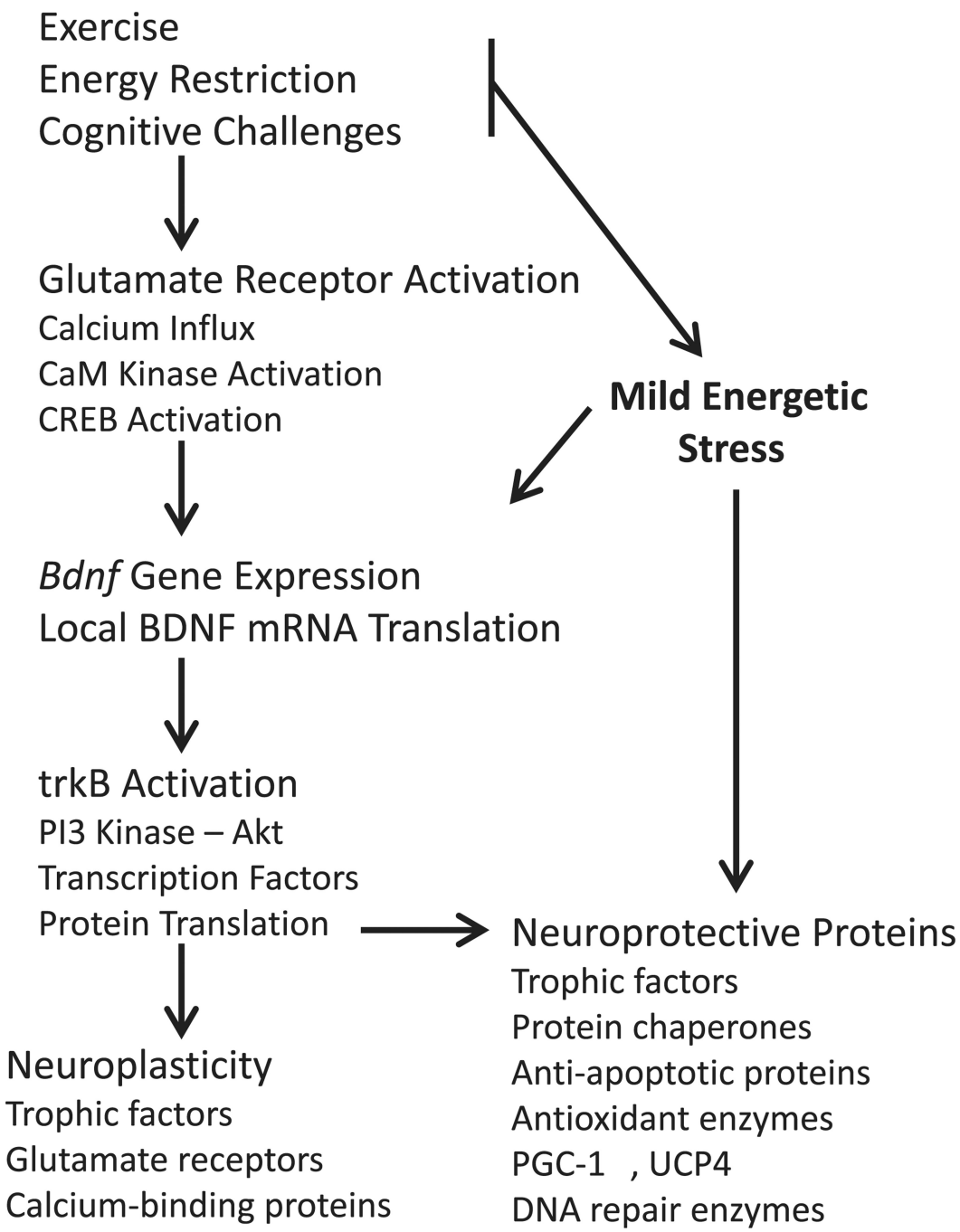

Fig. 1.

Central roles for BDNF in the beneficial effects of exercise, dietary energy restriction and cognitive challenges on brain health. Vigorous intermittent exercise, energy restriction and cognitive challenges activate excitatory neuronal circuits that employ glutamate at their synapses. Glutamate receptor activation results in calcium influx and activation of calcium/calmodulin (CaM)-dependent kinases. CaM kinases can stimulate local translation of BDNF mRNA in dendrites, and can also activate the transcription factor CREB which induces the expression of the *Bdnf* gene. BDNF activates high affinity receptors (trkB) in both the neuron in which it is produced and in adjacent neurons. Activated trkB engages the PI3 kinase–Akt kinase pathway which up-regulates the production of the indicated proteins

involved in neuroplasticity (synaptic plasticity and neurogenesis) and neuroprotection. BDNF-independent adaptive stress response signaling pathways are also activated by exercise, energy restriction and cognitive challenges.

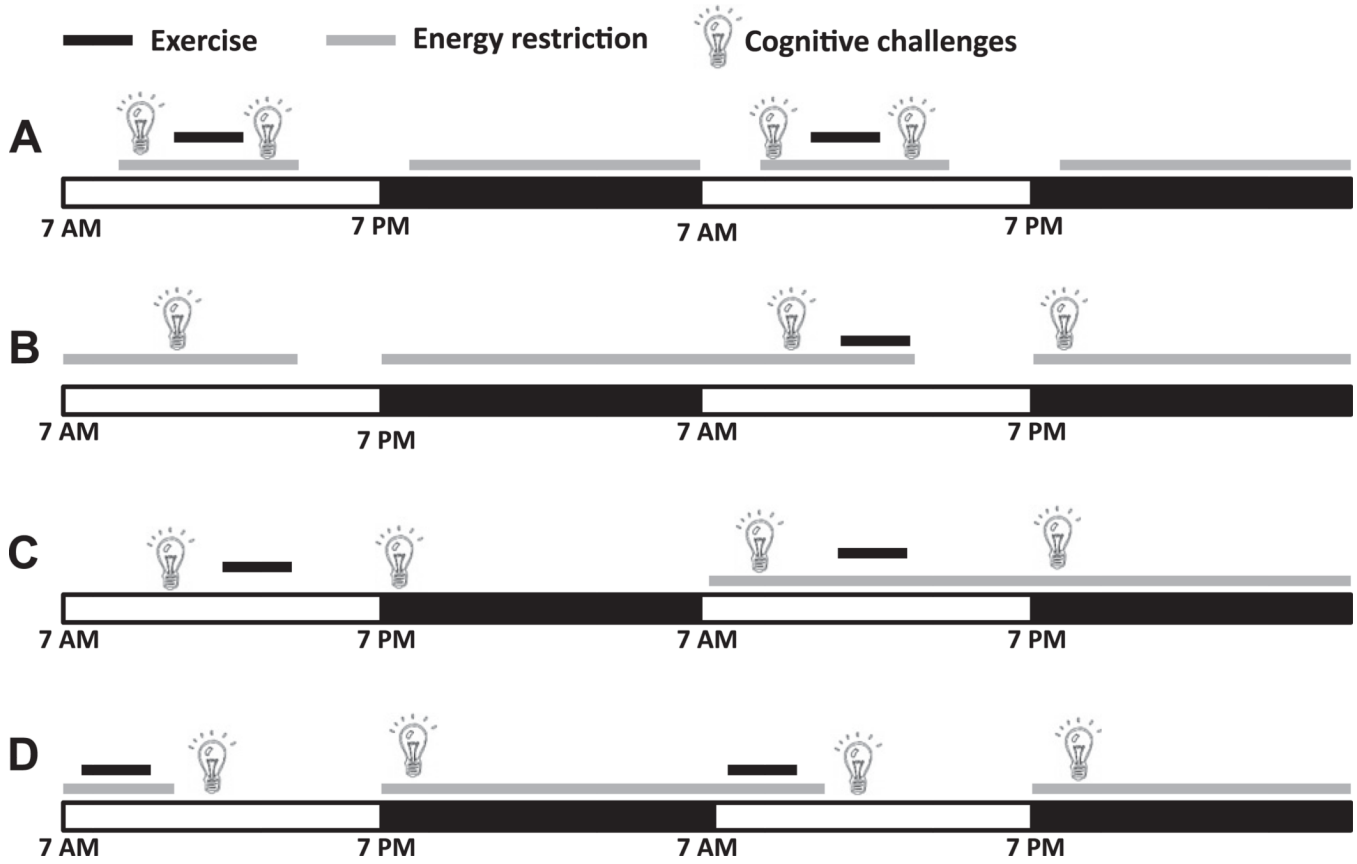

Fig. 2.

Prescriptions for optimal brain health. Findings from studies of animal models and human subjects suggest that intermittent dietary energy restriction, exercise and cognitive challenges (the BFT) increase BDNF production and signaling, and can protect the brain against a range of neurological disorders including anxiety, depression, stroke, and Alzheimer's and Parkinson's diseases. Based upon existing knowledge from human studies we set parameters of the BFT as follows: exercise – at least 20 min of vigorous aerobic exercise; energy restriction – zero calories for restriction periods of 8–12 h, and no more than 600 calories for a 24-h restriction period; cognitive challenges – learning new concepts, integrating information, and generating new ideas. (A) Eat breakfast and dinner – do not eat lunch – exercise during midday – critical thinking and reading prior to and after exercise. Do this every day of the workweek. (B) During the workweek do not eat breakfast or lunch – eat in the early evening – exercise in the afternoon on Monday, Wednesday and Friday. (C) Exercise in the afternoon every other day – fast every other day – maintain intake of water or other non-caloric beverages. (D) On a daily basis: do not eat breakfast – exercise in the early morning – eat lunch and dinner.