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Brain Derived Neurotrophic Factor: A novel neurotrophin involved in psychiatric and neurological disorders

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ABSTRACT

Brain Derived Neurotrophic Factor (BDNF) is a unique member of the neurotrophin family with potent and plethoric effects on the proliferation, differentiation, survival and death of neuronal and non-neuronal cells, thereby making it critical in the health and well being of the nervous system. Studies of various neurological and psychiatric disorders implicate BDNF aberration as a predisposing and perpetuating factor with predictive utility in treatment outcomes. BDNF therapies have yielded good results in animal models of disease states and studies in human subjects are underway. BDNF may be the "missing-link" that mediates the interaction between gene and environment, synaptic plasticity and apoptosis and transgenerational transmission of disease vulnerability. There is theoretical and empirical support for a model in which BDNF underpins the integrity of the central nervous system and this may herald a quantum leap in the way we approach disorders of the mind and brain. Understanding and developing therapies centered on the role of BDNF may lead to paradigm shifts in current practice and treatment of psychiatric and neurological disorders.

Contents

1. Introduction

Psychiatric and neurological disorders are complex heterogeneous disorders, which have multiple risk factors, causes, treatments and outcomes. Clinicians of various specialties have extensively studied various aspects of these disorders and various relationships and overlaps have been identified. For example, neurotransmitter abnormalities seem to be a primary research interest in psychiatry whereas macroarchitectural and neuropathological changes are emphasized in neurological research. Increasingly, researchers have become interested in the genetic aspects of disease processes, both in terms of vulnerability, factors that lead to phenotypic expression and familial transmission.

The first aim of this selective literature review is to highlight the role of BDNF as an emerging candidate in linking together the development and clinical course of varied neurological and psychiatric disorders. This neurotrophin is becoming increasingly recognized as a critical backbone in the functioning and well-being of the central nervous system. The review begins with an overview of this unique neurotrophin with a brief description of the structure, function and genetics. The second aim of this review is to characterize the role of BDNF in the interplay between the environment and genetics. The idea of BDNF linking adverse events in childhood, changes to genetic architecture and development of altered behavioral phenotypes is explored. Recent developments linking BDNF to a wide array of neurological and psychiatric disorders and their treatment outcomes are highlighted. This review concludes on BDNF as a novel therapeutic

Abbreviations: AD, Alzheimer's Disease; BDNF, Brain Derived Neurotrophic Factor; BDNFMet, Valine to Methionine substitution at position 66 in the pro-domain of BDNF gene; CSF, Cerebrospinal fluid; DT, Delirium Tremens; HD, Huntington's Disease; mBDNF, Proteolytically processed mature protein; MDD, Major Depressive Disorder; ProBDNF, Uncleaved precursor BDNF protein; Trk, Tropomyosin related Kinase family; TrkB, Tyrosine kinase receptor B.

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approach that could radically change and progress our understanding and treatment of severe neurological and psychiatric disorders.

1.1. Brain Derived Neurotrophic Factor, a unique member of the nerve growth family

Neurotrophins are considered to play a pivotal role in various aspects of neural function including survival, development, function, and plasticity. The first neurotrophin identified was Nerve Growth Factor (NGF), which was found during a search for such survival factors (Levi-Montalcini, 1987). Currently, four groups of neurotrophins are identified in humans: NGF, Brain-Derived Neurotrophic Factor (BDNF), Neurotrophin-3 (NT-3), and Neurotrophin-4 (NT-4). All of these are considered to be from a common ancestral gene, exhibit similarities in sequence and structure, and are therefore collectively named neurotrophins (Huang & Reichardt, 2001). BDNF is the most abundant and widely distributed neurotrophin in the mammalian CNS. Since the purification of BDNF protein, definitive evidence has emerged for its key role in mammalian brain development, physiology, and pathology.

1.2. Structure and function of Brain Derived Neurotrophic Factor

There is growing evidence for the role of BDNF in the survival, differentiation and plasticity of neurons throughout the brain and spinal cord. BDNF is thought to do this, at least in part, by inhibiting apoptosis (Riccio et al., 1999) and stimulating sprouting and neuronal reorganization (McAllister et al., 1999). The cellular actions of BDNF are mediated through tyrosine kinase receptor B (TrkB) and by p75NTR (p75 neurotrophin receptor), a member of the TNF (tumor necrosis factor) receptor superfamily (Chao, 2003).

All neurotrophins bind to p75NTR receptor but selectively interact with their individual high-affinity protein kinase receptors of the Trk (tropomyosin-related kinase) family. p75NTR is a receptor that binds to all neurotrophins with a very similar affinity (Rodriguez-Tebar et al., 1991). An accumulating body of work has shown that this protein transmits signals important for determining which neurons survive during development. Subsequently, a second class of neurotrophin receptors was identified as three members of the Trk receptor tyrosine kinase family (Bothwell, 1995). Neurotrophins have been shown to directly bind and dimerize these receptors, resulting in activation of the tyrosine kinases present in their cytoplasmic domains. NGF is specific for TrkA. BDNF and NT-4 are specific for TrkB. NT-3 activates TrkC and is also able to activate less efficiently each of the other Trk receptors.

The most important site at which Trk receptors interact with neurotrophins has been localized to the most proximal immunoglobulin (Ig) domain of each receptor (Ultsch et al., 1999). Via tyrosine kinases, neurotrophins are thought to regulate functions such as neuronal proliferation and survival, axonal and dendritic growth and remodeling, assembly of the cytoskeleton, membrane trafficking and fusion, and synapse formation and function (Huang & Reichardt, 2001).

BDNF is secreted in response to neuronal activity, largely via the regulated pathway and derived from both pre- and postsynaptic sites. BDNF is translated as a precursor protein (ProBDNF) and then proteolytically processed to generate a small mature protein (mBDNF). Both ProBDNF and mBDNF are active via two different receptor systems. The biological action of the neurotrophins can be regulated by proteolytic cleavage, with pro-forms preferentially activating p75NTR to mediate apoptosis and mature forms selectively activating Trk receptors to promote survival. Neurotrophins may use a death receptor to prune neurons efficiently during periods of developmental cell death. In the event of mis-targeting, neurons may undergo apoptosis if the appropriate trophic factors are not encountered. In this case, a neurotrophin may fail to activate Trk receptors and eliminate cells by an active killing process through p75NTR (Chao et al., 2006). Cell death mediated by p75NTR may be important for the refinement of correct target innervation during development. In addition, p75-mediated cell death is associated with inflammation, injury, seizure and nerve lesion.

The majority of BDNF effects are mediated through binding of mBDNF to TrkB. Both BDNF and its specific receptor TrkB are highly expressed in the adult brain and they are essential in survival of mature and immature neurons and neurotransmission. In immature neurons, BDNF is involved in growth, differentiation, maturation, and survival. In mature neurons, BDNF plays an important role in synaptic plasticity, augmentation of neurotransmission, and regulation of receptor sensitivity (Numakawa et al., 2010).

The other effects of BDNF are via ProBDNF, which preferentially binds p75NTR, thereby activating a different set of intracellular signaling cascades linked to the activation of apoptotic signaling and initiation of N-methyl-D-aspartic acid (NMDA) receptor-dependent synaptic depression in the hippocampus (Lu & Chang, 2004). p75NTR receptor signaling is involved in cell survival, neurogenesis, cell cycle effects, and apoptosis during developmental cell death and after nervous system injury (Roux & Barker, 2002). Pro-apoptotic p75NTR triggered cell death has been observed during stress, inflammation and injury conditions (Chao et al., 2006).

1.3. Genomics of Brain Derived Neurotrophic Factor

BDNF genomic structure is quite complex and the expression of BDNF gene depends on several regulatory regions. The two forms of BDNF proteins are as follows: uncleaved precursor BDNF protein (ProBDNF) and mBDNF protein each of which has altered binding characteristics and distinct biological activity in comparison with the other (Teng & Hempstead, 2004). Individually regulated upstream promoters drive a short exon that is alternatively spliced onto a common exon encoding the pre-proBDNF protein (Martinowich & Lu, 2008). These promoters of individual transcripts are regulated by diverse and varied physiological stimuli, and these transcripts are distributed in different brain regions, different cell types and even different parts of the cell (e.g. soma vs. dendrites) (Pattabiraman et al., 2005). The most studied promoter is the Rat Promoter III, which is regulated by neuronal activity in the amygdala, hippocampus, and cortex. Alterations in transcription of BDNF via promoter III have been heavily studied as a mediator of activity-dependent processes including synapse development, plasticity, learning, and memory.

In the mouse brain, BDNF mRNA and protein expression becomes detectable during embryonic development, reaching the highest levels by postnatal days 10–14. In the adult mouse, BDNF is expressed throughout the brain, with the highest levels in the neurons of hippocampus. Neuronal BDNF expression is affected by many stimuli, such as γ-aminobutyric acid and glutamate neurotransmission and membrane depolarization through calcium-mediated channels (Aid et al., 2007).

BDNF mRNA is translated in the endoplasmic reticulum into a precursor protein, which is folded in the trans-Golgi and then packaged into secretory vesicles (Lu & Chang, 2004). Upon correct folding, BDNF can be sorted into two forms: the constitutive (spontaneous release) form, or more frequently, the regulatory (release in response to stimuli) form. The trafficking and localization of BDNF appears to be controlled by its pro-domain. A significant single-nucleotide polymorphism in the pro-domain of BDNF has been identified, where the 66th amino acid valine has been converted into methionine (BDNFMet). This polymorphism has been observed to affect dendritic trafficking and synaptic localization of BDNF as well as to impair its secretion.

Studies have previously indicated that the prodomain of neurotrophins plays an important role in regulating their intracellular trafficking to secretory pathways. A recent review described the effect of alteration of the site in the prodomain as leading to decreased variant BDNF targeting to secretory granules and subsequent regulated secretion cells and primary cultured neurons (Chao et al., 2006). In addition, BDNFMet

alters the trafficking of wild-type BDNF through the formation of heterodimers that are less efficiently sorted into the regulated secretory pathway (Chen et al., 2004). These in vitro processing studies with BDNFMet point to the presence of a specific trafficking signal in the BDNF prodomain region encompassing the methionine substitution, which is required for efficient BDNF sorting to the regulated secretory pathway. The perturbations of this secretory pathway may lead to selective impairments in central nervous system function.

Human subjects carrying the BDNFMet polymorphism exhibit deficits in short-term episodic memory and show abnormal hippocampal activation (Egan et al., 2003). This has been associated with memory impairments as well as altered susceptibility to neuropsychiatric disorders, such as Alzheimer's Disease, Parkinson's disease, affective disorders and Schizophrenia as described below, perhaps through a common clinical symptom of impairment of higher cognitive abilities (Egan et al., 2003). Given established knowledge of BDNF role in mediating processes related to learning and memory, this susceptibility to cognitive impairment may lead to multiple disorders affecting nervous system functioning.

1.4. Brain Derived Neurotrophic Factor as a mediating factor in epigenesis

A significant body of research highlights the sensitivity of the developing brain to environmental effects during early, critical periods of brain plasticity, with subsequent long-term modifications of structural and functional aspects of brain activity. Many psychiatric disorders have their antecedents in childhood trauma, maltreatment or loss and studies have linked these events with later depression, anxiety and psychosis (Bremner, 2003). Rodent and non-primate animal models provide a means of studying lasting neurobiological correlates as a sequela of adverse childhood experiences, highlighting vulnerabilities on a macroarchitectural level (hippocampus, amygdala, HPA-Axis, prefrontal cortex) as well as on a cellular level (Korosi & Baram, 2009).

Animal studies have shown that BDNF expression is affected by both acute and chronic stress. These stress paradigms are evoked in the laboratory in various ways including immobilization stress, foot shocks, social defeat, and early maternal deprivation, all of which significantly decrease BDNF expression in the hippocampus, especially in the dentate gyrus (Smith et al., 1995). This is similar to monoamine systems including serotonin, which are significantly affected by stress. It has been proposed that the effects of serotonin on the central nervous system may be mediated, in part, by BDNF with the therapeutic structural and functional changes at a synaptic level as a result of antidepressant therapy being due to changes in the expression, secretion and functioning of BDNF (Martinowich & Lu, 2008). It seems clear that BDNF and serotonin are interconnected in neural circuits implicated in mood disorders and antidepressant response.

It has been proposed that brain changes may result from epigenetic modifications of early adverse life conditions (Murgatroyd et al., 2009). Epigenetic gene regulation is achieved through covalent modifications—methylation or acetylation—of either the DNA itself or of the histone skeleton around which it is packaged into chromatin. Such modifications of key genes are a mechanism whereby early experiences can have longlasting—potentially lifelong—influences on gene expression and, consequently, on brain function and behavior. DNA methylation is the most commonly studied mechanism whereby modifications made to DNA and the associated histone proteins that help regulate transcription of the genome may lead to understanding early-life experiences and neurobiological outcomes. The direct covalent modification of DNA, where at least three encoded enzymes known as DNA methyltransferases are known to catalyze the addition of a $-CH_3$ group to cytosine residues at the 5-position of the pyrimidine ring (Bird, 2007) is a common mechanism of DNA methylation. DNA methylation is increasingly being recognized for its role in mediating gene–environment interplay throughout the lifespan, as studies have now documented both dynamic and static effects and it has been recognized for its role in a number of developmental processes and neurodevelopmental disorders that are associated with long-lasting phenotypic changes (cellular differentiation, X-chromosome inactivation, Rett syndrome, and Fragile X mental retardation). DNA methylation in concert with other associated enzymatic machinery is increasingly thought to have an important role in regulating and promoting gene transcription in the central nervous system (Marmorstein & Trievel, 2009).

The BDNF gene has been the focus of numerous developmental studies aimed at understanding the relationship between early-life stress, brain responses and behavioral outcome, given BDNF's vital role in brain development and plasticity. Various animal models of early-life adversity have consistently indicated that altered behavioral outcomes are well correlated with stable changes in both BDNF gene transcription and protein expression. For example, infant mice that are exposed to higher levels of maternal care have an increased propensity for social interaction in adulthood that is correlated with increased hippocampal BDNF protein levels (Branchi, 2009) whereas infant isolation from the mother and or nest has been shown to alter an array of behaviors, with reduced levels of both mRNA and protein in the prefrontal cortex, amygdala, and hippocampus (Lippmann et al., 2007). Aberrant BDNF gene activity continues to receive attention as a mediating molecular mechanism through which early-life adversity may produce stable modifications in brain and behavioral plasticity (Alleva & Francia, 2009).

A recent review of this summarized the robust outcome of experience-driven changes in BDNF DNA methylation by early-life adverse experiences (Roth & Sweatt, 2011). They highlighted three findings: (1) that adverse social interactions and environmental conditions during the first week of life can alter cortical BDNF gene expression through epigenetic mechanisms, (2) this epigenetic molecular mechanism may potentially underlie not only lifelong but transgenerational effects incited by early-life adverse conditions and (3) Zebularine administration may potentially modify the epigenetic effects of early-life adversity (this is a demethylating agent used in chemotherapy which was able to reverse aberrant DNA methylation and gene expression patterns incited by early-life adversity in rat models).

2. Clinical and therapeutic aspects of Brain Derived Neurotrophic Factor

Neurotrophic factors regulate numerous neuronal functions in development and adult life and in response to neuronal injury (Chao et al., 2006). As a result, neurotrophins have been implicated in the pathophysiology of a wide variety of neurodegenerative and psychiatric disorders and have been considered as a therapeutic strategy for these disorders.

2.1. Brain Derived Neurotrophic Factor and neurological disorders

Alzheimer's Disease (AD) is a neurodegenerative disorder that leads to impairment of memory, judgment and executive functions. Although the exact cause of AD is not known, studies have revealed BDNF alterations in post mortem brains of those afflicted by this disorder. AD is characterized by the accumulation of 2 hallmark lesions, Aβ plaques and neurofibrillary tangles, which are accompanied by gliosis and widespread neuronal and synaptic loss, causing progressive loss of memory and cognitive function. BDNF is produced in the entorhinal cortex and hippocampus in adulthood, which are sites for neuronal loss in AD. The majority of studies have reported reduction in BDNF levels in the brains of those suffering from AD (Peng et al., 2005). A recent study found that serum BDNF levels were significantly increased in Mild Cognitive Impairment (MCI) and AD patients when compared to control subjects and that this was independent of treatment with acetylcholinesterase inhibitor or antidepressant

medication (Angelucci et al., 2010). These opposing data on levels of BDNF in AD patients may reflect differences in patient recruitment and stage of the disease. It may also support an emerging hypothesis that BDNF is upregulated in both preclinical phase (MCI) and clinical phase of dementia (AD).

Restoration of BDNF in transgenic mice with amyloid precursor protein overexpression (an AD model) led to some repair in gene expression that were disturbed in entorhinal cortex and hippocampus with corresponding improvement in learning and memory (Nagahara et al., 2009). BDNF restoration was accomplished by BDNF protein infusion intrathecally. Similarly, neural stem cell transplantation in aged triple transgenic mice that express pathogenic forms of amyloid precursor protein, presenilin, and tau led to improvement in spatial learning and memory deficits without reversing these neuropathological markers. The authors considered that a robust enhancement of hippocampal synaptic density, mediated by BDNF, was the cause of improvement of cognitive function in AD mice models (Blurton-Jones et al., 2011). Overall, emerging studies demonstrate that BDNF exerts substantial protective effects on crucial neuronal circuitry involved in AD and reverses cognitive impairment, acting through amyloid-independent mechanisms.

The involvement of BDNF in neurodegenerative disorders such as Parkinson's disease (PD) and Huntington's disease (HD) have received some attention. The pathological hallmark in PD is the loss of dopaminergic neurons from the striatum, which is replicated in mice with selective BDNF deletion from the midbrain and hindbrain that show early phenotype of PD (Baquet et al., 2005). This is in agreement with earlier studies that showed reduced BDNF mRNA expression in dopaminergic neurons of substantia nigra of those suffering from PD by up to 70% (Howells et al., 2000). Animal studies have demonstrated BDNF induced improvement in anatomical and behavioral effects in non human primates with demonstrated reversal of histological changes in the substantia nigra (Tsukahara et al., 1995). Similar effect was observed in rodent models with reduction of dopaminegic loss in substantia nigra with implanted fibroblasts genetically enhanced to express BDNF (Levivier et al., 1995). In HD, BDNF depletion leading to reduced trophic support and subsequent striatal degeneration has been put forward as a hypothesis in mediating the age of onset and severity of this condition (Strand et al., 2007). Cultured neurons that have been transfected with huntingtin protein show reduced cell death as a result of BDNF treatment (Zala et al., 2005). Infusion of BDNF into the striatum of mice expressing huntingtin protein led to improvement in motor abnormalities (Canals et al., 2004). Although trials of BDNF administration in humans with PD and HD are yet to be undertaken, BDNF offers the hope of stopping or delaying progression of neurodegenerative disorders.

Amyotrophic lateral sclerosis (ALS) is a severe neurodegenerative disorder, characterized by selective loss of motor neurons with progressive paralysis and death by respiratory failure. Trophic support from neurotrophins including BDNF is understood to be necessary for growth and survival of the developing nervous system. In a 6-month phase I/II trial, ALS patients treated with BDNF revealed a significant slowing of the decline in walking speed and a slowing of decline of respiratory function. A larger phase III trial of subcutaneous BDNF administration is underway to replicate these results (Schulte-Herbrüggen et al., 2007).

BDNF applied peripherally into the spinal cord promotes regeneration of ascending sensory neurons and functional recovery whereas direct injection of BDNF does not appear to have this effect (Song et al., 2008). The lack of effect is thought to be due to the suppressive effect of TrkB, which is found in astrocytes throughout the spine and central nervous system. BDNF applied to the peripheral nerve is transported transganglionically to the spinal cord and central nervous system, offering a practical and accessible vehicle for transport. Rats with spinal cord injuries showed significant improvement in locomotive tests after the injury when administered gels containing BDNF (Park et al., 2010). Hence, BDNF combined with a matrix of biogenic scaffolds or a cellular matrix has led to positive results in regenerative growth following spinal cord injury.

2.2. Brain Derived Neurotrophic Factor and psychiatric disorders

Given that neurotrophic factors are thought to modulate cell survival and promote neuronal plasticity, BDNF dysfunction may contribute to, or be a consequence of, mental illness. Human polymorphisms in BDNF gene are linked to increased risk of mood disorder including bipolar disorder.

Bipolar disorder (BPD) is characterized by episodes of elevated or depressed mood. Typically, depressive episodes predominate over manic episodes and in some cases, the episodes of elevated mood may be hypomanic episodes (Saunders & Goodwin, 2010). Recently, it was reported that decreased BDNF and impaired neuroplasticity may play a role in the pathophysiology of BPD (Duffy, 2010). Furthermore, no difference in BDNF levels was found between unaffected relatives and controls, which had higher levels compared with the related proband patient. This suggests that upregulation of BDNF may be a protective mechanism in those at genetic risk who do not develop the illness. Serum BDNF levels are decreased in depressive and manic episodes, returning to normal levels in euthymic states. BPD patients displayed reduced BDNF levels as a result of factors that negatively influence the course of this disorder, such as life stress and trauma (Kapczinski et al., 2008).

The pathophysiology of depressive disorders may be considered to be due to aberrant regulation of neuronal plasticity, including neurogenesis mediated by neurotrophic factors in the hippocampus and other limbic nuclei resulting in maladaptive changes in neural networks. Some authors have advanced a neurotrophin theory of depression, stating that the failure of neurogenesis and neuronal plasticity is an etiological factor for stress induced disorders such as Major Depressive Disorder (MDD) (Duman, 2002). Studies have suggested that MDD may be precipitated by low production of BDNF (Karege et al., 2002) and medication free patients with MDD and healthy subjects with depressive personality traits (Lang et al., 2006) have decreased serum BDNF level than healthy subjects. These studies also showed that greater depression severity is associated with a lower serum BDNF level and that antidepressant therapy can normalize BDNF levels (Gonul et al., 2005).

The gene encoding BDNF, located on chromosome 11p13 (Maisonpierre et al., 1990) is one of several candidate genes that have been described for MDD (Levinson, 2006). BDNF is a neurotrophin that is highly expressed in the central nervous system, especially in the hippocampus, which is coded for by this BDNF gene (Martinowich et al., 2007). A single nucleotide polymorphism (rs6265) in exon 11 of the BDNF gene results in an amino-acid substitution from valine to methionine at codon 66 (BDNFMet) in the prodomain of BDNF (Schumacher et al., 2005). BDNFMet is a common polymorphism with a higher frequency reported in Asian populations than Caucasian populations (Shimizu et al., 2004). Studies have suggested that the BDNFMet allele is associated with poorer episodic memory performance and reduced hippocampal activity, both of which are evident in MDD (Egan et al., 2003). Some studies have found lower serum BDNF levels during depression and that metcarriage had an effect in reducing serum BDNF levels, regardless of gender and depression (Ozan et al., 2010).

Recent review of BDNF in postmortem brains of suicide victims revealed low BDNF levels in the hippocampus and prefrontal cortex, but increased BDNF levels where victims of suicide were treated with antidepressant medications (Karege et al., 2005). Other studies have refuted this association (Oswald et al., 2005). The inconsistencies in association studies have been explained by some as resulting from the lack of statistical power in studies of small sample size and from variation across studies in inclusion criteria, such as the definition of psychiatric phenotype, or ethnicity (Verhagen et al., 2010).

BDNF is thought to play an important role in the pathophysiology of schizophrenia. The prefrontal cortex appears to be critical from a structural and functional point of view in controlling higher order cognitive and executive functions, the impairment of which is considered to be a core feature of the "negative syndrome" of schizophrenia (Dalley et al., 2004). A recent study demonstrated an inverse correlation between BDNF and cortisol levels in both postmortem human brains and animal models of schizophrenia (Issa et al., 2010). This builds on significant evidence suggesting lower BDNF levels in serum and prefrontal cortex of those suffering with schizophrenia, reversed by treatment with the antipsychotic agent olanzapine in prenatal rat models (Pillai, 2008). Studies of patients affected by episode psychosis also detected decreased BDNF levels (Pillai et al., 2010). The key findings from this study were: (1) BDNF protein levels are low in plasma and cerebrospinal fluid (CSF) of first episode psychotic subjects; (2) plasma and CSF BDNF protein levels show a significant negative correlation with scores of the baseline PANSS positive symptom subscales and (3) a strong positive correlation exists between plasma and CSF BDNF protein levels in first episode psychotic subjects. Hence, this provides strong support for BDNF as being a mediating factor in stress related paradigm models in the pathogenesis of schizophrenia (with elevated cortisol levels resulting from dysfunction of the hypothalamic-pituitary-adrenal axis being the biological marker for stress and BDNF being the final common pathway for altered neural plasticity and providing support for the aberrant neurodevelopmental changes found in schizophrenia patients).

That positive symptoms of schizophrenia as measured by the PANSS are inversely correlated with BDNF levels suggests that BDNF may assist with diagnosis and treatment of psychosis, even though the exact mechanism for change remains unknown. A recent study showed significant correlation between reduced levels of an isomeric form of BDNF (truncated-BDNF) and higher scores on negative subscale of PANSS and neuropsychological testing deficits (Carlino et al., 2011). The authors suggested that isomeric forms of BDNF (truncated-BDNF) might be better than serum total BDNF in brain pathology and might explain equivocal findings of BDNF levels in some studies of patients suffering with schizophrenia. Nevertheless, there is growing support for measuring BDNF levels as an empirical method of predicting positive and negative symptoms in schizophrenia.

A recent meta-analysis of BDNF levels in patients suffering with schizophrenia found that both drug naive and medicated patients had lower BDNF levels when compared to healthy controls (Green et al., 2011). Low BDNF levels are also inversely correlated with the duration of untreated psychosis (Rizos et al., 2010) as well as positive and negative symptoms of schizophrenia (Rizos et al., 2008). Hence, low BDNF may confer a poorer prognosis in schizophrenia and hold the key to understanding neurobiological mechanisms of this complex disease.

Studies of drug reward and dependence in rodent models revealed interesting and mixed findings regarding the role of BDNF in various phases of addiction (initiation, maintenance or abstinence/relapse). These experiments have revealed varying results depending on drug type, brain site, phase of addiction and time elapsed since injection of BDNF into the rodent brain and measurement of behavioral outcomes. BDNF is considered to be important in drug addiction as it provides trophic support to midbrain dopaminergic neurons, which are critically important in mediating drug reward and relapse (Chao, 2003). A recent summary of key research in this area revealed various outcomes (Ghitza et al., 2010): activating BDNF signaling in dorsal striatum decreases alcohol intake, stimulation of BDNF in the ventral tegmental area facilitates cocaine intake and a similar effect is produced by stimulating BNDF in the terminal mesocorticolimbic dopaminergic neurons, which potentiates cocaine intake.

A recent study compared BDNF levels among those suffering with alcohol dependence vs. healthy controls (Huang et al., 2011). The alcohol dependent group was further stratified into those exhibiting delirium tremens (DT) and those not. This study demonstrated that the lowest levels of BDNF (statistically significant) were in the DT group, followed by non DT group and highest in the control group. Furthermore, BDNF levels for both alcohol dependent groups increased within one week of alcohol withdrawals, implicating BDNF in recovery. Additionally, BDNF levels in the non-DT group were comparable to controls after withdrawal, but this did not occur in the DT group whose BDNF levels remained low. Some have proposed that BDNF is a haemostatic agent that is elevated acutely in alcohol abuse as a neuroprotective agent to counteract the rewarding effects of alcohol, but is reduced in chronic alcohol exposure (McGough et al., 2004). Hence, Huang et al. (2011) concluded that "It is plausible that the more inadequate BDNF expression to act against addiction is associated with more severe alcohol dependence and withdrawal. Therefore, alcoholic patients with weakened BDNF expression and ensued poor neurotrophic protection are likely to be susceptible to alcohol induced neurotoxicity and DTs". The role of endogenous BDNF and modifying it in drug addiction therapies are areas of future research where many questions remain unanswered.

BDNF and TrkB, its receptor are highly expressed in the hypothalamus and strongly implicated in a range of functions related to metabolism and food regulation such as appetite, weight and food consumption (Kernie et al., 2000). Obesity, hyperhagia, hyperinsulinemia and hyperglycemia have been demonstrated in mice heterozygous for BDNF or with BDNF deletion (Fox & Byerly, 2004). Recent reports have confirmed human cases where alterations in BDNF gene have led to childhood obesity and hyperphagia (Gray et al., 2006). Low BDNF levels are found in patients with diabetes compared to non-diabetic controls suggesting the possibility that BDNF may be linked to other biomarkers of diabetic control (Fujinami et al., 2008). It is possible to administer BDNF to mice centrally and peripherally and demonstrate physiological changes such as reduction of food intake, increase in energy expenditure, control of hyperglycemia and hyperinsulinemia and weight reduction in diabetic mice (Nakagawa et al., 2000; Tsuchida et al., 2001).

2.3. Brain Derived Neurotrophic Factor and psychopharmacology

Most classes of antidepressant medication have been found to increase BDNF levels in animal models (Duman & Monteggia, 2006). A similar effect is seen with Electroconvulsive Therapy (ECT) and transcranial magnetic stimulation (Müller et al., 2000; Altar et al., 2004). BDNF mutant mice with the BDNFMet variation exhibited higher levels of anxiety which could not be reversed with the antidepressant fluoxetine, implicating BDNF in the therapeutic efficacy of antidepressant medication (Chen et al., 2006). Using a double mutant mouse model without any copies of serotonin transporter gene, BDNF reduction led to excerbation of monoamine deficiency and increased stress abnormalities (Ren-Patterson et al., 2005). Mice with overexpressed TrkB receptors and enhanced BDNF signaling showed resistance in animal models of depression such as increased latency to immobility in the forced swim test. This was similar to wild-type mice that were administered fluoxetine (Koponen et al., 2005).

Chronic antidepressant treatment (21 days) has been shown to increase BDNF levels by 10–30% and repeated daily administration of electroconvulsive therapy over 10 days increased BDNF levels by 40–100% in rat forebrain regions (Balu et al., 2008). This is in contrast to 1 day of antidepressant or ECT treatment where there were no appreciable increases in BDNF levels observed. The duration of antidepressant medication treatment leading to initial therapeutic effect correlated well with the findings in wild type mice that 21 days of repeated drug treatment were required in increase expression of BDNF and TrkB (Nibuya et al., 1995). Human studies have demonstrated lower BDNF levels in those suffering with depression (Piccinni et al., 2008) in contrast to generally revealed elevated serum or plasma BDNF levels in depressed patients who have responded to therapy

with antidepressant medication (Brunoni et al., 2008). A recent pilot study also demonstrated that non increase in serum BDNF levels associated with non improvement by day 14 predicted later non response and non remission of MDD to antidepressant therapy with moderate to high specificity (Tadic et al., 2011). Hence, it may be considered that neuroplasticity, neurogenesis and synpatogenesis induced by antidepressant therapy may be mediated, at least in part, via BDNF (Lee & Kim, 2010).

Recent studies have confirmed previous findings that BDNF levels are decreased in BPD patients and these are normalized in lithium responders (Rybakowski & Suwalska, 2010). The neuropsychological performance and BDNF levels of patients in this study who responded to lithium were compared to control group, but better than those who did not respond to lithium. Other studies have shown that the severity of manic episodes is significantly negatively correlated with plasma BDNF levels, raising the possibility of BDNF being a potential biological marker or measure of disease severity in BPD patients (Machado-Vieira et al., 2007). This may also explain Lithium's actions as a neuroprotective agent. Hence, a study of AD patients treated with lithium showed significant increase of BDNF serum levels combined with significant decrease of ADAS-Cog sum scores in comparison to placebo-treated patients (Leyhe et al., 2009). Improvement of cognitive impairment was inversely correlated with lithium serum concentration. Animal studies also reported that lithium can increase BDNF levels in rat brain (Fukumoto et al., 2001).

Studies of BNDF levels with antipsychotic therapy have yielded inconsistent results. A recent study showed that clozapine, in comparison to first-generation antipsychotics (FGAs), was positively correlated with serum BDNF levels (Pedrini et al., 2011). The authors speculated that this may explain the superiority of clozapine when compared with FGAs, particularly in the domain of cognitive function. Another recent study showed that risperidone and clozapine treatment correlated with elevated BDNF levels, and patients treated with risperidone showed a significant increase compared to those treated with clozapine with a specific increase in male patients (Chen & Huang, 2011). Rats subjected to immobility stress showed significant decrease in BDNF levels, which were attenuated by the administration of antipsychotic medication, particularly olanzapine and aripiprazole (Park et al., 2011). BDNF phenotypes have also been implicated in antipsychotic induced weight gain with the BDNFMet variant implicated in weight gain among male patients and low BDNF levels implicated in weight gain in females, suggesting that BDNF may play a central role in appetite stimulation and metabolic homeostasis (Zhang et al., 2008).

2.4. Future directions in Brain Derived Neurotrophic Factor therapy research

Working with the assumption that impaired neurotrophic factors lead to neurological and psychiatric conditions, therapies have been considered that target neurotrophin signaling. The hypothesis is that disease states result in (i) decreased availability of neurotrophins for the affected neurons, (ii) decreased number of neurotrophin receptors on the affected neurons, and/or (iii) decreased neuronal survival. It is hoped that these deficits can be ameliorated by the addition of neurotrophic factors exogenously and at least provide symptomatic treatment for the disease state rather than a cure for these nervous system disorders (Chao et al., 2006). Therefore, a key task of future research endeavors lies in overcoming challenges associated with the delivery of BDNF to the central nervous system. These challenges may help explain why trials involving BDNF administration in human subjects have led to equivocal results with side effects (Thoenen & Sendtner, 2002).

BDNF protein does not readily cross the blood brain barrier when administered peripherally (Nagahara & Tuszynski, 2011). Hence, it must be administered centrally by intraventricular or intrathecal infusion which still may not penetrate the brain parenchyma beyond superficial layers (Ankeny et al., 2001). Infusion of BDNF via implanted pumps has been tried, but these studies struggled to achieve the balance between adequate flow rates that lead to effective BDNF distribution at target sites without causing damage to tissue and excessive flow rates that may lead to side effects (Lang et al., 2006). There are also the risks of reflux, infection and obstruction. Indiscriminate infusion of BDNF into the nervous system may lead to significant side effects including epilepsy, dysesthesias and migration/proliferation of Schwann cells into subpial space (Nagahara & Tuszynski, 2011). Therefore, to deliver adequate doses of BDNF to specific targets in the nervous system that can be controlled and measured with predictable pharmacokinetics for adequate duration (perhaps years in chronic neurodegenerative disorders) is a formidable challenge that remains to be met by future research.

Adenovirus vectors have been used in-vivo to genetically transfer BDNF into the central nervous system, usually in animal models (Koda et al., 2004). Various regions of the vector genome are deleted and then genetically engineered to express BDNF, after which the vector is directly injected into the injured neural site and initiates expression of transferred genes. These are incorporated into the axon terminals and transported retrogradely to the cell body, enabling a high degree of transferred gene expression (Liu et al., 1997). This contrasts with ex-vivo gene therapy where cells transfected with genes encoding therapeutic molecules as grafted to the lesion site such as fibroblasts that have been genetically modified to express BDNF (Liu et al., 1999). The main concerns with in-vivo gene delivery are the neurosurgical intervention required (the surgical procedure may take up to 4 h) and the challenges of accurate targeting and turning off genetic activation if side effects develop. Nagahara and Tuszynski (2011) have recently summarized six trials of in-vivo gene delivery to the brain, which are still in progress in patients suffering from PD and AD.

Mimetic analogs are small molecules that activate neurotrophic receptors and the subsequent cascades leading to neurogenesis and neuroplastic changes. A recent report heralded the development of a TrkB agonist which reduces neutrophin related neuronal loss in vitro and improves motor dependent learning after trauma in rodents (Massa et al., 2010). This prototype compound, named as LM22A-4, is believed to be the first reported small molecule to mimic a specific neurotrophin domain, capable of functioning as a ligand to selectively and potently activate the TrkB receptor. Studies of tolerability and efficacy in human subjects are awaited.

The neurotrophin system can also be transactivated by other receptor signaling systems such as G-protein-coupled receptors, purine adenosine A_{2A} receptor and pituitary adenylate cyclase-activating polypeptide neuropeptide receptor, even in the absence of neurotrophins (Lee & Chao, 2001). Recent reports confirm this finding in experimental situations where activating of A_{2A} receptor led to increased levels of TrkB receptor and potentiated the effects of BDNF with functional consequences for TrkB phosphorylation and BDNF-induced modulation of neurotransmitter release and hippocampal plasticity (Assaife-Lopes et al., 2010). Although there are no data on humans, intracellular signaling interactions between adenosine and Trk receptors therefore provide a new avenue for developing novel treatments for neurological disorders. By targeting populations of neurons that express adenosine and Trk receptors, small molecules such as adenosine, may be contemplated as potential treatments for a wide number of nervous system disorders, including cerebral ischemia, ALS, PD, and other neurodegenerative conditions.

3. Conclusion

This paper highlights convergence of recent research interests on BDNF (Table 1). The primary reason for understanding BDNF is that it may constitute attractive target for better understanding disease pathology and treatment. It seems to play a homeostatic role that

Table 1
Summary of effects of BDNF in human and animal models of disease.

Disease model	Pathology	Intervention	Effect on BDNF and outcome
Alcohol dependence	Low levels of BDNF in alcohol dependent patients with Delirium Tremens		Improvement in BDNF levels in detoxified patients
Alzheimer's Disease	BDNF levels increased in mild cognitive impairment—possible compensatory upregulation of BDNF in preclinical phase of Alzheimer's Disease. BDNF levels decreased in Alzheimer's Disease.	Lithium therapy in patients with Alzheimer's Disease associated with increased BDNF levels	Improved cognitive functioning with decreased ADAS-Cog scores in patients with Alzheimer's Disease treated with lithium
Amyotrophic lateral sclerosis—selective loss of motor neurons	? Related to lack of trophic support from BDNF	6 month phase I/II trial in humans of BDNF treatment	Slowing of decline in walking speed and respiratory function
Bipolar Disorder	Reduction in serum BDNF levels in manic and depressive episodes in human subjects; inverse correlation with severity of manic episodes and serum BDNF levels	Lithium administration	Normal BDNF levels in same subjects during euthymic states Normal BDNF levels in lithium responders
Huntington's Disease	BDNF depletion	BDNF infusion into striatum	BDNF treatment reduced cell death in cultured neurons infected with huntingtin protein with resultant improvement in motor abnormalities in mice
Metabolic function	Mice with BDNF deletion or heterozygous BDNF likely to demonstrate obesity, hyperphagia, hyperinsulinemia Low BDNF levels in diabetes	Central and peripheral BDNF administration to mice	Reduction in food intake, increased energy expenditure, weight loss in mice
Parkinson's disease	Mice with BDNF deletion from midbrain/hindbrain showing phenotypic changes of Parkinson's Disease	Fibroblast implantation genetically enhanced to overexpress BDNF	Reversal of BDNF reduction and reversal of histological changes in substantia nigra in animal models, reduction of dopaminergic loss
Resilience paradigm	Infant mice exposed to higher levels of maternal care		Increased hippocampal BDNF leading to increased social interaction in adulthood
Schizophrenia	Lower BDNF levels in serum, cerebrospinal fluid and prefrontal cortex of those suffering with schizophrenia	Antipsychotic treatment (olanzapine) administered to rats Clozapine administered to humans	Reversal of low BDNF levels in rat models Increased BDNF levels with clozapine therapy
Spinal cord injury	Rats with spinal cord injury	BDNF applied to peripheral nerve via gels	Improvement in locomotive activity
Stress paradigm	Immobilization stress, foot shock, social defeat, early maternal deprivation Infant mice isolation from mother and nest		Decreased BDNF in dentate gyrus of hippocampus. Reduced mRNA and protein in prefrontal cortex, amygdala and hippocampus
Suicide	Lower BDNF levels in postmortem brains of those who died by suicide		
Unipolar depression	Reduced BDNF levels during depressive episodes BDNFMet allele associated with poorer episodic memory	Antidepressant therapy, electroconvulsive therapy, transcranial magnetic stimulation	BDNF levels normalized by antidepressant therapy; reversal of anxiety in mice models

spans appetite regulation, memory, affect, perceptions and sensorimotor systems. This is due to its potent effects on proliferation, differentiation, survival and death of neuronal and non-neuronal cells, thereby making it critical in the health and well-being of the nervous system. BDNF both serves as a promoter of neuronal growth and regeneration as well as a key regular of neuronal apoptosis. It appears to mediate the interplay between gene expression and environmental stress. Studies of various neurological and psychiatric disease processes implicate BDNF aberration and promising therapeutic approaches have yielded good results in animal models of disease states. BDNF helps understand the effects of current pharmacological agents such as antidepressants, antipsychotics, lithium and ECT and promises to be a novel approach to treatment if it can be directly administered to critical brain sites. Although the development of rational therapies that engage neurotrophin signaling are in their early stages, there is much incentive to develop and study safe and effective ways of increasing BDNF levels in the central nervous system.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

References

Aid, T., Kazantseva, A., Piirsoo, M., Palm, K., & Timmusk, T. (2007). Mouse and rat BDNF gene structure and expression revisited. *J Neurosci Res 85*, 525–535.

Alleva, E., & Francia, N. (2009). Psychiatric vulnerability: suggestions from animal models and role of neurotrophins. *Neurosci Biobehav Rev 33*, 525–536.

Altar, C. A., Laeng, P., Jurata, L. W., Brockman, J. A., Lemire, A., Bullard, J., et al. (2004). Electroconvulsive seizures regulate gene expression of distinct neurotrophic signaling pathways. *J Neurosci 24*, 2667–2677.

Angelucci, F., Spalletta, G., Iulio, F. d., Ciaramella, A., Salani, F., Varsi, A. E., et al. (2010). Alzheimers Disease (AD) and Mild Cognitive Impairment (MCI) patients are characterized by increased BDNF serum levels. *Curr Alzheimer Res 7*, 15–20.

Ankeny, D. P., McTigue, D. M., Guan, Z., Yan, Q., Kinstler, O., Stokes, B. T., et al. (2001). Pegylated brain-derived neurotrophic factor shows improved distribution into the spinal cord and stimulates locomotor activity and morphological changes after injury. *Exp Neurol 170*, 85–100.

Assaife-Lopes, N., Sousa, V. C., Pereira, D. B., Ribeiro, J. A., Chao, M. V., & Sebastiao, A. M. (2010). Activation of adenosine A(2A) receptors induces TrkB translocation and increases BDNF-mediated phospho-TrkB localization in lipid rafts: implications for neuromodulation. *J Neurosci 30*, 8468–8480.

Balu, D. T., Hoshaw, B. A., Malberg, J. E., Rosenzweig-Lipson, S., Schechter, L. E., & Lucki, I. (2008). Differential regulation of central BDNF protein levels by antidepressant and non-antidepressant drug treatments. *Brain Res 1211*, 37–43.

Baquet, Z. C., Bickford, P. C., & Jones, K. R. (2005). Brain-derived neurotrophic factor is required for the establishment of the proper number of dopaminergic neurons in the substantia nigra pars compacta. *J Neurosci 25*, 6251–6259.

Bird, A. (2007). Perceptions of epigenetics. *Nature 447*, 396–398.

Blurton-Jones, M., Kitazawa, M., Martinez-Coria, H., Castello, N. A., Müller, F., Loring, J. F., Yamasaki, T. R., Poon, W. W., Green, K. N., & LaFerla, F. M. (2009). Neural stem cells improve cognition via BDNF in a transgenic model of Alzheimer's Disease. *Proc Natl Acad Sci 106*, 13549–13599.

Bothwell, M. (1995). Functional interactions of neurotrophins and neurotrophin receptors. *Annu Rev Neurosci 18*, 223–253.

Branchi, I. (2009). The mouse communal nest: investigating the epigenetic influences of the early social environment on brain and behavior development. *Neurosci Biobehav Rev 33*, 551–559.

Bremner, J. (2003). Long-term effects of childhood abuse on brain and neurobiology. *Child Adolesc Psychiatr Clin N Am 12*, 271–292.

Brunoni, A. R., Lopes, M., & Fregni, F. (2008). A systematic review and meta-analysis of clinical studies on major depression and BDNF levels: implications for the role of neuroplasticity in depression. *Int J Neuropsychopharmacol 11*, 1169–1180.

Canals, J. M., Pineda, J. R., Torres-Peraza, J. F., Bosch, M., Martin-Ibanez, R., Munoz, M. T., et al. (2004). Brain-derived neurotrophic factor regulates the onset and severity of motor dysfunction associated with enkephalinergic neuronal degeneration in Huntington's disease. *J Neurosci 24*, 7727–7739.

Carlino, D., Leone, E., Di Cola, F., Baj, G., Marin, R., Dinelli, G., et al. (2011). Low serum truncated-BDNF isoform correlates with higher cognitive impairment in schizophrenia. *J Psychiatr Res 45*, 273–279.

Chao, M. V. (2003). Neurotrophins and their receptors: a convergence point for many signalling pathways. *Nat Rev Neurosci 4*, 299–309.

Chao, M. V., Rajagopal, R., & Lee, F. S. (2006). Neurotrophin signalling in health and disease. *Clin Sci 110*, 167–173.

Chen, C. -C., & Huang, T. -L. (2011). Effects of antipsychotics on the serum BDNF levels in schizophrenia. *Psychiatry Res 189*, 327–330.

Chen, Z. -Y., Jing, D., Bath, K. G., Ieraci, A., Khan, T., Siao, C. -J., et al. (2006). Genetic variant BDNF (Val66Met) polymorphism alters anxiety-related behavior. *Science 314*, 140–143.

Chen, Z. -Y., Patel, P. D., Sant, G., Meng, C. -X., Teng, K. K., Hempstead, B. L., et al. (2004). Variant Brain-Derived Neurotrophic Factor (BDNF) (Met66) alters the intracellular trafficking and activity-dependent secretion of wild-type BDNF in neurosecretory cells and cortical neurons. *J Neurosci 24*, 4401–4411.

Dalley, J. W., Cardinal, R. N., & Robbins, T. W. (2004). Prefrontal executive and cognitive functions in rodents: neural and neurochemical substrates. *Neurosci Biobehav Rev 28*, 771–784.

Duffy, A. (2010). The early stages of bipolar disorder and recent developments in the understanding of its neurobiology. *Future Neurol 5*, 317–323.

Duman, R. S. (2002). Pathophysiology of depression: the concept of synaptic plasticity. *Eur Psychiatry 17*(Supplement 3), 306–310.

Duman, R. S., & Monteggia, L. M. (2006). A neurotrophic model for stress-related mood disorders. *Biol Psychiatry 59*, 1116–1127.

Egan, M. F., Kojima, M., Callicott, J. H., Goldberg, T. E., Kolachana, B. S., Bertolino, A., et al. (2003). The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell 112*, 257–269.

Fox, E. A., & Byerly, M. S. (2004). A mechanism underlying mature-onset obesity: evidence from the hyperphagic phenotype of brain-derived neurotrophic factor mutants. *Am J Physiol Regul Integr Comp Physiol 286*, R994–R1004.

Fujinami, A., Ohta, K., Obayashi, H., Fukui, M., Hasegawa, G., Nakamura, N., et al. (2008). Serum brain-derived neurotrophic factor in patients with type 2 diabetes mellitus: relationship to glucose metabolism and biomarkers of insulin resistance. *Clin Biochem 41*, 812–817.

Fukumoto, T., Morinobu, S., Okamoto, Y., Kagaya, A., & Yamawaki, S. (2001). Chronic lithium treatment increases the expression of brain-derived neurotrophic factor in the rat brain. *Psychopharmacology 158*, 100–106.

Ghitza, U. E., Zhai, H., Wu, P., Airavaara, M., Shaham, Y., & Lu, L. (2010). Role of BDNF and GDNF in drug reward and relapse: a review. *Neurosci Biobehav Rev 35*, 157–171.

Gonul, A., Akdeniz, F., Taneli, F., Donat, O., Eker, Ç., & Vahip, S. (2005). Effect of treatment on serum brain-derived neurotrophic factor levels in depressed patients. *Eur Arch Psychiatry Clin Neurosci 255*, 381–386.

Gray, J., Yeo, G. S. H., Cox, J. J., Morton, J., Adlam, A. -L. R., Keogh, J. M., et al. (2006). Hyperphagia, severe obesity, impaired cognitive function, and hyperactivity associated with functional loss of one copy of the Brain-Derived Neurotrophic Factor (BDNF) gene. *Diabetes 55*, 3366–3371.

Green, M. J., Matheson, S. L., Shepherd, A., Weickert, C. S., & Carr, V. J. (2011). Brain-derived neurotrophic factor levels in schizophrenia: a systematic review with meta-analysis. *Mol Psychiatry 16*, 960–972.

Howells, D. W., Porritt, M. J., Wong, J. Y. F., Batchelor, P. E., Kalnins, R., Hughes, A. J., et al. (2000). Reduced BDNF mRNA expression in the Parkinson's disease substantia nigra. *Exp Neurol 166*, 127–135.

Huang, E., & Reichardt, L. (2001). Neurotrophins: roles in neuronal development and function. *Annu Rev Neurosci 24*, 677–736.

Huang, M. -C., Chen, C. -H., Liu, H. -C., Chen, C. -C., Ho, C. -C., & Leu, S. -J. (2011). Differential patterns of serum brain-derived neurotrophic factor levels in alcoholic patients with and without delirium tremens during acute withdrawal. *Alcohol Clin Exp Res 35*, 126–131.

Issa, G., Wilson, C., Terry, A. V., Jr., & Pillai, A. (2010). An inverse relationship between cortisol and BDNF levels in schizophrenia: data from human postmortem and animal studies. *Neurobiol Dis 39*, 327–333.

Kapczinski, F., Frey, B. N., Kauer-Sant'Anna, M., & Grassi-Oliveira, R. (2008). Brain-derived neurotrophic factor and neuroplasticity in bipolar disorder. *Expert Rev Neurother 8*, 1101–1113.

Karege, F., Perret, G., Bondolfi, G., Schwald, M., Bertschy, G., & Aubry, J. M. (2002). Decreased serum brain-derived neurotrophic factor levels in major depressed patients. *Psychiatry Res 109*, 143–148.

Karege, F., Vaudan, G., Schwald, M., Perroud, N., & La Harpe, R. (2005). Neurotrophin levels in postmortem brains of suicide victims and the effects of antemortem diagnosis and psychotropic drugs. *Mol Brain Res 136*, 29–37.

Kernie, S. G., Liebl, D. J., & Parada, L. F. (2000). BDNF regulates eating behavior and locomotor activity in mice. *EMBO J 19*, 1290–1300.

Koda, M., Hashimoto, M., Murakami, M., Shirasawa, H., Sakao, S., Ino, H., et al. (2004). Adenovirus vector-mediated in vivo gene transfer of brain-derived neurotrophic factor (BDNF) promotes rubrospinal axonal regeneration and functional recovery after complete transection of the adult rat spinal cord. *J Neurotrauma 21*, 329–337.

Koponen, E., Rantamaki, T., Voikar, V., Saarelainen, T., MacDonald, E., & Castren, E. (2005). Enhanced BDNF signaling is associated with an antidepressant-like behavioral response and changes in brain monoamines. *Cell Mol Neurobiol 25*, 973–980.

Korosi, A., & Baram, T. Z. (2009). The pathways from mother's love to baby's future. *Front Behav Neurosci 3*.

Lang, A. E., Gill, S., Patel, N. K., Lozano, A., Nutt, J. G., Penn, R., et al. (2006). Randomized controlled trial of intraputamenal glial cell line-derived neurotrophic factor infusion in Parkinson disease. *Ann Neurol 59*, 459–466.

Lee, B., & Kim, Y. (2010). The roles of BDNF in the pathophysiology of major depression and in antidepressant treatment. *Psychiatry Invest 7*, 231–235.

Lee, F. S., & Chao, M. V. (2001). Activation of Trk neurotrophin receptors in the absence of neurotrophins. *Proc Natl Acad Sci U S A 98*, 3555–3560.

Levi-Montalcini, R. (1987). The nerve growth factor 35 years later. *Science 237*, 1154–1162.

Levinson, D. (2006). The genetics of depression: a review. *Biol Psychiatry 60*, 84–92.

Levivier, M., Przedborski, S., Bencsics, C., & Kang, U. J. (1995). Intrastriatal implantation of fibroblasts genetically engineered to produce Brain Derived Neurotrophic factor prevents degeneration of dopaminergic neurons in a rat model of Parkinson's Disease. *J Neurosci 15*(12), 7810–7820.

Leyhe, T., Eschweiler, G. W., Stransky, E., Gasser, T., Annas, P., Basun, H., et al. (2009). Increase of BDNF serum concentration in lithium treated patients with early Alzheimer's Disease. *J Alzheimers Dis 16*, 649–656.

Lippmann, M., Bress, A., Nemeroff, C., Plotsky, P., & Monteggia, L. (2007). Long-term behavioural and molecular alterations associated with maternal separation in rats. *Eur J Neurosci 25*, 3091–3098.

Liu, Y., Himes, B. T., Moul, J., Huang, W. L., Chow, S. Y., Tessler, A., et al. (1997). Application of recombinant adenovirus for in vivo gene delivery to spinal cord. *Brain Res 768*, 19–29.

Liu, Y., Kim, D., Himes, B., Chow, S., Murray, M., Tessler, A., et al. (1999). Transplants of fibroblasts genetically modified to express BDNF promote regeneration of adult rat rubrospinal axons and recovery of forelimb function. *J Neurosci 19*, 4370–4387.

Lu, B., & Chang, J. H. (2004). Regulation of neurogenesis by neurotrophins: implications in hippocampus-dependent memory. *Neuron Glia Biol 1*, 377–384.

Machado-Vieira, R., Dietrich, M. O., Leke, R., Cereser, V. H., Zanatto, V., Kapczinski, F., et al. (2007). Decreased plasma brain derived neurotrophic factor levels in unmedicated bipolar patients during manic episode. *Biol Psychiatry 61*, 142–144.

Maisonpierre, P. C., Belluscio, L., Squinto, S., Ip, N. Y., Furth, M. E., Lindsay, R. M., et al. (1990). Neurotrophin-3—a neurotrophic factor related to NGF and BDNF. *Science 247*, 1446–1451.

Marmorstein, R., & Trievel, R. C. (2009). Histone modifying enzymes: structures, mechanisms, and specificities. *Biochim Biophys Acta, Gene Regul Mech 1789*, 58–68.

Martinowich, K., & Lu, B. (2008). Interaction between BDNF and serotonin: role in mood disorders. *Neuropsychopharmacology 33*, 73–83.

Martinowich, K., Manji, H., & Lu, B. (2007). New insights into BDNF function in depression and anxiety. *Nat Neurosci 10*, 1089–1093.

Massa, S. M., Yang, T., Xie, Y., Shi, J., Bilgen, M., Joyce, J. N., et al. (2010). Small molecule BDNF mimetics activate TrkB signaling and prevent neuronal degeneration in rodents. *J Clin Invest 120*, 1774–1785.

McAllister, A. K., Katz, L. C., & Lo, D. C. (1999). Neurotrophins and synaptic plasticity. *Annu Rev Neurosci 22*, 295–318.

McGough, N. N. H., He, D. Y., Logrip, M. L., Jeanblanc, J., Phamluong, K., Luong, K., et al. (2004). RACK1 and brain-derived neurotrophic factor: a homeostatic pathway that regulates alcohol addiction. *J Neurosci 24*, 10542–10552.

Müller, M. B., Toschi, N., Kresse, A. E., Post, A., & M.E., K. (2000). Long-term repetitive transcranial magnetic stimulation increases the expression of brain-derived neurotrophic factor and cholecystokinin mRNA, but not neuropeptide tyrosine mRNA in specific areas of rat brain. *Neuropsychopharmacology 23*, 205–215.

Murgatroyd, C., Patchev, A. V., Wu, Y., Micale, V., Bockmuehl, Y., Fischer, D., et al. (2009). Dynamic DNA methylation programs persistent adverse effects of early-life stress. *Nat Neurosci 12* 1559-U1108.

Nagahara, A. H., Merrill, D. A., Coppola, G., Tsukada, S., Schroeder, B. E., Shaked, G. M., et al. (2009). Neuroprotective effects of brain-derived neurotrophic factor in rodent and primate models of Alzheimer's disease. *Nat Med 15*, 331–337.

Nagahara, A. H., & Tuszynski, M. H. (2011). Potential therapeutic uses of BDNF in neurological and psychiatric disorders. *Nat Rev Drug Discov 10*, 209–219.

Nakagawa, T., Tsuchida, A., Itakura, Y., Nonomura, T., Ono, M., Hirota, F., et al. (2000). Brain-derived neurotrophic factor regulates glucose metabolism by modulating energy balance in diabetic mice. *Diabetes 49*, 436–444.

Nibuya, M., Morinobu, S., & Duman, R. S. (1995). Regulation of BDNF and trkB messenger-MRNA in rat-brain by chronic electroconvulsive seizure and antidepressant drug treatments. *J Neurosci 15*, 7539–7547.

Numakawa, T., Suzuki, S., Kumamaru, E., Adachi, N., Richards, M., & Kunugi, H. (2010). BDNF function and intracellular signaling in neurons. *Histol Histopathol 25*, 237–258.

Oswald, P., Del-Favero, J., Massat, I., Souery, D., Claes, S., Van Broeckhoven, C., et al. (2005). No implication of brain-derived neurotrophic factor (BDNF) gene in unipolar affective disorder: evidence from Belgian first and replication patient-control studies. *Eur Neuropsychopharmacol 15*, 491–495.

Ozan, E., Okur, H., Eker, C., Eker, O. D., Gonul, A. S., & Akarsu, N. (2010). The effect of depression, BDNF gene val66met polymorphism and gender on serum BDNF levels. *Brain Res Bull 81*, 61–65.

Park, J., Lim, E., Back, S., Na, H., Park, Y., & Sun, K. (2010). Nerve regeneration following spinal cord injury using matrix metalloproteinase-sensitive, hyaluronic acid-based biomimetic hydrogel scaffold containing brain-derived neurotrophic factor. *J Biomed Mater Res A 93A*, 1091–1099.

Park, S. W., Phuong, V. T., Lee, C. H., Lee, J. G., Seo, M. K., Cho, H. Y., et al. (2011). Effects of antipsychotic drugs on BDNF, GSK-3β, and β-catenin expression in rats subjected to immobilization stress. *Neurosci Res 71*, 335–340 Dec.

Pattabiraman, P. P., Tropea, D., Chiaruttini, C., Tongiorgi, E., Cattaneo, A., & Domenici, L. (2005). Neuronal activity regulates the developmental expression and subcellular localization of cortical BDNF mRNA isoforms in vivo. *Mol Cell Neurosci 28*, 556–570.

Pedrini, M., Chendo, I., Grande, I., Lobato, M. I., Belmonte-de-Abreu, P. S., Lersch, C., et al. (2011). Serum brain-derived neurotrophic factor and clozapine daily dose in patients with schizophrenia: a positive correlation. *Neurosci Lett 491*, 207–210.

Peng, S., Wuu, J., Mufson, E. J., & Fahnestock, M. (2005). Precursor form of brain derived neurotrophic factor and mature brain derived neurotrophic factor are decreased in the pre clinical stages of Alzheimer's disease. *J Neurochem 93*, 1412–1421.

Piccinni, A., Marazziti, D., Catena, M., Domenici, L., Del Debbio, A., Bianchi, C., et al. (2008). Plasma and serum brain-derived neurotrophic factor depressed patients during 1 year of antidepressant (BDNF) in treatments. *J Affect Disord 105*, 279–283.

Pillai, A. (2008). Brain-derived neurotropic factor/TrkB signaling in the pathogenesis and novel pharmacotherapy of schizophrenia. *Neurosignals 16*, 183–193.

Pillai, A., Kale, A., Joshi, S., Naphade, N., Raju, M., Nasrallah, H., et al. (2010). Decreased BDNF levels in CSF of drug-naive first-episode psychotic subjects: correlation with plasma BDNF and psychopathology. *Int J Neuropsychopharmacol 13*, 535–539.

Ren-Patterson, R. F., Cochran, L. W., Holmes, A., Sherrill, S., Huang, S. J., Tolliver, T., et al. (2005). Loss of brain-derived neurotrophic factor gene allele exacerbates brain monoamine deficiencies and increases stress abnormalities of serotonin transporter knockout mice. *J Neurosci Res 79*, 756–771.

Riccio, A., Ahn, S., Davenport, C. M., Blendy, J. A., & Ginty, D. D. (1999). Mediation by a CREB family transcription factor of NGF-dependent survival of sympathetic neurons. *Science 286*, 2358.

Rizos, E. N., Michalopoulou, P. G., Siafakas, N., Stefanis, N., Douzenis, A., Rontos, I., et al. (2010). Association of serum brain-derived neurotrophic factor and duration of untreated psychosis in first-episode patients with schizophrenia. *Neuropsychobiology 62*, 87–90.

Rizos, E. N., Rontos, I., Laskos, E., Arsenis, G., Michalopoulou, P. G., Vasilopoulos, D., et al. (2008). Investigation of serum BDNF levels in drug-naive patients with schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry 32*, 1308–1311.

Rodriguez-Tebar, A., Dechant, G., & Barde, Y. -A. (1991). Neurotrophins: structural relatedness and receptor interactions. *Philos Trans R Soc Lond B Biol Sci 331*, 255–258.

Roth, T. L., & Sweatt, J. D. (2011). Epigenetic marking of the BDNF gene by early-life adverse experiences. *Horm Behav 59*, 315–320.

Roux, P. P., & Barker, P. A. (2002). Neurotrophin signaling through the p75 neurotrophin receptor. *Prog Neurobiol 67*, 203–233.

Rybakowski, J. K., & Suwalska, A. (2010). Excellent lithium responders have normal cognitive functions and plasma BDNF levels. *Int J Neuropsychopharmacol 13*, 617–622.

Saunders, K. E. A., & Goodwin, G. M. (2010). The course of bipolar disorder. *Adv Psychiatr Treat 16*, 318–328.

Schulte-Herbrüggen, O., Braun, A., Rochlitzer, S., Jockers-Scherübl, M. C., & Hellweg, R. (2007). Neurotrophic factors—a tool for therapeutic strategies in neurological, neuropsychiatric and neuroimmunological diseases? *Curr Med Chem 14*, 2318–2329.

Schumacher, J., Jamra, R. A., Becker, T., Ohlraun, S., Klopp, N., Binder, E. B., et al. (2005). Evidence for a relationship between genetic variants at the brain-derived neurotrophic factor (BDNF) locus and major depression. *Biol Psychiatry 58*, 307–314.

Shimizu, E., Hashimoto, K., & Iyo, M. (2004). Ethnic difference of the BDNF 196G/A (val66met) polymorphism frequencies: the possibility to explain ethnic mental traits. *Am J Med Genet B Neuropsychiatr Genet 126B*, 122–123.

Smith, M. A., Makino, S., Kvetnansky, R., & Post, R. M. (1995). Stress and glucocorticoids affect the expression of brain-derived neurotrophic factor and neu-rotrophin-3 mRNAs in the hippocampus. *J Neurosci 15*, 1768–1777.

Song, X. -Y., Li, F., Zhang, F. -H., Zhong, J. -H., & Zhou, X. -F. (2008). Peripherally-derived BDNF promotes regeneration of ascending sensory neurons after spinal cord injury. *PLoS One 3*.

Strand, A. D., Baquet, Z. C., Aragaki, A. K., Holmans, P., Yang, L., Cleren, C., et al. (2007). Expression profiling of Huntington's disease models suggests that brain-derived neurotrophic factor depletion plays a major role in striatal degeneration. *J Neurosci 27*, 11758–11768.

Tadic, A., Wagner, S., Schlicht, K. F., Peetz, D., Borysenko, L., Dreimueller, N., et al. (2011). The early non-increase of serum BDNF predicts failure of antidepressant treatment in patients with major depression: a pilot study. *Prog Neuropsychopharmacol Biol Psychiatry 35*, 415–420.

Teng, K. K., & Hempstead, B. L. (2004). Neurotrophins and their receptors: signaling trios in complex biological systems. *Cell Mol Life Sci 61*, 35–48.

Thoenen, H., & Sendtner, M. (2002). Neurotrophins: from enthusiastic expectations through sobering experiences to rational therapeutic approaches. *Nat Neurosci 5*, 1046–1050.

Tsuchida, A., Nonomura, T., Ono-Kishino, M., Nakagawa, T., Taiji, M., & Noguchi, H. (2001). Acute effects of brain-derived neurotrophic factor on energy expenditure in obese diabetic mice. *Int J Obes 25*, 1286–1293.

Tsukahara, T., Takeda, M., Shimohama, S., Ohara, O., & Hashimoto, N. (1995). Effects of brain-derived neurotrophic factor on 1 methyl 4 phenyl 1,2,3,6 tetrahydropyridine induced parkinsonism in monkeys. *Neurosurgery 37*, 733–739.

Ultsch, M. H., Wiesmann, C., Simmons, L. C., Henrich, J., Yang, M., Reilly, D., et al. (1999). Crystal structures of the neurotrophin-binding domain of TrkA, TrkB and TrkC1. *J Mol Biol 290*, 149–159.

Verhagen, M., van der Meij, A., van Deurzen, P. A. M., Janzing, J. G. E., Arias-Vasquez, A., Buitelaar, J. K., et al. (2010). Meta-analysis of the BDNF Val66Met polymorphism in major depressive disorder: effects of gender and ethnicity. *Mol Psychiatry 15*, 260–271.

Zala, D., Benchoua, A., Brouillet, E., Perrin, V., Gaillard, M. C., Zurn, A. D., et al. (2005). Progressive and selective striatal degeneration in primary neuronal cultures using lentiviral vector coding for a mutant huntingtin fragment. *Neurobiol Dis 20*, 785–798.

Zhang, X. Y., Zhou, D. F., Wu, G. Y., Cao, L. Y., Tan, Y. L., Haile, C. N., et al. (2008). BDNF levels and genotype are associated with antipsychotic-induced weight gain in patients with chronic schizophrenia. *Neuropsychopharmacology 33*, 2200–2205.