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Mini Review

Brain-derived Neurotrophic Factor

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HISTORY

Nerve growth factor (NGF) was discovered in the early 1950s due to its trophic (survival- and growth-promoting) effects on sensory and sympathetic neurons (Levi-Montalcini and Hamburger, 1951). In 1982, brain-derived neurotrophic factor (BDNF), the second member of the "neurotrophin" family of neurotrophic factors, was shown to promote survival of a subpopulation of dorsal root ganglion neurons, and subsequently purified from pig brain (Barde *et al.*, 1982). Since then, other members of the neurotrophin family such as neurotrophin-3 (NT-3) (Maisonpierre *et al.*, 1990) and neurotrophin-4/5 (NT-4/5) (Hallbook *et al.*, 1991; Ip *et al.*, 1992) have been described, each with a distinct profile of trophic effects on subpopulations of neurons in the peripheral and central nervous systems.

GENE AND PROTEIN STRUCTURE

The BDNF gene (in humans mapped to chromosome 11p) has four 5′ exons (exons I–IV) that are associated with distinct promoters, and one 3′ exon (exon V) that encodes the mature BDNF protein (Metsis *et al.*, 1993; Timmusk *et al.*, 1993). Eight distinct mRNAs are transcribed, with transcripts containing exons I–III expressed predominantly in brain and exon IV found in lung and heart (Timmusk *et al.*, 1993).

BDNF shares about 50% amino acid identity with NGF, NT-3 and NT-4/5. Each neurotrophin consists of a noncovalently-linked homodimer and contains (1) a signal peptide following the initiation codon; and (2) a pro-region containing an N-linked glycosylation site. Initially produced as proneurotrophins, prohormone convertases such as furin cleave the proneurotrophins (M.W. ~30 kDa) to the mature neurotrophin (M.W. ~14 kDa) (Chao and Bothwell, 2002). Proneurotrophins have altered binding characteristics and distinct biologic activity in comparison with mature neurotrophins (Lee *et al.*, 2001a,b). Neurotrophins also share a distinctive three-dimensional structure containing two pairs of antiparallel β-strands and cysteine residues in a cystine knot motif.

BDNF SIGNAL TRANSDUCTION

Each neurotrophin binds one or more of the tropomyosin-related kinase (trk) receptors, members of the family of receptor tyrosine kinases (Patapoutian and Reichardt, 2001). Ligand-induced receptor dimerization results in kinase activation; subsequent receptor autophosphorylation on multiple tyrosine residues creates specific binding sites for intracellular target proteins, which bind to the activated receptor via SH2 domains (Barbacid, 1994; Patapoutian and Reichardt, 2001). These include PLCγ1 (phospholipase C), p85 (the noncatalytic subunit of PI-3 kinase) and Shc (SH2-containing sequence); activation of these target proteins can then lead to a variety of intracellular signalling cascades such as the Ras-MAP (mitogen-activated protein) kinase cascade and phosphorylation of cyclic AMP-response element binding protein (CREB) (Patapoutian and Reichardt, 2001; Segal, 2003).

TrkA binds NGF (with low-affinity binding by NT-3 in some systems); trkB binds BDNF and NT-4/5 with lower-affinity binding by NT-3; and trkC binds NT-3 (Barbacid, 1994). Trk receptors exist in both a full-length (trkB.FL) form as well as truncated (trkB.T1, trkB.T2) forms lacking the kinase domain (Eide *et al.*, 1996; Fryer *et al.*, 1997).

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Although most functions attributed to BDNF are associated with full-length trkB, several roles have been suggested for truncated receptors, including growth and development (Fryer *et al.*, 1997; Yacoubian and Lo, 2000; Luikart *et al.*, 2003) and negative modulation of trkB receptor expression and function (Eide *et al.*, 1996; Haapasalo *et al.*, 2001; Haapasalo *et al.*, 2002). Expression of truncated trk receptors on astrocytes is upregulated following injury (Frisen *et al.*,1993) and may modulate neuronal vulnerability (Saarelainen *et al.*, 2000a,b) and sequestration of BDNF in astrocytes (Biffo *et al.*, 1995; Roback *et al.*, 1995; Alderson *et al.*, 2000). Recent studies have shown that BDNF activates glial calcium signalling by truncated trk receptors (Climent *et al.*, 2000; Rose *et al.*, 2003).

In addition, all of the neurotrophins bind to the p75 receptor, designated $p75^{NTR}$. $p75^{NTR}$, related to proteins of the tumor necrosis factor (TNFR) superfamily, has a glycosylated extracellular region involved in ligand binding, a transmembrane region, and a short cytoplasmic sequence lacking intrinsic catalytic activity (Chao and Hempstead, 1995; Dechant and Barde, 2002). Neurotrophin binding to $p75^{NTR}$ is linked to several intracellular signal transduction pathways, including nuclear factor-κB (NF-κB), Jun kinase and sphingomyelin hydrolysis (Dechant and Barde, 2002). $P75^{NTR}$ signalling mediates biologic actions distinct from those of the trk receptors, notably the initiation of programmed cell death (apoptosis) (Casaccia-Bonnefil *et al.*, 1996; Frade *et al.*, 1996; Roux *et al.*, 1999; Dechant and Barde, 2002). It has also been suggested that p75 may serve to determine neurotrophin binding specificity (Esposito *et al.*, 2001; Lee *et al.*, 2001a,b; Zaccaro *et al.*, 2001).

BDNF GENE REGULATION

A multitude of stimuli have been described that alter BDNF gene expression in both physiologic and pathologic states (Lindholm *et al.*, 1994). For example, light stimulation increases BDNF mRNA in visual cortex (Castrén *et al.*, 1992), osmotic stimulation increases BDNF mRNA in the hypothalamus (Castrén *et al.*, 1995; Dias *et al.*, 2003), and whisker stimulation increases BDNF mRNA expression in somatosensory barrel cortex (Rocamora *et al.*, 1996). Electrical stimuli that induce long-term potentiation (LTP) in the hippocampus, a cellular model of learning and memory, increase BDNF and NGF expression (Patterson *et al.*, 1992; Castrén *et al.*, 1993; Bramham *et al.*, 1996). Even physical exercise has been shown to increase NGF and BDNF expression in hippocampus (Neeper *et al.*, 1995). Interestingly, BDNF levels vary across the estrous cycle, which correlate with its effects on neural excitability (Scharfman *et al.*, 2003).

Distinct BDNF 5′ exons are differentially regulated by stimuli such as neural activity. For example, exons I–III, but not exon IV, increase after kainic acid-induced seizures (Timmusk *et al.*, 1993) or other stimuli that increase activity (Lauterborn *et al.*, 1996; Tao *et al.*, 2002). Protein synthesis is required for the effects of activity on exons I and II, but not III and IV, raising the possibility that the latter act as immediate early genes (Lauterborn *et al.*, 1996; Castrén *et al.*, 1998). The transcription factor CaRF activates transcription of exon III under the control of a calcium response element, CaRE1 (Tao *et al.*, 2002). CREB, which can be stimulated by diverse stimuli ranging from activity to chronic antidepressant treatment (Nibuya *et al.*, 1995, 1996; Shieh *et al.*, 1998; Tao *et al.*, 1998; Shieh and Ghosh, 1999), also modulates exon III transcription. Recent evidence also indicates that neural activity triggers calcium-dependent phosphorylation and release of methyl-CpG binding protein 2 (MeCP2) from BDNF promoter III to depress transcription (Chen *et al.*, 2003).

LOCALIZATION, TRANSPORT AND RELEASE

BDNF and trkB mRNA have a widespread distribution in the central nervous system (Merlio *et al.*, 1993; Conner *et al.*, 1997). BDNF and trkB protein immunoreactivity is also widespread (Conner *et al.*, 1997; Yan *et al.*, 1997a, b; Drake *et al.*, 1999). Like BDNF mRNA, constitutive BDNF protein expression is particularly high in the hippocampus, where the mossy fibre axons of dentate granule cells display BDNF immunoreactivity (Conner *et al.*, 1997).

Unlike the classical target-derived trophic factor model in which neurotrophins—such as NGF—are retrogradely transported, there is now abundant evidence that BDNF is also anterogradely transported in brain. First, BDNF protein is localized to nerve terminals (Conner *et al.*, 1997), and pathway transection or axonal transport inhibition abrogates this terminal expression (Altar *et al.*, 1997; Conner *et al.*, 1997; Altar and DiStefano, 1998). Second, higher-resolution studies have shown that BDNF is associated with dense-core vesicles (Fawcett *et al.*, 1997; Altar and DiStefano, 1998), which are the primary site for neuropeptide storage and release from nerve terminals. Third, further functional studies have supported the anterograde transport hypothesis (Fawcett *et al.*, 1998, 2000). Fourth, pro-BDNF is shuttled from the trans-Golgi network into secretory granules, where it is cleaved by prohormone convertase 1 (PC1) (Farhadi *et al.*, 2000).

In addition, emerging evidence suggests that both BDNF and trk receptors may undergo regulated intracellular transport. For example, seizures lead to redistribution of BDNF mRNA from hippocampal CA3 cell bodies to their apical dendrites (Bregola *et al.*, 2000; Simonato *et al.*, 2002). Trk signalling is now thought to include retrograde transport of intact neurotrophin–trk complexes to the neuronal cell body (Miller and Kaplan, 2001; Ginty and Segal, 2002).

Recent evidence indicates that neurotrophins are released acutely following neuronal depolarization

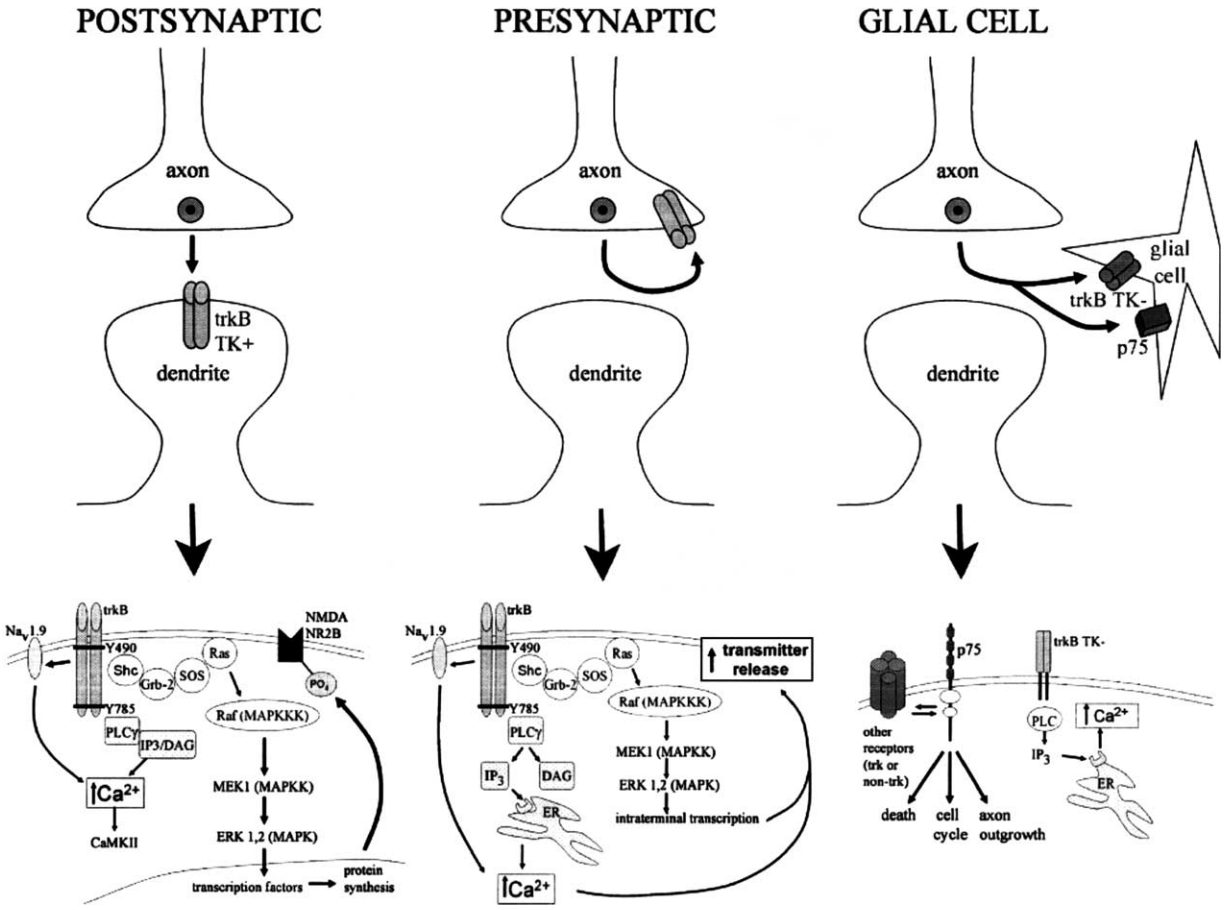

FIGURE 1 Multiple potential effects of local BDNF release at glutamatergic synapses. LEFT: Postsynaptic mechanisms. *Top*: BDNF released from dense core vesicles diffuses across the synaptic cleft to activate full-length trkB receptors (shown dimerized, trkB TK+) located at synapses on postsynaptic dendritic spines. *Bottom*: Postsynaptic signal transduction leads to protein phosphorylation, such as the NR2B subunit of the NMDA receptor, as well as other actions, leading to enhanced synaptic transmission. Note that the site of transcription could be the nucleus, as shown, or occur locally in the dendrite. CENTER: Presynaptic mechanisms. *Top*: BDNF activates, in an autocrine fashion, full-length trkB receptors on the plasma membrane of the axon terminal. *Bottom*: Presynaptic trkB activation leads to increased neurotransmitter release by several potential mechanisms. RIGHT: Synaptic modulation by glial cells. *Top*: When BDNF is released into the synaptic cleft, it may bind to receptors on juxtaposed glial cells, such as truncated trkB (trkB TK −), possibly full-length trkB (not shown) or p75 receptors. Bottom: Activation of truncated trkB has the potential to modulate glial Ca^{2+} signalling, and p75 activation can initiate other pathways; both could ultimately lead to changes in synaptic transmission.

(Griesbeck *et al.*, 1999; Mowla *et al.*, 1999; Goggi *et al.*, 2003). In fact, direct activity-dependent pre- to post-synaptic transneuronal transfer of BDNF has recently been demonstrated using fluorescently-labelled BDNF (Kohara *et al.*, 2001). The released form of BDNF is thought to be proBDNF (Mowla *et al.*, 2001), raising the possibility of postsecretory proteolytic processing by membrane-associated or extracellular proteases in the modulation of BDNF action (Lee *et al.*, 2001a,b).

BDNF AND DEVELOPMENT

BDNF has survival- and growth-promoting actions on a variety of neurons, including dorsal root ganglion cells (Acheson *et al.*, 1995) and hippocampal and cortical neurons (Huang and Reichardt, 2001). Certain peripheral sensory neurons, especially those in vestibular and nodose-petrosal ganglia, depend on the presence of BDNF because BDNF homozygous (−/−) knockout mice lack these neurons (Huang and Reichardt, 2001). Unlike NGF, sympathetic neurons are not affected, nor are motor neurons. BDNF homozygous (−/−) knockout mice fail to survive past 3 weeks, but heterozygous BDNF knockout (+/−) mice are viable, and exhibit a variety of phenotypes, including obesity (Lyons *et al.*, 1999; Kernie *et al.*, 2000), decreased seizure susceptibility (Kokaia *et al.*, 1995) and impaired spatial learning (Linnarsson *et al.*, 1997). Interestingly, conditional postnatal BDNF gene deletion (Rios *et al.*, 2001) and reduction in trkB expression (Xu *et al.*, 2003) also cause obesity.

Physiologic regulation of BDNF gene expression may be very important in the development of the brain. For example, BDNF contributes to activity-dependent development of the visual cortex. Provision of excess BDNF (Cabelli *et al.*, 1995) or blockade of BDNF signalling (Cabelli *et al.*, 1997) leads to abnormal patterning of ocular dominance columns during a critical

period of visual cortex development. This suggests a role for BDNF in axonal path-finding during development. BDNF also has powerful effects on dendritic morphology (McAllister *et al.*, 1997; Murphy *et al.*, 1998; Horch and Katz, 2002; Tolwani *et al.*, 2002).

EFFECTS ON SYNAPTIC TRANSMISSION

The first studies of BDNF effects on synaptic transmission showed that BDNF increased the frequency of miniature excitatory postsynaptic currents (EPSCs) in Xenopus cultures (Lohof *et al.*, 1993). Since then, numerous studies have examined the actions of BDNF. Overall, BDNF appears to strengthen excitatory (glutamatergic) synapses and weaken inhibitory (GABAergic) synapses. Schuman and colleagues demonstrated that exposure of adult rat hippocampal slices to BDNF led to a long-lasting potentiation of afferent input to hippocampal pyramidal cells (Kang and Schuman, 1995). Subsequent studies have supported a role of BDNF in LTP (Korte *et al.*, 1995, 1996; Patterson *et al.*, 1996; Kang, 1997; Xu *et al.*, 2003). For example, incubation of hippocampal or visual cortical slices with trkB inhibitors inhibits LTP (Figurov *et al.*, 1996), and hippocampal slices from BDNF knockout animals exhibit impaired LTP induction (Korte *et al.*, 1995) which is restored by reintroduction of BDNF (Korte *et al.*, 1996; Patterson *et al.*, 1996).

Whether BDNF-induced synaptic potentiation occurs primarily by a presynaptic action (e.g. through enhancement of glutamate release) or postsynaptically (e.g. via phosphorylation of neurotransmitter receptors) is intensely debated (Schinder and Poo, 2000) (Fig. 1). A number of studies have provided evidence for a presynaptic locus (Xu *et al.*, 2000; Tyler *et al.*, 2002) (see also, Kafitz *et al.* (1999)), yet evidence for postsynaptic actions has also been obtained (Black, 1999; Thakker-Varia *et al.*, 2001) (reviewed in Poo (2001)). Both pre- and postsynaptic trkB receptors in the hippocampus may be important (Drake *et al.*, 1999).

A role for BDNF in GABAergic synapses was first raised by studies showing that BDNF influences GABAergic neuronal phenotype (Marty *et al.*, 1996). Subsequently, BDNF was shown to decrease inhibitory (GABAergic) synaptic transmission (Tanaka *et al.*, 1997; Frerking *et al.*, 1998; Wardle and Poo, 2003), perhaps in part via modulation of $GABA_A$ receptor phosphorylation (Jovanovic *et al.*, 2004). Interestingly, BDNF may also regulate the efficacy of GABAergic synapses by direct downregulation of the neuronal K^+–Cl^- co-transporter, which would impair neuronal Cl^- extrusion and weaken GABAergic inhibition (Rivera *et al.*, 2002). Similarly, a recent paper found differential effects of BDNF on GABA-mediated currents in excitatory and inhibitory neuron subpopulations, selectively decreasing the efficacy of inhibitory neurotransmission by downregulation of Cl^- transport (Wardle and Poo, 2003).

NEUROGENESIS

BDNF has also been found to enhance neurogenesis. For example, intraventricular infusion of BDNF or adenoviral-induced BDNF activity increases the number of neurons in the adult olfactory bulb, striatum, septum and thalamus (Zigova *et al.*, 1998; Benraiss *et al.*, 2001; Pencea *et al.*, 2001), which can be potentiated by concurrent inhibition of glial differentiation of subependymal progenitor cells (Chmielnicki *et al.*, 2004). Studies of cultured progenitor cells have elucidated some of the signalling mechanisms, which appear to involve trkB activation, followed by activation of the MAP kinase and PI3-kinase pathways (Barnabe-Heider and Miller, 2003) and downstream modification of basic helix-loop-helix transcription factors (Ito *et al.*, 2003). Although some studies have concluded that the primary effect of BDNF is on proliferation (Katoh-Semba *et al.*, 2002), other experiments suggest an important effect on survival (Lee *et al.*, 2002). The effects of BDNF may depend on a previous history of ischemic damage (Larsson *et al.*, 2002; Gustafsson *et al.*, 2003).

LEARNING AND MEMORY

Since BDNF appears to be involved in activity-dependent synaptic plasticity, there is great interest in its role in learning and memory (Yamada and Nabeshima, 2003). The hippocampus, which is required for many forms of long-term memory in humans and animals, appears to be an important site of BDNF action. Rapid and selective induction of BDNF expression in the hippocampus during contextual learning has been demonstrated (Hall *et al.*, 2000), and function-blocking antibodies to BDNF (Alonso *et al.*, 2002), BDNF knockout (Linnarsson *et al.*, 1997), knockout of forebrain trkB signalling (Minichiello *et al.*, 1999), or overexpression of truncated trkB (Saarelainen *et al.*, 2000a,b) in mice impairs spatial learning. Another study demonstrated upregulation of BDNF in monkey parietal cortex associated with tool-use learning (Ishibashi *et al.*, 2002). In humans, a valine to methionine polymorphism at the 5′ pro-region of the human BDNF protein was found to be associated with poorer episodic memory; *in vitro*, neurons transfected with met-BDNF-GFP exhibited reduced depolarization-induced BDNF secretion (Egan *et al.*, 2003).

BDNF AND EPILEPSY

The discovery that limbic seizures increase NGF mRNA levels (Gall and Isackson, 1989) led to the idea that seizure-induced expression of neurotrophic factors may contribute to the lasting structural and functional changes underlying epileptogenesis (Gall *et al.*, 1991; 1997; Jankowsky and Patterson, 2001). Recent *in vitro*

and *in vivo* findings implicate BDNF in the cascade of electrophysiologic and behavioural changes underlying the epileptic state. BDNF mRNA and protein are markedly upregulated in the hippocampus by seizure activity in animal models (Ernfors *et al.*, 1991; Isackson *et al.*, 1991; Lindvall *et al.*, 1994; Nibuya *et al.*, 1995), and infusion of anti-BDNF agents (Binder *et al.*, 1999a,b) or use of BDNF knockout (Kokaia *et al.*, 1995) or truncated trkB-overexpressing (Lahteinen *et al.*, 2002) mice inhibits epileptogenesis in animal models. Conversely, direct application of BDNF induces hyperexcitability *in vitro* (Scharfman, 1997; Scharfman *et al.*, 1999), overexpression of BDNF in transgenic mice leads to spontaneous seizures (Croll *et al.*, 1999), and intrahippocampal infusion of BDNF is sufficient to induce seizure activity *in vivo* (Scharfman *et al.*, 2002) (but see, Reibel *et al.* (2000)). The hippocampus and closely associated limbic structures are thought to be particularly important in the pro-epileptogenic effects of BDNF (Binder *et al.*, 1999a,b), and indeed increased BDNF expression in the hippocampus is found in specimens from patients with temporal lobe epilepsy (Mathern *et al.*, 1997; Takahashi *et al.*, 1999). It is hoped that understanding of the hyperexcitability associated with BDNF in epilepsy animal models may lead to novel anticonvulsant or antiepileptic therapies (Binder *et al.*, 2001).

BDNF AND PAIN

BDNF also may play an important neuromodulatory role in pain transduction (Malcangio and Lessmann, 2003). BDNF is synthesized by dorsal horn neurons and markedly upregulated in inflammatory injury to peripheral nerves (along with NGF) (Fukuoka *et al.*, 2001). BDNF acutely sensitizes nociceptive afferents and elicits hyperalgesia which is abrogated by BDNF inhibitors (Kerr *et al.*, 1999; Thompson *et al.*, 1999; Pezet *et al.*, 2002). Central pain sensitization is an activity-dependent increase in excitability of dorsal horn neurons leading to a clinically intractable condition termed "neuropathic pain" in which normally nonpainful somatosensory stimuli (touch and pressure) become exquisitely painful (allodynia). Electrophysiological and behavioural data demonstrate that inhibition of BDNF signal transduction inhibits central pain sensitization (Kerr *et al.*, 1999; Pezet *et al.*, 2002).

BDNF AND NEURODEGENERATIVE DISEASES

The idea that degenerative diseases of the nervous system may result from insufficient supply of neurotrophic factors has generated great interest in BDNF as a potential therapeutic agent. Many reports have documented evidence of decreased expression of BDNF in neurological disease (Murer *et al.*, 2001). Selective reduction of BDNF mRNA in the hippocampus has been reported in Alzheimer's disease specimens (Phillips *et al.*, 1991; Ferrer *et al.*, 1999), although selective upregulation appears to occur in plaque-related glial cells in an animal model (Burbach *et al.*, 2004). Decreased BDNF protein has been demonstrated in the substantia nigra in Parkinson's disease (Howells *et al.*, 2000). Interestingly, recent work has implicated BDNF in Huntington's disease as well. Huntingtin, the protein mutated in Huntington's disease, upregulates BDNF transcription, and loss of Huntingtin-mediated BDNF transcription leads to loss of trophic support to striatal neurons which subsequently degenerate in the hallmark pathology of the disorder (Zuccato *et al.*, 2001). A recent study has demonstrated that Huntingtin normally inhibits the neuron restrictive silencer element (NRSE) involved in tonic repression of transcription from BDNF promoter II (Zuccato *et al.*, 2003). In all of these disorders, provision of BDNF or increasing endogenous BDNF production may conceivably be therapeutic if applied in the appropriate spatiotemporal context (Spires *et al.*, 2004).

BDNF AND NEUROPSYCHIATRIC DISEASE

BDNF signalling may also be involved in affective behaviours (Altar, 1999). Environmental stresses such as immobilization that induce depression also decrease BDNF mRNA (Smith *et al.*, 1995). Conversely, physical exercise is associated with decreased depression and increased BDNF mRNA (Russo-Neustadt *et al.*, 1999; Cotman and Berchtold, 2002). Existing treatments for depression are thought to act primarily by increasing endogenous monoaminergic (i.e. serotonergic and noradrenergic) synaptic transmission, and recent studies have shown that effective antidepressants increase BDNF mRNA (Dias *et al.*, 2003) and protein (Chen *et al.*, 2001; Altar *et al.*, 2003). Exogenous delivery of BDNF promotes the function and sprouting of serotonergic neurons in adult rat brains (Mamounas *et al.*, 1995), and BDNF-deficient mice are also deficient in serotonergic innervation (Lyons *et al.*, 1999). Thus, new pharmacologic strategies are focused on the potential antidepressant role of BDNF.

It has also been hypothesized that BDNF may be involved in bipolar disorder (Tsai, 2004). Interestingly, lithium, a major drug for the treatment of bipolar disorder, increases BDNF and trkB activation in cerebral cortical neurons (Hashimoto *et al.*, 2002). BDNF is an attractive candidate gene for susceptibility to bipolar disorder, and some (Neves-Pereira *et al.*, 2002; Sklar *et al.*, 2002) but not other (Hong *et al.*, 2003; Nakata *et al.*, 2003) studies suggest linkage between BDNF polymorphisms and disease susceptibility (Green and Craddock, 2003). How alterations in BDNF activity may relate to fluctuating bouts of mania and depression in bipolar disorder is still a matter of speculation.

SUMMARY

Since the purification of BDNF in 1982, a great deal of evidence has mounted for its central roles in development, physiology, and pathology. Aside from its importance in neural development and cell survival, BDNF appears essential to molecular mechanisms of synaptic plasticity. Basic activity-related changes in the central nervous system are thought to depend on BDNF modification of synaptic transmission, especially in the hippocampus and neocortex. Pathologic levels of BDNF-dependent synaptic plasticity may contribute to conditions such as epilepsy and chronic pain sensitization, whereas application of the trophic properties of BDNF may lead to novel therapeutic options in neurodegenerative diseases and perhaps even in neuropsychiatric disorders.

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