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CHAPTER 22

Neurotrophins in the dentate gyrus

Devin K. Binder*

Department of Neurological Surgery, University of California, Irvine, CA 92868, USA

Abstract: Since the discovery of nerve growth factor (NGF) in the 1950s and brain-derived neurotrophic factor (BDNF) in the 1980s, a great deal of evidence has mounted for the roles of neurotrophins (NGF; BDNF; neurotrophin-3, NT-3; and neurotrophin-4/5, NT-4/5) in development, physiology, and pathology. BDNF in particular has important roles in neural development and cell survival, as well as appearing essential to molecular mechanisms of synaptic plasticity and larger scale structural rearrangements of axons and dendrites. Basic activity-related changes in the central nervous system (CNS) are thought to depend on BDNF modulation of synaptic transmission. 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. In this chapter, I review neurotrophin structure, signal transduction mechanisms, localization and regulation within the nervous system, and various potential roles in disease. Modulation of neurotrophin action holds significant potential for novel therapies for a variety of neurological and psychiatric disorders.

Keywords: brain-derived neurotrophic factor; neurotrophin-3; neurotrophin-4/5; nerve growth factor; epilepsy

Introduction to neurotrophins

Neurotrophin structure

Each neurotrophin (including nerve growth factor, NGF; brain-derived neurotrophic factor, BDNF; neurotrophin-3, NT-3; neurotrophin-4/5, NT-4/5; see below) consists of a noncovalently linked homodimer and contains (1) a signal peptide following the initiation codon; (2) a pro-region containing an N-linked glycosylation site and a proteolytic cleavage site for furin-like pro-protein convertases, followed by the mature sequence; (3) a distinctive three-dimensional structure containing two pairs of antiparallel β-strands and cysteine residues in a *cystine knot motif*. Initially produced as proneurotrophins, prohormone convertases such as furin cleave the proneurotrophins (molecular weight, MW ~30 kDa) to the mature neurotrophin (MW ~14 kDa) (Chao and Bothwell, 2002). Proneurotrophins have altered binding characteristics and distinct biologic activity in comparison with mature neurotrophins (Lee et al., 2001b). Mature neurotrophins are noncovalently linked homodimers with MW approximately 28 kDa. Dimerization appears essential for neurotrophin (NT) receptor activation. BDNF shares approximately 50% amino acid identity with NGF, NT-3, and NT-4/5.

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′

*Corresponding author. Tel.: +1 (714) 456-6966; Fax: +1 (714) 456-8212; E-mail: dbinder@uci.edu

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exon (exon V) that encodes the mature BDNF protein (Metsis et al., 1993; Timmusk et al., 1993b). 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., 1993b).

Neurotrophin signal transduction

Each NT binds one or more of the tropomyosin-related kinase (trk) receptors, members of the family of receptor tyrosine kinases (RTKs) (Patapoutian and Reichardt, 2001). Trk proteins are transmembrane RTKs homologous to other RTKs such as the epidermal growth factor (EGF) receptor and insulin receptor family. 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 signaling 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).

Binding specificity is conferred via the juxtamembrane Ig-like domain of the extracellular portion of the receptor in the following pattern (Urfer et al., 1995). 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). 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, 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) 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 signaling by truncated trk receptors (Climent et al., 2000; Rose et al., 2003).

In addition, all of the NTs 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). NT 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). $p75^{NTR}$ signaling mediates biologic actions distinct from those of the trk receptors, notably the initiation of programed 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 NT binding specificity (Esposito et al., 2001; Lee et al., 2001a; Zaccaro et al., 2001).

Nerve growth factor (NGF)

NGF was discovered in the early 1950s by Rita Levi-Montalcini and Viktor Hamburger due to its trophic (survival and growth-promoting) effects on sensory and sympathetic neurons (Levi-Montalcini and Hamburger, 1951). In addition, NGF supports the survival and neurotransmitter synthesis of cholinergic neurons in the central nervous system (CNS). In the brain, it is synthesized primarily in cholinergic target tissues such as the cortex, hippocampal pyramidal layer, and striatum (Gall and Isackson, 1989; Rylett and Williams, 1994). The trkA NT receptor is expressed primarily on the axons of NGF-dependent cholinergic neurons (Sobreviela et al., 1994).

Table 1. Seizure regulation of NGF expression

Reference	Methods	Results
NGF mRNA		
Gall and Isackson (1989)	Hilar electrolytic lesion	Increases in DG (4 h) and cortex (17 h)
Gall and Lauterborn (1992)	Hilar electrolytic lesion	Increase in DG, max at 6 h (10 ×) and 24 h (6 ×) (biphasic)
Ernfors et al. (1991)	Rapid kindling (ventral hippocampal stimulation)	Increase max at 1 h (DG), 4 h (PC)
Bengzon et al. (1993)	Traditional kindling (ventral hippocampal stimulation CA1–CA2)	Increase — did not do time course but studied relationship between development of kindling and neurotrophin induction — found similar NGF induction (approximately 2 × at 2 h time point) regardless of kindling stage
Schmidt-Kastner et al. (1996)	Pilocarpine	Increase in DG max at 3–6 h
Mudo et al. (1996)	Pilocarpine	Increase in DG max at 3 h (approximately 2.5 ×)
Sato et al. (1996)	Traditional amygdala kindling	Increase in CA1, CA3, perirhinal cortex 1 h after stage 5 kindled seizure
Morimoto et al. (1998)	Traditional amygdala kindling	Increase in DG, max at 2 h (2 ×)
NGF protein		
Bengzon et al. (1992)	Rapid hippocampal kindling (ventral hippocampal stimulation) NGF ELISA	After 40 stimulations, NGF protein levels (measured by 2-site ELISA) increased to 150% in DG at 7 days, 260% in PC at 12 h, and 170% in parietal cortex at 24 h

NGF gene regulation

NGF expression levels are regulated by activity. This has been most clearly demonstrated following the intense activity associated with seizures (Table 1). Hilar electrolytic lesion-induced (Gall and Isackson, 1989; Gall and Lauterborn, 1992; Lauterborn et al., 1994) or kindled seizures (Ernfors et al., 1991; Bengzon et al., 1993; Sato et al., 1996; Morimoto et al., 1998) induce a rapid and transient expression of NGF mRNA in dentate gyrus granule cells as well as piriform cortex. Similarly, pilocarpine-induced status epilepticus increases NGF mRNA expression in dentate gyrus, maximum at approximately 3 h (Mudo et al., 1996; Schmidt-Kastner et al., 1996).

Basal levels of NGF protein in the hippocampus are very low (Narisawa-Saito and Nawa, 1996). Studies with NGF ELISAs indicate that NGF protein levels do increase following kindling, especially in dentate gyrus, piriform cortex, and parietal cortex (Bengzon et al., 1992). In contrast to the mRNA increases, NGF protein levels remain elevated for at least 7 days (Bengzon et al., 1992).

Basal levels of trkA mRNA in the hippocampus are very low (Cellerino, 1996; Mudo et al., 1996), and do not appear to increase following kindling (Bengzon et al., 1993; Merlio et al., 1993) or pilocarpine status epilepticus (Mudo et al., 1996) (Table 2).

Brain-derived neurotrophic factor (BDNF)

In 1982, BDNF, the second member of the "NT" 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). The amino acid sequence of BDNF was found to have a strong homology with NGF. Since then, other members of the NT family such as NT-3 (Maisonpierre et al., 1990b) and 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 CNS.

BDNF mRNA has a widespread distribution in the CNS (Merlio et al., 1993; Conner et al., 1997),

Table 2. Seizure regulation of trk receptor expression

Reference	Methods	Results
TrkA mRNA		
Cellerino (1996)	Basal hippocampal	Basal not detectable by ^{35}S; can only detect with ^{33}P
Mudo et al. (1996)	Pilocarpine	Basal not detectable and pilocarpine status did not increase levels
Bengzon et al. (1993)	Hippocampal kindling	No change
Merlio et al. (1993)	Rapid hippocampal kindling	No change
TrkB mRNA		
Bengzon et al. (1993)	Rapid hippocampal kindling (ventral hippocampal stimulation)	Increased in DG 2 h (2 ×) after focal or generalized seizures
Merlio et al. (1993)	Rapid hippocampal kindling (ventral hippocampal stimulation)	Increased threefold in DG at 30 min after 40 stimulations
Elmer et al. (1996a, b)	Rapid hippocampal kindling (ventral hippocampal stimulation)	Increased in DG max at 2 h
Humpel et al. (1993)	PTZ	Increased twofold in DG at 3 h
Nibuya et al. (1995)	ECS	Increased fivefold (DG) at 2 h
Schmidt-Kastner et al. (1996)	Pilocarpine	Increase in DG, CA1–3 at 3–6 h
Mudo et al. (1996)	Pilocarpine	Increase in DG, amygdala, PC at 3 h
Hughes et al. (1998)	Hippocampal afterdischarge	Increase in DG at 4 h
TrkC mRNA		
Bengzon et al. (1993)	Rapid hippocampal kindling (ventral hippocampal stimulation)	Increased in DG 2 h (1.5 ×) after focal or generalized seizures
Merlio et al. (1993)	Rapid hippocampal kindling (ventral hippocampal stimulation)	No change after 40 rapid K stimulations
Mudo et al. (1995)	ICV KA or ICV bicuculline	Increase max at 3 h (bicuculline) or 12 h (KA) confined to DG

including limbic forebrain, neocortex, and is abundant in all principal neurons of the hippocampus (Ernfors et al., 1990; Hofer et al., 1990; Wetmore et al., 1990). Like BDNF mRNA, constitutive BDNF protein expression is widespread (Conner et al., 1997; Yan et al., 1997b), localized on neuronal cell bodies, axons, and dendrites. The mossy-fiber axons of hippocampal dentate granule cells display especially intense BDNF immunoreactivity (Conner et al., 1997). The principal receptor for BDNF, trkB, is a receptor tyrosine kinase, which is found in both catalytic and truncated forms in the adult forebrain (Fryer et al., 1996; Drake et al., 1999). TrkB mRNA and protein are found in hippocampus (Merlio et al., 1992; Altar et al., 1994; Yan et al., 1997a). Truncated trkB is also found in the ependymal cells lining the ventricular cavities, effectively limiting diffusion of intraventricularly administered BDNF (Yan et al., 1994; Anderson et al., 1995).

Localization, transport and release

Unlike the classical target-derived trophic factor model in which NTs — 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 signaling is now thought to include retrograde transport of intact NT-trk complexes to the neuronal cell body (Miller and Kaplan, 2001; Ginty and Segal, 2002).

Recent evidence indicates that NTs are released acutely following neuronal depolarization (Griesbeck et al., 1999; Mowla et al., 1999; Hartmann et al., 2001; Egan et al., 2003; Goggi et al., 2003; Brigadski et al., 2005). In fact, direct activity-dependent pre- to postsynaptic transneuronal transfer of BDNF has been demonstrated using fluorescently labeled BDNF (Kohara et al., 2001). The released form of BDNF is thought to be pro-BDNF (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., 2001b).

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). Physiologic stimuli are known to increase BDNF mRNA content. 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., 1993b) or other stimuli that increase activity (Lauterborn et al., 1996; Tao et al., 2002). Protein synthesis is required for the effects of activity on exon 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 (calcium response factor) 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 MeCP2 (methyl-CpG binding protein 2) from BDNF promoter III to derepress transcription (Chen et al., 2003).

Pathologic states are also associated with alteration in BDNF gene expression. For example, seizures dramatically upregulate BDNF mRNA (Table 3). A wide variety of seizure paradigms (kindling; kainic acid; pilocarpine; pentylenetetrazol, PTZ; electroconvulsive shock, ECS) rapidly and dramatically increase expression of BDNF mRNA in dentate gyrus as well as in other areas of the hippocampus and cortex (Ernfors et al., 1991; Isackson et al., 1991; Gall and Lauterborn, 1992; Dugich-Djordjevic et al., 1992a, b; Bengzon et al., 1993; Humpel et al., 1993; Nibuya et al., 1995; Mudo et al., 1996; Sato et al., 1996; Schmidt-Kastner et al., 1996). This is associated with a transient upregulation of BDNF protein (Nawa et al., 1995; Elmer et al., 1996b; Hughes et al., 1998).

TrkB mRNA and protein in the dentate gyrus are also upregulated following various seizure protocols (Bengzon et al., 1993; Merlio et al., 1993; Elmer et al., 1996a) (Table 2). TrkB mRNA expression is increased in dentate granule cells 2–6 h after rapid electrical kindling, hippocampal after discharge, PTZ kindling, ECS, or pilocarpine

Table 3. Seizure regulation of BDNF expression

Reference	Methods	Results
BDNF mRNA		
Isackson et al. (1991)	Hilar electrolytic lesion	Increase, onset <1.5 h, max at 6 h ($12\times$)
Gall and Lauterborn (1992)	Perforant path stimulation (1 AD)	Increase, onset 20 min, max at 4 h ($12\times$)
Ernfors et al. (1991)	Rapid kindling (ventral hippocampal stimulation)	Increase max at 30 min (DG/PC), 1 h (CA1)
Dugich-Djordjevic et al. (1992b)	KA	Increase in all hippocampus (P21, P40), no change despite seizures (P8)
Dugich-Djordjevic et al. (1992a)	KA	Increase max at 30 min ($10\times$ in DG, 2–$6\times$ in CA1, CA3, CA4); later in cortex
Bengzon et al. (1993)	Traditional kindling (ventral hippocampal stimulation CA1–2)	Increase — did not do time course but studied relationship between development of kindling and neurotrophin induction — found similar BDNF induction (approximately $9\times$ at 2 h time point) regardless of kindling stage
Humpel et al. (1993)	PTZ kindling (30 mg/kg i.p. followed by convulsive dose (50 mg/kg))	Increase max at 3 h (DG, PC, amygdala) after acute convulsive PTZ
Nibuya et al. (1995)	ECS	Increase 30-fold 2 h after ECS (DG), fivefold (PC)
Schmidt-Kastner et al. (1996)	Pilocarpine	Increase max at 3–6 h (DG, other hippocampal, neocortex, PC, striatum, thalamus)
Mudo et al. (1996)	Pilocarpine	Increase max at 3–6 h (DG, amygdala, PC)
Sato et al. (1996)	Traditional amygdala kindling	4–5-fold increase in DG 1 h after stage 5 kindled seizure
BDNF protein		
Nawa et al. (1995)	Hilar electrolytic lesion	Highest levels of basal BDNF in hippocampus (followed by hypothalamus, neocortex, cerebellum, thalamus and striatum)
	BDNF ELISA	Fourfold induction of BDNF protein levels in hippocampus, maximum at 24 h after HL, down by 1 week
Elmer et al. (1996a, b)	Rapid kindling (ventral hippocampal stimulation)	Basal levels of BDNF highest in DGCA3 > CA1 > PC
	BDNF ELISA	After 1 AD: increase to 150% in DG at 6 h, 200% in CA3 at 12 h, 50% in PC at 6 h After 40 ADs: increase to 200% in DG at 6 and 24 h, 150% in CA3 at 6 h, 300% in PC at 2 and 6 h After 7 ADs: increase to 200% in CA3 at 24 h
Hughes et al. (1998)	Hippocampal after discharge	Increase in DG at 4 h

status epilepticus (Bengzon et al., 1993; Humpel et al., 1993; Nibuya et al., 1995; Elmer et al., 1996a; Mudo et al., 1996; Schmidt-Kastner et al., 1996; Hughes et al., 1998). Subcellular studies have demonstrated targeting of BDNF and trkB mRNAs to dendrites in CA3 neurons following kindled seizures (Simonato et al., 2002).

Role(s) of BDNF during development

In vitro and in vivo studies have demonstrated that BDNF has survival- and growth-promoting actions on a variety of CNS neurons, including dorsal root ganglion cells, dopaminergic and cholinergic neurons, retinal ganglion cells, and

hippocampal and cortical neurons (Johnson et al., 1986; Alderson et al., 1990; Hyman et al., 1991; Knusel et al., 1991; Acheson et al., 1995; Patel and McNamara, 1995; 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 ($BDNF^{-/-}$) mice lack these neurons (Huang and Reichardt, 2001). Unlike NGF, sympathetic neurons are not affected, nor are motor neurons. $BDNF^{-/-}$ mice fail to thrive, demonstrate lack of proper coordination of movement and balance, and ultimately die by 3 weeks of age. However, heterozygous BDNF knockout ($BDNF^{+/-}$) 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 signaling (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 pathfinding 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

BDNF has an enormous range of physiologic actions at both developing and mature synapses, overall enhancing synaptic transmission by both pre- and postsynaptic mechanisms. The first studies of BDNF effects on synaptic transmission showed that BDNF increased the frequency of miniature excitatory postsynaptic currents (EPSCs) at *Xenopus* neuromuscular synapses (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 synaptic strength at Schaffer collateral-CA1 synapses (Kang and Schuman, 1995). Subsequent studies have supported a role of BDNF in LTP (Korte et al., 1995; Korte et al., 1996; Patterson et al., 1996; Kang et al., 1997; Xu et al., 2000). For example, incubation of hippocampal or visual cortical slices with trkB inhibitors inhibits LTP (Figurov et al., 1996), and hippocampal slices from $BDNF^{-/-}$ mice 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). 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; McLean Bolton et al., 2000). Subsequently, BDNF was shown to decrease inhibitory (GABAergic) synaptic transmission (Tanaka et al., 1997; Frerking et al., 1998; Wardle and Poo, 2003). Recent evidence shows that BDNF can modulate the function of $GABA_A$ receptors via modulation of phosphorylation state (Jovanovic et al., 2004). Interestingly, BDNF may also regulate the efficacy of GABAergic synapses by direct downregulation of the neuronal K^+-Cl^- cotransporter, 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).

Effect on neurogenesis

An important feature of the dentate gyrus is the lifelong production of new granule cells from progenitor cells located in the subgranular zone (Gould and McEwen, 1993; Scharfman, 2004). BDNF has also been found to enhance neurogenesis. 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). Intrahippocampal infusion of BDNF into adult rats leads to increased dentate gyrus neurogenesis, accompanied by increased numbers of ectopic granule cells (Scharfman et al., 2005). $BDNF^{+/-}$ mice show decreased numbers of BrdU-labeled cells in the dentate gyrus (Lee et al., 2002). Studies of cultured progenitor cells have elucidated some of the signaling 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).

Effects on learning and memory

Learning and memory depend on persistent selective modification of synapses between CNS neurons. 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 signaling (Minichiello et al., 1999), or overexpression of truncated trkB (Saarelainen et al., 2000b) 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-green fluorescence protein (GFP) exhibited reduced depolarization-induced BDNF secretion (Egan et al., 2003).

Neurotrophin-3 (NT-3)

NT-3, first described in 1990 (Maisonpierre et al., 1990b), is similar to BDNF in several ways. Like BDNF, NT-3 mRNA and protein are widely distributed in the adult CNS (Maisonpierre et al., 1990a, b, Zhou and Rush, 1994; Katoh-Semba et al., 1996). While the preferred receptor for NT-3 is trkC, NT-3 can also bind to trkA and trkB (Barbacid, 1994; Ryden and Ibanez, 1996; Huang and Reichardt, 2003). Like BDNF, NT-3 is involved in synaptic transmission and neuronal excitability (Thoenen, 1995). Addition of NT-3 to hippocampal slices enhances synaptic strength at Schaffer collateral-CA1 synapses (Kang and Schuman, 1995). NT-3 enhances paired-pulse facilitation in the perforant path-dentate gyrus pathway (Kokaia et al., 1998; Asztely et al., 2000). Like BDNF, NT-3 reduces GABAergic inhibition (Kim et al., 1994). Also like BDNF, NT-3 enhances the survival and differentiation of neural progenitor cells (Barnabe-Heider and Miller, 2003).

NT-3 gene regulation

However, whereas NGF and BDNF levels increase after seizures, NT-3 levels are reduced in dentate

Table 4. Seizure regulation of NT-3 and NT-4 expression

Reference	Methods	Results
NT-3 mRNA		
Gall and Lauterborn (1992)	Hilar electrolytic lesion	Decrease, onset 12 h max 12 h (20%) in DG
Bengzon et al. (1993)	Traditional kindling (ventral hippocampal stimulation CA1-CA2)	Decrease — did not do time course but studied relationship between development of kindling and neurotrophin induction — found similar NT-3 decrease (~50%) regardless of kindling stage
Schmidt-Kastner and Olson (1995)	Pilocarpine	Decrease max at 3 h
Mudo et al. (1996)	Pilocarpine	Decrease max at 12–24 h (40–50%)
Kim et al. (1998)	Amygdala kindling	Decrease in DG
NT-4 mRNA		
Timmusk et al. (1993a, b)	RNAse protection analysis from different tissues	Could not detect NT-4 by in situ but did find very low levels in adult brain using RNAse protection No increase in NT-4 mRNA following either systemic KA or hippocampal stimulation
Mudo et al. (1996)	Pilocarpine	Basal not detectable and pilocarpine status did not increase levels

gyrus granule neurons (Gall and Lauterborn, 1992; Bengzon et al., 1993; Schmidt-Kastner and Olson, 1995; Mudo et al., 1996; Kim et al., 1998) (Table 4). This suggests that the potential role of NT-3 in seizure progression is different. Whether trkC is elevated appears to depend on the model used; rapid kindling induces no change (Merlio et al., 1993) or a transient increase (Bengzon et al., 1993) in trkC mRNA levels, and ICV KA or ICV bicuculline transiently increase trkC mRNA in dentate granule cells (Mudo et al., 1995).

Neurotrophin-4/5

The fourth member of the NT family, NT-4/5, was discovered after NGF, BDNF, and NT-3 (Hallbook et al., 1991; Ip et al., 1992). Levels of NT-4/5 in the brain are very low at baseline (Timmusk et al., 1993a; Katoh-Semba et al., 2003) and are not increased by seizures (Timmusk et al., 1993a; Mudo et al., 1996) (Table 4). NT-4/5$^{-/-}$ mice, unlike BDNF$^{-/-}$ mice, are normal and long-lived with no obvious neurological deficits (Conover et al., 1995; Liu et al., 1995). The only loss of neurons in NT-4/5$^{-/-}$ mice appears to be a reduction in the number of sensory neurons in the nodose-petrosal and geniculate ganglia (Conover et al., 1995; Liu et al., 1995). Provision of NT-4/5 protects hippocampal and cortical neurons against energy deprivation-induced injury (Cheng et al., 1994) and adrenalectomy-induced apoptosis of hippocampal granule cells (Qiao et al., 1996). Application of NT-4/5 enhances excitatory synaptic transmission in cultured hippocampal neurons (Lessmann et al., 1994).

Roles of neurotrophins in epilepsy models

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).

NGF and epilepsy

Is there a functional role for NGF gene upregulation in epileptogenesis? Indeed, intraventricular administration of NGF antibodies retards amygdala kindling (Funabashi et al., 1988) and blocks kindling-induced mossy-fiber sprouting (Van der Zee et al., 1995). Similarly, an NGF inhibitory peptide inhibits amygdala kindling and mossy-fiber sprouting (Rashid et al., 1995). Conversely, intraventricular NGF infusion was found to facilitate amygdala

and hippocampal kindling and increase mossy-fiber sprouting (Adams et al., 1997).

Whether NGF exerts its effects on kindling and kindling-induced morphological changes via trkA or $p75^{NTR}$ has been investigated. Inhibition of Ras, a downstream effector of trkA, inhibits kindling and kindling-associated mossy-fiber sprouting (Li et al., 2003). Peptide inhibitors of NGF binding to trkA but not to $p75^{NTR}$ can inhibit kindling, whereas both trkA and $p75^{NTR}$ inhibition can inhibit mossy-fiber sprouting (Li et al., 2005).

What is the locus of effects of NGF on hippocampal kindling? As described above, there is little evidence for trkA expression in hippocampus (Sobreviela et al., 1994; Cellerino, 1996). Similarly, there is little expression of p75 in hippocampus at baseline (Pioro and Cuello, 1990; Sobreviela et al., 1994). It is likely that NGF-dependent effects are due to modulation of the cholinergic system, as both trkA and $p75^{NTR}$ (Hofer et al., 1990) receptors are most strongly expressed in the basal forebrain cholinergic neurons which project to hippocampus (Sobreviela et al., 1994). Consistent with this hypothesis is that cholinergic agonists and antagonists produce effects on kindling and sprouting parallel to those of NGF (Adams et al., 2002).

BDNF and epilepsy

Abundant in vitro and in vivo evidence implicates BDNF in the cascade of electrophysiologic and behavioral changes underlying the epileptic state (Binder et al., 2001). 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). Infusion of trkB receptor body (a chimera of human IgG-Fc domain and the extracellular domain of the trkB receptor) (Binder et al., 1999b) or use of $BDNF^{+/-}$ (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).

A separate group of experiments has demonstrated that chronic BDNF infusion can inhibit kindling (Larmet et al., 1995; Osehobo et al., 1996; Reibel et al., 2000b). These inhibitory effects appear to be due to trkB receptor downregulation following chronic BDNF administration, and hence are still consistent with the "pro-epileptogenic BDNF" hypothesis. This interpretation is supported by the observation that chronic exposure to BDNF in vitro leads to downregulation of trkB mRNA and protein (Knusel et al., 1997). Similarly, continuous in vivo intrahippocampal BDNF infusion results in downregulation of trkB protein by as much as 80% (Frank et al., 1996). Thus, whereas chronic BDNF infusion inhibits kindling progression, acute microinjections of BDNF enhance epileptogenesis in the absence of effect on trkB expression (Xu et al., 2004). Furthermore, chronic infusions of BDNF may upregulate the inhibitory neuropeptide Y (NPY) (Reibel et al., 2000a).

Whether BDNF has a significant effect on seizure-associated mossy-fiber sprouting is not clear. While mossy-fiber sprouting has been reported in $BDNF^{+/-}$ mice and following BDNF infusion (Kokaia et al., 1995; Scharfman et al., 2002), there is no effect on mossy-fiber sprouting in BDNF-overexpressing mice or following chronic infusion or bolus injection of BDNF in other studies (Qiao et al., 2001; Xu et al., 2004). However, BDNF overexpression does increase dendritic length and complexity in the hippocampus (Tolwani et al., 2002). The relative role of BDNF on effect synaptic changes vs. larger scale morphological changes during epileptogenesis remains to be clarified.

The anatomic locus of action of NTs during epileptogenesis has been clarified with the study of trk receptor activation (see below).

NT-3 and epilepsy

In comparison with BDNF, what is the evidence for a role of NT-3 in epileptogenesis? In $NT\text{-}3^{+/-}$

mice, which have ~30% reduction in basal NT-3 mRNA levels, amygdala kindling was markedly retarded (Elmer et al., 1997). However, compensatory changes in BDNF and trkB mRNA levels in these mice made these data difficult to interpret (Elmer et al., 1997). Chronic intraventricular infusion of NT-3 retards the development of behavioral seizures (Xu et al., 2002), probably in part via downregulation of trk phosphorylation (Xu et al., 2002).

What about the effects of NT-3 on kindling-induced mossy-fiber sprouting in the dentate gyrus? Chronic infusion of NT-3 inhibits kindling-associated mossy-fiber sprouting (Xu et al., 2002). However, this effect is unclear as infusion of NT-3 in the absence of kindling actually enhances sprouting of mossy fibers in the inner molecular layer of the dentate gyrus and CA3 stratum oriens (Xu et al., 2002).

NT-4 and epilepsy

Unlike NGF, BDNF, and NT-3 levels, levels of NT-4/5 do not appear to be regulated by seizure activity (Timmusk et al., 1993a; Mudo et al., 1996). The amygdala kindling phenotype of NT-4/$5^{-/-}$ mice was studied (He et al., 2006). No aspect of the development or persistence of amygdala kindling was different between NT-4/$5^{-/-}$ and wild-type mice (He et al., 2006).

Trk receptor activation following seizure activity

The ability to monitor trk receptor activation following seizures using phospho-specific trk antibodies enabled identification of the anatomy, time course, and threshold characteristics of trk receptor activation in the hippocampus following seizure activity (Binder et al., 1999a). Kainate-induced status epilepticus or hippocampal electrographic seizures increase phospho-trk immunoreactivity selectively in the hippocampus, primarily confined to the dentate hilus and CA3 stratum lucidum. This seizure-induced phospho-trk immunoreactivity is marked but transient, maximal at 24–48 h but back to baseline by 1 week. The seizure duration threshold for increase in phospho-trk immunoreactivity appears to correspond to the previously reported threshold for increase in BDNF gene expression. These observations are examined in greater detail in the next few sections.

Anatomy of seizure-induced phospho-trk immunoreactivity

Following seizure activity, phospho-trk immunoreactivity is selectively increased in dentate hilus and CA3 stratum lucidum of hippocampus (Binder et al., 1999a). This distribution precisely coincides with the "mossy fiber" pathway of dentate granule cell axon terminals. In addition, this anatomic pattern coincides with the distribution of both basal and seizure-induced BDNF protein. Basal BDNF protein is also localized in hilus and CA3 stratum lucidum (Conner et al., 1997), and seizures increase levels of BDNF protein in dentate gyrus and CA3 (Elmer et al., 1998) and BDNF immunoreactivity in hilus and CA3 stratum lucidum (Smith et al., 1997; Yan et al., 1997b; Rudge et al., 1998; Vezzani et al., 1999). This precise anatomic colocalization of increased phospho-trk immunoreactivity and increases in BDNF protein suggests that the phospho-trk immunoreactivity is caused by seizure-induced increases in BDNF. BDNF, but not NGF, is known to increase levels of NPY (Croll et al., 1994), and kindling and kainate-induced seizures increase NPY immunoreactivity in hilus and CA3 stratum lucidum (Marksteiner et al., 1990; Tønder et al., 1994), further implicating seizure-induced BDNF acting in the mossy-fiber pathway. While NGF mRNA content is upregulated by seizures, the anatomic distribution of increased NGF protein is not known. Thus, these anatomic considerations are most consistent with a role for BDNF.

Time course of seizure-induced phospho-trk immunoreactivity

The time course of known BDNF upregulation following seizures coincides temporally with increased phospho-trk immunoreactivity. Using hippocampal microdissection and a two-site ELISA for BDNF, Elmer et al. showed that after seven

ventral hippocampal electrographic seizures, the maximum increase in BDNF protein occurs at 12 h in dentate gyrus and 24 h in CA3 (Elmer et al., 1998). Similarly, maximum increases in BDNF protein following hilus lesion-induced (Nawa et al., 1995) or kainate-induced (Rudge et al., 1998) seizures occur at approximately 24 h in hippocampus. Importantly, BDNF protein levels in both of these studies returned to baseline after 1 week, similar to phospho-trk immunoreactivity. In contrast, Bengzon et al. found maximal NGF protein content (measured by two-site immunoassay) 7 days after a similar rapid kindling protocol (Bengzon et al., 1992) and did *not* see NGF protein increases at earlier time points. Similarly, Lowenstein et al. found maximal NGF-like neurotrophic activity of hippocampal extracts from animals 1 week after KA treatment (Lowenstein et al., 1993). Thus, the time-course data favor a role for BDNF rather than NGF in seizure-induced phospho-trk immunoreactivity.

Seizure duration threshold for increased phospho-trk immunoreactivity

The seizure duration threshold for increase in phospho-trk immunoreactivity further supports a role for BDNF. Consistently, increased phospho-trk immunoreactivity was observed only in hippocampal kindled animals with ESD~70 s (Binder et al., unpublished data). In a similar ventral hippocampal stimulation protocol, Bengzon et al. observed increases in BDNF mRNA content in dentate granule cells in an all-or-none manner above an electrographic seizure duration of approximately 70 s (Bengzon et al., 1993). Like the increases in mRNA content, increases in phospho-trk immunoreactivity appeared to be "all-or-none" as no differences were noted in intensity of immunoreactivity between kainate-treated and 7 hippocampal ES-treated animals despite marked differences in seizure duration (hours for kainate vs. seconds for 7 hippocampal ESs) (Binder et al., unpublished data). This strong similarity between thresholds as well as all-or-none characteristics suggests that such prior increases in BDNF mRNA content may not only be necessary for any increase in phospho-trk immunoreactivity but also sufficient for maximal increase in phospho-trk immunoreactivity following seizures.

Evidence that the trk receptor activated by seizures is trkB

Indirect evidence suggests that BDNF-induced trkB activation is responsible for the increased phospho-trk immunoreactivity following seizures. First, the mRNA content of NGF and BDNF is increased following seizures (Ernfors et al., 1991; Isackson et al., 1991; Lindvall et al., 1994; Nibuya et al., 1995) whereas dentate granule NT-3 mRNA content is decreased (Gall et al., 1991; Gall and Lauterborn, 1992; Bengzon et al., 1993; Schmidt-Kastner and Olson, 1995; Mudo et al., 1996). Second, protein levels of NGF and BDNF increase after seizure activity (Bengzon et al., 1992; Elmer et al., 1998). Third, the time-course data described above implicate BDNF rather than NGF. Fourth, mRNA levels of the other NT known to activate trkB, NT-4, are very low in adult brain (Timmusk et al., 1993a) and do not increase after seizures (Mudo et al., 1996). Fifth, unlike trkB and trkC, levels of expression of trkA in hippocampus are barely detectable (Barbacid, 1994; Cellerino, 1996), suggesting that trkA is unlikely to mediate seizure-induced increases in phospho-trk immunoreactivity.

In order to more directly analyze the role of the trkB receptor in seizure-induced trk receptor activation, He et al. studied trk receptor phosphorylation in a mouse mutant with a single point mutation at the shc site (Y490 in humans, Y515 in mice) of the trkB receptor (He et al., 2002). Homozygous $trkB^{shc/shc}$ (Y515F) mice were generated by Minichiello et al. and interestingly display loss of NT-4-dependent neurons but have no major effects on BDNF responses (Minichiello et al., 1999). He et al. found that following amygdala kindling stimulation, phospho-trk immunoreactivity is increased in wild-type mice in a similar pattern (hilus and CA3 stratum lucidum) to that seen in the rat experiments (described above). The

trkB$^{shc/shc}$ homozygous mice displayed absence of seizure-induced phospho-trk immunoreactivity, and the heterozygotes displayed intermediate immunoreactivity (He et al., 2002). These experiments suggest that the trk receptor activated during kindling stimulation is indeed trkB.

Interestingly, the Y515F point mutation had no effect on kindling development in the same study (He et al., 2002). This is remarkably consistent with the lack of effect of this mutation on synaptic LTP (Korte et al., 2000). More recently, this group has generated a distinct mouse with a point mutation at the PLC site. Unlike trkB$^{shc/shc}$ mice, trkB$^{PLC/PLC}$ mice exhibit impaired LTP (Minichiello et al., 2002). This direct comparison of distinct trkB tyrosine mutants implicates the PLC signaling pathway as opposed to the MAPK pathway in trkB activation-induced synaptic plasticity.

Similarly, other studies have shown that specific stimuli may cause tyrosine-specific phosphorylation of the trkB receptor (i.e. at other tyrosines but not at the shc site). For example, Saarelainen et al., in studying the role of endogenous BDNF and trkB signaling in the mechanism of action of antidepressant drugs, found that acute and chronic antidepressant treatment caused trkB receptor phosphorylation and activation, but the pY674/5 site was selectively phosphorylated compared to the pY490 (shc) site (Saarelainen et al., 2003). The further development of phosphorylation state-specific antibodies to distinct tyrosines (pY674/5, pY785) may prove to be of use in dissecting tyrosine site-specific trkB signal transduction in vivo in a variety of paradigms. Furthermore, these results can be compared with antibodies that recognize activated intracellular signaling pathways (e.g. phosphoCREB) (Finkbeiner et al., 1997).

Cellular site of seizure-induced phospho-trk immunoreactivity

What is the likely cellular site of seizure-induced phospho-trk immunoreactivity? The light microscopic distribution of phospho-trk immunoreactivity after seizure (dentate hilus and CA3 stratum lucidum of hippocampus) corresponds to the mossy-fiber pathway of dentate granule cell axon terminals (Binder et al., 1999a). This suggests that the cellular site of phospho-trk immunoreactivity is either on mossy-fiber axons and/or targets. Localization on mossy-fiber axons represents a parsimonious explanation for both hilar and CA3 stratum lucidum immunoreactivity. In contrast, localization on targets requires immunoreactivity on both targets in hilus (hilar interneurons) and in CA3 stratum lucidum (pyramidal cell dendrites and/or stratum lucidum interneurons).

Anatomic consideration of trkB-like immunoreactivity may lend insight into the likely cellular site of phospho-trk immunoreactivity. In some published experiments, an affinity-purified antibody directed against an extracellular trkB peptide sequence was used, which does not distinguish between full-length and truncated (Barbacid, 1994) trkB receptors. The earlier studies (using light microscopy) demonstrated that trkB-like immunoreactivity is preferentially distributed on cell bodies and dendrites of both cortical and hippocampal neurons (Fryer et al., 1996; Yan et al., 1997a). Pyramidal neurons in hippocampus in particular demonstrate marked trkB immunoreactivity on cell bodies and dendrites in comparison with axons (Fryer et al., 1996; Yan et al., 1997a). These studies utilized an antibody raised against the extracellular portion of trkB (trkB$_{23-36}$) common to both full-length and truncated forms. A more recent and comprehensive study of cellular and subcellular localization of trkB immunoreactivity was carried out by Drake et al. (1999). These investigators used acytoplasmic-domain antibody (trkB-in) to selectively label the full-length form of trkB and carried out both light and electron microscopic analysis. Their conclusion was that full-length trkB immunoreactivity exists in glutamatergic granule and pyramidal cells and was most intense in axons, axon terminals, and dendritic spines and to a lesser extent in somata and dendritic shafts. Occasionally, interneurons were also labeled. Thus, phospho-trkB immunoreactivity could represent pre- and/or postsynaptic activation of trkB receptors in the mossy-fiber pathway.

Potential models for induction of phospho-trk immunoreactivity by seizure activity

Throughout the brain, BDNF immunoreactivity appears to be preferentially localized in cell bodies and axons compared to dendrites (Conner et al., 1997). In addition, unlike the classical target-derived trophic factor model in which NTs are retrogradely transported, abundant recent evidence suggests that CNS BDNF appears to be anterogradely transported (Von Bartheld et al., 1996a; Zhou and Rush, 1996; Altar et al., 1997; Conner et al., 1997; Fawcett et al., 1998; Tonra et al., 1998). This evidence, together with the anatomic distribution of BDNF immunoreactivity in hippocampus in a mossy fiber-like pattern, suggests that BDNF protein in hilus and CA3 stratum lucidum was synthesized in granule cell bodies and anterogradely transported to mossy-fiber terminals.

Furthermore, following seizures there may be increased anterograde transport of BDNF. First, using hippocampal microdissections of dentate gyrus (which contained hilus) and CA3 (which contained stratum lucidum), Elmer et al. showed that maximal BDNF protein levels after seizures were at 12 h in dentate gyrus but 24 h in CA3 (Elmer et al., 1998). This suggests anterograde transport of seizure-induced BDNF protein. More recent evidence regarding the time course of BDNF immunoreactivity following seizures demonstrates that there is increased BDNF immunoreactivity in dentate granule cells at 4 h followed by subsequent increases in hilus and finally increases in CA3 stratum lucidum at about 24 h (Vezzani et al., 1999) (C. Gall, personal communication). Furthermore, this anterograde "movement" of BDNF immunoreactivity was abrogated by the axonal transport inhibitor colchicine (C. Gall, personal communication).

These considerations lead to a model in which CA3 stratum lucidum phospho-trk immunoreactivity is a consequence of seizure-induced BDNF release from mossy-fiber axons activating trkB receptors on dendrites of CA3 pyramidal cells and hilar interneurons. Supporting a postsynaptic site for trk receptor activation is the evidence that full-length trkB receptors are localized to the postsynaptic density (Wu et al., 1996). Alternatively, dendritic BDNF mRNA targeting may underlie another potential cellular mechanism for BDNF translation, release, and trk receptor activation (Simonato et al., 2002). Determining the ultrastructural distribution of phospho-trk immunoreactivity would be necessary to distinguish these possibilities.

Since the other primary target of mossy-fiber axons in CA3 is dendrites of stratum lucidum interneurons (Spruston et al., 1997), it is possible that phospho-trk immunoreactivity in stratum lucidum could reflect activation of trk receptors on interneurons as well as CA3 pyramidal cell dendrites. Indeed, quantitative analysis of mossy-fiber targets in CA3 suggests that the number of synaptic contacts onto GABAergic interneurons vastly outnumbers those onto CA3 dendrites (Acsady et al., 1998). Indeed, any interneuron with dendrites traversing stratum lucidum could be a target of mossy-fiber axons. However, it is unclear whether functional trkB receptors exist on stratum lucidum interneurons, as in situ hybridization studies show trkB mRNA localization predominantly in granule and pyramidal cells of hippocampus (Bengzon et al., 1993) and only occasional interneurons were found to be trkB-immunoreactive in the EM study (Drake et al., 1999).

Furthermore, recent evidence indicates that activated trk receptors may be endocytosed and retrogradely transported while still tyrosine phosphorylated (Grimes et al., 1996; Von Bartheld et al., 1996b; Bhattacharyya et al., 1997; Riccio et al., 1997; Senger and Campenot, 1997). Therefore, mossy fiber-like phospho-trk immunoreactivity could in part reflect not only distal synaptic sites of trk activation but also in-progress retrograde transport of activated trk from CA3 within the mossy fibers. Thus, the increase in phospho-trk immunoreactivity observed in the dentate hilus may represent activated trk from mossy-fiber terminals in hilus or CA3.

Role of BDNF in other pathologic conditions

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 behavioral data demonstrate that inhibition of BDNF signal transduction inhibits central pain sensitization (Kerr et al., 1999; Pezet et al., 2002).

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). BDNF promotes survival of all major neuronal types affected in Alzheimer's and Parkinson's disease, such as hippocampal and neocortical neurons, cholinergic septal and basal forebrain neurons, and nigral dopaminergic neurons.

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).

Rett syndrome

Rett syndrome is an X-linked postnatal neurodevelopmental disorder that strikes approximately 1 in 10,000 girls. It is characterized by regression of normal development after about the age of 1 year and eventually leads to several mental and physical impairment, including cognitive and movement deficits and breathing abnormalities. In 1999, Rett syndrome was linked to mutations in the *MECP2* gene on the X chromosome (Amir et al., 1999). MeCP2, the protein product of the *MECP2* gene, is a methyl-CpG binding protein, known to bind DNA regulatory regions to silence gene expression. In 2003, it was discovered that one of the genes normally turned off by MeCP2 is BDNF (Chen et al., 2003; Martinowich et al., 2003). Recently, a strain of mice missing the mouse version of *MECP2* (*Mecp2*) has been found to have abnormally low levels of BDNF (Chang et al., 2006). These mice exhibit several features of human Rett syndrome. Increasing BDNF production in mice lacking *Mecp2* restored mobility and extended life span (Chang et al., 2006). Neural activity triggers phosphorylation of MeCP2 that detaches it from the regulatory region of the BDNF gene and allows BDNF transcription (Zhou et al., 2006). Further study of MeCP2–BDNF interactions may lead to novel insights and treatment strategies for Rett syndrome. Interestingly, *MECP2* abnormalities are starting to be found in other neurodevelopmental disorders such as autism, suggesting that BDNF dysregulation may also have a more widespread role in the pathophysiology of these conditions.

Neuropsychiatric disease

BDNF signaling may also be involved in affective behaviors (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). Acute local BDNF infusion has antidepressant-like effects in rats (Shirayama et al., 2002). 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.

Perspective

Since the discovery of NGF in the 1950s and BDNF in the 1980s, a great deal of evidence has mounted for the roles of NGF, BDNF, NT-3, and NT-4/5 in development, physiology, and pathology. BDNF in particular has important roles in neural development and cell survival, as well as appearing essential to molecular mechanisms of synaptic plasticity and larger scale structural rearrangements of axons and dendrites. Basic activity-related changes in the CNS are thought to depend on BDNF modulation of synaptic transmission. 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.

The role of BDNF in epilepsy provides a particularly good example of the pleiotropic effects of BDNF on excitability. The hippocampus and closely associated limbic structures are thought to be particularly important in the pro-epileptogenic effects of BDNF (Binder et al., 1999a), and 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).

Of course, simple up- or downregulation of NTs may lead to many nonspecific effects. For ultimate clinical application in specific conditions, it will be very helpful to elucidate the mechanisms of action of each of the effects of NT receptor activation. Therefore, much recent research has focused on downstream targets of the NT signaling pathways responsible for specific phenotypic effects. For example, BDNF activation of trkB down-regulates hippocampal KCC2, a K^+-Cl^- cotransporter (Rivera et al., 2002); this suppresses chloride-dependent fast GABAergic inhibition and may partially account for BDNF modulation of GABAergic synapses (Wardle and Poo, 2003). In addition, BDNF phosphorylates specific subunits of both, the NMDA receptor and the $GABA_A$ receptor, altering their function (Suen et al., 1997; Lin et al., 1998; Jovanovic et al., 2004). Long-term effects of BDNF must take into account the fact that it upregulates many other plasticity-related genes, such as NPY (Croll et al., 1994; Nawa et al., 1994). NPY, for example, may not only modulate excitability (Baraban et al., 1997; Reibel et al., 2000a) but also other phenomena such as neurogenesis (Howell et al., 2003).

New methods of modulation/upregulation of NTs may be required to achieve translational control of diseases of NT deficiency. ''Ampakines'' represent a new class of compounds that have been shown to upregulate BDNF over a long period of time (Lauterborn et al., 2003). Of course, proper dosing so as not to trigger downregulation of important NT signaling pathways will be critical to avoiding deleterious side effects of these potential new therapies. Nevertheless, these and similar compounds are under active clinical investigation as cognitive and memory enhancing drugs (Danysz, 1999; Johnson and Simmon, 2002).

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