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Brain-Derived Neurotrophic Factor and the Development of Structural Neuronal Connectivity

Susana Cohen-Cory, **Adhanet H. Kidane**, **Nicole J. Shirkey**, and **Sonya Marshak**
Department of Neurobiology and Behavior, University of California Irvine, Irvine CA 92697, USA

Abstract

During development, neural networks are established in a highly organized manner which persists throughout life. Neurotrophins play crucial roles in the developing nervous system. Among the neurotrophins, brain-derived neurotrophic factor (BDNF) is highly conserved in gene structure and function during vertebrate evolution, and serves an important role during brain development and in synaptic plasticity. BDNF participates in the formation of appropriate synaptic connections in the brain, and disruptions in this process contribute to disorders of cognitive function. In this review, we first briefly highlight current knowledge on the expression, regulation, and secretion of BDNF. Further, we provide an overview of the possible actions of BDNF in the development of neural circuits, with an emphasis on presynaptic actions of BDNF during the structural development of central neurons.

Neurotrophins are growth factors with crucial roles in the developing and mature nervous system. They are initially synthesized as precursor proteins (pro-neurotrophins), which are processed intracellularly to be secreted mostly in a mature, biologically active form (Mowla et al., 1999; Mowla et al., 2001; Matsumoto et al., 2008; for review see Lu et al., 2005). Pro-neurotrophins can also influence developing and mature neural circuits, and may be released in a developmentally regulated manner (Lee et al., 2001; Lu et al., 2005; Teng et al., 2005; Yang et al., 2009). Neurotrophins bind two classes of membrane receptors, the tropomyosin receptor kinase (Trk) family of receptors and the p75 neurotrophin receptor (p75NTR) (for a review see Chao, 2003). The actions of mature neurotrophins are mediated by the high affinity full-length Trk receptors, which signal through their intrinsic tyrosine kinase activity to promote growth. Trk receptors signal by dimerization of receptor molecules, leading to intracellular phosphorylation and activation of intracellular signaling cascades (Ullrich and Schlessinger, 1990; Jing et al., 1992). Truncated Trk receptors (Trk.T) are splice variants of full-length Trks, which lack the intracellular tyrosine kinase domain, and are thought to act as negative effectors of full-length receptors (Luikart et al., 2003), although they may also have their own signaling properties (Rose et al., 2003; Ohira et al., 2006). The neurotrophins show binding specificity for particular Trk receptors: nerve growth factor (NGF) binds to TrkA, brain-derived neurotrophic factor (BDNF) and neurotrophin 4 (NT4) to TrkB, and neurotrophin 3 (NT3) to TrkC (Chao, 2003). The p75NTR has low affinity for the mature neurotrophins, but can form a complex with Trk receptors to form high affinity binding sites for neurotrophins, enabling the receptor to participate in the stimulation of growth processes (Esposito et al., 2001). Moreover, p75NTR displays high affinity binding with pro-neurotrophins, and induces apoptosis by interacting with sortilin (Lee et al., 2001; Nykjaer et al., 2004). Thus, pro-neurotrophins and mature neurotrophins may utilize distinct receptors to mediate divergent neuronal actions. This review focuses on the actions of mature BDNF, highlighting the role that BDNF plays in the development of synaptic

Corresponding Author: Susana Cohen-Cory, Ph.D.Department of Neurobiology and Behavior University of California, Irvine 2205 McGaugh Hall Irvine, CA 92697-4550 phone: (949)824-8188 Fax:(949) 824-2447 scohenco@uci.edu.

connectivity in the central nervous system (CNS). Evidence supporting presynaptic actions by target-released BDNF, and the influence that BDNF exerts during the structural development of neurons are reviewed here.

BDNF synthesis and release

A number of neurodevelopmental, neurodegenerative and neuropsychiatric disorders, which are characterized by abnormalities in synaptic plasticity, have been associated with deficits in BDNF function (Alberch et al., 2004; Mattson et al., 2004; Chang et al., 2006; Arancio and Chao, 2007; Mattson, 2008). BDNF expression and secretion require well regulated mechanisms, and this can be achieved through the complex organization of its gene. In addition to regulated transcription, differential targeting of distinct *Bdnf* transcripts may provide a controlled mechanism for modulating BDNF availability and function at distinct cellular locations (Tongiorgi et al., 2006; Chiaruttini et al., 2008; Tongiorgi, 2008). Local regulation of BDNF protein synthesis is also essential for its function, since BDNF does not diffuse a long distance, and is likely to act on local receptors (Horch and Katz, 2002). Understanding the transcriptional and translational regulation of BDNF, as well as its regulated secretion, can thus provide better insight into developmental mechanisms of BDNF action, and how altered BDNF expression and release can impact neuronal circuit function.

The *Bdnf* gene consists of multiple alternative exons (ten in human, eight in rodents and six in lower vertebrates), and a single exon coding for the entire pro-BDNF protein. Transcription of the *Bdnf* gene can be initiated by multiple promoters, which are regulated in a developmental, tissue specific, and activity-dependent manner (Aid et al., 2007). The activity dependent transcription of *Bdnf* is controlled mainly by promoters I and IV (Tao et al., 2002; Rattiner et al., 2004; Kidane et al., 2009). The complex organization of the *Bdnf* gene is well conserved among species, from fish to mammals (Heinrich and Pagtakhan, 2004; Aid et al., 2007; Pruunsild et al., 2007), suggesting that the control of its expression has a strong functional significance. In addition to regulated transcription, regulated polyadenylation at either of two alternative sites in the *Bdnf* gene results in the synthesis of two distinct populations of mRNAs: transcripts with a short 3'untranslated region (UTR), and transcripts with a long 3'UTR (Timmusk et al., 1993). *Bdnf* mRNA transcripts with a short 3'UTR are restricted to the soma, whereas those with a long 3'UTR are targeted to dendrites for local translation (An et al., 2008). Approximately 1–4% of all mRNA species in neurons localize to dendrites. Not surprisingly, most of the dendritically localized mRNAs code for proteins involved in synaptic plasticity (Steward and Schuman, 2001). Dendritically localized mRNAs remain untranslated until stimulation (Bramham and Wells, 2007), so that translation of mRNAs in response to activity would restrict newly synthesized proteins to the active postsynaptic sites. Even though the translational regulation of *Bdnf* mRNA is yet to be fully understood, the highly conserved and complex *Bdnf* gene organization is thought to be necessary for the tight regulation of BDNF expression.

All of the distinct *Bdnf* mRNA transcripts, each of which is transcribed by its own promoter, contain multiple 5' upstream translation initiation codons (uAUGs). Given the biological significance of BDNF, it is surprising that little attention has been given to the translational regulation of BDNF. The functional significance of upstream open reading frames (uORFs) and uAUGs in the *Bdnf* gene is of particular interest since recent studies show that the 5'UTRs of *Xenopus* BDNF transcripts I and IV, which have highly conserved uORFs, can decrease translational efficiency (Kidane et al., 2009). Functional uORFs have been found upstream of genes that encode potent regulatory proteins, such as cytokines, growth factors, kinases and G protein-coupled receptors (Kozak, 1991; Morris and Geballe, 2000). The inhibitory features of uORFs in those genes can serve as regulatory elements by modulating

the translatability of the respective mRNAs, regulating genes implicated in cell proliferation and damage (Xu et al., 2001; Bastide et al., 2008). Therefore, control of BDNF translation through regulatory elements such as uORFs may serve as an additional mechanism to control the synthesis of this important protein which can be harmful when misexpressed (Croll et al., 1999; Cunha et al., 2009).

The secretion of BDNF occurs through both a regulated, and a constitutive pathway. Constitutive secretion occurs mainly at the soma, while regulated secretion occurs in distal neural processes (Brigadski et al., 2005). Efficient BDNF sorting to the regulated secretory pathway is controlled by a region in the *pro*-domain of BDNF (Chen et al., 2005). Mature BDNF is proposed to be released in an activity-dependent manner from both axons and dendrites. However, direct evidence demonstrating site-specific endogenous BDNF release is still missing. Methods that measure BDNF secretion have relied on exogenous expression of BDNF tagged with GFP (Kojima et al., 2001; Matsuda et al., 2009), or on immunochemical assays measuring endogenous BDNF secreted to the extracellular medium (Balkowiec and Katz, 2002). Although these studies have been valuable for understanding BDNF release, they either provide little information on whether the release of excess BDNF represents endogenous BDNF secretion, or give no spatiotemporal information on BDNF secretion. A recently developed cell-based indicator that allows measurement of picomolar concentrations of endogenous BDNF secreted from living neurons (Nakajima et al., 2008), may help define the precise site(s) of BDNF release. Collectively, most findings point to a predominant, postsynaptic mechanism of BDNF release (for detail reviews on this topic see Kuczewski et al., 2009; Lessmann and Brigadski, 2009). The actions of postsynaptically released BDNF, and the signaling mechanisms implicated in local activation of TrkB receptors at developing axon terminals, are summarized in Figure 1 and reviewed below.

BDNF and the guidance of central axons to their targets: *in vivo* versus *in vitro* studies

Roles for neurotrophins as axon guidance molecules have been supported by evidence dating back to early observations that NGF and other members of the neurotrophin family can induce neurite outgrowth in culture (Levi-Montalcini, 1964; Davies et al., 1986; Thanos et al., 1989). Over the years, assays that examine roles of neurotrophins, and in particular of BDNF in axon guidance, have not only become more innovative and sophisticated, but have also supported such a role. Early observations of increased neurite outgrowth in neurons exposed to BDNF in culture suggested that BDNF participates in the growth and branching of axon terminals of both peripheral and central neurons (Davies et al., 1986; Thanos et al., 1989). Elegant stripe and growth cone turning assays have since then shown that axon growth cones can indeed respond to extracellular gradients of BDNF (Ming et al., 2001; Chen et al., 2006). A direct role for BDNF in axon pathfinding, however, remains to be demonstrated (see below, and also Guthrie, 2007).

Accumulating evidence indicates that BDNF, signaling through its receptor TrkB, can influence the morphological development of neurons as well as their synaptic connectivity (Huang and Reichardt, 2001; Poo, 2001; Zweifel et al., 2005). Observations made *in vivo* support the idea that axon guidance and pathfinding are independent of BDNF, but that wiring events that follow successful axon pathfinding depend on BDNF. Specifically, studies that used loss of function approaches (heterozygote mutant mice and conditional knockouts), have been particularly useful to demonstrate the consequence of altered TrkB signaling in the intact brain. No deficits in the guidance of major afferent projections in key neural circuits in the brain, including the hippocampus, cerebellum, somatosensory cortex and visual system, have been found in mutant mice deficient in TrkB expression, even though synaptic connectivity at the target is affected (Martinez et al., 1998; Rico et al., 2002;

Lush et al., 2005; Rodger and Frost, 2009). Similarly, homozygote BDNF mutant mice, in which neuronal populations are rescued from cell death by a mutation in a pro-apoptotic gene (Bax), show normal sensory neuron projections to their targets, though target innervation is abnormal (Hellard et al., 2004). Studies in simple organisms confirm observations made in TrkB mutant mice and argues against an axon guidance role for BDNF. In *Xenopus*, retinal ganglion cells with cell-specific alterations in TrkB signaling show no defects in optic axon pathfinding, but exhibit significant abnormalities in the morphology of their growth cones and branching of axon terminals at the target (Fig. 2) (Marshak et al., 2007). Similarly, BDNF does not influence *Xenopus* trigeminal axon pathfinding, but is necessary to promote target innervation (Huang et al., 2007). In this particular study, axonal arborization of trigeminal sensory neurons that innervate the cement gland was significantly reduced in embryos with BDNF knockdown early in development, but was induced when the target tissue was replaced with ectopic grafts expressing BDNF. Localized effects of neurotrophins on axon terminals have also been demonstrated by studies that examined the behavior of GFP-labeled sensory and motor axons that innervate the limb bud in mouse embryos (Tucker et al., 2001). By placing neurotrophin-coated beads ectopically, but near axon pathways in an embryo slice preparation, Trucker and colleagues showed that axons from sensory neurons, but not motor neurons, elongated and stopped at the focal source of BDNF. In these studies, normal axon elongation was also prevented when placing a cocktail of function-blocking antibodies against all neurotrophins along the pathway, but not when antibodies to BDNF alone were used. These findings therefore support the idea that axon growth of some neuronal populations *in vivo* can be influenced by BDNF, but that axon pathfinding is independent of BDNF. Collectively, the *in vivo* studies support the idea that BDNF functions as a short-range signal to stimulate axon terminal arborization at the target. Effects of BDNF on axon growth and guidance *in vitro* may therefore reflect potential changes in the axon terminal that are triggered locally *in vivo*, when growing axons have already reached their target, such as filopodial extension and collateral axon branching. The low expression levels of BDNF during development, and its regulated secretion, further support the notion that BDNF exerts spatially restricted actions on presynaptic axon terminals upon release from a local, target-derived source.

Signaling mechanisms mediating the effects of BDNF on growing axons

Studying effects of neurotrophins *in vitro* has been useful for elucidating the signaling mechanisms that control axon growth and differentiation, and for manipulating downstream effects on neurons (Arevalo and Chao, 2005; Reichardt, 2006). Studies that have examined growth cone responses *in vitro* have revealed that BDNF activates intracellular signaling cascades that are shared with classical axon guidance molecules. Responses of growing axons to extracellular gradients of BDNF trigger activation of the phosphatidylinositol-3 (PI3) kinase, mitogen-activated protein (MAP) kinase and phospholipase C-γ (PLC-γ) pathways, and depend on intracellular cAMP levels (Song et al., 1997; Wang and Zheng, 1998; Ming et al., 1999; Ming et al., 2002; Nishiyama et al., 2003; Jin et al., 2005; Mai et al., 2009); for review see (Huang and Reichardt, 2003; Huber et al., 2003). Accumulating evidence indicates that neurotrophins regulate the activity of the Rho family of small GTPases that influence actin cytoskeleton dynamics (Yamashita et al., 1999; Reichardt, 2006). Regulated activity of the protein kinase Akt, activated through the PI3 Kinase pathway by neurotrophin signaling, in turn influences the activity of downstream effectors that include Rho, Rac and Cdc42 (Hall, 1998; Dickson, 2001). BDNF, in particular, activates Rac1 and Cdc42 in *Xenopus* neurons in culture and *in vivo*, in turn affecting actin polymerization and myosin activity within the growth cone (Ruchhoeft et al., 1999; Yuan et al., 2003). These signaling pathways are also targets of more common axon guidance molecules that include netrin-1, Wnts, and ephrin-B3 that affect the actin cytoskeleton and directionality of growth (Kishida et al., 2004; Arevalo and Chao, 2005; Iwasato et al., 2007;

Moore et al., 2008). Lipid rafts in the membrane may mediate growth cone responses to both BDNF and netrin-1, by localizing or coupling their specific receptors to downstream effectors that influence actin cytoskeletal dynamics (Guirland et al., 2004). Recent *in vitro* evidence indeed supports that TrkB receptor localization within the membrane, or graded receptor activation by BDNF along discrete sites down the axon, may also polarize growth, presumably by triggering differential gradients of cytoplasmic second messengers such as iCa2+ and cAMP (Mai et al., 2009). Thus, polarized signaling may differentially affect cytoskeletal dynamics and therefore influence branch initiation and/or growth. Indeed, application of BDNF to neurons in culture rapidly influences filopodia and lamellipodia dynamics along the axon shaft, by inducing localized changes in the actin cytoskeleton (Gibney and Zheng, 2003; Menna et al., 2009). Collectively, observations of BDNF-mediated growth cone responses *in vitro* support the localized recruitment of signaling pathways, often shared by other guidance molecules, which can affect local axon growth and branching in the living organism.

Roles for BDNF in the branching, synaptic differentiation, and maintenance of presynaptic axon arbors

The selection of potential synaptic partners depends on structural and functional interactions between developing axons and dendrites at nascent synaptic sites (Ziv and Smith, 1996; Wong and Wong, 2000; Cohen-Cory, 2002; Yuste and Bonhoeffer, 2004; Mumm et al., 2006; Lohmann and Bonhoeffer, 2008). Imaging studies have revealed that the initial branching of axons and dendritic terminals is a dynamic process that involves the active extension and retraction of branches (O'Rourke et al., 1994; Jontes and Smith, 2000; Cline, 2001; Niell et al., 2004). These dynamic interactions between developing axons and dendrites precede synapse formation in the developing brain and are subject to modulation by neurotrophic activity (Alsina et al., 2001; Lang et al., 2007) (see Fig 2). *In vivo* imaging studies first performed in simple organisms, and more recently in the mammalian brain, have also revealed an association between synapse stabilization and branch extension in both developing axon and dendritic terminals (Alsina et al., 2001; Niell et al., 2004; Hu et al., 2005; Portera-Cailliau et al., 2005; Meyer and Smith, 2006; Ruthazer et al., 2006). The ability of neurotrophins, in particular BDNF, to induce localized structural and functional changes in axon and dendritic terminals has supported its participation in such important developmental events. Here, we briefly review recent data supporting a presynaptic role of BDNF on developing axon arbors.

In vivo studies in the *Xenopus* visual circuit, where BDNF levels were manipulated at key stages of synaptic development, provided the first direct demonstration that BDNF modulates the morphological maturation of presynaptic axon arbors at their target and their synaptic connectivity (Cohen-Cory and Fraser, 1995; Alsina et al., 2001). In this system, acute treatment with BDNF at the retinal axon target, the optic tectum, rapidly induced the extension of new branches and the formation of new presynaptic specializations on axonal arbors of individual retinal ganglion cells imaged *in vivo* (Alsina et al., 2001). Structural changes in retinal axon arbors coincide with ultrastructural and functional changes at individual synapses, and with downstream changes in the presynaptic connectivity of these neurons (Du and Poo, 2004; Marshak et al., 2007; Nikolakopoulou et al, 2009). Thus, BDNF can shape both neuronal structure and function in the developing brain. Imaging and electrophysiological studies performed in *Xenopus*, as well as in mutant mice deficient in TrkB receptor expression, have suggested that threshold levels of BDNF may tip the balance between enhanced axon arbor growth and connectivity versus increased destabilization and pruning of axon terminals. In *Xenopus*, manipulations that decrease endogenous BDNF levels at the retinal axon target induce presynaptic site destabilization and axon arbor pruning (Hu et al., 2005). Specifically, retinal ganglion cell axons, identified by their

expression of GFP-tagged synaptic markers and red fluorescent proteins, respond to acute treatment with function-blocking antibodies to BDNF by disassembling GFP-tagged presynaptic sites and by retracting axonal branches (Hu et al., 2005). These acute, dynamic changes in axon arbor stabilization observed in *Xenopus* may represent, at least in part, some of the long term events that significantly impact axon terminal connectivity in the mammalian brain.

Presynaptic defects on axon terminals at their target in the absence of TrkB signaling were also revealed by studies that analyzed mutant mice with conditional deletion of TrkB. Specifically, in conditional knockout mice with presynaptic deletion of TrkB, the number of presynaptic terminals and the number of excitatory synapses formed by Schaffer collaterals in the hippocampus was reduced (Luikart et al., 2005). Similarly, presynaptic defects in mossy fiber connectivity result from conditional deletion of TrkB specifically in hippocampal granule cells (Danzer et al., 2008). Aberrant branching and pruning of thalamic axon terminals that innervate the somatosensory cortex are also observed in knockout mice with conditional deletion of TrkB within the thalamus (Lush et al., 2005). However, conditional deletion of TrkB in cortical neurons, rather than in thalamic neurons, does not result in aberrant thalamic axon segregation or growth. Collectively, studies that manipulate TrkB signaling in subsets of neurons rather than in the entire organism support earlier observations that thalamic axon segregation and branching locally at the target can be modulated by BDNF, as was initially demonstrated in the visual system during ocular dominance column formation (Cabelli et al., 1995; Cabelli et al., 1997). Recent studies that took advantage of a mouse model in which neurotransmitter release can be blocked in single olfactory sensory neurons to effectively block axon arbor competition have further demonstrated that, the total levels of BDNF, as well as that regulated by activity, are important for the activity-dependent pruning of axon terminals during development (Cao et al., 2007). Thus, BDNF may provide a molecular mechanism of synaptic competition during development, as was originally proposed more than a decade ago (Katz and Shatz, 1996; Snider and Lichtman, 1996).

In vivo studies have demonstrated that BDNF impacts, not only axon arbor morphology, but also shapes the synaptic connectivity of axons that become morphologically more complex in response to BDNF. Presynaptic, cell-autonomous effects of BDNF on developing synapses are supported by studies that examined the effects of altered BDNF expression or TrkB signaling in specific neuronal populations in living embryos. Conditional presynaptic deletion of TrkB during development results in decreased axonal varicosities, decreased synapse number, and altered ultrastructural morphology of synapses made by hippocampal CA1 neuron axon terminals in the adult mouse (Luikart et al., 2005). This indicates that cell-autonomous TrkB signaling, during early neural circuit formation, can impact synaptic connectivity in the more mature brain. Studies that examined the consequence of overexpression of dominant negative TrkB in single neurons in *Xenopus* tadpoles further support an early role for presynaptic TrkB signaling during the synaptic differentiation of axon terminals in the living brain (Marshak et al., 2007). Expression of a truncated form of TrkB tagged with GFP (TrkB.T1-GFP) in retinal ganglion cells was used to visualize changes in individual axon terminals with altered TrkB signaling in an otherwise intact brain. Altered TrkB signaling influenced not only axon branch initiation, but also the stability of the axon arbor and the number of synaptic contacts that each axon established (Marshak et al., 2007). Elegant *in vitro* studies, where BDNF expression was manipulated in single neurons in the mammalian visual cortex, also support target-derived effects of BDNF on presynaptic terminal arbors (Kohara et al., 2007). In these experiments, single-cell conditional deletion of BDNF was used to restrict BDNF influence to only a subset of cortical neurons in slice cultures. A specific decrease in inhibitory postsynaptic currents, and in the number of GABAergic synapses made onto pyramidal neurons deficient in BDNF

expression, indicates that BDNF promotes the formation and/or maintenance of inhibitory synapses in the cortex through a direct effect on GABAergic presynaptic terminals. Together, these studies indicate that target-derived BDNF can exert very localized presynaptic actions on both excitatory and inhibitory neurons as they make appropriate synaptic connections in the brain.

Observations that fine structural changes at the level of individual synapses result from manipulation of TrkB signaling are consistent with a modulatory role for BDNF in the synaptic differentiation of axon terminals. Most studies that analyzed how BDNF modulates synapses collectively within a circuit, or within specific cell types, show effects on synapse ultrastructure that vary slightly among vertebrate species and synapse type. A common observation is that the total synaptic vesicle pool and the number of synaptic vesicles docked at active zones can be altered upon perturbations in BDNF signaling (Vicario-Abejon et al., 2002; Shen et al., 2006). In the hippocampus, deficits in TrkB signaling result in decreased expression of synaptic proteins responsible for synaptic vesicle docking and fusion, decreased number of docked vesicles at active zones, and downregulation of neurotransmitter release at synaptic sites (Martinez et al., 1998; Pozzo-Miller et al., 1999; Lin and Scheller, 2000; Otal et al., 2005). In contrast, exposure to BDNF increases the number of synaptic vesicles docked in excitatory synapses in hippocampal neurons in culture (Tyler and Pozzo-Miller, 2001; Tyler et al., 2006). Cerebellar inhibitory synapses are also modulated by BDNF, where alterations in TrkB signaling in knockout mice reduce the numbers of GABAergic boutons and synaptic specializations (Rico et al., 2002), and targeted deletion of the BDNF gene decreases the number of vesicles that are docked (Carter et al., 2002). In the visual system of chicks and frogs, alterations in BDNF levels within the target optic tectum can also affect the total synaptic vesicle pool and the number of docked synaptic vesicles (Wang et al., 2003; Nikolakopoulou et al., 2009). Studies that utilized cell-specific conditional deletion of TrkB, or dominant negative approaches to alter TrkB signaling in afferent neurons, further demonstrate that BDNF can directly impact the synaptic structure of axon terminals in a cell-autonomous way (Luikart et al., 2005; Marshak et al., 2007). Effects of altered TrkB signaling at the level of individual synapses were demonstrated by a decrease in the number of docked synaptic vesicles in those synapses formed by GFP-identified, individual *Xenopus* retinal axons expressing dominant negative TrkB, in an otherwise intact brain (Marshak et al., 2007). Changes in the fine structure of TrkB-deficient retinotectal synapses in *Xenopus* also resemble effects observed after conditional ablation of TrkB in the hippocampus *in vivo*, where the density of presynaptic elements is reduced by the cell-specific, presynaptic deletion of TrkB (Luikart et al., 2005). Because neurotransmitter release probability is proportional to the number of docked synaptic vesicles (Pozzo-Miller et al., 1999; Schikorski and Stevens, 2001; Tyler and Pozzo-Miller, 2001), the ultrastructural changes observed at individual synapses are consistent with specific modulation of presynaptic function. Indeed, electrophysiological studies showing persistent potentiation of synapses after acute increase in target BDNF levels in the *Xenopus* brain support this notion (Du and Poo, 2004).

BDNF and the development of dendrites and synaptic specializations

It has been suggested that the transport and local synthesis of BDNF in dendrites may serve as a mechanism to precisely regulate BDNF function in space and time (Tongiorgi, 2008). Indeed, an increasing number of studies demonstrate the ability of BDNF to control, not only the maintenance of dendritic arbor structure, but also to act as a modifying factor for the shape and number of dendritic spines (Murphy et al., 1998; Shimada et al., 1998; Horch et al., 1999; Matsutani and Yamamoto, 2004; Ji et al., 2005; Chakravarthy et al., 2006; An et al., 2008; Gao et al., 2009). Accumulating evidence demonstrates that BDNF is involved in the branching of both axons and dendrites, and suggests that these structural changes

correlate with the ability to foster functional development of synaptic circuits. Even though BDNF can influence the branching and differentiation of dendritic arbors both in culture and *in vivo* (for review see McAllister et al., 1999; McAllister, 2000), direct modulation of dendritic arbor growth by BDNF has been demonstrated only for a few neuronal populations *in vivo* (Luikart et al., 2005).

Early studies showed that the development of dendritic arbors of cortical pyramidal neurons is modulated by neurotrophins when applied to neurons grown in explant cultures, with recombinant BDNF influencing apical and basal dendritic branching in opposite ways (McAllister et al., 1995; McAllister et al., 1997). Thus, neurotrophins can act positively to promote dendritic branching (McAllister et al., 1995; Horch and Katz, 2002; Wirth et al., 2003), but they can also limit the size of a neuron's dendritic arbor (McAllister et al., 1997; see also Lom and Cohen-Cory, 1999). Culture studies also demonstrate that effects of BDNF on cortical pyramidal neuron dendritic growth and branching are spatially restricted, require neural activity, and occur rapidly after exposure to BDNF (McAllister et al., 1996; Horch and Katz, 2002). In the hippocampus, a modulatory role for BDNF in the morphological differentiation of dendritic arbors was demonstrated in experiments showing increased number of primary dendrites and in dendritic spines in cultured neurons grown in the presence of BDNF (Ji et al., 2005). However, hippocampal neurons in adult mice with conditional deletion of TrkB show no deficits in dendrite branch number or dendritic arbor length, although synapse formation in these neurons is affected (Luikart et al., 2005). It is possible that differences in responses to manipulations in BDNF levels and/or signaling may result from differences in the developmental timing and the local microenvironment in which neurons grow. For some neuronal populations, however, observations made in culture and *in vivo* are more consistent. For example, the shape and number of spines on dendrites of cerebellar Purkinje cells grown in culture are influenced by BDNF, but not the branching or complexity of their dendritic arbor (Shimada et al., 1998). Similarly, in the cerebellum of mutant mice lacking all isoforms of TrkB, Purkinje cells show no deficits in dendritic arbor branching, but have deficits at the level of individual synapses, with synapse elimination being affected (Bosman et al., 2006). Thus, it is clear that BDNF influences the synaptic connectivity of some developing neurons, while the growth of their dendritic arbor may be independent of BDNF.

It remains an open question whether the localized effects of BDNF on postsynaptic neurons and at specific postsynaptic sites are mediated through a direct activation of postsynaptic TrkB receptors and/or whether these effects are mediated through presynaptic TrkB signaling (feedback mechanisms) (Segal, 2001). It has been difficult to differentiate the precise site(s) of BDNF action since most studies have relied on the analysis of neurons grown in isolation and treated with drugs, or on the analysis of transgenic or mutant mice with large populations of affected neurons. Elegant work in culture using neurons from BDNF knockout mice, but engineered to express and release BDNF, supports a postsynaptic role for BDNF in the development of inhibitory neurons of the visual cortex (Kohara et al., 2003). Specific regulation of dendritic arbor growth of cortical GABAergic interneurons, through controlled presynaptic release of BDNF, was demonstrated in studies that used single-cell expression to directly manipulate BDNF release from only a subset of identified neurons. These observations, together with the notion that TrkB can be localized to dendrites of neurons in cortex and hippocampus, as well as other circuits in the brain, further support the possibility of a direct postsynaptic action by BDNF (Drake et al., 1999; Aoki et al., 2000; Swanwick et al., 2004; Gomes et al., 2006).

The influence that BDNF exerts on dendritic arbors, especially those of neurons developing in culture, may reflect changes in local signaling at the dendrite that in turn influence dendritic filopodial density, motility and/or connectivity. A role for BDNF during the

differentiation of postsynaptic specializations was recently demonstrated for hippocampal neurons in culture, where mature spine synapses were formed within 10–15 hours of initial contact by nascent spines at existing presynaptic sites (Nagerl et al., 2007). The modulation of spine formation by BDNF may reflect a transition from an early filopodial-mediated contact that involved the accumulation of pre- and postsynaptic components at the nascent synaptic site, to the later maturation of a synapse. Thus, BDNF may control both pre- and postsynaptic site differentiation in a spatially and temporally regulated manner (Alsina et al., 2001; Kossel et al., 2001; Lang et al., 2007). Imaging experiments also demonstrate that focal delivery of BDNF onto dendrites can induce fast, localized calcium transients at nascent synaptic sites along the dendrite, while blocking TrkB signaling reduces the frequency of calcium transients specifically at synaptic sites (Lang et al., 2007). Thus, local signaling by BDNF at nascent synaptic sites can regulate synapse formation and plasticity.

Even though changes in dendritic arbor morphology have been taken to imply direct changes in the synaptic connectivity of postsynaptic neurons (Cline, 2001), it is clear that alterations that significantly impact synapse number may not always shape dendritic arbor growth. For example, TrkB exerts a cell-autonomous role in the formation of spines and postsynaptic specializations in hippocampal neurons *in vivo* but has no influence on the morphology of the dendritic arbor (Luikart et al., 2005). In the *Xenopus* visual system, BDNF can influence the synaptic differentiation of tectal neurons, the postsynaptic partners of retinal ganglion cells, though indirectly, without shaping dendritic arbor morphology. Specifically, the density of GFP-tagged postsynaptic specializations (through expression of the postsynaptic density protein 95 (PSD-95) tagged with GFP) was increased or decreased, along tectal neuron dendrites, when the levels of endogenous BDNF within the tadpole optic tectum were acutely increased or decreased, respectively, by treatment with recombinant BDNF or blocking antibodies to BDNF (Sanchez et al., 2006). These changes in postsynaptic site number were independent of dendritic arbor growth, and transpired several hours after BDNF induced significant changes in presynaptic site differentiation and axon arbor growth in retinal ganglion cell axons exposed to the same treatment (Alsina et al., 2001; Hu et al., 2005). Thus, BDNF influences postsynaptic arbor structure in a manner and a time scale that differ from its effects on presynaptic retinal ganglion cells. Experiments that specifically altered TrkB signaling in individual neurons in the *Xenopus* brain further demonstrate that BDNF is not directly involved in the synaptic differentiation of postsynaptic tectal neurons (Marshak et al., 2007). Consequently, at least for some developing neuronal circuits, effects of BDNF on the morphological and synaptic differentiation of dendritic arbors can be secondary to effects on presynaptic axon terminals that are responsive to BDNF.

Roles for BDNF in the maturation and refinement of dendritic arbors

Studies that have analyzed conditional BDNF knockout mice suggest that BDNF is involved in the maintenance of dendritic morphology rather than in the developmental formation of dendritic arbors of neurons in the neocortex (Xu et al., 2000; Gorski et al., 2003). Recent studies that manipulated the expression of Ankyrin Repeat-Rich Membrane Spanning/Kidins 220 (ARMS/Kidins220), a scaffolding protein that is a direct substrate of BDNF signaling, also demonstrate a role for BDNF during dendritic branch and spine stability *in vivo* (Wu et al., 2009). Specifically, neurons in ARMS/Kidins220 mature mutant mice possess dendritic arbors that are less complex and have fewer spines than neurons in younger mice that harbor the same mutation. Neurons deficient in ARMS expression, moreover, extend fewer primary dendrites in response to BDNF. Thus, these studies demonstrate that hippocampal and cortical neuron dendritic arbors are affected by the mutation only after the period of synaptic refinement, and not earlier during development, when dendritic arbors begin to form. Collectively, studies that integrate the analysis of mutant mice deficient in BDNF or TrkB signaling support a role for BDNF during the refinement and/or stabilization of dendritic

arbors. Developmental roles for BDNF in the refinement of synaptic connectivity are also supported by evidence from the visual system of mammals showing that BDNF and NT-3 control both the branching and the laminar refinement of dendritic arbors of distinct subtypes of retinal ganglion cells (Liu et al., 2007; Liu et al., 2009). Overexpression of BDNF in transgenic mice accelerates the visual experience-dependent laminar refinement of retinal ganglion cell dendrites, and this developmental maturation of dendritic arbors is delayed in the absence of TrkB signaling. It remains unclear, however, to what extent BDNF is directly responsible for retinal ganglion cell dendritic arbor refinement, as some of its effects may be secondary to its modulation of retinal activity or synaptic connectivity at the target (Landi et al., 2007; Liu et al., 2007). Certainly, BDNF can exert acute effects on retinal ganglion cell dendritic arbor growth, and these can differ depending on whether TrkB activation occurs locally within the retina or at the axon's target (Lom and Cohen-Cory, 1999; Lom et al., 2002; Landi et al., 2007).

In addition to its developmental role, BDNF participates in the activity-dependent structural rearrangement of synapses in the adult brain. Cell-autonomous TrkB signaling is necessary for maintaining spine morphology and number in dendrites of pyramidal neurons in the adult visual cortex (Chakravarthy et al., 2006). BDNF has also been implicated in balancing the number of excitatory and inhibitory synapses in the adult brain, as a normal shift in excitatory/inhibitory balance triggered by controlled sensory stimulation is absent in the cortex of heterozygote BDNF mutant mice (Genoud et al., 2004). Recent studies further indicate that locally translated BDNF may act to promote dendritic spine pruning and remodeling later in postnatal development (An et al., 2008). The role that local translation and release of BDNF protein plays in the synaptic morphological rearrangements and in synaptic plasticity in the mature brain is currently a topic of high interest in the field (for review see (Tongiorgi et al., 2006; Greenberg et al., 2009; Waterhouse and Xu, 2009).

Signaling pathways implicated in the modulation of dendritic arbor structure by BDNF

Recent studies have implicated local TrkB activation of the Ras and PI3K pathways in dendrites, in the control of filopodial motility and the subsequent formation of synapses in the mammalian brain (Luikart et al., 2008). Specifically, these studies showed that alterations in dendritic filopodial motility in the absence of TrkB signaling correlate with a decrease in the number of spines and synapses in hippocampal neurons in culture and *in vivo* (Luikart et al., 2005; Luikart et al., 2008). Additional work in culture has shown that the observed effects of BDNF on dendrite extension may involve activation of the PI3 kinase and MAP kinase pathways (Dijkhuizen and Ghosh, 2005), again similar to the signaling pathways activated by BDNF on axon terminals (see above). The extension of primary dendrites by hippocampal neurons in culture, however, does not depend on cAMP (Ji et al., 2005). The effects of BDNF on dendritic arbors seem to involve the transport of TrkB to dendritic filopodia and distal dendrites (Gomes et al., 2006; Luikart et al., 2008), where the receptor may localize to lipid rafts (Suzuki et al., 2004). The BDNF-induced increase in primary dendrite number in hippocampal neurons in culture can be prevented by treatment with cholesterol synthesis inhibitors that modify lipid rafts (Suzuki et al., 2004). As is the case for axon terminals that respond to BDNF, activation of Rho GTPases has also been implicated in the induction of activity-dependent dendritic filopodial formation and branching (Ruchhoeft et al., 1999; Li et al., 2000; Sin et al., 2002; for review see Van Aelst and Cline, 2004). Recent studies demonstrate that BDNF stimulates Cdc42 activity in hippocampal neurons in culture and contributes to the increase in primary dendrites in these neurons (Cheung et al., 2007). Rho GTPases are also involved in TrkB signaling at the dendrite, as alterations in Rac1 and RhoA, or interfering Rho GTPase activation, alter the BDNF-induced effects on dendrite branching and filopodial formation in developing

neurons (Cheung et al., 2007; Luikart et al., 2008; Zhou et al., 2008). Thus, it is possible that BDNF may mediate effects on the extension of filopodia, branching of dendrites, and/or the formation of synapses on those dendrites, through local activation of signal transduction pathways that modify the actin and microtubule cytoskeleton (Bramham, 2008; Gu et al., 2008).

Interactions between BDNF/TrkB signaling and guidance molecules in the growth and branching of axon terminals at their target

While most *in vivo* evidence argues against an axon pathfinding role for BDNF as discussed in this review, it does not rule out the possibility that neurotrophins may cooperate with classical axon guidance molecules that work as short range signals to fine tune neuronal connectivity at the target. Ephrins and their respective receptors, Ephs, through expression of complementary gradients of both ligands and receptors, can provide the positional information needed for axon terminals to organize topographically at their target (for review see Flanagan, 2006). While Eph receptors trigger intracellular signaling cascades upon ligand binding via phosphorylation of the intracellular tyrosine kinase domain, ephrin ligands can also induce signaling cascades through what is known as reverse signaling (Klein, 2009). Both the glycosylphosphatidil-inositol (GPI)-anchored ephrin-A ligands, and the transmembrane ephrin-B ligands, can induce reverse signaling. Recent evidence demonstrates that *cis* interactions between TrkB and ephrin ligands expressed in axon terminals can influence the branching of axons at the appropriate target. Specifically, ephrin-A reverse signaling in TrkB-expressing retinal axons prevents the early branching of anterior retinal axons that normally project to the posterior optic tectum, in the inappropriate, anterior portion of the brain (Marler et al., 2008). Molecular interactions between ephrin-A and TrkB recruit activation of the PI3 kinase pathway, and have been shown to be important for the branching of axons not only in the visual system but also in the hippocampus. Molecular interactions and/or shared signaling mechanisms between ephrin ligands and TrkB may also be responsible for the synaptic differentiation of axon arbors through ephrin-B reverse signaling, as recently demonstrated for retinal ganglion cells (Lim et al., 2008).

Ephrin ligands, Trk receptors, and receptors that bind other classical axon guidance molecules, activate similar intracellular signaling pathways, such as the PI3 kinase pathway, and share downstream adaptor molecules that possibly integrate to influence branching (Huber et al., 2003). Activation of these pathways seems to be necessary, not only for TrkB-induced axonal filopodia motility, but also the motility of dendritic filopodia and may be responsible for their collaborative effects. Rho GTPases, that control both retinal ganglion cell dendritic and axonal branching (Ruchhoeft et al., 1999; Li et al., 2000; Wong et al., 2000; Sin et al., 2002), have also been implicated in the signaling mechanisms induced by the binding of neurotrophins to p75NTR (Yamashita et al., 1999). p75NTR and ephrin ligands may also interact to modulate axon targeting through activation of signaling pathways that affect the actin cytoskeleton (Lim et al., 2008). Consequently, neurotrophins and their receptors may employ multiple interactive mechanisms to modulate the development of functional neuronal circuits. These interactive mechanisms remain open to further investigation.

A second molecule with which BDNF may collaborate, either directly or indirectly, in modulating synaptic connections at the target is the classical axon guidance molecule netrin-1. In the visual system, netrin-1 is involved in guiding retinal axons at the optic nerve head as they exit the eye (Deiner et al., 1997; Hopker et al., 1999), and possibly in axon target recognition at the optic tectum (Shewan et al., 2002). Recent evidence indicates that after successful targeting, netrin-1 also impacts axon arbor differentiation, through a

mechanism that involves deleted-in-colorectal cancer (DCC) receptor signaling (Manitt et al., 2009). Time-lapse imaging of fluorescently labeled retinal axons in live *Xenopus* tadpoles revealed that netrin treatment significantly increases the presynaptic and morphological differentiation of axons in their target optic tectum, similar to the effects of BDNF (Cohen-Cory and Fraser, 1995; Alsina et al., 2001). Even though both netrin and BDNF increase retinal ganglion cell axon arbor complexity, these two molecules influence the dynamic formation, elimination, and stabilization of branches and presynaptic sites in distinct manners. BDNF increases arbor complexity by the simultaneous addition and stabilization of both presynaptic sites and axon branches within two hours of treatment (Alsina et al., 2001). In contrast, netrin increases the complexity of the arbor by first adding presynaptic specializations followed by the induction of new branch formation, whereas it has no significant effect on synapse or branch stabilization. Given that BDNF and netrin share many of the same signaling mechanisms (Ming et al., 1999; Ming et al., 2002; Guirland et al., 2004; Jin et al., 2005), it is interesting that they can both produce complex axon arbors, but in their own distinct ways. It is possible that both molecules induce common signaling pathways to modulate axon arbor differentiation, but that there is a degree of fine tuning inherent to each molecule's signaling which allows for utilization of complementary dynamic strategies to reach a morphologically differentiated and stable arbor (Fig. 3). Future investigation will be necessary to understand how cues, like BDNF and netrin, might work in concert to shape neural circuit formation.

Concluding Remarks

Significant knowledge on the actions and functions of neurotrophins has been gathered in the last fifty years since the discovery of NGF, by Rita Levi-Montalcini and Stanley Cohen (for a very interesting, autobiographical account of this discovery read “In Praise of Imperfection” by Levi-Montalcini, 1989). The breakthrough that BDNF, a potent modulator of neuronal development in the CNS, is related to NGF (Leibrock et al., 1989), further advanced neurotrophin research. The cloning of additional members of the neurotrophin family, together with the identification of the Trk family of receptor tyrosine kinases as the high affinity receptors for neurotrophins, then rapidly transformed the field of developmental neuroscience and advanced the study of learning and memory and cognitive function. It is now evident that neurotrophins work in concert with many developmental signals to modulate synaptic development and plasticity in the CNS. One of these important interactions is the reciprocal regulation of neuronal activity and neurotrophic function. While we have not addressed these interactions directly in this review, this is a topic of great interest in neuroscience that has received significant attention in the last few years. For comprehensive reviews see Poo, 2001; Nagappan and Lu, 2005; Carvalho et al., 2008.

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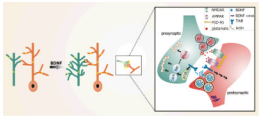

Figure 1.

Synthesis and release of BDNF, and molecular cascades that influence presynaptic structure. A simplified schematic view of BDNF action at sites of pre- and postsynaptic contact (yellow dots). Presynaptic activity induces glutamate release leading to the activation of postsynaptic NMDA (N-methyl-D-aspartate) and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors. Local BDNF mRNA, selectively transported into the spine, is translated and released in an activity dependent manner from the postsynaptic site. BDNF binds to presynaptic TrkB receptors and activates intracellular signal transduction pathways, influencing among many downstream signals the activity of the RhoGTPases, RhoA, Rac and Cdc42 which affect the actin cytoskeleton. Rac and Cdc42 are positive regulators that promote growth and branching, whereas RhoA is a negative regulator that causes the collapse of the growth cone. BDNF can also act in an autocrine fashion through postsynaptic TrkB. PSD-95, postsynaptic density protein 95; PI3K, Phosphatidylinositol 3-kinase.

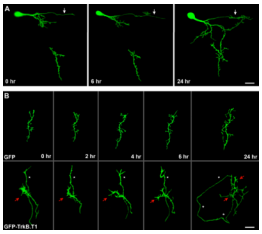

Figure 2.

The visual system of *Xenopus laevis* as a model to understand roles for BDNF during synaptic circuit formation in the living brain **(A)** Dynamic interactions between axon and dendritic terminals during retinotectal circuit development. A series of time-lapse confocal microscopy images of the optic tectum of a live, developing tadpole show the growth and arborization of a tectal neuron (*top*) and a retinal axon (*bottom*) both expressing GFP. Over time, the tectal neuron dendrites and the retinal axon actively and coordinately, branch and grow toward one another, as formation of the retinotectal circuit proceeds. This image series exemplifies the dynamic structural rearrangements occurring in presynaptic as well as postsynaptic neurons, a process that is modulated by BDNF (see Fig. 1 and also Alsina et al., 2001;Hu et al., 2005;Sanchez et al., 2006). The small white arrows point to the tectal neuron's axon. Scale bar = 20 μm. **(B)** TrkB signaling influences retinal axon growth cone morphology and branch initiation at the target. Representative retinal axons expressing GFP (*top*), or dominant negative TrkB tagged with GFP (GFP-TrkB.T1; *bottom*), illustrate the dynamic changes in axon growth cones as they begin to branch in the target optic tectum. Axons expressing dominant negative TrkB display dynamic behavior and growth cone morphologies that differ from the GFP expressing control axons. The two retinal axons expressing GFP-TrkB.T1 in this tadpole brain illustrate the variability in growth cone dynamics and structure. Axons may possess growth cones with uncharacteristically long filopodia and large lamellipodia (*red arrows*), or show dynamic growth cone behavior but fail to branch (*asterisks*). Axons that express dominant negative TrkB, and eventually branch, continue to bear multiple abnormal growth cone-like structures (*red arrows*; 24 hr). Interfering with TrkB signaling also results in axons with decreased density of presynaptic specializations and higher axon degeneration rate (for details see Marshak et al., 2007). Scale bar = 20 μm.

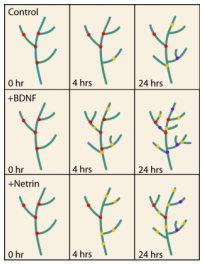

Figure 3. Neurotrophins and classical axon guidance cues are capable of inducing axonal differentiation in similar, yet distinct ways

BDNF and netrin-1 have a common, but unique ability to modulate retinal ganglion cell axon arbor complexity. This cartoon represents the change in arbor structure over time of retinal ganglion cell axons branching at their target, acutely treated with BDNF or netrin-1 (see Alsina et al., 2001 and Manitt et al., 2009). Red dots represent presynaptic specializations present before treatment, yellow represent newly added specializations and purple represents specializations added and stabilized over time. Both BDNF and netrin treated retinal axons significantly increase the complexity of their arbors by 24 hours following treatment. BDNF rapidly increases axon branch and presynaptic site formation and stabilization in the same time scale, while netrin increases presynaptic site addition and subsequent branching.