Neuropharmacology 76 (2014) 603–609

Contents lists available at SciVerse ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Invited review

Shaping neurons: Long and short range effects of mature and proBDNF signalling upon neuronal structure

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ARTICLE INFO

Article history:
Received 28 February 2013
Received in revised form
23 April 2013
Accepted 25 April 2013

Keywords:
BDNF
proBDNF
Neuronal morphology
Cytoskeleton
Rho GTPases
Signalling

ABSTRACT

Both mature BDNF and its precursor, proBDNF, play a crucial role in shaping neurons and contributing to the structural basis for neuronal connectivity. They do so in a largely opposing manner, and through differential engagement with their receptors. In this review, we will summarise the evidence that BDNF modulates neural circuit formation *in vivo* both within the central and peripheral nervous systems, through the control of neuronal morphology. The underlying intracellular mechanisms that translate BDNF signalling into changes of neuronal cell shape will be described. In addition, the signalling pathways that act either locally at the site of BDNF action, or over long distances to influence gene transcription will be discussed. These mechanisms begin to explain the diversity of actions that BDNF carries out on neuronal morphology.

This article is part of the Special Issue entitled 'BDNF Regulation of Synaptic Structure, Function, and Plasticity'.

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1. Introduction

The development of the peripheral nervous system (PNS) includes a phase of widespread programmed cell death in order to selectively maintain appropriate connections. During this period, neurons approaching the same target compete for limited amounts of target-derived survival factors, which accounts for the selective survival of those neurons that projected to the correct target (Levi-Montalcini, 1987). Neurotrophins, such as BDNF, act as target-derived growth factors. BDNF was originally isolated from pig brain (Barde et al., 1982) and represented the second member of the neurotrophin family after NGF. Neurotrophins mediate axonal growth and neuronal survival of select subpopulations of peripheral neurons, such as cultured chick embryonic dorsal root ganglia neurons (Lindsay et al., 1985). Accordingly, BDNF null mice display reduced cell numbers in a variety of sympathetic and sensory ganglia, including the trigeminal, vestibular, dorsal root and superior cervical ganglia (Ernfors et al., 1994). BDNF has been shown to act on the nervous system in multiple ways, including promoting the differentiation, survival, growth and arborisation of neurons, as well as strengthening synaptic function (Yano et al., 2006; Park and Poo, 2013).

Similar to other secreted factors, all neurotrophins, including BDNF, are initially synthesized as proneurotrophins, which are then cleaved by proteases to mature proteins of 118–120 amino acids (Chao and Bothwell, 2002). The prodomain of neurotrophins is essential for the correct folding of the mature ligand and for its targeting to the secretory pathway. In fact, a frequent human polymorphism within the BDNF prodomain, Val66Met, interferes with BDNF sorting to the regulated secretory pathway, and consequently leads to a reduced level of activity-dependent secretion of BDNF without affecting constitutive release (Chen et al., 2004; Egan et al., 2003). This is thought to be due to a disrupted interaction with the sorting receptor sortilin, which interacts with BDNF in a region encompassing the Val66Met substitution. Accordingly, downregulation of sortilin leads to a decrease in BDNF secretion from the regulated pathway, without affecting constitutive secretion (Chen et al., 2005). A separate study identified the carboxypeptidase E binding motif $I_{16}E_{18}I_{105}D_{106}$ within the mature domain of BDNF, and mutation of the acidic residues within this motif, or loss of carboxypeptidase E, also led to missorting of BDNF into the constitutive secretory pathway (Lou et al., 2005).

The prodomain of neurotrophins acts not only to aid in the folding and secretion of the mature neurotrophin, but the precursor can also act as an active signalling molecule itself. Intriguingly,

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http://dx.doi.org/10.1016/j.neuropharm.2013.04.054

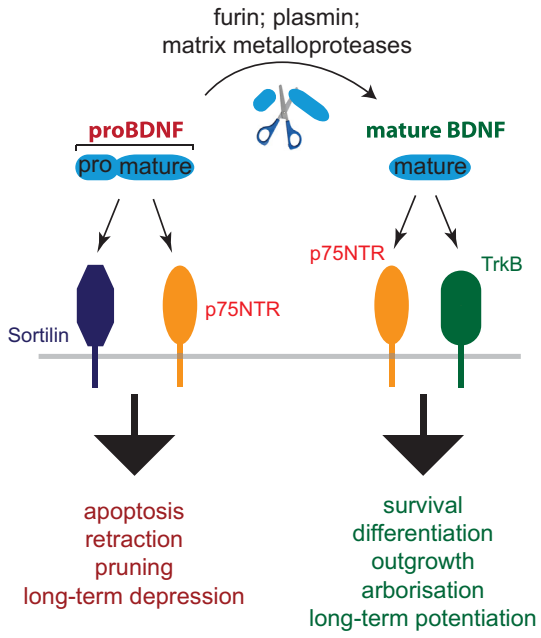


Fig. 1. Both BDNF and its precursor, proBDNF are biologically active. Mature BDNF is generated through elimination of the prodomain from the precursor, either intra- or extracellularly, and signals through TrkB to mediate neuronal growth and survival. Unprocessed proBDNF is also biologically active, signalling through p75NTR and Sortilin or related Vps10p family members to mediate process pruning and apoptosis.

proneurotrophins display largely opposing effects compared to their mature counterparts (Fig. 1) (Lu et al., 2005). The possible secretion of proBDNF was initially controversial (Matsumoto et al., 2008; Yang et al., 2009) due to detection issues, but a function for endogenous proBDNF during development is now established. For example, in contrast to the survival-promoting effects of target-derived mature BDNF, proBDNF can play an active role in developmental motor neuron programmed cell death and motor axon pruning of rejected connections (Je et al., 2012; Taylor et al., 2012). In addition, abundant evidence exists to show that proNGF is upregulated in a variety of injury and neurodegenerative paradigms, and both proneurotrophins can contribute to neuronal cell death (Friedman, 2010; Lee et al., 2001b; Teng et al., 2005, 2010).

The opposing actions of mature and proBDNF are mediated through differential receptor engagement. Mature BDNF preferentially binds and activates the receptor tyrosine kinase, TrkB. Activity-dependent release of synaptic BDNF acting on TrkB receptors results in enhanced synaptic transmission and synaptic plasticity (Nagappan and Lu, 2005; Park and Poo, 2013). In addition, BDNF can bind to the p75 pan-neurotrophin receptor ($p75^{NTR}$), a member of the tumour necrosis factor (TNF) family of transmembrane receptors. Like Fas and TNF receptor, $p75^{NTR}$ possesses a canonical death domain in its C-terminus. The precursor form proBDNF binds with high affinity to $p75^{NTR}$, and also engages sortilin and other members of the Vps10p family of sorting receptors, which are transmembrane proteins involved in protein trafficking (Fig. 1). Thus, the cellular responses to pro- and mature neurotrophins can either engage Trk receptors, $p75^{NTR}$ and sortilin family members (Teng et al., 2010) in different combinations.

In this chapter, we will describe the actions of the precursor and the mature forms of BDNF upon neuronal morphology. Specifically, we will discuss short-range responses to growth factors that modulate neuronal shape locally, together with signalling cascades that are relayed back to the soma, which utilize different Trk, $p75^{NTR}$ and sortilin family members.

2. Building the underlying scaffold – BDNF action on axonal and dendritic growth is context dependent

The activities of neurotrophins extend well beyond neuronal survival and death, and include the initiation of molecular mechanisms underlying neuronal growth and arborisation, as well as the strengthening of synaptic transmission (Park and Poo, 2013). The overlapping expression of multiple neurotrophin receptors and their cognate ligands allows for the creation and remodelling of multiple modes of connectivity, a process that extends into adulthood. A major mechanism is through the modulation of neuronal morphology (Fig. 2). BDNF and its precursor can signal through TrkB and $p75^{NTR}$ differentially to promote neural circuit formation. TrkB is widely expressed throughout the central nervous system (CNS), as well as in select populations of the PNS, such as parasympathetic and subpopulations of sensory neurons. The $p75^{NTR}$ protein, on the other hand, is expressed in most PNS neurons, but expression within the CNS is restricted to early development. Later on, $p75^{NTR}$ expression can be upregulated following injury, inflammation or traumatic circumstances (Lee et al., 2001a). Accordingly, genetic deletion of $p75^{NTR}$ in mice interferes with developmental axon pruning (Park et al., 2010; Singh et al., 2008) and ameliorates cell death after injury or damage (Harrington et al., 2004).

BDNF is best described for its ability to promote neuronal growth and as an activity dependent gene. A consequence is that the underlying structure allows a neuron to connect with multiple targets and to form elaborate networks affected by BDNF (Fig. 2A). For example, early experiments showed that treatment of organotypic slices of the ferret visual cortex with BDNF greatly enhances the dendritic complexity of layer 4 pyramidal neurons (McAllister et al., 1995). In addition, manipulating BDNF levels in the optic tectum of living *Xenopus laevis* tadpoles results in rapid changes in axonal complexity in retinal ganglion cells. Raising BDNF levels by supplementing exogenous BDNF leads to an increase in axonal arbour formation, while reducing BDNF by injecting blocking antibodies results in a decrease in complexity (Cohen-Cory and Fraser, 1995). In line with these experiments, targeted deletion of BDNF in mice from differentiated excitatory CNS neurons leads to neuronal growth defects. In this model, deficits in dendritic growth and spine density were observed most prominently in the striatum and to a lesser degree also in the hippocampus (Rauskolb et al., 2010).

These observations indicate that alterations in the amounts of BDNF can result in different morphological outcomes. Interestingly, raising retinal BDNF levels in *X. laevis* tadpoles has an opposing effect to that of raising tectal BDNF, in that retinal BDNF inhibits dendritic complexity of retinal ganglion cells, without affecting axonal arborisation (Lom et al., 2002). The fact that retinal ganglion cells thus respond differentially to BDNF depending on whether the signal was initiated at the post- or presynaptic site suggests that the location of signal initiation is crucial. This might be due to either differential expression of alternative receptors for BDNF, or to differential engagement of downstream signalling components as a result of distinct intracellular availability.

The mechanisms that foster process retraction and degeneration have been of considerable interest (Kaplan and Miller, 2003; Luo and O'Leary, 2005). A prominent example of differential BDNF action is on the degeneration of axons, which has been shown to take place in sympathetic neurons through binding to $p75^{NTR}$ (Singh et al., 2008). BDNF-induced axonal pruning in mouse superior cervical ganglion neurons requires activity-dependent secretion of BDNF. In this scenario, BDNF engages $p75^{NTR}$ in the absence of TrkB receptor expression to mediate developmental axon pruning (Fig. 2C). Specifically, activity-dependent BDNF synthesis by appropriately connected superior cervical ganglion axons has been postulated to

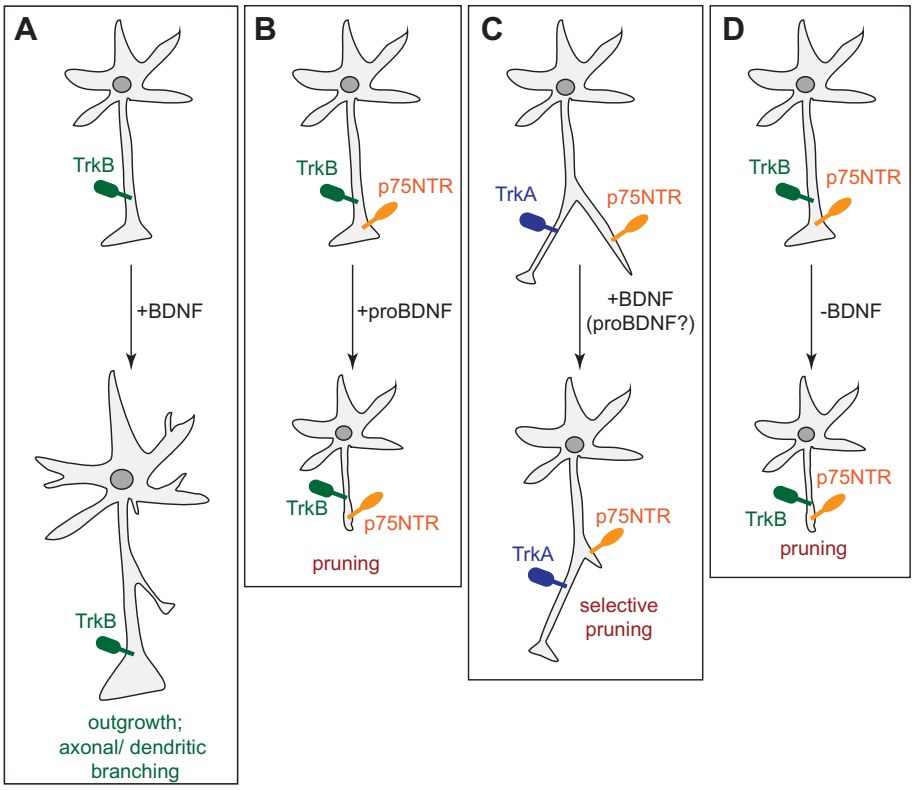


Fig. 2. Different modes of BDNF action on neuronal growth. (A) BDNF signals through TrkB to enhance axonal and dendritic growth and arborisation. (B) The BDNF precursor proBDNF has an opposing effect. It signals through p75NTR to decrease neurite outgrowth and initiate growth cone collapse. (C) In absence of TrkB, BDNF activates p75NTR to induce axonal pruning. (D) Sudden withdrawal of BDNF not only stops enhancing outgrowth, but also leads to dying back of axons.

initiate the degeneration of neighbouring, inactive axons via activation of $p75^{NTR}$ (Singh et al., 2008).

Although these studies show that BDNF binding to $p75^{NTR}$ exerts a negative effect upon sympathetic neurons in the absence of TrkB, proneurotrophins also play a role in degeneration or pruning. In dissociated chick retinal ganglion cells, axonal repulsion and reduced branching were facilitated by an interaction between $p75^{NTR}$ and the ephrinA ligand (Lim et al., 2008), a repellent cue. The BDNF precursor, proBDNF, was found to activate $p75^{NTR}$ and ephrinA5 to mediate axonal repulsion and reduce axonal arborisation (Marler et al., 2010) (Fig. 2B). Therefore, while BDNF binding to TrkB enhances retinal axon branching, proBDNF decreases the level of branching. Hence, the two forms of BDNF protein produce antagonistic results in the same population of retinal cells.

Another way that BDNF can shape neural circuits occurs after loss or sudden withdrawal of BDNF from sensory axons (Fig. 2D). A recent study demonstrated that sensory innervation of the mammary glands at early developmental stages depends upon sex hormone-dependent regulation of BDNF signalling. At E13, upregulation of gonad-derived androgen signalling in male embryos initiates mesenchymal expression of truncated TrkB (Liu et al., 2012), which sequesters the available BDNF and therefore blocks normal BDNF-TrkB signalling. Lack of growth-promoting BDNF-TrkB signalling in turn leads to degeneration of male sensory axons and ultimately to regression of mammary glands in the male embryos. Interestingly, the axonal degeneration observed in male, and not female, embryos was independent of apoptosis, arguing for a localised action. Thus, neurotrophin signalling can produce a sexually dimorphic pattern of sensory innervation leading to regression of neural circuits (Liu et al., 2012). An interesting question is whether in the absence of growth-promoting BDNF-signalling, there may be an active $p75^{NTR}$-dependent pruning mechanism operating to mediate the axonal degeneration that was observed in the male embryos.

3. Molecular mechanisms underlying BDNF action on growth and pruning

The intracellular mechanisms that BDNF uses to alternatively promote growth or pruning of axons depend upon the extent of TrkB or $p75^{NTR}$ activation. These mechanisms must feed into the cytoskeletal rearrangements required for axonal and dendritic outgrowth and arborisation. In the following sections, we will summarise recent work on the mechanisms that underlie axonal growth and growth arrest.

3.1. BDNF induces collateral branch formation via a combination of local and long-range signals

The formation and maintenance of axonal branches is tightly coupled to activity- dependent events. In this regard, BDNF provides an example of a highly regulated growth factor that links to intracellular processes to change axon structure. One pathway leading to collateral branching in cortical axons requires a combination of local and long-range signalling events to locally impact on microtubule function (Jeanneteau et al., 2010). In this mechanism, BDNF-mediated TrkB activation at the distal axon was shown to induce a retrograde Erk1/2 signal, which in turn activates immediate early gene transcription in the nucleus. Among the multiple immediate early genes induced by BDNF signalling is a MAPK phosphatase, MKP-1 (DUSP1). Basal MKP-1 expression is low both *in vitro* and *in vivo*, but BDNF-Erk1/2 signalling induces a quick rise in MKP-1 protein levels, followed by rapid turnover through the ubiquitin/proteasome pathway (Brondello et al., 1999). However, in

addition to initiating MKP-1 protein synthesis, continuing BDNF-Erk1/2 signalling also results in MKP-1 phosphorylation locally, which interferes with MKP-1 degradation.

One target of MKP-1 action in neurons is c-Jun N-terminal kinase (JNK). Prolonged MKP-1 activity locally shuts down JNK activity near sites of continuing BDNF signalling and thus affects the phosphorylation status of JNK substrates (Jeanneteau et al., 2010), many of which are involved in cytoskeletal dynamics. Indeed, lack of JNK activity leads to decreased microtubule stability and increased microtubule dynamics in a temporally and spatially controlled manner. Therefore, MKP-1 provides a tightly regulated signalling mechanism for promoting local cytoskeletal remodelling that is required for collateral branch formation (Jeanneteau and Deinhardt, 2011; Jeanneteau et al., 2010). The action of MKP-1 downstream of BDNF provides a dual role for BDNF signalling in axonal branch formation. First, BDNF initiates immediate early gene activation. This leads to transcriptional and translational changes that have the potential to affect the morphology of the neuron. Second, long lasting BDNF-TrkB signalling leads to the stabilisation and continued activity of MKP-1, an immediate early gene product that acts proximal to the site of signal initiation (Fig. 3A). The stabilisation of MKP-1 by activity-dependent BDNF explains the ability of BDNF to act in a localized manner in neurons.

A closely related neurotrophin, NT-3, displays another mechanism for promoting branching and growth of processes through increasing the levels of β-catenin (Kundel et al., 2009), a component of the Wnt signalling pathway and of cadherin-based adherens junctions (Valenta et al., 2012). NT-3 activates the local translation of β-catenin in hippocampal neurons, specifically in growth cones to increase growth (Kundel et al., 2009). Interestingly, NT-3 binds not only to TrkC receptors, but also to TrkB and $p75^{NTR}$ receptors. proNT-3 acts similarly to proBDNF in promoting cell death of sympathetic neurons (Yano et al., 2009). In addition, it is likely protein synthesis-dependent processes are regulated by mature neurotrophins to influence neuronal morphogenesis.

3.2. BDNF-$p75^{NTR}$ signalling induces axonal degeneration, but not cell death

In addition to axonal growth, BDNF can mediate degeneration of sympathetic axons, which express the NGF-receptor TrkA and $p75^{NTR}$. Interestingly, sympathetic neurons do not express the BDNF receptor TrkB. Nevertheless, BDNF can be secreted from active axons to exclusively signal via $p75^{NTR}$. The two receptors in sympathetic neurons, $p75^{NTR}$ and TrkA, can form high affinity binding sites for NGF depending upon the ratio of the two receptors

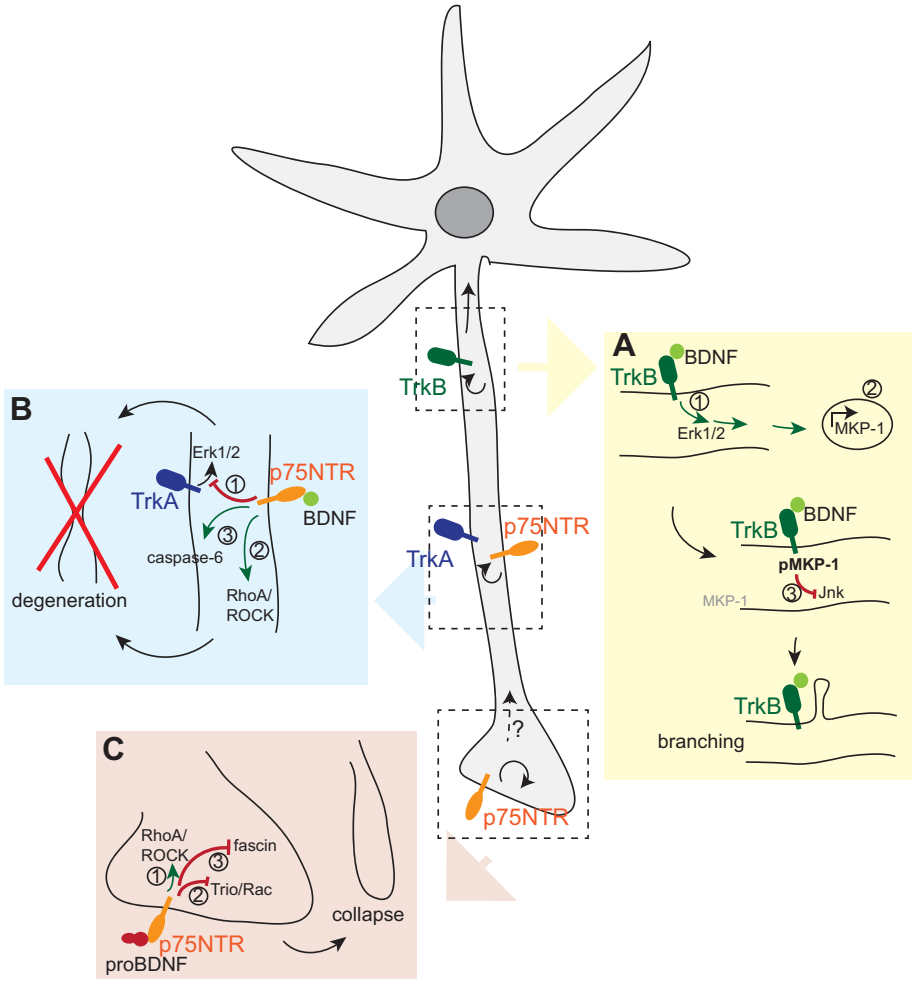


Fig. 3. Intracellular mechanisms of BDNF action on neuronal morphology. BDNF and its precursor signal locally (curved arrows) as well as over long distances (straight arrows) to modify neuronal morphology. (A) BDNF-TrkB elicit a retrograde Erk1/2 signal (1) to initiate immediate early gene expression (2). Continuing BDNF-TrkB signalling stabilises one of the immediate early genes, MKP-1, through phosphorylation and thus locally inhibits Jnk signalling (3), leading to collateral branch formation. (B) In absence of TrkB, BDNF signals through p75NTR to (1) dampen TrkA signaling, (2) activate the RhoA/ROCK pathway and (3) activate caspase-6 to initiate axonal degeneration. (C) ProBDNF signals through p75NTR to (1) activate the RhoA-ROCK pathway or inactivate (2) Rac and (3) fascin to initiate growth cone collapse.

(Chao and Hempstead, 1995; Hempstead et al., 1991). However, BDNF can act through $p75^{NTR}$ alone, which accumulates within the inactive, degenerating axon, where it can suppress NGF-TrkA signals (Singh et al., 2008) (Fig. 3B). This produces an alternative consequence, in which Erk1/2 activation is reduced in response to the sympathetic *bona fide* trophic factor, NGF. In this scenario, the BDNF-$p75^{NTR}$ signal is restricted to the degenerating axon, where the target-derived growth signal is suppressed. On the other hand, the surviving axon remains intact and is appropriately connected.

Another mechanism of negative control of axonal growth involves components of myelin, which are largely responsible for inhibitory signalling during regeneration (Filbin, 2003). BDNF-$p75^{NTR}$ signalling plays a role in myelin-induced axonal degeneration of sympathetic axons. In limiting amounts of NGF, sympathetic axons retract when grown on myelin. This is a localised phenomenon, as the degeneration is limited to the axon segment in direct contact with myelin, and does not spread to affect the entire axon. Myelin/BDNF/$p75^{NTR}$ signalling was shown to activate the RhoA-ROCK-cofilin pathway (Park et al., 2010), which mediates axonal retraction (Fig. 3B). The Rho family of GTPases, Rho, Rac and Cdc42, are regulators of the actin cytoskeleton and directly influences neurite growth (Hall, 2005; Murakoshi et al., 2011). Interestingly, blocking the RhoA pathway inhibited axonal degeneration, but did not rescue BDNF-$p75^{NTR}$/myelin-induced growth inhibition. Similarly, BDNF also led to caspase-6 activation, and blocking caspase activity rescued degeneration, but not the myelin-induced growth inhibition. Therefore, BDNF-$p75^{NTR}$ signalling can potentially lead to axonal degeneration via multiple pathways. In this instance, $p75^{NTR}$ signalling predominates over Trk tyrosine kinase activity.

3.3. ProBDNF discourages outgrowth

Proneurotrophins have been shown to inhibit neurite outgrowth and to collapse neuronal growth cones in dorsal root ganglia neurons, cortical and hippocampal neurons (Deinhardt et al., 2011; Sun et al., 2012). The growth inhibiting activities assigned to mature BDNF signalling through $p75^{NTR}$ may also be a consequence of the precursor to BDNF rather than mature BDNF, which promotes growth cone turning and growth. The responses of growth cones to proBDNF and mature BDNF are at least partially derived from local protein synthesis. For example, BDNF initiates phosphorylation of mRNA binding proteins such as zipcode binding protein, thus leading to local translation of β-actin to stimulate BDNF-induced growth cone turning (Sasaki et al., 2010).

Interestingly, hippocampal neurons secrete pro- rather than mature BDNF in response to activity (Pang et al., 2004), raising the possibility that a pruning signal may be initiated by the precursor of BDNF. Proneurotrophins achieve their growth-dampening action by signalling to the actin cytoskeleton. ProNGF for example signals through a complex of $p75^{NTR}$ and the Vps10p-domain containing sorting receptor, SorCS2, to mediate growth cone collapse in cultured hippocampal neurons (Deinhardt et al., 2011). Downstream of proNGF, the Rac activator Trio dissociates from the receptor complex, thus leading to a decrease in active Rac, which is a member of the family of Rho GTPases that normally mediates actin filament assembly and growth. In parallel, proNGF binding also leads to an inactivation of the actin filament bundling protein fascin, thus destabilising existing filaments. The combination of both proneurotrophin activities initiates a robust growth cone collapse response (Deinhardt et al., 2011) (Fig. 3C). These mechanisms are equally activated downstream of proBDNF, suggesting that in certain scenarios, proneurotrophins may substitute for each other. An alternative mechanism of proBDNF action on the actin cytoskeleton is the activation of the RhoA/ROCK/cofilin pathway downstream of $p75^{NTR}$ (Sun et al., 2012), which is also activated in sympathetic axon degeneration (Park et al., 2010). RhoA signalling led to a decrease in neurite outgrowth both in DRG and cortical neurons in response to proBDNF (Sun et al., 2012) (Fig. 3C). Interestingly, local axonal RhoA protein synthesis is required for growth cone collapse in response to the guidance molecule, semaphorin 3A (Wu et al., 2005), raising the possibility that local translation may also be part of the proneurotrophin response.

4. Building synapses – molecular mechanisms underlying BDNF-mediated filopodia and spine formation

The conversion of pro- to mature BDNF occurs through many different proteolytic mechanisms. A prominent mechanism is via the tissue plasminogen activator (tPA)/plasmin system, which has potent enzymatic activity that cleaves proBDNF to mature BDNF. It is also critically required for the late-phase long-term potentiation (L-LTP) of hippocampal synapses (Baranes et al., 1998; Pang et al., 2004). Accordingly, reduced levels of BDNF as well as the lack of the plasmin precursor, plasminogen, or its activator, tPA abolish the expression of L-LTP (Pang et al., 2004). This suggests that BDNF is released in its proform upon neuronal activity in hippocampal neurons. Interestingly, a complementary study showed that proBDNF-$p75^{NTR}$ signalling promotes hippocampal long-term depression (LTD) (Woo et al., 2005). However, LTD was found to be unaffected in slices prepared from mice lacking BDNF in excitatory neurons (Matsumoto et al., 2008), suggesting that the source of proBDNF might be non-neuronal. Together, these studies suggest a bidirectional control for pro- and mature BDNF in hippocampal synaptic plasticity. In fact, tPA was found to be co-released with proBDNF during a high-frequency stimulation, but not during low frequency stimulation, implying that the relative extracellular amount of pro- versus mature BDNF is controlled through the regulated secretion of converting proteases in response to neuronal activity (Nagappan et al., 2009). This allows for a spatially tightly controlled mechanism to regulate pro- versus mature BDNF action at individual synapses, and thus the precise strengthening or weakening of synaptic connections. This is at least in part achieved through changes in the underlying structure.

4.1. BDNF enhances filopodial growth and dendritic spine formation

In addition to promoting or inhibiting growth and branching of entire axons and dendrites, BDNF and proBDNF also differentially modulate finer structures, such as spines, that form the basis of connectivity in established neurons. They do so largely by signalling to the actin cytoskeleton. For example, BDNF-TrkB activates Erk1/2 signalling, which leads to the phosphorylation and thus inactivation of the actin capping protein, Eps8. This in turn disinhibits actin filament growth and thus increases the number of axonal filopodia in hippocampal neurons (Menna et al., 2009). A second study showed that BDNF/TrkB signalling enhances dendritic filopodial motility through a phosphatidylinositol–3 kinase dependent pathway (Luikart et al., 2008). Filopodia are largely thought to be the precursors of synaptic contacts, with dendritic filopodia maturing into spines and axonal filopodia maturing into presynaptic specialisations upon stabilisation. Thus, enhanced filopodial activity may amplify the number of synaptogenic contacts and therefore precede increased synaptic connectivity. Moreover, it was shown that BDNF stimulates the growth of existing dendritic spine heads, which is correlated with a strengthening of the synaptic contact. It does so by stimulating a Rac activator, the guanine nucleotide exchange factor Vav2, therefore leading to increased Rac activity. Conversely, deletion of Vav impairs spine head growth and leads to deficits in hippocampal long-term plasticity (Hale et al., 2011).

4.2. proBDNF reduces dendritic spine formation

Since an increase in active Rac downstream of BDNF leads to spine head growth in mature hippocampal cultures, and proBDNF leads to a decrease of Rac activity in young hippocampal neurons, it is tempting to speculate the proBDNF may have adverse effects on spines in a more mature system. Indeed, application of a cleavage-resistant version of proBDNF to mature hippocampal cultures leads to a decrease in spine density over the course of two to three days, while mature BDNF increases spine density in the same setting (Koshimizu et al., 2009). The decrease in spine density is accompanied by a decrease in the amplitude of synaptic currents, and requires $p75^{NTR}$ (Koshimizu et al., 2009). Curiously, Rac activity was increased rather than decreased downstream of proBDNF in cerebellar granule neurons, and was accompanied by activation of JNK and caspase-3 to initiate cell death (Koshimizu et al., 2010). These differences observed may either be a consequence of different cell types assessed, or of the severity of the insult to the neuron. ProBDNF has been found to be capable of initiating apoptosis in peripheral neurons (Teng et al., 2005), and proNGF induces cell death in the hippocampus following seizures (Le and Friedman, 2012; Volosin et al., 2008). However, proneurotrophin effects upon neuronal morphology do not necessarily lead to cell death (Deinhardt et al., 2011). Additionally, in hippocampal neurons the activation of JNK and caspase-3 has been shown to function in the removal of synaptic AMPA receptors during the depression of synapses and for the generation of LTD (Li et al., 2010; Zhu et al., 2005). Therefore, in hippocampal neurons the activation of the Rac-Jnk and caspase pathways by proBDNF might affect synaptic efficacy independently of inducing apoptosis and of proBDNF's action on synaptic structure.

5. Conclusions

We have discussed the roles of BDNF and its precursor in modulating neuronal connectivity through modifying the morphology of individual neurons. BDNF's growth promoting effects have been well characterised in the past, and comprise both local activities to fine-tune the structure, such as in the case of locally activating Rac to promote spine head growth and inactivating eps8 to initiate filopodia formation. In addition, BDNF signalling also triggers a robust transcriptional response, as well as local translational events, which in turn have the potential to affect the morphology and physiology of the entire cell, including sites distant to the initial signal. Therefore, a combination of local and long-range signals may ultimately determine the cellular response, such as in the case of MKP-1 induction to promote axonal branch formation.

In contrast, the degeneration signals initiated by BDNF, such as the activation of RhoA/ROCK pathway, are largely locally restricted. For example, selectively the part of the axon growing on myelin degenerates, or the less active axon is pruned, without affecting growth in other areas of the cell. Similarly, proBDNF acts specifically on the growth cone or spine. To what extend proneurotrophins also signal over long distances to prime a whole cellular response on morphology, as they do to initiate apoptosis, remains to be investigated.

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