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REVIEW

Activity-dependent dendritic secretion of brain-derived neurotrophic factor modulates synaptic plasticity

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Abstract

During the last decade, a major role has emerged for brain-derived neurotrophic factor (BDNF) in the translation of intrinsic or sensory-driven synaptic activities into the neuronal network plasticity that sculpts neural circuits. BDNF is released from dendrites and axons in response to synaptic activity and modulates many aspects of synaptic function. Although the importance of BDNF in synaptic plasticity has been clearly established, direct evidence for a specific contribution of the activity-dependent dendritic secretion of BDNF has been difficult to obtain. This review summarizes recent advances that have established specific effects of postsynaptic BDNF secretion on synapse efficacy and development. We will also discuss these data in the light of their functional and pathological significance.

Introduction

The activity-dependent regulation of synaptic efficacy is one of the mechanisms that enable neuronal networks to develop appropriate connections or form memories. Modifications of synaptic efficacy also contribute to the progression of pathological conditions. One strategy developed by many neurons to modulate synapse formation and function is to release substances from their cell bodies and dendrites in response to synaptic activity. This target-derived messenger strategy enables the delivery of appropriate amounts of messenger 'on demand' according to the level and/or pattern of postsynaptic neuronal activity. The messenger can be released locally or globally to control the refinement and strength of synaptic connections. This strategy further allows the postsynaptic target to act on both active and inactive synapses.

Brain-derived neurotrophic factor (BDNF) belongs to the neurotrophin family of structurally related proteins originally identified as a crucial target-derived neuronal survival factor (Barde *et al.*, 1982). Since this pioneering observation, in addition to its role in promoting the proliferation and differentiation of neurons, BDNF has been shown to contribute to synaptic plasticity through both functional and structural changes (Lu *et al.*, 2005; Gottmann *et al.*, 2009). Meanwhile, several studies using the over-expression of tagged BDNF have shown that this neurotrophin is released from neurons in an activity-dependent manner (Lessmann & Brigadski, 2009). These findings have led to the hypothesis that BDNF acts as a target-derived messenger in synaptic plasticity and development. However, both dendrites (Kolarow *et al.*, 2007) and axons (Kohara *et al.*, 2001) release BDNF and in many early studies it was difficult to determine the source of release. Direct evidence for a role of the activity-dependent dendritic secretion of BDNF in synaptic plasticity and development has been obtained only recently in studies in which the postsynaptic expression or release of BDNF has been selectively eliminated or enhanced.

The mechanism of BDNF release, processing and action has been reviewed previously (Lu *et al.*, 2005; Gottmann *et al.*, 2009) and is beyond the scope of this article. Here, we summarize current advances in establishing the impact that postsynaptic BDNF secretion has on synapse development and function both during development and in the adult central nervous system. We will also highlight recent evidence suggesting a sub-cellular postsynaptic compartmentalization of postsynaptic BDNF secretion. Finally we will consider the physiological role of activity-dependent postsynaptic BDNF secretion.

Brain-derived neurotrophic factor is an activity-dependent and target-derived messenger of synaptic plasticity

To be considered as a target-derived messenger of synaptic plasticity, a molecule should satisfy at least two criteria. The first criterion that must be satisfied is that the appropriate machinery for synthesis and release of the molecule is present in the postsynaptic neuron. A dendritic localization of BDNF mRNA transcripts has been reported previously (Chiaruttini *et al.*, 2008). Moreover, alterations of dendritic mRNA targeting lead to a local decrease in dendritic BDNF level (An *et al.*, 2008; Chiaruttini *et al.*, 2009), demonstrating a local dendritic synthesis of BDNF. The sub-cellular distribution of endogenous BDNF has been difficult to study because of the low level of the protein. However, a patchy dendritic and axonal distribution was reported for endogenous BDNF in dissociated neuronal cultures where detection is more sensitive (Brigadski *et al.*, 2005; Adachi *et al.*, 2005).

The over-expression of green fluorescent protein-tagged BDNF (BDNF-GFP) in neuronal culture has been used to obtain evidence regarding its sub-cellular localization. Although the expression of tagged protein may have altered binding to sorting partners, the distribution of BDNF-GFP is similar to that observed for endogenous

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BDNF, i.e. a dendritic and axonal patchy distribution (Hartmann *et al.*, 2001; Adachi *et al.*, 2005). In the dendrites, BDNF-GFP is packaged into secretory granules of the regulated pathway of secretion (Gottmann *et al.*, 2009), thus suggesting that dendritic secretion of BDNF can occur. This was confirmed using BDNF-GFP expression combined with time-lapse fluorescence imaging in dissociated neuronal cultures. Several different synaptic signals leading to the Ca^{2+}-dependent dendritic release of BDNF have been directly identified in neuronal cultures (Fig. 1): (i) tetanic stimulation of presynaptic glutamatergic fibres and subsequent activation of ionotropic glutamatergic receptors (Hartmann *et al.*, 2001); (ii) prolonged depolarization of the postsynaptic neurons (Magby *et al.*, 2006); (iii) action potentials that propagate backwards into the dendrites (Kuczewski *et al.*, 2008b; Matsuda *et al.*, 2009); and (iv) activation of metabotropic glutamate (Canossa *et al.*, 2001) and γ-aminobutyric acid (GABA) (Fiorentino *et al.*, 2009) receptors. This approach was also extremely useful to study the intracellular signalling cascades that mediate BDNF secretion (Lessmann *et al.*, 2003; Lessmann & Brigadski, 2009). Depending on the location of the release site and/or stimuli used, several sources of Ca^{2+} contribute to BDNF release: *N*-methyl-D-aspartate (NMDA) channels, voltage-dependent Ca^{2+} channels and intracellular Ca^{2+} stores (Fig. 1). Such diversity in the Ca^{2+} source leading to BDNF secretion again supports the idea that multiple modalities of neuronal BDNF secretion can coexist.

The expression of fluorescent protein-tagged BDNF has also been used to demonstrate the activity-dependent axonal secretion of BDNF. In a seminal study, Kohara *et al.* (2001) used a micropipette to transfect individual cells with a plasmid encoding either BDNF-GFP or a non-releasable red fluorescent protein. Only one neuron per culture was injected. At 2 days after the transfection, the authors found that the axon of the BDNF-GFP/red fluorescent protein-expressing neuron was surrounding newly fluorescent BDNF-GFP-positive soma. The number of these newly BDNF-GFP-positive soma was reduced in cultures treated with the BDNF scavenger tropomyosin-related kinase (type B) (TrkB)-IgG or when the level of synaptic activity was decreased with tetrodotoxin. Thus, BDNF is secreted from the axons in an activity-dependent manner and can move trans-synaptically to postsynaptic neurons. In a recent study using BDNF tagged with a pH-sensitive form of the green fluorescent protein, the pHluorin, Matsuda *et al.* (2009) found that brief spiking activity in cultured hippocampal neurons triggered transient fusion pore opening, followed by immediate retrieval of BDNF-containing granules in the axon. In contrast, the same spiking activity induced a complete granular fusion in the dendrites, suggesting that the postsynaptic cell is the main source of secreted BDNF. A similar complete dendritic secretion and partial axonal secretion of BDNF-pHluorin has been observed when the neuronal cultures were depolarized with high potassium concentration (Dean *et al.*, 2009). Matsuda *et al.* (2009) further showed that a brief period of theta burst stimulation, a protocol frequently used to trigger long-term potentiation at glutamatergic synapses, was highly effective for inducing dendritic secretion of BDNF but was ineffective at the axon, again suggesting a predominant dendritic secretion. This issue is, however, not yet clear. Indeed, the activity-dependent presynaptic release of endogenous BDNF has been revealed in rat hippocampal organotypic slice cultures. Thus, theta burst stimulation of Schaffer collaterals or mossy fibres in the presence of glutamatergic and GABAergic receptor antagonists evokes a postsynaptic current in, respectively, CA1 (Amaral & Pozzo-Miller, 2007) and CA3 (Li *et al.*, 2010) pyramidal neurons that was sensitive to the BDNF scavenger TrkB-IgG. Moreover, both the presynaptic secretion of BDNF from the Schaffer collaterals (Zakharenko *et al.*, 2003) and postsynaptic expression in the CA1 pyramidal neurons (An *et al.*, 2008) have been reported to be crucial for the induction of theta burst stimulation-induced long-term potentiation in the CA1 hippocampus.

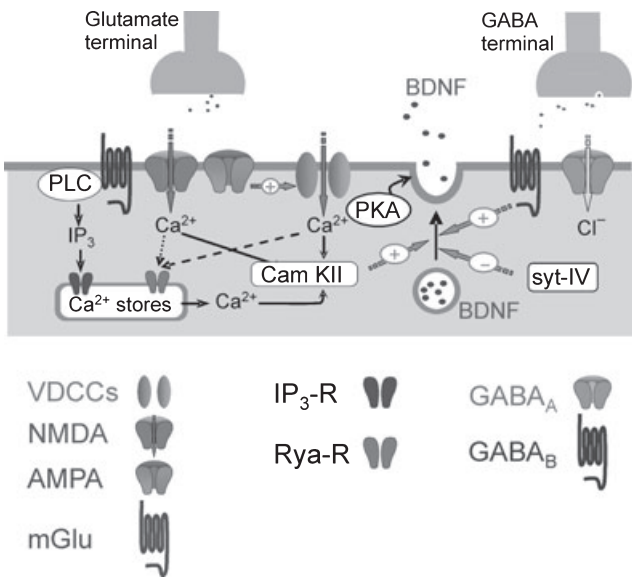

FIG. 1. Mechanism of dendritic BDNF secretion and synaptic triggers. BDNF secretion requires a postsynaptic rise in intracellular Ca^{2+} concentration. This Ca^{2+} rise can result from an influx through voltage-dependent Ca^{2+} channels (VDCCs) or *N*-methyl-D-aspartate (NMDA) receptors upon membrane depolarization, or from the activation of internal Ca^{2+} stores (Inositol trisphosphate receptor, IP_3-R) following the activation of metabotropic glutamatergic (mGlu) receptors. The initial Ca^{2+} rise can be amplified by Ca^{2+}-induced Ca^{2+} secretion via ryanodine receptors (Rya-Rs). Ca^{2+} activates Calcium/Calmodulin-dependent kinase II (CamKII) leading to the fusion of secretory granules. Basal levels of Protein kinase A (PKA) activation 'gate' BDNF secretion. The activation of metabotropic $GABA_B$ receptors also triggers a secretion of BDNF through an as yet unknown mechanism. The postsynaptic release of BDNF is inhibited by a membrane trafficking protein, synaptotagmin-IV (syt-IV). PLC, phospholipase C.

The second criterion that must be satisfied to consider a molecule as a target-derived messenger is that modifications of the synthesis or release of the molecule from the postsynaptic neuron have biological effects. Single cell over-expression or knock-out of BDNF in dissociated neuronal or organotypic slice cultures are tools used to test this criterion. Neurons over-expressing BDNF within cortical organotypic slice cultures exhibit a more complex dendritic arborization when compared with control neurons (Horch *et al.*, 1999; Wirth *et al.*, 2003). Using the same approach, Horch & Katz (2002) further showed that BDNF released from dendrites and soma of 'donor' BDNF-expressing cells acts directly on nearby 'recipient' neurons to increase their dendritic branching These effects were prevented by TrkB-IgG (i.e. extracellular scavengers of released BDNF), showing that released BDNF can act in an autocrine and paracrine manner to modulate dendritic development. A similar approach was used to show that BDNF released from postsynaptic

target neurons can increase the presynaptic expression of Glutamate decarboxylase 65 (GAD65) and GABAergic synaptic activity (Ohba *et al.*, 2005; Singh *et al.*, 2006). In contrast, when a small number of BDNF-deficient neurons is created by single-cell gene knock-out in organotypic slice cultures of visual cortex, the number of GAD65-positive terminals established on these neurons as well as miniature GABAergic activity are reduced (Kohara *et al.*, 2007). A similar decrease in the number of presynaptic GABAergic terminals and level of miniature GABAergic synaptic activity has been observed after a selective deletion of the gene promoter IV that controls the activity-dependent synthesis of BDNF (Hong *et al.*, 2008).

Glutamatergic as well as GABAergic synaptic transmission is modulated by the postsynaptic secretion of BDNF. Altered spine morphology and a selective impairment of dendritic glutamatergic long-term potentiation are observed in mutant mice in which the level of dendritic BDNF protein was selectively reduced (An *et al.*, 2008). A loss-of-function strategy also demonstrates that BDNF released from one target neuron can selectively modify the rate of vesicle exocytosis from presynaptic fibres contacting that neuron. Thus, in a study aimed at determining the function of synaptotagmin-IV, Dean *et al.* (2009) found that synaptotagmin-IV colocalizes with dendritic and axonal BDNF-containing granules and negatively regulates BDNF secretion. Using a coculture assay, in which 5% of the cultured neurons were derived from synaptotagmin-IV knock-out mice and the remaining 95% from wild type, the authors showed that BDNF released from a target neuron could control presynaptic vesicle dynamics (Dean *et al.*, 2009).

Another tool to investigate the activity-dependent postsynaptic release of endogenous BDNF is to monitor functional or morphological changes as an assay for endogenous BDNF release after stimulations of single cells. This approach provides information on endogenous BDNF secretion and action. Using this approach, it has been shown that back-propagating action potentials in CA3 pyramidal neurons induce a BDNF-dependent potentiation of GABAergic synapses in newborn hippocampal slices (Gubellini *et al.*, 2001; 2005). A BDNF-dependent persistent enhancement of GABA release at developing mossy fibres has also been reported when the stimulation of these fibres is coincident with postsynaptic action potentials generated in the target CA3 hippocampal neurons (Sivakumaran *et al.*, 2009). As this plasticity is prevented in neurons loaded with 1,2-bis (o-aminophenoxy)ethane-N,N,N′,N′-tetra-acetic acid, a chelator Ca^{2+}, by L-type voltage-dependent Ca^{2+} channel blockers, or in the presence of extracellular TrkB-IgG, it was proposed that the Ca^{2+}-dependent release of native BDNF from the target pyramidal neurons is required to trigger GABAergic plasticity (Fig. 2). Using a similar approach, Magby *et al.* (2006) have demonstrated that a tonic depolarization of one single hippocampal neuron in culture elicits a potentiation of glutamatergic transmission. The induction of this potentiation is prevented by a postsynaptic disruption of $[Ca^{2+}]_i$ rise or BDNF release (Fig. 2). Finally, Tanaka *et al.* (2008) have shown that repetitive pairing of postsynaptic spikes with glutamate uncaging triggers a long-lasting structural spine plasticity prevented by the BDNF scavenger TrkB-IgG (Fig. 2). Moreover, although bath-applied BDNF does not by itself alter spine morphology, it results in long-lasting spine plasticity when paired with glutamate uncaging. Thus, exogenous BDNF is able to replace postsynaptic spikes, supporting the idea that a postsynaptic secretion of BDNF during the spike-timing protocol is required to induce long-lasting changes in spine morphology.

Collectively, these observations show that BDNF fulfils the criteria to qualify as a target-derived messenger and that, once released from the target, BDNF can modulate many aspects of synapse development and function.

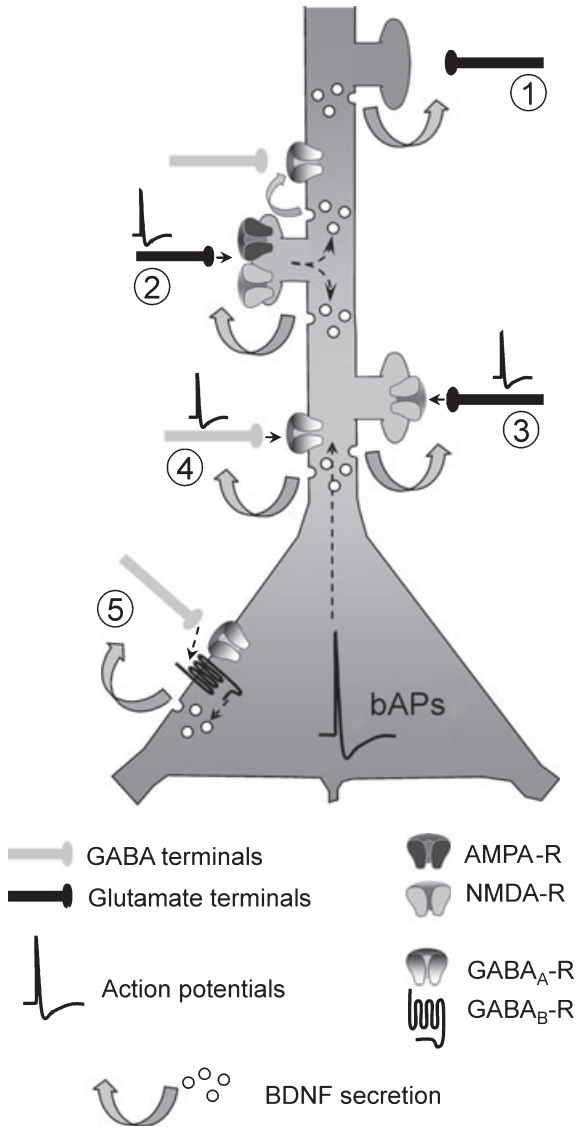

FIG. 2. Multiple sites of postsynaptic BDNF secretion and consequences on glutamatergic and GABAergic synapses. (1) A prolonged postsynaptic depolarization elicits a calcium-dependent postsynaptic release of BDNF that enhances glutamate release probability acting on presynaptic TrkB receptors (Magby *et al.*, 2006). (2) Synaptic activation of AMPA and/or *N*-methyl-D-aspartate (NMDA) receptors elicits a calcium-dependent postsynaptic secretion of BDNF that potentiates glutamatergic synaptic transmission (Hartmann *et al.*, 2001; An *et al.*, 2008). BDNF secreted after the synaptic activation of AMPA and/or NMDA receptors can also potentiate GABAergic synaptic transmission acting of postsynaptic (Kuczewski *et al.*, 2008a) or presynaptic (Liu *et al.*, 2007) TrkB receptors. (3) Pairing presynaptic back-propagating action potentials (bAPs) with NMDA receptor activation triggers a calcium-dependent postsynaptic release of BDNF leading to a selective postsynaptic spine enlargement (Tanaka *et al.*, 2008). (4) bAPs paired (Sivakumaran *et al.*, 2009) or not (Gubellini *et al.*, 2005) with presynaptic stimulation trigger a BDNF-dependent potentiation of GABAergic synaptic transmission. (5) Activation of metabotropic $GABA_B$ receptor elicits a calcium-dependent postsynaptic release of BDNF that promotes the formation of functional perisomatic GABAergic synapses (Fiorentino *et al.*, 2009).

Postsynaptic compartmentalization of brain-derived neurotrophic factor synthesis, secretion and actions

The regulated activity-dependent postsynaptic secretion of BDNF can therefore modulate multiple processes that are important for synaptic plasticity in the developing and adult central nervous system.

However, BDNF diffusion is very limited due to its sticky nature (the isoelectric point of BDNF is roughly 10, so that the molecule is positively charged at physiological pH and, hence, strongly interacts with surrounding negatively charged molecules). The presence of full or truncated TrkB receptors, which can bind and internalize BDNF, further restricts BDNF diffusion. Therefore, to function biologically, BDNF has to be released near the target. Given the large number of segregated terminals along the somato-dendritic axis, these observations suggest that multiple postsynaptic sites of BDNF secretion coexist. Depending on the pattern of synaptic activity, these multiple sites of release enable BDNF to selectively control the development of different sub-populations of synapses and neurons.

Direct proof of the compartmentally restricted dendritic secretion of BDNF is lacking and awaits real-time imaging of BDNF-GFP release in brain slices. However, different BDNF mRNA transcripts generated by the neurons are targeted to distinct cellular compartments (Chiaruttini *et al.*, 2008; An *et al.*, 2008; Chiaruttini *et al.*, 2009) and in mutant mice, where the dendritic targeting of BDNF mRNA is selectively impaired, long-term potentiation of distal, but not proximal, glutamatergic synapses of hippocampal neurons is impaired (An *et al.*, 2008). Given the important role of BDNF in GABAergic synapse development, it will be interesting in future experiments to investigate the fate of dendritic and perisomatic GABAergic synaptic transmission in these mutant mice. In mutant mice in which the activity-dependent expression of BDNF has been selectively down-regulated, the development of cortical GABAergic innervation is selectively impaired, with no effect on the number of glutamatergic synapses or the extent of dendritic arborization (Hong *et al.*, 2008). Therefore, the selective local targeting and expression of BDNF transcripts along the somato-dendritic axis might be a mechanism used by neurons to deliver BDNF protein to specific sub-sets of synapses.

In agreement with a sub-cellular compartmentalization of postsynaptic BDNF release, time-lapse fluorescence imaging studies have shown that the synaptic activation of ionotropic glutamatergic (Hartmann *et al.*, 2001) or metabotropic $GABA_B$ (Fiorentino *et al.*, 2009) receptors can induce a postsynaptic secretion of BDNF in neuronal cultures (Fig. 2). Interestingly, mutant mice that display a complete loss of functional $GABA_B$ receptors exhibit a BDNF-dependent reduction in perisomatic GABAergic synaptic innervation, whereas dendritic GABAergic and glutamatergic synaptic transmission are not affected (Fiorentino *et al.*, 2009). Given that the synaptic activation of AMPA receptors induces localized dendritic BDNF release (Hartmann *et al.*, 2001) and that secreted BDNF controls the formation of functional glutamatergic synapses (Walz *et al.*, 2006) and spine-head morphology (Tanaka *et al.*, 2008), glutamate and GABA must be playing a self-regulating role in excitatory and inhibitory synapse development, respectively, through a local postsynaptic release of BDNF. Further experiments will be required to confirm this.

Glutamate-induced BDNF dendritic release can control the strength of nearby GABAergic synapses (Liu *et al.*, 2007; Kuczewski *et al.*, 2008a) (Fig. 2). Such a mechanism might be important for the formation of functionally balanced local dendritic excitatory and inhibitory inputs. Alternatively, the action potentials triggered by a suprathreshold excitatory postsynaptic potential could provide the depolarization necessary for BDNF release at distant GABAergic synapses (Kuczewski *et al.*, 2008b; Matsuda *et al.*, 2009) (Fig. 2). Indeed, because the action potentials and associated Ca^{2+} rise travel backward from the soma to invade the dendritic tree, BDNF delivered under these circumstances as well as the actions mediated by BDNF might not be restricted to specific synapses.

Therefore, in contrast to presynaptic release, which is confined to individual stimulated synapses, postsynaptic release provides a means to deliver BDNF locally or globally depending on the pattern or level of synaptic activity. It should be mentioned, however, that presynaptic activity concomitant with BDNF secretion can gate the BDNF-TrkB signalling cascade and restrict the action of BDNF to specific inputs (Fig. 2). Accordingly, bath-applied BDNF, at a concentration that by itself has no effect, resulted in marked enlargement in spine-heads when paired with un-caging of glutamate at single spines in hippocampal slice cultures (Tanaka *et al.*, 2008). This effect of BDNF was selective for the stimulated spines, not being observed on neighbouring spines. Similarly, in the developing rat visual cortex (Inagaki *et al.*, 2008) and *Xenopus* tectum (Liu *et al.*, 2007), exogenous application of BDNF, that by itself did not affect baseline GABAergic activity, induced a selective potentiation of stimulated GABAergic pathways.

Physiopathological implications of dendritic brain-derived neurotrophic factor synthesis and release

Most of the interest in BDNF secretion and actions stems from the possibility that it might play a role in brain development or function. With this in mind, the conditioning protocol used to trigger BDNF secretion deserves particular attention. Compelling evidence shows that physiological conditioning protocols can trigger dendritic secretion of BDNF. As few as 10 back-propagating action potentials are sufficient to trigger the release of endogenous dendritic BDNF in neuronal cultures (Kuczewski *et al.*, 2008b). In the developing hippocampus, ongoing synaptic activity is characterized by spontaneous patterned network-driven activity termed giant depolarizing potentials *in vitro* (Ben-Ari *et al.*, 1989) and sharp waves *in vivo* (Leinekugel *et al.*, 2002). When paired with presynaptic Schaffer collateral stimulation, the spontaneous giant depolarizing potentials lead to a persistent and selective increase in the efficacy of the stimulated glutamatergic synapses (Mohajerani *et al.*, 2007). This potentiation involves the activation of presynaptic and postsynaptic TrkB receptors by endogenous BDNF, the activation of the postsynaptic extracellular signal-regulated kinase pathway and is expressed as an increase in presynaptic glutamate release. giant depolarizing potentials have also been proposed to play an instructive role in the development of the hippocampal GABAergic circuit through the activity-dependent secretion of BDNF (Fiorentino *et al.*, 2009). Sensory-driven synaptic activity can also trigger a dendritic secretion of BDNF *in vivo*. For instance, a BDNF-dependent potentiation of GABAergic inputs to *Xenopus* tectal neurons can be induced *in vivo* by repetitive visual stimuli (Liu *et al.*, 2007).

Although the source of BDNF (dendritic and/or axonal) was not determined, studies show that learning-related activity can drive BDNF release to modify synaptic efficacy *in vivo*. Thus, the molecular mechanisms underlying the formation of long-term memory *in vivo* share remarkable similarities with those involved in long-term modifications of glutamatergic synaptic efficacy, an *in vitro* model of memory formation. The secretion of hippocampal BDNF, and proteolysis of pro-BDNF, appear to be required *in vivo* for the consolidation of hippocampal-dependent contextual fear memory (Lee *et al.*, 2004; Barnes & Thomas, 2008) and *in vitro* for the induction of long-term potentiation at hippocampal glutamatergic synapses (Pang *et al.*, 2004). Along the same lines, in mouse models of Alzheimer's disease and in aged primates, BDNF gene delivery in the entorhinal cortex has been reported to improve cognitive performance (Nagahara *et al.*, 2009). Therefore, although further studies are required to clarify the mechanisms involved, these findings provide important evidence that *in vivo* activity can lead to BDNF secretion.

The physiological significance of the activity-dependent secretion of BDNF has been highlighted by a number of studies showing that a single nucleotide polymorphism in the pro-region of BDNF (val66met) results in a marked decrease in both dendritic BDNF levels and regulated secretion of BDNF (Egan *et al.*, 2003). Such a decrease results, at least in part, from a deficit in dendritic BDNF mRNA trafficking (Chiaruttini *et al.*, 2009). The valine to methionine substitution in the pro-domain also impaired the regulated, but not constitutive, form of BDNF secretion (Egan *et al.*, 2003; Chen *et al.*, 2005). Human subjects carrying the BDNF single nucleotide polymorphism exhibit impairments in hippocampal specific short-term memory and a higher susceptibility to a variety of neuropsychiatric disorders (Egan *et al.*, 2003). A smaller hippocampal and cortical volume has also been reported in carriers of the BDNF single nucleotide polymorphism (Pezawas *et al.*, 2004). These differences may be related to the role of BDNF in synaptic plasticity and brain development, although it is difficult to establish causality between phenotypic changes and genetic modifications in such studies. A $BDNF_{Met}$ knock-in mouse that mimics the phenotypic hallmarks of humans with BDNF polymorphism was generated (Chen *et al.*, 2006). The dendritic complexity and performance in various behavioural paradigms used to access learning, memory and anxiety are altered in the $BDNF_{Met}$ mice (Chen *et al.*, 2006, 2008). The polymorphism in the BDNF gene therefore represents an important example of the role of secreted neurotrophins in behavioural and cognitive processes.

Conclusions and perspectives

The studies summarized above have established that the activity-dependent postsynaptic secretion of BDNF contributes to synapse plasticity and development. Several issues remain to be addressed. For example, although controversial (Matsumoto *et al.*, 2008), some studies have reported that a significant proportion of BDNF is secreted from hippocampal neurons in the pro-form (Bergami *et al.*, 2008; Yang *et al.*, 2009b), converted into mature BDNF by extracellular proteases (Nagappan *et al.*, 2009; Yang *et al.*, 2009b), and that released pro-BDNF is biologically active (Pang *et al.*, 2004; Woo *et al.*, 2005). Endogenous pro-BDNF can also be released from postsynaptic *Xenopus* myocytes in culture and causes synaptic depression and nerve terminal retraction at the developing neuromuscular junction (Yang *et al.*, 2009a). Thus, an important issue is to determine whether the dendritic release of pro-BDNF and/or mature BDNF also occurs in the central nervous system. Because pro-BDNF and mature BDNF have opposing biological effects on glutamatergic synapses, dendritic morphology and cell survival, addressing this issue will not only advance our basic understanding of BDNF release and actions, but will also have implications for the management of disorders in which BDNF release and signalling are disrupted.

A large number of studies suggest that BDNF can be used for the therapeutic treatment of neurodegenerative diseases or neurological disorders. However, results from preclinical and clinical trials have been largely disappointing or controversial. Strategies have included the delivery of neurotrophins or non-peptidyl small molecules that mimic the biological action of neurotrophins. The most probable weakness of this approach is that such uniform delivery is different from the spatially and temporally restricted activity-dependent secretion of BDNF occurring from multiple releasing sites. To overcome this drawback, it will be interesting in future experiments to discover selective modulators of the different modalities of BDNF secretion and to investigate the effects that these drugs might have on brain development, plasticity and pathology.

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Abbreviations

BDNF, brain-derived neurotrophic factor; BDNF-GFP, green fluorescent protein-tagged brain-derived neurotrophic factor; GABA, γ-aminobutyric acid; TrkB, tropomyosin-related kinase (type B).

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