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REVIEW

Role of the brain-derived neurotrophic factor at glutamatergic synapses

AL Carvalho, MV Caldeira, SD Santos and CB Duarte

Center for Neuroscience and Cell Biology, Department of Zoology, University of Coimbra, Coimbra, Portugal

The neurotrophin brain-derived neurotrophic factor (BDNF) plays an important role in the activity-dependent regulation of synaptic structure and function, particularly of the glutamatergic synapses. BDNF may be released in the mature form, which activates preferentially TrkB receptors, or as proBDNF, which is coupled to the stimulation of the p75^{NTR}. In the mature form BDNF induces rapid effects on glutamate release, and may induce short- and long-term effects on the postsynaptic response to the neurotransmitter. BDNF may affect glutamate receptor activity by inducing the phosphorylation of the receptor subunits, which may also affect the interaction with intracellular proteins and, consequently, their recycling and localization to defined postsynaptic sites. Stimulation of the local protein synthesis and transcription activity account for the delayed effects of BDNF on glutamatergic synaptic strength. Several evidences show impaired synaptic plasticity of glutamatergic synapses in diseases where compromised BDNF function has been observed, such as Huntington's disease, depression, anxiety, and the BDNF polymorphism Val66Met, suggesting that upregulating BDNF-activated pathways may be therapeutically relevant. This review focuses on recent advances in the understanding of the regulation of the glutamatergic synapse by BDNF, and its implications in synaptic plasticity.
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Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BDNF, brain-derived neurotrophic factor; CaMKII, calcium- and calmodulin-dependent protein kinase II; CREB, type 2 cAMP-response element binding; eIF4E, eukaryotic initiation factor 4E; LTD, long-term depression; LTP, long-term potentiation; mTOR, mammalian target of rapamycin; NMDA, *N*-methyl-D-aspartate; PI3K, phosphatidylinositol 3-kinase; PKC, protein kinase C; PLC γ, phospholipase C γ; Shc, Src homology 2-containing protein; TRPC3, transient receptor potential canonical subfamily 3; Trk, tropomyosin-related kinase

Introduction

Neurotrophins control survival, differentiation and synaptogenesis, and play important roles in activity-dependent forms of synaptic plasticity in the CNS. The physiological responses to neurotrophins are mediated by activation of two distinct classes of transmembrane receptors, the tropomyosin-related kinase (Trk) family of receptors and the p75^{NTR} (reviewed in: Reichardt, 2006; Manadas *et al*., 2007). The Trk family of receptor tyrosine kinases includes the TrkA, TrkB and TrkC receptors, which are activated preferentially by nerve growth factor, brain-derived neurotrophic factor (BDNF), NT-4/5 and NT-3, respectively. In contrast with the specificity displayed by the Trk family of receptors, the p75^{NTR} binds both the mature form of the neurotrophins and their uncleaved (precursor) forms (pro-neurotrophins) (Lee *et al*., 2001; Teng *et al*., 2005). Sortilin, a member of the Vps10p-domain family of transmembrane receptors, acts as a p75^{NTR} coreceptor to mediate pro-neurotrophin-induced cell death (Nykjaer *et al*., 2004; Teng *et al*., 2005).

The levels and secretion of BDNF can be regulated by activity, and BDNF colocalizes with its receptor, TrkB, at glutamatergic synapses both presynaptically and postsynaptically. This makes BDNF attractive as a bidirectional modulator of excitatory synaptic transmission and plasticity. GABAergic synapses are also regulated by BDNF, which has been shown to act pre- and postsynaptically (for example, Frerking *et al*., 1998; Wardle and Poo, 2003; Jovanovic *et al*., 2004; Baldelli *et al*., 2005; Matsumoto *et al*., 2006). Moreover, BDNF modulates growth and complexity of dendrites, and changes spine density and morphology. This review focuses on the role of BDNF as a synaptic modulator through its pre- and postsynaptic actions at the glutamate synapse. The following sections will consider how BDNF is produced, processed and released, the signalling pathways that are

Correspondence: Dr AL Carvalho, Center for Neuroscience and Cell Biology, Department of Zoology, University of Coimbra, Largo Marquês de Pombal, Coimbra 3004-517, Portugal.
E-mail: alc@ibili.uc.pt
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activated through activation of TrkB, how BDNF regulates glutamate release and how it regulates glutamate receptor function. The final sections summarize recent progress in understanding the role of BDNF in synapse formation and stabilization, and in synaptic plasticity. A model for some of the mechanisms of action of BDNF on the glutamatergic synapse is depicted in Figure 1.

BDNF transport and release

Neurotrophins, including BDNF, are synthesized as pre-pro-neurotrophin precursors that undergo post-translational modifications before giving rise to mature homodimeric proteins. proBDNF is present in many regions of the CNS, including the hippocampus, cerebral cortex, cerebellum, hypothalamus, substantia nigra, amygdala and spinal cord (Zhou *et al*., 2004). Expression of the *bdnf* gene is tightly controlled by neuronal activity, through mechanisms dependent on the $[Ca^{2+}]_i$ (reviewed in Mellstrom *et al*., 2004).

The pro-neurotrophins produced in the endoplasmic reticulum (ER) then transit to the Golgi apparatus and finally accumulate in the trans-Golgi network. A model was proposed according to which proBDNF binds to sortilin in the Golgi, facilitating the correct folding of the mature domain. In the appropriate conformation, the mature domain of BDNF binds to carboxipeptidase E, thereby sorting the neurotrophin to the regulated secretory pathway (Chen *et al*., 2005; Lou *et al*., 2005; Lu *et al*., 2005). The sorting of BDNF to this secretory pathway is impaired by a BDNF polymorphism consisting in a valine to methionine substitution at codon 66 in the prodomain, which affects human memory and hippocampal function (Egan *et al*., 2003). It remains to be determined whether the missorting phenotype of this BDNF polymorphism implies the existence of an additional, and independent, sorting motif in the prodomain of the neurotrophin. A recent study also suggested that huntingtin, a protein mutated in patients with Huntington's disease, plays an important role in the post-Golgi transport of BDNF (del Toro *et al*., 2006).

Brain-derived neurotrophic factor produced in the cell body is transported to postsynaptic dendrites, in secretory granules (Goodman *et al*., 1996; Haubensak *et al*., 1998; Hartmann *et al*., 2001; Kohara *et al*., 2001; Adachi *et al*., 2005; Brigadski *et al*., 2005). Alternatively, the neurotrophin contained within large dense core vesicles is delivered to the presynaptic axon terminals, by anterograde transport (Fawcett *et al*., 1998; Kohara *et al*., 2001; Adachi *et al*., 2005). Accordingly, BDNF was found in a vesicular fraction isolated from nerve endings (Fawcett *et al*., 1997), and electron microscopy studies showed that it is stored in dense core vesicles, together with neuropeptide transmitters, in the amygdala (Salio *et al*., 2007). The release of BDNF from the synaptic terminals of cerebellar granule neurons is mediated by Ca^{2+}-dependent activator protein for secretion, type 2, a protein that interacts with the secretory granules containing the neurotrophin (Kawaguchi *et al*., 2004; Sadakata *et al*., 2007). The BDNF vesicle clusters, pre- and postsynaptic, are found close to active synapses and their content is released in response to synaptic stimulation (Hartmann *et al*., 2001; Kohara *et al*., 2001; Kojima *et al*., 2001). Depolarization of cultured neurons with KCl or electrical stimulation, or stimulation with glutamate, induces the release of endogenous proBDNF/BDNF and BDNF-green fluorescent protein (GFP) fusion protein in a Ca^{2+}-dependent manner (Goodman *et al*., 1996; Hartmann *et al*., 2001; Kojima *et al*., 2001; Balkowiec and Katz, 2002; Lou *et al*., 2005). The specificity in the location of BDNF release, together with the fact that the release occurs by a regulated mechanism, is an important issue in determining the specificity of the effects of the neurotrophin in the modulation of synaptic activity and neuronal connectivity.

Interestingly, BDNF mRNA is accumulated in dendrites of cultured hippocampal neurons following KCl depolarization,

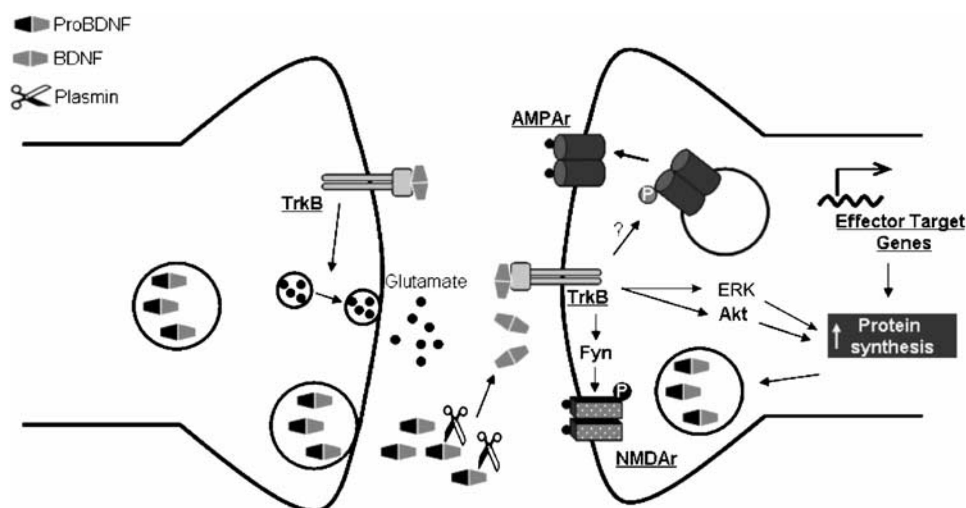

Figure 1 Brain-derived neurotrophic factor (BDNF) modulates glutamatergic synapses through pre- and postsynaptic targets. ProBDNF is secreted in an activity-regulated way, processed by extracellular proteases, such as plasmin, and acts on pre- and postsynaptic TrkB receptors. Presynaptically, BDNF regulates glutamate release, whereas the postsynaptic actions of BDNF include changes in glutamate receptor phosphorylation and synthesis, changes in gene expression and local alterations in protein synthesis. These effects of BDNF influence synaptic plasticity, and spine density and morphology.

by a mechanism involving Ca^{2+} influx, glutamate receptor activation and stimulation of TrkB receptors by endogenous BDNF (Tongiorgi *et al*., 1997; Righi *et al*., 2000). Under the same conditions there was an increase in dendritic BDNF immunoreactivity, even in the presence of dendritic transport blockers, suggesting that the neurotrophin is synthesized locally (Tongiorgi *et al*., 1997). Dendritic targeting of BDNF mRNA and accumulation of the neurotrophin were also observed in the rat hippocampus following epileptogenic stimuli, and may contribute to the cellular changes leading to epilepsy (Tongiorgi *et al*., 2004).

The 32 kDa proBDNF is the main form of the neurotrophin secreted from cultured neurons (Mowla *et al*., 1999, 2001; Chen *et al*., 2004), indicating that the mature form originates mainly from the extracellular cleavage of proBDNF by extracellular proteases. The most relevant extracellular protease in the cleavage of neurotrophins, including BDNF, is plasmin (Lee *et al*., 2001; Pang *et al*., 2004). This serine protease is expressed as an inactive zymogen, plasminogen, which becomes activated upon cleavage by tissue plasminogen activator (Plow *et al*., 1995). The cleavage of proBDNF by tPA/plasmin plays a key role in hippocampal long-term potentiation (LTP) (see below) (Pang *et al*., 2004). However, it remains to be determined whether the activation of plasmin can be regulated to tightly control the extracellular concentration of BDNF.

Brain-derived neurotrophic factor has also been found in some of the neurons that lack BDNF mRNA transcripts, which are unable to synthesize the neurotrophin (Conner *et al*., 1997). This indicates that extracellular BDNF may be taken up by pre- or postsynaptic neurons, as observed in cultured cortical neurons transfected with GFP-tagged BDNF (Kohara *et al*., 2001). *In vivo* studies also showed transneuronal transport of BDNF following injection of BDNF into the eyes of chick embryos (von Bartheld *et al*., 1996; Butowt and von Bartheld, 2001) or adult rodents (Caleo *et al*., 2000, 2003; Butowt and von Bartheld, 2005). Following uptake by retinal ganglion cells, BDNF is transported to the nerve terminals and released, increasing the survival of target neurons (von Bartheld *et al*., 1996; Caleo *et al*., 2000, 2003). In addition to the long-range transport to distal synapses, BDNF may also be recycled locally. In the hippocampus, the complex formed by BDNF and its receptor (TrkB) is internalized by Pincher (pinocytic chaperone)-mediated macroendocytosis-dependent mechanism, in axons and dendrites, and enters rapidly into a local recycling pathway independent of the ER and the Golgi (Valdez *et al*., 2005). The internalized BDNF may be released following stimulation of the neurons, allowing the recycling of the neurotrophin, and the recycled BDNF was shown to contribute to the maintenance of LTP (see below) (Santi *et al*., 2006).

TrkB receptors and signalling pathways

The TrkB receptors are activated by BDNF and NT-4/5 (reviewed in: Reichardt, 2006; Manadas *et al*., 2007). Neurotrophins bind to the Trk receptors as dimers, thus promoting receptor dimerization (Jing *et al*., 1992) and transphosphorylation on specific tyrosine residues located in the intracellular domain. This, in turn, creates docking sites for different adaptor proteins and signalling enzymes, setting in motion various parallel signal transduction cascades, with distinct functions (Atwal *et al*., 2000; Reichardt, 2006; Manadas *et al*., 2007). The signalling activity of the various Trk receptors is rather similar, due to the high homology between their intracellular domains (Atwal *et al*., 2000). Phosphorylation of two tyrosine residues located outside the kinase activation domain of the Trk receptors mediates the interaction with Shc (Src homology 2-containing protein) and phospholipase C γ (PLC γ; reviewed in: Reichardt, 2006; Manadas *et al*., 2007). Shc recruitment to the active Trk receptors is followed by phosphorylation of the adaptor protein, leading to the activation of the Ras/extracellular signal-regulated kinase (ERK) signalling pathway through recruitment of Grb2 and SOS. The Shc docking site on active Trk receptors may also allow binding of the adaptor protein fibroblast growth factor receptor substrate 2, which becomes phosphorylated on tyrosine residues, thus creating binding sites for the adaptor proteins Grb2 and Crk, the phosphatase SH-PTP2, the tyrosine kinase Src and the cyclin-dependent kinase substrate p13 suc 1. Crk binds and activates the exchange factor C3G, which in turn stimulates a small G protein, Rap-1, thereby activating the downstream kinase B-raf and the MEK/ERK signalling cascade (Reichardt, 2006). Alternatively, CrkL can be recruited to the activated Trk receptor through binding to the tyrosine-phosphorylated ARMS/Kidins220 (ankyrin-rich membrane spanning domain), resulting in the activation of Rap1 through C3G (Arevalo *et al*., 2006). Activation of ERK influences transcription events, such as the activation of cAMP-response element binding (CREB) transcription factor (Shaywitz and Greenberg, 1999).

Binding of Shc to the Trk receptors also activates the phosphatidylinositol 3-kinase (PI3K) pathway, either by direct interaction of Ras with PI3K or through recruitment of the adaptor protein Gab1. Activation of PI3K changes the composition of inositol phospholipids in the inner leaflet of the plasma membrane, resulting in the translocation of PKB (also known as Akt) to the plasma membrane, where it is activated through phosphorylation by upstream kinases, including phosphoinositide-dependent protein kinases 1 and 2 (possibly the rictor–mTOR complex; Sarbassov *et al*., 2005). Akt may change transcription activity, but may also induce rapid and local changes in the proteome by regulating the translation machinery (Takei *et al*., 2001, 2004). This signalling pathway plays an important role in cell survival (Brunet *et al*., 2001; Almeida *et al*., 2005; Manadas *et al*., 2007).

Phosphorylation of TrkB on Tyr785 recruits PLC γ to the receptors, and the enzyme becomes activated upon tyrosine phosphorylation (Pereira *et al*., 2006; Reichardt, 2006). A recent study showed that full activation of this signalling pathway requires TrkB translocation to lipid rafts, possibly through a Fyn-dependent mechanism (Pereira and Chao, 2007). PLCγ hydrolyses phosphatidylinositol 4,5-bisphosphate, giving rise to diacylglycerol, which activates protein kinase C (PKC), and inositol 1,4,5-trisphosphate ($Ins(1,4,5)P_3$), which releases Ca^{2+} from intracellular stores. In cultured cerebellar granule cells, the BDNF-induced

mobilization of intracellular Ca^{2+} stores acts together with the diacylglycerol generated by PLCγ in the activation of plasma membrane transient receptor potential canonical subfamily 3/6 (TRPC3/6) channels. The influx of Ca^{2+} through these channels contributes to ERK and CREB activation, increasing cell survival (Jia *et al*., 2007). Activation of this pathway also plays a key role in synaptic plasticity (see below; Minichiello *et al*., 2002).

Little is known about the role of the $p75^{NTR}$ in the regulation of the glutamatergic synapses. These receptors lack intracellular catalytic activity and, therefore, their signalling activity is initiated by binding to several adaptor proteins, including Traf6, neurotrophin receptor-interacting factor, melanoma-associated antigen, neurotrophin receptor p75-interacting melanoma-associated antigen homologue, Schwann cell factor 1, RhoGDI and other proteins (reviewed in: Harrington *et al*., 2004; Nykjaer *et al*., 2005; Schor, 2005). Activation of $p75^{NTR}$ by proBDNF facilitates long-term depression (LTD) in the hippocampus, but the signalling mechanism involved is still unknown (Woo *et al*., 2005).

Subcellular distribution of TrkB receptors and regulation of glutamate release by BDNF

The TrkB mRNA and protein are widely distributed throughout the brain, including the cerebral cortex, hippocampus, striatum, septal nuclei, substantia nigra, cerebellar Purkinje neurons, brain stem and spinal cord motor neurons (Kokaia *et al*., 1993; Zhou *et al*., 1993; Muragaki *et al*., 1995; Shelton *et al*., 1995; Fryer *et al*., 1996; Yan *et al*., 1997). The subcellular localization of these receptors has been investigated in great detail in the hippocampus and cerebral cortex, given their role in synaptic plasticity (see below). In the adult rat hippocampus, the TrkB receptors are present in the glutamatergic pyramidal and granule cells, mainly in axons, nerve terminals and dendritic spines. The receptors are also present to a lower extent in the cell bodies and dendritic shafts (Drake *et al*., 1999), and in dendritic spines of the rat brain cortex (Aoki *et al*., 2000). Subcellular fractionation of the rat hippocampus showed that TrkB receptors are present in about one-third of the glutamatergic nerve terminals, being evenly distributed between the presynaptic active zone and the postsynaptic density (Pereira *et al*., 2006). However, with the exception of the dendritic spines, most of the TrkB receptors appear to be intracellular and, therefore, should not respond to extracellular BDNF (Drake *et al*., 1999; Pereira *et al*., 2006). Interestingly, the cellular response to BDNF may depend on the recent history of the cell since plasma membrane depolarization and an increase in the intracellular cAMP concentration rapidly increase the amount of receptors associated with the plasma membrane (Meyer-Franke *et al*., 1998). Local protein synthesis also contributes to the increase in BDNF and TrkB protein levels in distal dendrites following depolarization of cultured hippocampal neurons (Tongiorgi *et al*., 1997).

In agreement with the presynaptic expression of TrkB receptors, BDNF was shown to potentiate the depolarization-evoked Ca^{2+}-dependent release of glutamate from isolated hippocampal and cerebrocortical nerve terminals (Sala *et al*., 1998; Jovanovic *et al*., 2000; Gooney and Lynch, 2001;Canas *et al*., 2004; Pereira *et al*., 2006). This effect is mediated by mitogen-activated protein kinase (ERK1/2)-dependent phosphorylation of synapsin I/II, since it was significantly reduced in synaptosomes isolated from mice deficient in each or both synapsins (Jovanovic *et al*., 2000). Mitogen-activated protein kinase phosphorylation of synapsin I reduces its ability to promote G-actin polymerization into actin filaments (Jovanovic *et al*., 1996). In addition to the contribution of the mitogen-activated protein kinase pathway, PLC may also contribute to the effects of BDNF on the depolarization-evoked exocytotic release of glutamate, as shown in cultured cerebrocortical neurons (Matsumoto *et al*., 2001). Furthermore, a recent study showed that BDNF-induced potentiation of neurotransmitter release depends on the interaction of myosin VI, a minus end-directed actin-based motor, and the GIPC1 adaptor protein. GIPC1 binds directly to myosin VI and the Trk receptors (Yano *et al*., 2006).

In cultured neurons from the cerebral cortex, cerebellum, striatum and hippocampus, BDNF induces the release of glutamate in the absence of other depolarizing stimuli, and this effect is dependent on the mobilization of Ca^{2+} from Ins(1,4,5)P_3-sensitive stores (Takei *et al*., 1998; Numakawa *et al*., 1999, 2001). The BDNF-induced release of glutamate in cultured neurons is mainly mediated by reversal of the plasma membrane transporter and is dependent on extracellular Na^+ (Numakawa *et al*., 2001), suggesting that it may be secondary to the activation of the Na^+/Ca^{2+} exchanger. Studies using cultured hippocampal neurons also showed an increase in the frequency, but not amplitude, of miniature excitatory postsynaptic current (mEPSC) following stimulation with BDNF, showing a presynaptic effect of the neurotrophin on excitatory synapses (Li *et al*., 1998).

Control of glutamate receptors by BDNF

AMPA receptor structure, diversity and traffic

Ionotropic glutamate receptors mediate most of the excitatory synaptic transmission in the brain where they also play key roles in synaptic plasticity and pathology. In view of pharmacological and electrophysiological criteria, ionotropic glutamate receptors have been classified into three major subtypes: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainate and *N*-methyl-D-aspartate (NMDA) receptors, named after their most selective agonist (Watkins *et al*., 1981). AMPA receptors (AMPARs) are responsible for the primary depolarization in glutamate-mediated neurotransmission. They are largely Ca^{2+} impermeable, display exceptionally fast kinetics and mediate moment-to-moment synaptic signalling (Jonas, 2000). These characteristic functional properties depend on the subunit composition and on subunit modifications introduced by alternative splicing. AMPARs assemble in tetrameric structures of four subunits, GluR1–GluR4 (or GluRA–GluRD), in various combinations (Laube *et al*., 1998; Mano and Teichberg, 1998; Rosenmund *et al*., 1998). The subunit stoichiometry determines channel function (that is desensitization/resensitization kinetics and conductance properties) (Ozawa *et al*., 1998) and trafficking

to synapses (Malinow *et al*., 2000). Stargazin and other transmembrane AMPAR regulatory proteins also coassemble stoichiometrically with native AMPARs. The transmembrane AMPAR regulatory proteins act as auxiliary subunits that are required for AMPAR maturation, trafficking and channel function (Korber *et al*., 2007; Ziff, 2007). The C-terminus of AMPAR subunits is intracellular and shows differences between the subunits. GluR1, GluR4 and an alternative splice form of GluR2 (GluR2L) have longer cytoplasmic tails that are homologous. In contrast, the predominant splice form of GluR2, GluR3 and an alternative splice form of GluR4 (GluR4c) have shorter, homologous cytoplasmic tails. Receptors composed of subunits with short cytoplasmic C-termini (GluR2/3) cycle continuously in and out of the synapse with a time constant of $\sim$15 min (Passafaro *et al*., 2001; Shi *et al*., 2001), whereas receptors that contain long C-termini (GluR1/2 and GluR2/4) are added into synapses in an activity-dependent manner (Hayashi *et al*., 2000; Shi *et al*., 2001). Through their C-terminal tail, each subunit interacts with specific cytoplasmic proteins, which play important roles in controlling the trafficking of AMPARs and/or their stabilization at the synapses.

AMPAR subunits are synthesized and assembled in the rough ER and then inserted into the plasma membrane after crossing the Golgi apparatus. The final step of insertion of the receptors in the synaptic membrane involves tightly regulated events that depend on the subunit composition of the receptor and on specific signals contained within the C-termini. Several PDZ domain-containing proteins, such as SAP97, glutamate receptor-interacting protein (GRIP1), AMPAR-binding protein (ABP) and protein interacting with C-kinase-1 (PICK1), have been shown to participate in the process. GluR2 also binds *N*-ethylmaleimide-sensitive factor, an ATPase required for membrane fusion events, which interacts with a membrane proximal segment of the C-terminus of GluR2. This protein helps to maintain the synaptic expression of GluR2-containing AMPARs. Several recent reviews summarize in detail the literature in this field (Bredt and Nicoll, 2003; Gomes *et al*., 2003; Derkach *et al*., 2007; Elias and Nicoll, 2007; Greger and Esteban, 2007).

Phosphorylation is a key post-translational modification in regulating AMPAR function (Carvalho *et al*., 2000). It can regulate the physiological properties of the channel as well as protein trafficking. GluR1 subunit has been described to be phosphorylated at three sites located in the intracellular C-terminus: serine 831 (Ser831) can be phosphorylated by both PKC (Roche *et al*., 1996) and calcium- and calmodulin-dependent protein kinase II (CaMKII) (Mammen *et al*., 1997); serine 845 (Ser845) is a protein kinase A (PKA) phosphorylation site (Roche *et al*., 1996) and serine 818 (Ser818) is a substrate for PKC (Boehm *et al*., 2006). LTP induction increases the CaMKII-dependent phosphorylation of GluR1 at Ser831 (Mammen *et al*., 1997). Although such phosphorylation may enhance the function of synaptic receptors (Benke *et al*., 1998), it does not seem to be required for receptor delivery, since mutations on GluR1–Ser831 that prevent its phosphorylation by CaMKII do not prevent delivery of the receptor to synapses by active CaMKII (Hayashi *et al*., 2000). Interestingly, mutations at Ser845, the PKA phosphorylation site of GluR1 (Roche *et al*., 1996), do prevent delivery of GluR1 to synapses by active CaMKII or LTP (Esteban *et al*., 2003). On the other hand, PKA activity is necessary but not sufficient for the CaMKII-driven incorporation of GluR1 into synapses (Esteban *et al*., 2003). It is important to note that both Ser831 and Ser845 are necessary, but not sufficient to deliver AMPARs into synapses, which requires the activation of the CaMKII-Ras-mitogen-activated protein kinase (Esteban, 2003). Phosphorylation of GluR1–Ser818 by PKC is critical in LTP-driven incorporation of AMPARs into the postsynaptic membrane and is suggested to exert its function by facilitating the interaction between GluR1 and a delivery or tethering protein (Boehm *et al*., 2006).

Regulation of AMPAR expression and traffic by BDNF

In addition to the presynaptic effects of BDNF on glutamatergic synapses, the neurotrophin may also act postsynaptically, through regulation of the abundance of the plasma-membrane-associated glutamate receptors. Stimulation of cultured hippocampal neurons with BDNF increases the amount of GluR1 associated with the plasma membrane, by a protein synthesis-dependent mechanism, without affecting the distribution of GluR2. BDNF also promotes the synaptic delivery of homomeric GluR1 AMPARs in cultured organotypic hippocampal slices by a mechanism dependent on the activation of Trk receptors (presumably TrkB) (Caldeira *et al*., 2007a). The synaptic delivery of GluR1 induced by BDNF is associated with the phosphorylation of the protein in Ser831, the CaMKII and PKC phosphorylation site, but no phosphorylation was detected in Ser845 (Caldeira *et al*., 2007a). Because GluR1 phosphorylation in Ser831 is not sufficient to induce synaptic delivery of AMPARs (Hayashi *et al*., 2000), the effect of BDNF may require GluR1 phosphorylation on Ser818, a PKC phosphorylation site (Boehm *et al*., 2006), or changes in a protein involved in GluR1 traffic.

Similarly, BDNF induces the synaptic delivery of GluR1-containing AMPARs in cultured cerebrocortical neurons, from a local pool, and by a mechanism dependent on the mobilization of Ca^{2+} from Ins(1,4,5)P_3-sensitive internal stores (Nakata and Nakamura, 2007). [^{3}H]AMPA-binding studies showed that the surface translocation of AMPARs to the membrane induced by BDNF requires intracellular Ca^{2+} and is sensitive to blockers of exocytosis (Narisawa-Saito *et al*., 2002). It remains to be determined whether the population of GluR1-containing AMPARs recruited to the synapse following stimulation with BDNF is synthesized locally. This may occur by TrkB-induced activation of the mammalian target of rapamycin (mTOR)-PI3K-dependent pathway, as shown in isolated rat forebrain synaptoneurosomes (Schratt *et al*., 2004).

Activation of Trk receptors, presumably TrkB, increases the protein expression of the AMPAR subunits GluR1, GluR2 and GluR3 in cultured hippocampal neurons, by a mechanism dependent on transcription activation (Caldeira *et al*., 2007a). Chronic stimulation with BDNF also increases GluR1 and GluR2/3 protein levels in cultured rat neocortical neurons, probably by activation of Fyn, a non-receptor-type tyrosine kinase of the Src family, which is known to be

activated by Trk receptors (Narisawa-Saito *et al*., 1999). Under the same conditions, there is an upregulation of several postsynaptic density proteins known to interact with AMPARs, including SAP97, GRIP1, PICK1, and an increase in the interaction between GluR1 and SAP97, and GluR2/3 with GRIP1 (Jourdi *et al*., 2003), which may in turn stabilize AMPARs at the membrane. However, the mechanisms that act downstream of the Trk receptors in the upregulation of the expression of AMPAR subunits in hippocampal and cerebrocortical neurons remain to be determined. In agreement with the observed upregulation of AMPAR subunits following long-term stimulation of cultured neurons with BDNF, chronic treatment with BDNF increases the inward membrane currents evoked by AMPA and, consequently, AMPA-triggered GABA release in neocortical GABAergic neurons (Nagano *et al*., 2003). Also, long-term treatment of hippocampal cultures with BDNF potentiates excitatory transmission by augmenting the amplitude of AMPAR-mediated miniature EPSCs (Bolton *et al*., 2000). In contrast, BDNF was shown to strongly inhibit postsynaptic AMPAR-mediated currents in a large subset of newborn nucleus tractus solitarius neurons (Balkowiec *et al*., 2000). These BDNF induced-changes in synaptic activity may be due to the insertion or removal of AMPARs from potentiated and depressed synapses (Carroll *et al*., 1999; Lissin *et al*., 1999), respectively, or to changes in the phosphorylation state of AMPA-type glutamate receptors (Wu *et al*., 2004).

NMDA receptor structure, diversity and traffic

N-Methyl-D-aspartate receptors are glutamate, glycine (or D-serine) and voltage-dependent receptors that mediate a relatively slow and long-lasting excitatory postsynaptic current component (reviewed in Chen and Wyllie, 2006). These receptors are ligand-gated cation channels characterized by their high Ca^{2+} permeability (Ascher and Nowak, 1988). The NMDA receptor family is made of NR1, NR2 and NR3 subunits. NR1 contains the glycine-binding site and is essential for the NMDA receptor function, but the glutamate-binding site is contained within the NR2 subunits. Therefore, functional NMDA receptors are thought to be tetramers of two NR1 and two NR2 subunits, and their activity requires the binding of the co-agonists glycine and glutamate (or NMDA) (Kew and Kemp, 2005; Chen and Wyllie, 2006). The NR3 subunits can assemble with NR1–NR2 complexes to depress NMDA receptor responses, and may interact with NR1 subunits to form excitatory glycine receptors, insensitive to glutamate or NMDA, calcium impermeable and resistant to Mg^{2+} blockade (Chatterton *et al*., 2002; Kew and Kemp, 2005). NMDA receptor diversity arises from alternative splicing at three sites in the NR1 mRNA, giving rise to eight distinct functional splice variants, and one non-functional truncated splice variant of NR1 (McBain and Mayer, 1994). The existence of four NR2 subunits (NR2A–NR2D), and two NR3 subunits (NR3A and NR3B) further contributes to the diversity of NMDA receptors. Each NR2 subunit is encoded by its own gene, and is unable to form functional channels on its own, but greatly enhances NMDA receptor function when coexpressed with NR1 (Cull-Candy *et al*., 2001). Regional and developmental regulation of NR2 subunit expression underlies much of the diversity of NMDA receptor responses in the CNS (Wenthold *et al*., 2003). Thus, during development there is a general trend towards a decreasing contribution of NR2B, associated with an increasing contribution of NR2A-containing NMDA receptors to the synaptic currents. This shift in the subunit composition of the NMDA receptors causes a significant decrease in the deactivation time of the NMDA receptors (Cull-Candy *et al*., 2001).

NMDA receptors are targeted to the postsynaptic sites in glutamatergic synapses at an initial stage after the contact between axons and dendrites (Friedman *et al*., 2000). NMDA receptors are synthesized in the ER and delivered to the synapse, and localization signals at the intracellular C-terminal tail of the NR1 and NR2 subunits regulate NMDA receptors delivery to and retrieval from the plasma membrane. Longer splice variants of NR1 are retained in the ER due to the presence of an ER retention motif in the alternatively spliced C1 cassette present in these forms. Assembly of these NR1 forms with the NR2 subunits masks the retention motif and allows traffic of the assembled receptors to the cell surface and targeting to dendritic spines (for a review, see Wenthold *et al*., 2003).

The targeting of NMDA receptors to the synapse and their stabilization at the synapse depend on interactions with other proteins, and many of these interactions involve the intracellular C-terminus of the receptor subunits. Accordingly, mice expressing NR2A or NR2B subunits truncated at the C-terminus show compromised synaptic localization of NMDA receptors (Mori *et al*., 1998; Steigerwald *et al*., 2000). The NR2 subunits have been shown to bind, through PDZ recognition motifs at the distal end of the C-terminal tail, to the first two PDZ domains of PSD95, PSD93 and SAP102. These scaffolding proteins bind other intracellular proteins and can therefore link NMDA receptors to other glutamate receptors and to ion channels in the postsynaptic reticulum. Moreover, PSD95 promotes the surface expression and clustering of NMDA receptors containing NR2A, enhances NMDA channel opening, reduces the desensitization of NMDA responses and links synaptic NMDA receptors to downstream signalling molecules, such as neuronal nitric oxide synthase (for a review, see Lau and Zukin, 2007).

Phosphorylation of NMDA receptors is another major mechanism for regulating receptor trafficking at the synapse. Phosphorylation of NR1 by PKC at serine residues near the ER retention motif promotes NMDA receptor traffic to the cell surface on a timescale of hours (Scott *et al*., 2001). In parallel, activation of PKC increases NMDA channel opening and plasma membrane expression of NMDA receptors in hippocampal neurons, through a mechanism not involving direct phosphorylation of the receptors (Lan *et al*., 2001). PKA phosphorylates NR1, NR2A and NR2B (Leonard and Hell, 1997), and mediates activity-regulated synaptic targeting of NMDA receptors (Crump *et al*., 2001). PKA is anchored to NMDA receptors via yotiao, a protein that binds to the C1 cassette present in the C-terminus of some splice variants, and therefore counteracts constitutive type I protein phosphatase activity, and enhances NMDA receptor currents (Westphal *et al*., 1999). Fyn, a kinase of the Src protein tyrosine kinase family, phosphorylates NR2A in a

PSD95-dependent manner (Tezuka *et al*., 1999), and PSD95 is required for Src-mediated potentiation of the NR1/NR2A receptor currents in *Xenopus* oocytes (Liao *et al*., 2000). Moreover, Fyn phosphorylates NR2B (Nakazawa *et al*., 2001). Finally, NMDA receptors are regulated by cyclin-dependent kinase-5, which phosphorylates NR2A. In fact, roscovitine, a selective cyclin-dependent kinase-5 inhibitor, blocks both LTP induction and NMDA-evoked currents in rat CA1 hippocampal neurons (Li *et al*., 2001), suggesting that cyclin-dependent kinase-5 upregulates NMDA receptors.

N-Methyl-D-aspartate receptors are relatively stable at the synapse when compared to AMPARs, but recent evidences indicate that NMDA receptors are internalized in a regulated manner (for a review, see Lau and Zukin, 2007). NMDA receptor internalization is mediated by the tyrosine-based internalization motifs in the C-terminus of NR2 subunits, and NR2B shows stronger internalization, and sorting to recycling endosomes. Phosphorylation of this internalization motif in NR2B by Fyn suppresses internalization of NMDA receptors. Moreover, endocytic motifs present in the membrane-proximal region of the C-terminus of NR1, NR2A and NR2B also drive internalization, and drive receptors to recycling endosomes.

The activity-dependent changes in NMDA receptor traffic may provide an additional mechanism for regulating synaptic efficacy. In fact, the primary mechanism for LTP and LTD involves alterations in the number of synaptic AMPARs, but there are also evidences for changes in the currents conducted by NMDA receptors triggered by LTP and LTD (Lau and Zukin, 2007). Moreover, the forms of synaptic plasticity that operate over longer timescales, such as synaptic scaling and metaplasticity, seem to rely on mechanisms that involve activity-dependent alterations in NMDA receptor trafficking (Perez-Otano and Ehlers, 2005).

BDNF modulation of NMDA receptors

The current understanding of the regulation of NMDA receptors by BDNF is not as extensive as for AMPARs. BDNF increases the amount of NR1, NR2A and NR2B NMDA receptor subunits associated with the plasma membrane in cultured hippocampal neurons (Caldeira *et al*., 2007b). The BDNF-induced delivery of NMDA receptors to the plasma membrane is correlated with an increase in the activity of the receptors, as measured by the $[Ca^{2+}]_i$ response to NMDA stimulation. However, in addition to the effect of the neurotrophin on the number of receptors associated with the plasma membrane, BDNF may also change the responses to NMDA by regulating the biophysical properties of the receptors. Activation of TrkB receptors was shown to potentiate NMDA receptor currents in *Xenopus* oocytes micro-transplanted with rat forebrain postsynaptic densities (Sandoval *et al*., 2007). Furthermore, BDNF increases NMDA receptor single channel open probability in cultured hippocampal neurons (Levine *et al*., 1998), presumably through phosphorylation of the receptors. BDNF induces tyrosine phosphorylation of NR1 and NR2B subunits in hippocampal and cortical neurons, but not NR2A (Suen *et al*., 1997; Lin *et al*., 1998; Alder *et al*., 2005), and the effects of BDNF on the NMDA receptor open probability depend on the presence of NR2B subunits (Levine and Kolb, 2000). Phosphorylation of NR2B may be mediated by Fyn, a member of the Src family of non-receptor tyrosine kinases, since this kinase is activated by TrkB receptors (Narisawa-Saito *et al*., 1999), phosphorylates this NMDA receptor subunit (Nakazawa *et al*., 2001) and contributes to BDNF-induced increase in synaptic transmission (Wang and Salter, 1994; Alder *et al*., 2005). CaMKII and PKC may also contribute to the potentiation of NMDA receptors by BDNF, as demonstrated in cultured hippocampal neurons (Crozier *et al*., 1999; Lan *et al*., 2001). Both kinases are activated downstream of TrkB, following stimulation of PLC, which gives rise to $Ins(1,4,5)P_3$ and DAG. The $Ins(1,4,5)P_3$ mobilizes Ca^{2+} from intracellular stores and DAG stimulates PKC (see above).

In addition to the effects on the activity and trafficking of NMDA receptors, BDNF upregulates the expression of NR1, NR2A and NR2B NMDA receptor subunits in cultured hippocampal neurons, by a transcription-dependent mechanism (Caldeira *et al*., 2007b). NR2A mRNA and protein levels are also upregulated in cultured cerebrocortical neurons stimulated with BDNF (Small *et al*., 1998), and the neurotrophin regulates NR2A expression in the developing visual cortex (Margottil and Domenici, 2003). In fact, NR1 expression is regulated by different transcription factors, including the NF-κB (Liu *et al*., 2004) and CREB (Lau *et al*., 2004), and the latter is a major mediator of neuronal neurotrophin responses (Finkbeiner *et al*., 1997). NR2B expression is also regulated by CREB (Rani *et al*., 2005) and AP-1 (Qiang and Ticku, 2005), which may be activated by BDNF-induced signalling (Li *et al*., 2004). Recent studies have also shown that BDNF increases the translation of the NR1 subunit mRNA in cultured cerebrocortical neurons (Schratt *et al*., 2004), suggesting that the neurotrophin may regulate the abundance of NMDA receptors in the hippocampus by acting at the translation level.

Role of BDNF in synapse formation and stabilization

The fast changes in synaptic efficacy triggered by BDNF may be translated to structural changes if the synapses are exposed to BDNF for longer periods. These alterations include axonal branching and dendritic growth (McAllister *et al*., 1999), but there is also ample evidence that BDNF influences the formation, stability and morphology of excitatory synapses, probably through presynaptic as well as postsynaptic mechanisms. TrkB receptors have been found in postsynaptic densities in adult rat cerebral cortex and hippocampus (Wu *et al*., 1996), and surface TrkB was found to be enriched at glutamatergic synapses in cultured cortical neurons (Gomes *et al*., 2006). In this preparation, before synapse formation some TrkB puncta in dendrites colocalize with NMDA receptors, and almost all TrkB puncta in axons colocalize with synaptic vesicle proteins; moreover, surface TrkB is found in structures that participate in synapse formation, such as axonal growth cones and dendritic filipodia (Gomes *et al*., 2006). The distribution of TrkB in cortical neurons in culture suggests that TrkB is correctly localized to play a role in glutamatergic synapse formation.

The first evidence that BDNF is involved in regulating synapse number came from a study using electron microscopy to analyse the phenotype of hippocampal connections in Trkb-knockout mice, which showed lower densities of synaptic contacts and important structural alterations of presynaptic boutons, such as decreased density of synaptic vesicles, in P13–P14 Trkb (−/−) mice when compared to wild-type littermates (Martinez *et al*., 1998). Another early study using hippocampal cultures prepared from embryonic day 16 rat embryos, which form presynaptically silent synapses, showed that functional connectivity between these neurons could be established by 1–3 days exposure of the culture to BDNF (Vicario-Abejon *et al*., 1998).

Later studies using organotypic hippocampal slice cultures from postnatal rats showed that exogenous BDNF application increases the number of synapses per neuron, and the number of docked vesicles at the active zone of excitatory synapses onto CA1 pyramidal neurons (Tyler and Pozzo-Miller, 2001). Using the same system, Tyler and Pozzo-Miller (2003) found that BDNF increases the proportion of short stubby spines, which are thought to promote synchronous widespread of Ca^{2+} transients among adjacent spines (Nimchinsky *et al*., 2002). Moreover, it was found that spontaneous, action potential-independent, synaptic transmission is sufficient for BDNF to induce spine formation and increase the proportion of stubby spines (Tyler and Pozzo-Miller, 2003), and that ERK1/2 activation is necessary for BDNF to increase dendritic spine density in hippocampal CA1 pyramidal neurons (Alonso *et al*., 2004). A recent study from the laboratory of Pozzo-Miller showed that BDNF elicits a postsynaptic slowly developing and sustained non-selective cationic current in hippocampal CA1 pyramidal neurons, which was blocked by anti-TRPC3 channel antibodies, and that functional TRPC3 channels are required for BDNF to increase dendritic spine density (Amaral and Pozzo-Miller, 2007). On the other hand, in dissociated cultures of hippocampal neurons, cAMP was found to specifically facilitate the increase in dendritic spine density induced by BDNF, and to recruit TrkB to the postsynaptic densities (Ji *et al*., 2005).

Exogenous BDNF application for 2 weeks to cocultures of cerebellar Purkinje and granular cells increased the density of Purkinje cell dendritic spines, without causing alterations in the spine morphology, whereas treatment with TrkB-immunoglobulin G alone increased the length of spine necks (Shimada *et al*., 1998).

In the visual cortex, overexpression of BDNF caused destabilization of dendritic spines, suggesting that BDNF allows for activity-dependent morphological changes in dendritic spines by causing local dendritic instability (Horch *et al*., 1999). A recent study shows that BDNF treatment of cultured visual cortical neurons increases the size of synaptic PSD95 puncta, and that dendritic transport of PSD95 is facilitated by a pathway initiated by NMDA receptor stimulation of BDNF-TrkB signalling (Yoshii and Constantine-Paton, 2007).

Taken together, the evidences provided by these studies using several different systems indicate a contribution of BDNF to sculpture synapses through both pre- and postsynaptic effects.

Role of BDNF in synaptic plasticity

The role of BDNF and TrkB in LTP is well documented in the adult hippocampus and visual cortex (Bramham and Messaoudi, 2005). Thus, LTP in the hippocampus is attenuated by the TrkB-immunoglobulin G fusion protein, which sequesters endogenous BDNF, and is also reduced in BDNF- or TrkB-knockout mice (Korte *et al*., 1995, 1998; Patterson *et al*., 1996; Chen *et al*., 1999; Minichiello *et al*., 1999; Xu *et al*., 2000). The impairment of LTP in BDNF-knockout mice can be rescued by acute application of BDNF (Figurov *et al*., 1996; Patterson *et al*., 1996; Pozzo-Miller *et al*., 1999) or by virus-mediated transfer of the neurotrophin (Korte *et al*., 1996a, b). A role for BDNF in synaptic potentiation in the hippocampus was also found in studies where stimulation with the neurotrophin was associated with synaptic stimulation that would not normally induce potentiation (Figurov *et al*., 1996; Kovalchuk *et al*., 2002). Acute application of BDNF to hippocampal slices also induces synaptic potentiation in the hippocampal CA1 region (Kang and Schuman, 1995; Kang *et al*., 1997), and similar results were obtained in the dentate gyrus following intrahippocampal infusion of the neurotrophin (Messaoudi *et al*., 1998). However, the effect in hippocampal slices was not occluded by tetanus-induced LTP (and vice versa), suggesting that the mechanism involved is distinct from the one involved in LTP (Kang and Schuman, 1995). Also, the acute effects of BDNF on the excitatory synaptic transmission have been controversial, with some groups reporting minimal or no effects (Frerking *et al*., 1998). Similar to the effects reported in the hippocampus, BDNF induces a long-lasting potentiation of synaptic transmission in the developing visual cortex (Jiang *et al*., 2001), and BDNF-heterozygous mice show an impairment of LTP in the visual cortex due, at least in part, to a reduction in glutamate release (Jiang *et al*., 2001; Abidin *et al*., 2006).

The role of BDNF in LTP is correlated with its contribution to the mechanisms of learning and memory. Thus, an impairment of spatial leaning was observed in BDNF- or TrkB-knockout mice, and in rats subjected to chronic injection of antibodies to BDNF, in contrast with the improved spatial learning and memory formation observed in transgenic mice overexpressing TrkB (Linnarsson *et al*., 1997; Minichiello *et al*., 1999; Mu *et al*., 1999; Koponen *et al*., 2004). Deletion of the BDNF gene in the hippocampus of adult mice impaired spatial learning and novel object recognition (Heldt *et al*., 2007). Animals with deletions in hippocampal BDNF also showed significantly reduced extinction of conditioned fear (Heldt *et al*., 2007). Interestingly, the BDNF val66met polymorphism that affects the activity-dependent release of BDNF is associated with poorer episodic memory in human subjects (Egan *et al*., 2003). Taken together, these evidences suggest that a decrease in hippocampal BDNF may account for the cognitive deficits and the impairment in extinction of aversive memory characteristic of depression and anxiety disorders (Heldt *et al*., 2007). Stimulation of the BDNF-activated pathways may, therefore, be therapeutically relevant under these conditions.

The rapid activity-dependent release of BDNF from the nerve terminals of hippocampal neurons may contribute to

the induction phase of LTP (Kohara *et al.*, 2001). This may be followed by postsynaptic release of the neurotrophin, but the relative role of the dendritic BDNF in synaptic potentiation remains to be determined. The BDNF pool that is relevant in LTP is thought to be released as proBDNF, and cleaved by the extracellular protease plasmin. This protease is activated by the tissue plasminogen activator (Plow *et al.*, 1995), which can also be secreted from stimulated nerve terminals in a Ca^{2+}-dependent manner (Krystosek and Seeds, 1981; Gualandris *et al.*, 1996). According to this hypothesis, tPA- or plasminogen-knockout mice show a severe impairment of late LTP, and this phenotype can be rescued by the mature form of BDNF (Pang *et al.*, 2004; Pang and Lu, 2004). The extracellular BDNF may be then internalized upon binding to the TrkB receptors, and this pool of endocytosed neurotrophin contributes to the release of BDNF necessary to maintain LTP (Santi *et al.*, 2006). However, the relative roles of anterograde and retrograde BDNF signalling in LTP remain to be determined.

The signalling mechanisms that operate downstream of the TrkB receptors in LTP have been investigated using mice with targeted mutations in either the Shc- or the PLCγ-binding sites of TrkB (Minichiello *et al.*, 2002). These studies showed that the early and late phases of LTP in the CA1 region of the hippocampus are dependent on the TrkB coupling to PLCγ, whereas mutation of the Shc docking site on TrkB was without effect on LTP. Selective pre- and postsynaptic expression of the PLCγ pleckstrin homology domain with viral vectors, which blocks PLCγ signalling and $Ins(1,4,5)P_3$ production, abrogated the effect of TrkB receptors on LTP. However, selective blockade of pre- or postsynaptic signalling alone did not result in a significant reduction of LTP, indicating that both sides contribute to the effects of BDNF (Gartner *et al.*, 2006; Gruart *et al.*, 2007). The role of TrkB coupling to PLCγ in LTP induced by high-frequency stimulation correlates with a role of this signalling pathway in associative learning (Gruart *et al.*, 2007).

The presynaptic role of BDNF in the early phase of LTP has been attributed to an enhancement in the synaptic responses to tetanic stimulation and to the facilitation in synaptic vesicle docking to the plasma membrane (Gottschalk *et al.*, 1998; Pozzo-Miller *et al.*, 1999; Jovanovic *et al.*, 2000; Xu *et al.*, 2000; Tyler and Pozzo-Miller, 2001). Furthermore, the induction of LTP by tetanic stimulation of hippocampal slices from P12–13 mice, which requires the addition of exogenous BDNF, depends on the presynaptic interaction of TrkB receptors with the minus end-directed actin-based motor myosin VI and its binding protein GIPC1 (Yano *et al.*, 2006). The presynaptic effects of BDNF enable sustained glutamate release during bursts of action potentials, thereby facilitating LTP induction in response to high-frequency stimulation.

Brain-derived neurotrophic factor also induces postsynaptic responses, some of them contributing to the development of late stages of LTP. Thus, pairing of a weak burst of synaptic stimulation with a brief dendritic application of BDNF induces a rapid and robust LTP, by a mechanism dependent on the activation of postsynaptic Ca^{2+} channels and NMDA receptors (Kovalchuk *et al.*, 2002). Furthermore, BDNF was shown to induce delivery of GluR1-containing AMPARs to the synapse in hippocampal slices (Caldeira *et al.*, 2007a), which may also account for the earlier postsynaptic effects of BDNF in LTP. Interestingly, the BDNF-induced delivery of AMPARs to the synapse depends on $Ins(1,4,5)P_3$ receptor and TRPC calcium signalling (Nakata and Nakamura, 2007), initiated by the PLCγ pathway, a mechanism that resembles the role of the TrkB–PLCγ coupling in LTP (Minichiello *et al.*, 2002). However, there is yet no direct evidence that BDNF regulates AMPAR trafficking during LTP.

Delayed BDNF signalling coupled to local dendritic protein synthesis and stimulation of transcription in the postsynaptic cell is also required for the late phase of LTP, which is mimicked by BDNF application to hippocampal slices and *in vivo* (Soule *et al.*, 2006). Anatomical evidences for the presence of ribosomes in dendrites date from several decades ago (Bodian, 1965; Steward and Levy, 1982), and were followed by evidences for the incorporation of radiolabelled amino acids into proteins in synaptosomes (Rao and Steward, 1991; Weiler and Greenough, 1991). Since then, many observations in several different systems support a role for local protein synthesis in dendrites in synaptic plasticity and memory (Sutton and Schuman, 2006). Interestingly, BDNF induced potentiation of the synaptic transmission between CA3 and CA1 neurons in hippocampal slices where the CA1 dendrites were surgically isolated from their cell bodies, in a manner dependent on protein synthesis (Kang and Schuman, 1996), suggesting that BDNF regulates synaptic function at least in part by activating dendritic protein synthesis. In an elegant study using a dendritic protein synthesis reporter, Aakalu *et al.* (2001) have shown that protein synthesis can be stimulated in dendrites by BDNF. The protein synthesis reporter consists of GFP flanked by the 5′ and 3′ untranslated regions from the CaMKII α-subunit, since these regions contain information sufficient for the dendritic localization of the mRNA. BDNF treatment for 4 h of hippocampal neurons expressing the reporter construct resulted in increased GFP synthesis in both the cell body and dendrites. BDNF also stimulates protein synthesis in mechanically or optically isolated dendrites, and the protein synthesis reporter is concentrated near sites of translation and synapses (Aakalu *et al.*, 2001).

Synaptic potentiation induced by BDNF injection into the rat dentate gyrus is accompanied by a rapid phosphorylation of two key translation factors, the eukaryotic initiation factor 4E (eIF4E) and elongation factor-2, and enhanced expression of eIF4E (Kanhema *et al.*, 2006). However, BDNF treatment of synaptoneurosomes, which contain the pre- and postsynaptic components, selectively induced a transient phosphorylation of eIF4E and upregulated the CaMKII, but had no effect on elongation factor-2. These evidences suggest that BDNF-induced translation is initiated at synapses, whereas initiation and elongation are regulated at non-synaptic sites (Kanhema *et al.*, 2006; see also Smart *et al.*, 2003; Schratt *et al.*, 2004). The regulation of eIF4E by BDNF also includes the translocation of the initiation factor to mRNA granules, by an F-actin-dependent mechanism (Smart *et al.*, 2003). *In vivo* studies suggested that the effects of BDNF on the initiation and elongation steps of translation in the dentate gyrus are mediated by ERK (Kanhema *et al.*, 2006). In contrast, several studies have indicated a role for the

mTOR-PI3K-dependent pathway in the regulation of dendritic protein synthesis by BDNF. A genome-wide screen for mRNAs whose translation is regulated by BDNF in a mTOR signalling-dependent manner in cortical neurons 4 and 14 DIV was performed using RNA associated with the polysomal fraction, presumably being translated, and using Affymetrix DNA microarrays (Schratt *et al*., 2004). This screening led to the identification of several genes whose transcripts are associated with polysomes in an mTOR-sensitive way and among them several transcripts are present in dendrites, such as those for CaMKIIα, Homer2 and NR1. Moreover, the BDNF-induced synthesis of activity-regulated cytoskeleton-associated protein (Arc) and CaMKII in synaptoneurosomes is partially blocked by rapamycin (Takei *et al*., 2004). This study describes how BDNF activates the translation machinery in dendrites, through the activation of mTOR and its downstream translation regulatory molecules, such as 3EBP, p70S6K and S6, in dendrites. The role proposed for the rapamycin (mTOR)-PI3K-dependent pathway and the ERK signalling pathway in activation of translation at the dendritic level contrasts with the key role proposed for the PLCγ in the signalling activity of TrkB coupled to synaptic potentiation (Minichiello *et al*., 2002).

Dendritic mRNAs are transported to synapto-dendritic compartments in RNA granules. The translation of these mRNA molecules may be suppressed during their transport and at synaptic sites until factors released during synaptic stimulation activate their translation. BDNF was recently found to induce the expression of *Limk1*, a protein kinase whose mRNA translation is inhibited by a brain-specific microRNA, miR-134 (Schratt *et al*., 2006). miR-134 is present within dendrites and partially colocalizes with synapsin, indicating that it is present near synaptic sites. Moreover, overexpression of miR-134 in hippocampal neurons in culture leads to a decrease in spine size, through repression of *Limk1* mRNA translation. The translation of *Limk1* mRNA is regulated by BDNF. In fact, BDNF treatment significantly increases the synthesis of Limk1 protein in isolated synaptoneurosomes, in a rapamycin-sensitive manner, and BDNF relieves the suppression of *Limk1* mRNA translation by miR-134 (Schratt *et al*., 2006). The regulation of translation in dendrites by microRNAs, in a BDNF-sensitive manner, may constitute a mechanism whereby the neurotrophin regulates the postsynaptic proteome during the late phases of LTP.

Studies performed in synaptoneurosomes showed that activation of the dendritic translation machinery by BDNF leads to the local synthesis of GluR1 (Schratt *et al*., 2004), Arc/Arg3.1 (Yin *et al*., 2002; Takei *et al*., 2004) and CaMKII (Takei *et al*., 2004). Moreover, intrahippocampal microinfusion of BDNF to trigger LTP at medial perforant path-granule cell synapses *in vivo* leads to the upregulation of mRNA and protein for Arc, and the Arc transcripts are rapidly delivered to granule cell dendrites after BDNF infusion (Ying *et al*., 2002). The synthesis of Arc in particular is necessary for the induction of BDNF-LTP and its time-dependent consolidation (Soule *et al*., 2005), and this protein was proposed to regulate actin polymerization contributing to the formation of stable LTP (Messaoudi *et al*., 2007). One or more proteins synthesized locally in response to activation of TrkB receptors may act locally as a 'synaptic tag' (Reymann and Frey, 2007) to specifically bind pre-existing or newly synthesized plasticity-related proteins at activated synapses expressing LTP.

Importantly, a recent study shows that the presymptomatic impairment in LTP in hippocampal slices from knock-in mouse models of Huntington's disease can be rescued with BDNF, suggesting that the upregulation of this neurotrophin and/or its signaling activity could be a possible treatment for cognitive deficits in asymptomatic carriers of Huntington's disease (Lynch *et al*., 2007). The role of BDNF in LTP contrasts with the effect of proBDNF in enhancing NR2B-dependent long-term synaptic depression, and NR2B-mediated synaptic currents, in the hippocampus (Woo *et al*., 2005). The effect of proBDNF in LTD is mediated by $p75^{NTR}$, but the signalling mechanisms involved remain to be determined.

Concluding remarks

Brain-derived neurotrophic factor is a strong molecular candidate for regulating synaptic plasticity, over short timescales, which requires the involvement of post-translational modifications of pre-existing synaptic components, and also over longer timescales, which requires changes in gene expression or in local protein synthesis. The direct roles for BDNF in synaptic plasticity require synapse-specific actions of the neurotrophin, and precise temporal resolution of these actions. At present, it is still unresolved how the spatial and temporal specificity of the actions of BDNF are assured. Elucidation of these issues is crucial for understanding the function of BDNF as a synaptic modulator.

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Conflict of interest

The authors state no conflict of interest.

References

Aakalu G, Smith WB, Nguyen N, Jiang C, Schuman EM (2001). Dynamic visualization of local protein synthesis in hippocampal neurons. *Neuron* **30**: 489–502.
Abidin I, Kohler T, Weiler E, Zoidl G, Eysel UT, Lessmann V *et al*. (2006). Reduced presynaptic efficiency of excitatory synaptic transmission impairs LTP in the visual cortex of BDNF-heterozygous mice. *Eur J Neurosci* **24**: 3519–3531.
Adachi N, Kohara K, Tsumoto T (2005). Difference in trafficking of brain-derived neurotrophic factor between axons and dendrites of cortical neurons, revealed by live-cell imaging. *BMC Neurosci* **6**: 42.
Alder J, Thakker-Varia S, Crozier RA, Shaheen A, Plummer MR, Black IB (2005). Early presynaptic and late postsynaptic components

contribute independently to brain-derived neurotrophic factor-induced synaptic plasticity. *J Neurosci* **25**: 3080–3085.

Almeida RD, Manadas BJ, Melo CV, Gomes JR, Mendes CS, Graos MM *et al.* (2005). Neuroprotection by BDNF against glutamate-induced apoptotic cell death is mediated by ERK and PI3-kinase pathways. *Cell Death Differ* **12**: 1329–1343.

Alonso M, Medina JH, Pozzo-Miller L (2004). ERK1/2 activation is necessary for BDNF to increase dendritic spine density in hippocampal CA1 pyramidal neurons. *Learn Mem* **11**: 172–178.

Amaral MD, Pozzo-Miller L (2007). TRPC3 channels are necessary for brain-derived neurotrophic factor to activate a nonselective cationic current and to induce dendritic spine formation. *J Neurosci* **27**: 5179–5189.

Aoki C, Wu K, Elste A, Len G, Lin S, McAuliffe G *et al.* (2000). Localization of brain-derived neurotrophic factor and TrkB receptors to postsynaptic densities of adult rat cerebral cortex. *J Neurosci Res* **59**: 454–463.

Arevalo JC, Pereira DB, Yano H, Teng KK, Chao MV (2006). Identification of a switch in neurotrophin signaling by selective tyrosine phosphorylation. *J Biol Chem* **281**: 1001–1007.

Ascher P, Nowak L (1988). The role of divalent cations in the *N*-methyl-D-aspartate responses of mouse central neurones in culture. *J Physiol* **399**: 247–266.

Atwal JK, Massie B, Miller FD, Kaplan DR (2000). The TrkB-Shc site signals neuronal survival and local axon growth via MEK and P13-kinase. *Neuron* **27**: 265–277.

Baldelli P, Hernandez-Guijo JM, Carabelli V, Carbone E (2005). Brain-derived neurotrophic factor enhances GABA release probability and nonuniform distribution of N- and P/Q-type channels on release sites of hippocampal inhibitory synapses. *J Neurosci* **25**: 3358–3368.

Balkowiec A, Katz DM (2002). Cellular mechanisms regulating activity-dependent release of native brain-derived neurotrophic factor from hippocampal neurons. *J Neurosci* **22**: 10399–10407.

Balkowiec A, Kunze DL, Katz DM (2000). Brain-derived neurotrophic factor acutely inhibits AMPA-mediated currents in developing sensory relay neurons. *J Neurosci* **20**: 1904–1911.

Benke TA, Luthi A, Isaac JT, Collingridge GL (1998). Modulation of AMPA receptor unitary conductance by synaptic activity. *Nature* **393**: 793–797.

Bodian D (1965). A suggestive relationship of nerve cell RNA with specific synaptic sites. *Proc Natl Acad Sci USA* **53**: 418–425.

Boehm J, Kang MG, Johnson RC, Esteban J, Huganir RL, Malinow R (2006). Synaptic incorporation of AMPA receptors during LTP is controlled by a PKC phosphorylation site on GluR1. *Neuron* **51**: 213–225.

Bolton MM, Lo DC, Sherwood NT (2000). Long-term regulation of excitatory and inhibitory synaptic transmission in hippocampal cultures by brain-derived neurotrophic factor. *Prog Brain Res* **128**: 203–218.

Bramham CR, Messaoudi E (2005). BDNF function in adult synaptic plasticity: the synaptic consolidation hypothesis. *Prog Neurobiol* **76**: 99–125.

Bredt DS, Nicoll RA (2003). AMPA receptor trafficking at excitatory synapses. *Neuron* **40**: 361–379.

Brigadski T, Hartmann M, Lessmann V (2005). Differential vesicular targeting and time course of synaptic secretion of the mammalian neurotrophins. *J Neurosci* **25**: 7601–7614.

Brunet A, Datta SR, Greenberg ME (2001). Transcription-dependent and -independent control of neuronal survival by the PI3K-Akt signaling pathway. *Curr Opin Neurobiol* **11**: 297–305.

Butowt R, von Bartheld CS (2001). Sorting of internalized neurotrophins into an endocytic transcytosis pathway via the Golgi system: ultrastructural analysis in retinal ganglion cells. *J Neurosci* **21**: 8915–8930.

Butowt R, von Bartheld CS (2005). Anterograde axonal transport of BDNF and NT-3 by retinal ganglion cells: roles of neurotrophin receptors. *Mol Cell Neurosci* **29**: 11–25.

Caldeira MV, Melo CV, Pereira DB, Carvalho R, Correia SS, Backos DS *et al.* (2007a). Brain-derived neurotrophic factor regulates the expression and synaptic delivery of alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor subunits in hippocampal neurons. *J Biol Chem* **282**: 12619–12628.

Caldeira MV, Melo CV, Pereira DB, Carvalho RF, Carvalho AL, Duarte CB (2007b). BDNF regulates the expression and traffic of NMDA receptors in cultured hippocampal neurons. *Mol Cell Neurosci* **35**: 208–219.

Caleo M, Medini P, von Bartheld CS, Maffei L (2003). Provision of brain-derived neurotrophic factor via anterograde transport from the eye preserves the physiological responses of axotomized geniculate neurons. *J Neurosci* **23**: 287–296.

Caleo M, Menna E, Chierzi S, Cenni MC, Maffei L (2000). Brain-derived neurotrophic factor is an anterograde survival factor in the rat visual system. *Curr Biol* **10**: 1155–1161.

Canas N, Pereira IT, Ribeiro JA, Sebastiao AM (2004). Brain-derived neurotrophic factor facilitates glutamate and inhibits GABA release from hippocampal synaptosomes through different mechanisms. *Brain Res* **1016**: 72–78.

Carroll RC, Lissin DV, von Zastrow M, Nicoll RA, Malenka RC (1999). Rapid redistribution of glutamate receptors contributes to long-term depression in hippocampal cultures. *Nat Neurosci* **2**: 454–460.

Carvalho AL, Duarte CB, Carvalho AP (2000). Regulation of AMPA receptors by phosphorylation. *Neurochem Res* **25**: 1245–1255.

Chatterton JE, Awobuluyi M, Premkumar LS, Takahashi H, Talantova M, Shin Y *et al.* (2002). Excitatory glycine receptors containing the NR3 family of NMDA receptor subunits. *Nature* **415**: 793–798.

Chen G, Kolbeck R, Barde YA, Bonhoeffer T, Kossel A (1999). Relative contribution of endogenous neurotrophins in hippocampal long-term potentiation. *J Neurosci* **19**: 7983–7990.

Chen PE, Wyllie DJ (2006). Pharmacological insights obtained from structure–function studies of ionotropic glutamate receptors. *Br J Pharmacol* **147**: 839–853.

Chen ZY, Ieraci A, Teng H, Dall H, Meng CX, Herrera DG *et al.* (2005). Sortilin controls intracellular sorting of brain-derived neurotrophic factor to the regulated secretory pathway. *J Neurosci* **25**: 6156–6166.

Chen ZY, Patel PD, Sant G, Meng CX, Teng KK, Hempstead BL *et al.* (2004). Variant brain-derived neurotrophic factor (BDNF) (Met66) alters the intracellular trafficking and activity-dependent secretion of wild-type BDNF in neurosecretory cells and cortical neurons. *J Neurosci* **24**: 4401–4411.

Conner JM, Lauterborn JC, Yan Q, Gall CM, Varon S (1997). Distribution of brain-derived neurotrophic factor (BDNF) protein and mRNA in the normal adult rat CNS: evidence for anterograde axonal transport. *J Neurosci* **17**: 2295–2313.

Crozier RA, Black IB, Plummer MR (1999). Blockade of NR2B-containing NMDA receptors prevents BDNF enhancement of glutamatergic transmission in hippocampal neurons. *Learn Mem* **6**: 257–266.

Crump FT, Dillman KS, Craig AM (2001). cAMP-dependent protein kinase mediates activity-regulated synaptic targeting of NMDA receptors. *J Neurosci* **21**: 5079–5088.

Cull-Candy S, Brickley S, Farrant M (2001). NMDA receptor subunits: diversity, development and disease. *Curr Opin Neurobiol* **11**: 327–335.

del Toro D, Canals JM, Gines S, Kojima M, Egea G, Alberch J (2006). Mutant huntingtin impairs the post-Golgi trafficking of brain-derived neurotrophic factor but not its Val66Met polymorphism. *J Neurosci* **26**: 12748–12757.

Derkach VA, Oh MC, Guire ES, Soderling TR (2007). Regulatory mechanisms of AMPA receptors in synaptic plasticity. *Nat Rev Neurosci* **8**: 101–113.

Drake CT, Milner TA, Patterson SL (1999). Ultrastructural localization of full-length trkB immunoreactivity in rat hippocampus suggests multiple roles in modulating activity-dependent synaptic plasticity. *J Neurosci* **19**: 8009–8026.

Egan MF, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, Bertolino A *et al.* (2003). The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell* **112**: 257–269.

Elias GM, Nicoll RA (2007). Synaptic trafficking of glutamate receptors by MAGUK scaffolding proteins. *Trends Cell Biol* **17**: 343–352.

Esteban JA (2003). AMPA receptor trafficking: a road map for synaptic plasticity. *Mol Interv* **3**: 375–385.

Esteban JA, Shi SH, Wilson C, Nuriya M, Huganir RL, Malinow R (2003). PKA phosphorylation of AMPA receptor subunits controls synaptic trafficking underlying plasticity. *Nat Neurosci* **6**: 136–143.

Fawcett JP, Aloyz R, McLean JH, Pareek S, Miller FD, McPherson PS *et al.* (1997). Detection of brain-derived neurotrophic factor in a

vesicular fraction of brain synaptosomes. *J Biol Chem* **272**: 8837–8840.
Fawcett JP, Bamji SX, Causing CG, Aloyz R, Ase AR, Reader TA *et al.* (1998). Functional evidence that BDNF is an anterograde neuronal trophic factor in the CNS. *J Neurosci* **18**: 2808–2821.
Figurov A, Pozzo-Miller LD, Olafsson P, Wang T, Lu B (1996). Regulation of synaptic responses to high-frequency stimulation and LTP by neurotrophins in the hippocampus. *Nature* **381**: 706–709.
Finkbeiner S, Tavazoie SF, Maloratsky A, Jacobs KM, Harris KM, Greenberg ME (1997). CREB: a major mediator of neuronal neurotrophin responses. *Neuron* **19**: 1031–1047.
Frerking M, Malenka RC, Nicoll RA (1998). Brain-derived neurotrophic factor (BDNF) modulates inhibitory, but not excitatory, transmission in the CA1 region of the hippocampus. *J Neurophysiol* **80**: 3383–3386.
Friedman HV, Bresler T, Garner CC, Ziv NE (2000). Assembly of new individual excitatory synapses: time course and temporal order of synaptic molecule recruitment. *Neuron* **27**: 57–69.
Fryer RH, Kaplan DR, Feinstein SC, Radeke MJ, Grayson DR, Kromer LF (1996). Developmental and mature expression of full-length and truncated TrkB receptors in the rat forebrain. *J Comp Neurol* **374**: 21–40.
Gartner A, Polnau DG, Staiger V, Sciarretta C, Minichiello L, Thoenen H *et al.* (2006). Hippocampal long-term potentiation is supported by presynaptic and postsynaptic tyrosine receptor kinase B-mediated phospholipase Cgamma signaling. *J Neurosci* **26**: 3496–3504.
Gomes AR, Correia SS, Carvalho AL, Duarte CB (2003). Regulation of AMPA receptor activity, synaptic targeting and recycling: role in synaptic plasticity. *Neurochem Res* **28**: 1459–1473.
Gomes RA, Hampton C, El-Sabeawy F, Sabo SL, McAllister AK (2006). The dynamic distribution of TrkB receptors before, during, and after synapse formation between cortical neurons. *J Neurosci* **26**: 11487–11500.
Goodman LJ, Valverde J, Lim F, Geschwind MD, Federoff HJ, Geller AI *et al.* (1996). Regulated release and polarized localization of brain-derived neurotrophic factor in hippocampal neurons. *Mol Cell Neurosci* **7**: 222–238.
Gooney M, Lynch MA (2001). Long-term potentiation in the dentate gyrus of the rat hippocampus is accompanied by brain-derived neurotrophic factor-induced activation of TrkB. *J Neurochem* **77**: 1198–1207.
Gottschalk W, Pozzo-Miller LD, Figurov A, Lu B (1998). Presynaptic modulation of synaptic transmission and plasticity by brain-derived neurotrophic factor in the developing hippocampus. *J Neurosci* **18**: 6830–6839.
Greger IH, Esteban JA (2007). AMPA receptor biogenesis and trafficking. *Curr Opin Neurobiol* **17**: 289–297.
Gruart A, Sciarretta C, Valenzuela-Harrington M, Delgado-Garcia JM, Minichiello L (2007). Mutation at the TrkB PLCgamma-docking site affects hippocampal LTP and associative learning in conscious mice. *Learn Mem* **14**: 54–62.
Gualandris A, Jones TE, Strickland S, Tsirka SE (1996). Membrane depolarization induces calcium-dependent secretion of tissue plasminogen activator. *J Neurosci* **16**: 2220–2225.
Harrington AW, Leiner B, Blechschmitt C, Arevalo JC, Lee R, Morl K *et al.* (2004). Secreted proNGF is a pathophysiological death-inducing ligand after adult CNS injury. *Proc Natl Acad Sci USA* **101**: 6226–6230.
Hartmann M, Heumann R, Lessmann V (2001). Synaptic secretion of BDNF after high-frequency stimulation of glutamatergic synapses. *EMBO J* **20**: 5887–5897.
Haubensak W, Narz F, Heumann R, Lessmann V (1998). BDNF-GFP containing secretory granules are localized in the vicinity of synaptic junctions of cultured cortical neurons. *J Cell Sci* **111** (Pt 11): 1483–1493.
Hayashi Y, Shi SH, Esteban JA, Piccini A, Poncer JC, Malinow R (2000). Driving AMPA receptors into synapses by LTP and CaMKII: requirement for GluR1 and PDZ domain interaction. *Science* **287**: 2262–2267.
Heldt SA, Stanek L, Chhatwal JP, Ressler KJ (2007). Hippocampus-specific deletion of BDNF in adult mice impairs spatial memory and extinction of aversive memories. *Mol Psychiatry* **12**: 656–670.
Horch HW, Kruttgen A, Portbury SD, Katz LC (1999). Destabilization of cortical dendrites and spines by BDNF. *Neuron* **23**: 353–364.
Ji Y, Pang PT, Feng L, Lu B (2005). Cyclic AMP controls BDNF-induced TrkB phosphorylation and dendritic spine formation in mature hippocampal neurons. *Nat Neurosci* **8**: 164–172.
Jia Y, Zhou J, Tai Y, Wang Y (2007). TRPC channels promote cerebellar granule neuron survival. *Nat Neurosci* **10**: 559–567.
Jiang B, Akaneya Y, Ohshima M, Ichisaka S, Hata Y, Tsumoto T (2001). Brain-derived neurotrophic factor induces long-lasting potentiation of synaptic transmission in visual cortex *in vivo* in young rats, but not in the adult. *Eur J Neurosci* **14**: 1219–1228.
Jing S, Tapley P, Barbacid M (1992). Nerve growth factor mediates signal transduction through trk homodimer receptors. *Neuron* **9**: 1067–1079.
Jonas P (2000). The time course of signaling at central glutamatergic synapses. *News Physiol Sci* **15**: 83–89.
Jourdi H, Iwakura Y, Narisawa-Saito M, Ibaraki K, Xiong H, Watanabe M *et al.* (2003). Brain-derived neurotrophic factor signal enhances and maintains the expression of AMPA receptor-associated PDZ proteins in developing cortical neurons. *Dev Biol* **263**: 216–230.
Jovanovic JN, Benfenati F, Siow YL, Sihra TS, Sanghera JS, Pelech SL *et al.* (1996). Neurotrophins stimulate phosphorylation of synapsin I by MAP kinase and regulate synapsin I–actin interactions. *Proc Natl Acad Sci USA* **93**: 3679–3683.
Jovanovic JN, Czernik AJ, Fienberg AA, Greengard P, Sihra TS (2000). Synapsins as mediators of BDNF-enhanced neurotransmitter release. *Nat Neurosci* **3**: 323–329.
Jovanovic JN, Thomas P, Kittler JT, Smart TG, Moss SJ (2004). Brain-derived neurotrophic factor modulates fast synaptic inhibition by regulating $GABA_A$ receptor phosphorylation, activity, and cell-surface stability. *J Neurosci* **24**: 522–530.
Kang H, Schuman EM (1995). Long-lasting neurotrophin-induced enhancement of synaptic transmission in the adult hippocampus. *Science* **267**: 1658–1662.
Kang H, Schuman EM (1996). A requirement for local protein synthesis in neurotrophin-induced hippocampal synaptic plasticity. *Science* **273**: 1402–1406.
Kang H, Welcher AA, Shelton D, Schuman EM (1997). Neurotrophins and time: different roles for TrkB signaling in hippocampal long-term potentiation. *Neuron* **19**: 653–664.
Kanhema T, Dagestad G, Panja D, Tiron A, Messaoudi E, Havik B *et al.* (2006). Dual regulation of translation initiation and peptide chain elongation during BDNF-induced LTP *in vivo*: evidence for compartment-specific translation control. *J Neurochem* **99**: 1328–1337.
Kawaguchi N, Kuwabara S, Nemoto Y, Fukutake T, Satomura Y, Arimura K *et al.* (2004). Treatment and outcome of myasthenia gravis: retrospective multi-center analysis of 470 Japanese patients, 1999–2000. *J Neurol Sci* **224**: 43–47.
Kew JN, Kemp JA (2005). Ionotropic and metabotropic glutamate receptor structure and pharmacology. *Psychopharmacology (Berl)* **179**: 4–29.
Kohara K, Kitamura A, Morishima M, Tsumoto T (2001). Activity-dependent transfer of brain-derived neurotrophic factor to postsynaptic neurons. *Science* **291**: 2419–2423.
Kojima M, Takei N, Numakawa T, Ishikawa Y, Suzuki S, Matsumoto T *et al.* (2001). Biological characterization and optical imaging of brain-derived neurotrophic factor–green fluorescent protein suggest an activity-dependent local release of brain-derived neurotrophic factor in neurites of cultured hippocampal neurons. *J Neurosci Res* **64**: 1–10.
Kokaia Z, Bengzon J, Metsis M, Kokaia M, Persson H, Lindvall O (1993). Coexpression of neurotrophins and their receptors in neurons of the central nervous system. *Proc Natl Acad Sci USA* **90**: 6711–6715.
Koponen E, Voikar V, Riekki R, Saarelainen T, Rauramaa T, Rauvala H *et al.* (2004). Transgenic mice overexpressing the full-length neurotrophin receptor TrkB exhibit increased activation of the TrkB–PLCgamma pathway, reduced anxiety, and facilitated learning. *Mol Cell Neurosci* **26**: 166–181.
Korber C, Werner M, Hoffmann J, Sager C, Tietze M, Schmid SM *et al.* (2007). Stargazin interaction with alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptors is critically

dependent on the amino acid at the narrow constriction of the ion channel. *J Biol Chem* **282**: 18758–18766.
Korte M, Carroll P, Wolf E, Brem G, Thoenen H, Bonhoeffer T (1995). Hippocampal long-term potentiation is impaired in mice lacking brain-derived neurotrophic factor. *Proc Natl Acad Sci USA* **92**: 8856–8860.
Korte M, Griesbeck O, Gravel C, Carroll P, Staiger V, Thoenen H *et al*. (1996a). Virus-mediated gene transfer into hippocampal CA1 region restores long-term potentiation in brain-derived neurotrophic factor mutant mice. *Proc Natl Acad Sci USA* **93**: 12547–12552.
Korte M, Kang H, Bonhoeffer T, Schuman E (1998). A role for BDNF in the late-phase of hippocampal long-term potentiation. *Neuropharmacology* **37**: 553–559.
Korte M, Staiger V, Griesbeck O, Thoenen H, Bonhoeffer T (1996b). The involvement of brain-derived neurotrophic factor in hippocampal long-term potentiation revealed by gene targeting experiments. *J Physiol (Paris)* **90**: 157–164.
Kovalchuk Y, Hanse E, Kafitz KW, Konnerth A (2002). Postsynaptic induction of BDNF-mediated long-term potentiation. *Science* **295**: 1729–1734.
Krystosek A, Seeds NW (1981). Plasminogen activator release at the neuronal growth cone. *Science* **213**: 1532–1534.
Lan JY, Skeberdis VA, Jover T, Grooms SY, Lin Y, Araneda RC *et al*. (2001). Protein kinase C modulates NMDA receptor trafficking and gating. *Nat Neurosci* **4**: 382–390.
Lau CG, Zukin RS (2007). NMDA receptor trafficking in synaptic plasticity and neuropsychiatric disorders. *Nat Rev Neurosci* **8**: 413–426.
Lau GC, Saha S, Faris R, Russek SJ (2004). Up-regulation of NMDAR1 subunit gene expression in cortical neurons via a PKA-dependent pathway. *J Neurochem* **88**: 564–575.
Laube B, Kuhse J, Betz H (1998). Evidence for a tetrameric structure of recombinant NMDA receptors. *J Neurosci* **18**: 2954–2961.
Lee R, Kermani P, Teng KK, Hempstead BL (2001). Regulation of cell survival by secreted proneurotrophins. *Science* **294**: 1945–1948.
Leonard AS, Hell JW (1997). Cyclic AMP-dependent protein kinase and protein kinase C phosphorylate *N*-methyl-D-aspartate receptors at different sites. *J Biol Chem* **272**: 12107–12115.
Levine ES, Crozier RA, Black IB, Plummer MR (1998). Brain-derived neurotrophic factor modulates hippocampal synaptic transmission by increasing *N*-methyl-D-aspartic acid receptor activity. *Proc Natl Acad Sci USA* **95**: 10235–10239.
Levine ES, Kolb JE (2000). Brain-derived neurotrophic factor increases activity of NR2B-containing *N*-methyl-D-aspartate receptors in excised patches from hippocampal neurons. *J Neurosci Res* **62**: 357–362.
Li BS, Sun MK, Zhang L, Takahashi S, Ma W, Vinade L *et al*. (2001). Regulation of NMDA receptors by cyclin-dependent kinase-5. *Proc Natl Acad Sci USA* **98**: 12742–12747.
Li YX, Zhang Y, Lester HA, Schuman EM, Davidson N (1998). Enhancement of neurotransmitter release induced by brain-derived neurotrophic factor in cultured hippocampal neurons. *J Neurosci* **18**: 10231–10240.
Li Z, Ding M, Thiele CJ, Luo J (2004). Ethanol inhibits brain-derived neurotrophic factor-mediated intracellular signaling and activator protein-1 activation in cerebellar granule neurons. *Neuroscience* **126**: 149–162.
Liao GY, Kreitzer MA, Sweetman BJ, Leonard JP (2000). The postsynaptic density protein PSD-95 differentially regulates insulin- and Src-mediated current modulation of mouse NMDA receptors expressed in *Xenopus* oocytes. *J Neurochem* **75**: 282–287.
Lin SY, Wu K, Levine ES, Mount HT, Suen PC, Black IB (1998). BDNF acutely increases tyrosine phosphorylation of the NMDA receptor subunit 2B in cortical and hippocampal postsynaptic densities. *Brain Res Mol Brain Res* **55**: 20–27.
Linnarsson S, Bjorklund A, Ernfors P (1997). Learning deficit in BDNF mutant mice. *Eur J Neurosci* **9**: 2581–2587.
Lissin DV, Carroll RC, Nicoll RA, Malenka RC, von Zastrow M (1999). Rapid, activation-induced redistribution of ionotropic glutamate receptors in cultured hippocampal neurons. *J Neurosci* **19**: 1263–1272.
Liu A, Hoffman PW, Lu W, Bai G (2004). NF-kappaB site interacts with Sp factors and up-regulates the NR1 promoter during neuronal differentiation. *J Biol Chem* **279**: 17449–17458.
Lou H, Kim SK, Zaitsev E, Snell CR, Lu B, Loh YP (2005). Sorting and activity-dependent secretion of BDNF require interaction of a specific motif with the sorting receptor carboxypeptidase E. *Neuron* **45**: 245–255.
Lu B, Pang PT, Woo NH (2005). The yin and yang of neurotrophin action. *Nat Rev Neurosci* **6**: 603–614.
Lynch G, Kramar EA, Rex CS, Jia Y, Chappas D, Gall CM *et al*. (2007). Brain-derived neurotrophic factor restores synaptic plasticity in a knock-in mouse model of Huntington's disease. *J Neurosci* **27**: 4424–4434.
Malinow R, Mainen ZF, Hayashi Y (2000). LTP mechanisms: from silence to four-lane traffic. *Curr Opin Neurobiol* **10**: 352–357.
Mammen AL, Kameyama K, Roche KW, Huganir RL (1997). Phosphorylation of the alpha-amino-3-hydroxy-5-methylisoxazole4-propionic acid receptor GluR1 subunit by calcium/calmodulin-dependent kinase II. *J Biol Chem* **272**: 32528–32533.
Manadas BJ, Melo CV, Gomes JR, Duarte CB (2007). Neurotrophin signaling and cell survival. In: Malva JO, Rego AC, Cunha RA, Oliveira CR (eds). *Interaction between Neurons and Glia in Aging and Disease*. Springer-Verlag: New York. pp 137–172.
Mano I, Teichberg VI (1998). A tetrameric subunit stoichiometry for a glutamate receptor-channel complex. *NeuroReport* **9**: 327–331.
Margottil E, Domenici L (2003). NR2A but not NR2B *N*-methyl-D-aspartate receptor subunit is altered in the visual cortex of BDNF-knock-out mice. *Cell Mol Neurobiol* **23**: 165–174.
Martinez A, Alcantara S, Borrell V, Del Rio JA, Blasi J, Otal R *et al*. (1998). TrkB and TrkC signaling are required for maturation and synaptogenesis of hippocampal connections. *J Neurosci* **18**: 7336–7350.
Matsumoto T, Numakawa T, Adachi N, Yokomaku D, Yamagishi S, Takei N *et al*. (2001). Brain-derived neurotrophic factor enhances depolarization-evoked glutamate release in cultured cortical neurons. *J Neurochem* **79**: 522–530.
Matsumoto T, Numakawa T, Yokomaku D, Adachi N, Yamagishi S, Numakawa Y *et al*. (2006). Brain-derived neurotrophic factor-induced potentiation of glutamate and GABA release: different dependency on signaling pathways and neuronal activity. *Mol Cell Neurosci* **31**: 70–84.
McAllister AK, Katz LC, Lo DC (1999). Neurotrophins and synaptic plasticity. *Annu Rev Neurosci* **22**: 295–318.
McBain CJ, Mayer ML (1994). *N*-Methyl-D-aspartic acid receptor structure and function. *Physiol Rev* **74**: 723–760.
Mellstrom B, Torres B, Link WA, Naranjo JR (2004). The BDNF gene: exemplifying complexity in Ca^{2+}-dependent gene expression. *Crit Rev Neurobiol* **16**: 43–49.
Messaoudi E, Bardsen K, Srebro B, Bramham CR (1998). Acute intrahippocampal infusion of BDNF induces lasting potentiation of synaptic transmission in the rat dentate gyrus. *J Neurophysiol* **79**: 496–499.
Messaoudi E, Kanhema T, Soule J, Tiron A, Dagyte G, Silva B, Bramham CR (2007). Sustained Arc/Arg3.1 synthesis controls long-term potentiation consolidation through regulation of local actin polymerization in the Dentate Gyrus *in vivo*. *J Neurosci* **27**: 10445–10455.
Meyer-Franke A, Wilkinson GA, Kruttgen A, Hu M, Munro E, Hanson Jr MG *et al*. (1998). Depolarization and cAMP elevation rapidly recruit TrkB to the plasma membrane of CNS neurons. *Neuron* **21**: 681–693.
Minichiello L, Calella AM, Medina DL, Bonhoeffer T, Klein R, Korte M (2002). Mechanism of TrkB-mediated hippocampal long-term potentiation. *Neuron* **36**: 121–137.
Minichiello L, Korte M, Wolfer D, Kuhn R, Unsicker K, Cestari V *et al*. (1999). Essential role for TrkB receptors in hippocampus-mediated learning. *Neuron* **24**: 401–414.
Mori H, Manabe T, Watanabe M, Satoh Y, Suzuki N, Toki S *et al*. (1998). Role of the carboxy-terminal region of the GluR epsilon2 subunit in synaptic localization of the NMDA receptor channel. *Neuron* **21**: 571–580.
Mowla SJ, Farhadi HF, Pareek S, Atwal JK, Morris SJ, Seidah NG *et al*. (2001). Biosynthesis and post-translational processing of the precursor to brain-derived neurotrophic factor. *J Biol Chem* **276**: 12660–12666.
Mowla SJ, Pareek S, Farhadi HF, Petrecca K, Fawcett JP, Seidah NG *et al*. (1999). Differential sorting of nerve growth factor and

brain-derived neurotrophic factor in hippocampal neurons. *J Neurosci* **19**: 2069–2080.

Mu JS, Li WP, Yao ZB, Zhou XF (1999). Deprivation of endogenous brain-derived neurotrophic factor results in impairment of spatial learning and memory in adult rats. *Brain Res* **835**: 259–265.

Muragaki Y, Timothy N, Leight S, Hempstead BL, Chao MV, Trojanowski JQ *et al.* (1995). Expression of trk receptors in the developing and adult human central and peripheral nervous system. *J Comp Neurol* **356**: 387–397.

Nagano T, Yanagawa Y, Obata K, Narisawa-Saito M, Namba H, Otsu Y *et al.* (2003). Brain-derived neurotrophic factor upregulates and maintains AMPA receptor currents in neocortical GABAergic neurons. *Mol Cell Neurosci* **24**: 340–356.

Nakata H, Nakamura S (2007). Brain-derived neurotrophic factor regulates AMPA receptor trafficking to post-synaptic densities via IP_3R and TRPC calcium signaling. *FEBS Lett* **581**: 2047–2054.

Nakazawa T, Komai S, Tezuka T, Hisatsune C, Umemori H, Semba K *et al.* (2001). Characterization of Fyn-mediated tyrosine phosphorylation sites on GluR epsilon 2 (NR2B) subunit of the *N*-methyl-D-aspartate receptor. *J Biol Chem* **276**: 693–699.

Narisawa-Saito M, Iwakura Y, Kawamura M, Araki K, Kozaki S, Takei N *et al.* (2002). Brain-derived neurotrophic factor regulates surface expression of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors by enhancing the *N*-ethylmaleimide-sensitive factor/GluR2 interaction in developing neocortical neurons. *J Biol Chem* **277**: 40901–40910.

Narisawa-Saito M, Silva AJ, Yamaguchi T, Hayashi T, Yamamoto T, Nawa H (1999). Growth factor-mediated Fyn signaling regulates alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor expression in rodent neocortical neurons. *Proc Natl Acad Sci USA* **96**: 2461–2466.

Nimchinsky EA, Sabatini BL, Svoboda K (2002). Structure and function of dendritic spines. *Annu Rev Physiol* **64**: 313–353.

Numakawa T, Matsumoto T, Adachi N, Yokomaku D, Kojima M, Takei N *et al.* (2001). Brain-derived neurotrophic factor triggers a rapid glutamate release through increase of intracellular Ca^{2+} and Na^{+} in cultured cerebellar neurons. *J Neurosci Res* **66**: 96–108.

Numakawa T, Takei N, Yamagishi S, Sakai N, Hatanaka H (1999). Neurotrophin-elicited short-term glutamate release from cultured cerebellar granule neurons. *Brain Res* **842**: 431–438.

Nykjaer A, Lee R, Teng KK, Jansen P, Madsen P, Nielsen MS *et al.* (2004). Sortilin is essential for proNGF-induced neuronal cell death. *Nature* **427**: 843–848.

Nykjaer A, Willnow TE, Petersen CM (2005). p75NTR—live or let die. *Curr Opin Neurobiol* **15**: 49–57.

Ozawa S, Kamiya H, Tsuzuki K (1998). Glutamate receptors in the mammalian central nervous system. *Prog Neurobiol* **54**: 581–618.

Pang PT, Lu B (2004). Regulation of late-phase LTP and long-term memory in normal and aging hippocampus: role of secreted proteins tPA and BDNF. *Ageing Res Rev* **3**: 407–430.

Pang PT, Teng HK, Zaitsev E, Woo NT, Sakata K, Zhen S *et al.* (2004). Cleavage of proBDNF by tPA/plasmin is essential for long-term hippocampal plasticity. *Science* **306**: 487–491.

Passafaro M, Piech V, Sheng M (2001). Subunit-specific temporal and spatial patterns of AMPA receptor exocytosis in hippocampal neurons. *Nat Neurosci* **4**: 917–926.

Patterson SL, Abel T, Deuel TA, Martin KC, Rose JC, Kandel ER (1996). Recombinant BDNF rescues deficits in basal synaptic transmission and hippocampal LTP in BDNF knockout mice. *Neuron* **16**: 1137–1145.

Pereira DB, Chao MV (2007). The tyrosine kinase Fyn determines the localization of TrkB receptors in lipid rafts. *J Neurosci* **27**: 4859–4869.

Pereira DB, Rebola N, Rodrigues RJ, Cunha RA, Carvalho AP, Duarte CB (2006). TrkB receptors modulation of glutamate release is limited to a subset of nerve terminals in the adult rat hippocampus. *J Neurosci Res* **83**: 832–844.

Perez-Otano I, Ehlers MD (2005). Homeostatic plasticity and NMDA receptor trafficking. *Trends Neurosci* **28**: 229–238.

Plow EF, Herren T, Redlitz A, Miles LA, Hoover-Plow JL (1995). The cell biology of the plasminogen system. *FASEB J* **9**: 939–945.

Pozzo-Miller LD, Gottschalk W, Zhang L, McDermott K, Du J, Gopalakrishnan R *et al.* (1999). Impairments in high-frequency transmission, synaptic vesicle docking, and synaptic protein distribution in the hippocampus of BDNF knockout mice. *J Neurosci* **19**: 4972–4983.

Qiang M, Ticku MK (2005). Role of AP-1 in ethanol-induced *N*-methyl-D-aspartate receptor 2B subunit gene up-regulation in mouse cortical neurons. *J Neurochem* **95**: 1332–1341.

Rani CS, Qiang M, Ticku MK (2005). Potential role of cAMP response element-binding protein in ethanol-induced *N*-methyl-D-aspartate receptor 2B subunit gene transcription in fetal mouse cortical cells. *Mol Pharmacol* **67**: 2126–2136.

Rao A, Steward O (1991). Evidence that protein constituents of postsynaptic membrane specializations are locally synthesized: analysis of proteins synthesized within synaptosomes. *J Neurosci* **11**: 2881–2895.

Reichardt LF (2006). Neurotrophin-regulated signalling pathways. *Philos Trans R Soc Lond B Biol Sci* **361**: 1545–1564.

Reymann KG, Frey JU (2007). The late maintenance of hippocampal LTP: requirements, phases, 'synaptic tagging', 'late-associativity' and implications. *Neuropharmacology* **52**: 24–40.

Righi M, Tongiorgi E, Cattaneo A (2000). Brain-derived neurotrophic factor (BDNF) induces dendritic targeting of BDNF and tyrosine kinase B mRNAs in hippocampal neurons through a phosphatidylinositol-3 kinase-dependent pathway. *J Neurosci* **20**: 3165–3174.

Roche KW, O'Brien RJ, Mammen AL, Bernhardt J, Huganir RL (1996). Characterization of multiple phosphorylation sites on the AMPA receptor GluR1 subunit. *Neuron* **16**: 1179–1188.

Rosenmund C, Stern-Bach Y, Stevens CF (1998). The tetrameric structure of a glutamate receptor channel. *Science* **280**: 1596–1599.

Sadakata T, Kakegawa W, Mizoguchi A, Washida M, Katoh-Semba R, Shutoh F *et al.* (2007). Impaired cerebellar development and function in mice lacking CAPS2, a protein involved in neurotrophin release. *J Neurosci* **27**: 2472–2482.

Sala R, Viegi A, Rossi FM, Pizzorusso T, Bonanno G, Raiteri M *et al.* (1998). Nerve growth factor and brain-derived neurotrophic factor increase neurotransmitter release in the rat visual cortex. *Eur J Neurosci* **10**: 2185–2191.

Salio C, Averill S, Priestley JV, Merighi A (2007). Costorage of BDNF and neuropeptides within individual dense-core vesicles in central and peripheral neurons. *Dev Neurobiol* **67**: 326–338.

Sandoval M, Sandoval R, Thomas U, Spilker C, Smalla KH, Falcon R *et al.* (2007). Antagonistic effects of TrkB and $p75^{NTR}$ on NMDA receptor currents in post-synaptic densities transplanted into *Xenopus* oocytes. *J Neurochem* **101**: 1672–1684.

Santi S, Cappello S, Riccio M, Bergami M, Aicardi G, Schenk U *et al.* (2006). Hippocampal neurons recycle BDNF for activity-dependent secretion and LTP maintenance. *EMBO J* **25**: 4372–4380.

Sarbassov DD, Guertin DA, Ali SM, Sabatini DM (2005). Phosphorylation and regulation of Akt/PKB by the rictor–mTOR complex. *Science* **307**: 1098–1101.

Schor NF (2005). The p75 neurotrophin receptor in human development and disease. *Prog Neurobiol* **77**: 201–214.

Schratt GM, Nigh EA, Chen WG, Hu L, Greenberg ME (2004). BDNF regulates the translation of a select group of mRNAs by a mammalian target of rapamycin-phosphatidylinositol 3-kinase-dependent pathway during neuronal development. *J Neurosci* **24**: 7366–7377.

Schratt GM, Tuebing F, Nigh EA, Kane CG, Sabatini ME, Kiebler M *et al.* (2006). A brain-specific microRNA regulates dendritic spine development. *Nature* **439**: 283–289.

Scott DB, Blanpied TA, Swanson GT, Zhang C, Ehlers MD (2001). An NMDA receptor ER retention signal regulated by phosphorylation and alternative splicing. *J Neurosci* **21**: 3063–3072.

Shaywitz AJ, Greenberg ME (1999). CREB: a stimulus-induced transcription factor activated by a diverse array of extracellular signals. *Annu Rev Biochem* **68**: 821–861.

Shelton DL, Sutherland J, Gripp J, Camerato T, Armanini MP, Phillips HS *et al.* (1995). Human trks: molecular cloning, tissue distribution, and expression of extracellular domain immunoadhesins. *J Neurosci* **15**: 477–491.

Shi S, Hayashi Y, Esteban JA, Malinow R (2001). Subunit-specific rules governing AMPA receptor trafficking to synapses in hippocampal pyramidal neurons. *Cell* **105**: 331–343.

Shimada A, Mason CA, Morrison ME (1998). TrkB signaling modulates spine density and morphology independent of

dendrite structure in cultured neonatal Purkinje cells. *J Neurosci* **18**: 8559–8570.

Small DL, Murray CL, Mealing GA, Poulter MO, Buchan AM, Morley P (1998). Brain derived neurotrophic factor induction of *N*-methyl-D-aspartate receptor subunit NR2A expression in cultured rat cortical neurons. *Neurosci Lett* **252**: 211–214.

Smart FM, Edelman GM, Vanderklish PW (2003). BDNF induces translocation of initiation factor 4E to mRNA granules: evidence for a role of synaptic microfilaments and integrins. *Proc Natl Acad Sci USA* **100**: 14403–14408.

Soule J, Messaoudi E, Bramham CR (2006). Brain-derived neurotrophic factor and control of synaptic consolidation in the adult brain. *Biochem Soc Trans* **34**: 600–604.

Soule J, Messaoudi E, Kanhema T, Tiron A, Dagyte G, da Silva B *et al.* (2005). Arc mediates a window of consolidation in long-term synaptic plasticity coupled to local actin polymerization in the rat dentate gyrus *in vivo*. *Abstr Soc Neurosci* **160**: 3.

Steigerwald F, Schulz TW, Schenker LT, Kennedy MB, Seeburg PH, Kohr G (2000). C-Terminal truncation of NR2A subunits impairs synaptic but not extrasynaptic localization of NMDA receptors. *J Neurosci* **20**: 4573–4581.

Steward O, Levy WB (1982). Preferential localization of polyribosomes under the base of dendritic spines in granule cells of the dentate gyrus. *J Neurosci* **2**: 284–291.

Suen PC, Wu K, Levine ES, Mount HT, Xu JL, Lin SY *et al.* (1997). Brain-derived neurotrophic factor rapidly enhances phosphorylation of the postsynaptic *N*-methyl-D-aspartate receptor subunit 1. *Proc Natl Acad Sci USA* **94**: 8191–8195.

Sutton MA, Schuman EM (2006). Dendritic protein synthesis, synaptic plasticity, and memory. *Cell* **127**: 49–58.

Takei N, Inamura N, Kawamura M, Namba H, Hara K, Yonezawa K *et al.* (2004). Brain-derived neurotrophic factor induces mammalian target of rapamycin-dependent local activation of translation machinery and protein synthesis in neuronal dendrites. *J Neurosci* **24**: 9760–9769.

Takei N, Kawamura M, Hara K, Yonezawa K, Nawa H (2001). Brain-derived neurotrophic factor enhances neuronal translation by activating multiple initiation processes: comparison with the effects of insulin. *J Biol Chem* **276**: 42818–42825.

Takei N, Numakawa T, Kozaki S, Sakai N, Endo Y, Takahashi M *et al.* (1998). Brain-derived neurotrophic factor induces rapid and transient release of glutamate through the non-exocytotic pathway from cortical neurons. *J Biol Chem* **273**: 27620–27624.

Teng HK, Teng KK, Lee R, Wright S, Tevar S, Almeida RD *et al.* (2005). ProBDNF induces neuronal apoptosis via activation of a receptor complex of p75NTR and sortilin. *J Neurosci* **25**: 5455–5463.

Tezuka T, Umemori H, Akiyama T, Nakanishi S, Yamamoto T (1999). PSD-95 promotes Fyn-mediated tyrosine phosphorylation of the *N*-methyl-D-aspartate receptor subunit NR2A. *Proc Natl Acad Sci USA* **96**: 435–440.

Tongiorgi E, Armellin M, Giulianini PG, Bregola G, Zucchini S, Paradiso B *et al.* (2004). Brain-derived neurotrophic factor mRNA and protein are targeted to discrete dendritic laminas by events that trigger epileptogenesis. *J Neurosci* **24**: 6842–6852.

Tongiorgi E, Righi M, Cattaneo A (1997). Activity-dependent dendritic targeting of BDNF and TrkB mRNAs in hippocampal neurons. *J Neurosci* **17**: 9492–9505.

Tyler WJ, Pozzo-Miller L (2003). Miniature synaptic transmission and BDNF modulate dendritic spine growth and form in rat CA1 neurones. *J Physiol* **553**: 497–509.

Tyler WJ, Pozzo-Miller LD (2001). BDNF enhances quantal neurotransmitter release and increases the number of docked vesicles at the active zones of hippocampal excitatory synapses. *J Neurosci* **21**: 4249–4258.

Valdez G, Akmentin W, Philippidou P, Kuruvilla R, Ginty DD, Halegoua S (2005). Pincher-mediated macroendocytosis underlies retrograde signaling by neurotrophin receptors. *J Neurosci* **25**: 5236–5247.

Vicario-Abejon C, Collin C, McKay RD, Segal M (1998). Neurotrophins induce formation of functional excitatory and inhibitory synapses between cultured hippocampal neurons. *J Neurosci* **18**: 7256–7271.

von Bartheld CS, Byers MR, Williams R, Bothwell M (1996). Anterograde transport of neurotrophins and axodendritic transfer in the developing visual system. *Nature* **379**: 830–833.

Wang YT, Salter MW (1994). Regulation of NMDA receptors by tyrosine kinases and phosphatases. *Nature* **369**: 233–235.

Wardle RA, Poo MM (2003). Brain-derived neurotrophic factor modulation of GABAergic synapses by postsynaptic regulation of chloride transport. *J Neurosci* **23**: 8722–8732.

Watkins JC, Davies J, Evans RH, Francis AA, Jones AW (1981). Pharmacology of receptors for excitatory amino acids. *Adv Biochem Psychopharmacol* **27**: 263–273.

Weiler IJ, Greenough WT (1991). Potassium ion stimulation triggers protein translation in synaptoneurosomal polyribosomes. *Mol Cell Neurosci* **2**: 305–314.

Wenthold RJ, Prybylowski K, Standley S, Sans N, Petralia RS (2003). Trafficking of NMDA receptors. *Annu Rev Pharmacol Toxicol* **43**: 335–358.

Westphal RS, Tavalin SJ, Lin JW, Alto NM, Fraser ID, Langeberg LK *et al.* (1999). Regulation of NMDA receptors by an associated phosphatase-kinase signaling complex. *Science* **285**: 93–96.

Woo NH, Teng HK, Siao CJ, Chiaruttini C, Pang PT, Milner TA *et al.* (2005). Activation of p75NTR by proBDNF facilitates hippocampal long-term depression. *Nat Neurosci* **8**: 1069–1077.

Wu K, Len GW, McAuliffe G, Ma C, Tai JP, Xu F *et al.* (2004). Brain-derived neurotrophic factor acutely enhances tyrosine phosphorylation of the AMPA receptor subunit GluR1 via NMDA receptor-dependent mechanisms. *Brain Res Mol Brain Res* **130**: 178–186.

Wu K, Xu JL, Suen PC, Levine E, Huang YY, Mount HT *et al.* (1996). Functional trkB neurotrophin receptors are intrinsic components of the adult brain postsynaptic density. *Brain Res Mol Brain Res* **43**: 286–290.

Xu B, Gottschalk W, Chow A, Wilson RI, Schnell E, Zang K *et al.* (2000). The role of brain-derived neurotrophic factor receptors in the mature hippocampus: modulation of long-term potentiation through a presynaptic mechanism involving TrkB. *J Neurosci* **20**: 6888–6897.

Yan Q, Radeke MJ, Matheson CR, Talvenheimo J, Welcher AA, Feinstein SC (1997). Immunocytochemical localization of TrkB in the central nervous system of the adult rat. *J Comp Neurol* **378**: 135–157.

Yano H, Ninan I, Zhang H, Milner TA, Arancio O, Chao MV (2006). BDNF-mediated neurotransmission relies upon a myosin VI motor complex. *Nat Neurosci* **9**: 1009–1018.

Yin Y, Edelman GM, Vanderklish PW (2002). The brain-derived neurotrophic factor enhances synthesis of Arc in synaptoneurosomes. *Proc Natl Acad Sci USA* **99**: 2368–2373.

Ying SW, Futter M, Rosenblum K, Webber MJ, Hunt SP, Bliss TV *et al.* (2002). Brain-derived neurotrophic factor induces long-term potentiation in intact adult hippocampus: requirement for ERK activation coupled to CREB and upregulation of Arc synthesis. *J Neurosci* **22**: 1532–1540.

Yoshii A, Constantine-Paton M (2007). BDNF induces transport of PSD-95 to dendrites through PI3K-AKT signaling after NMDA receptor activation. *Nat Neurosci* **10**: 702–711.

Zhou XF, Parada LF, Soppet D, Rush RA (1993). Distribution of TrkB tyrosine kinase immunoreactivity in the rat central nervous system. *Brain Res* **622**: 63–70.

Zhou XF, Song XY, Zhong JH, Barati S, Zhou FH, Johnson SM (2004). Distribution and localization of pro-brain-derived neurotrophic factor-like immunoreactivity in the peripheral and central nervous system of the adult rat. *J Neurochem* **91**: 704–715.

Ziff EB (2007). TARPs and the AMPA receptor trafficking paradox. *Neuron* **53**: 627–633.