TrkB signalling pathways in LTP and learning

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Abstract | Understanding the mechanisms that underlie learning is one of the most fascinating and central aims of neurobiological research. Hippocampal long-term potentiation (LTP) is widely regarded as a prime candidate for the cellular mechanism of learning. The receptor tyrosine kinase TrkB (also known as NTRK2), known primarily for its function during PNS and CNS development, has emerged in recent years as a potent regulator of hippocampal LTP. Here I describe efforts to understand the signalling pathways and molecular mechanisms that underlie the involvement of TrkB in LTP and learning.

Long-term potentiation
(LTP). A persistent increase in synaptic strength induced by brief high-frequency electrical stimulation of afferent fibres or coincident activation of pre- and postsynaptic neurons.

Synaptic plasticity
The ability of a synapse to change in strength.

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doi:10.1038/nrn2738

For many years, a major focus of neuroscience research has been to understand the cellular changes that occur during memory acquisition. In particular, this work has focused on changes in synaptic activity in the hippocampus, and long-term potentiation (LTP) has been identified as a prime candidate for mediating these changes[1,2].

Different types of LTP have been observed in different neural structures, including the hippocampus, cerebral cortex, amygdala and cerebellum, and LTP can be further divided into NMDA (*N*-methyl-D-aspartate) receptor (NMDAR)-dependent and -independent LTP. The most widely studied type of LTP is NMDAR-dependent LTP at the synapses between Schaffer collaterals and commissural neurons in area CA1 of the adult hippocampus[3], which is commonly used as a basic experimental synaptic model for learning and memory in vertebrates. LTP is generally split into three sequential phases: short-term potentiation, early LTP (E-LTP) and late LTP (L-LTP). Short-term potentiation is a preface to LTP and this and E-LTP are both transient and independent of gene transcription, whereas L-LTP requires changes in gene expression and *de novo* protein synthesis and lasts for hours (see below)[4,5].

In recent years, evidence has emerged for an important role for TrkB (also known as NTRK2), a member of the neurotrophin receptor tyrosine kinase family, and its ligand, brain-derived neurotrophic factor (BDNF), in LTP in the adult hippocampus. A full review of the literature on BDNF and synaptic plasticity has been provided elsewhere[6–9] and is beyond the scope of this article. Here, I discuss the evidence for the role of TrkB in CA1 hippocampal LTP and learning, and consider the signalling pathways and downstream mechanisms involved.

Mechanisms of LTP

We know much about the mechanisms that underlie LTP. Three distinct events characterize each phase: induction, maintenance and expression[4]. Induction is the event that triggers LTP in response to a brief signal elicited by the application of a few trains of high-frequency stimuli such as theta burst or tetanus, maintenance consists of persistent biochemical changes in the cell, and expression involves long-lasting cellular changes that result from these biochemical changes[4].

Postsynaptic Ca^{2+} influx, mediated by the activation of the NMDAR complex, is both necessary and sufficient for the induction of E-LTP[10]. In order for NMDAR channels to open, both sufficient membrane depolarization — which expels the Mg^{2+} block from NMDAR channels — and L-glutamate binding are required. Opening allows Ca^{2+} to flow into the cell. The rapid rise in intracellular Ca^{2+} concentration triggers the short-lasting activation of several enzymes that mediate the induction of E-LTP. Particularly important is the activation of protein kinases such as Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) and protein kinase C (PKC), which are crucial for E-LTP induction[4]. Whereas induction of E-LTP requires transient activation of CaMKII and PKC, maintenance is instead characterized by the persistent activation of these enzymes[2,10–12]. During the maintenance phase of E-LTP, which does not depend on Ca^{2+} influx, CaMKII and PKC become autonomously active, and are consequently able to perform the phosphorylation events that underlie E-LTP expression[4]. These events include the phosphorylation of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors, which increases their activity[3], their trafficking to and from the synaptic plasma membrane[13,14] and their insertion (particularly the GluR1 subunit) into the postsynaptic membrane. Membrane

insertion is facilitated by PKC-mediated phosphorylation of two serine residues in GluR1, which enhances the binding of protein 4.1R, an actin-binding protein[15]. Moreover, recent findings provide evidence that the number and subunit composition of synaptic NMDARs are not static, and that neuronal activity drives NMDAR trafficking to synapses, contributing to the expression mechanism of E-LTP[16]. This provides another dynamic and potentially powerful mechanism for regulating synaptic efficacy and remodelling[17].

E-LTP at CA3–CA1 synapses has also been associated with changes in the presynaptic cell, such as alterations in vesicular release[2]. Recent studies that have directly visualized transmitter release at CA3–CA1 excitatory synapses in rat hippocampal slices have demonstrated that induction of E-LTP can lead to a selective enhancement in presynaptic release of transmitter from the rapidly recycling vesicle pool (RRP)[18].

Postsynaptic action potentials that back-propagate from the axon into dendrites can also provide the depolarization at CA3–CA1 hippocampal dendritic synapses that is necessary for E-LTP induction[19]. However, because the action potential amplitude decreases as it travels from the axon to the distal dendrites, this mechanism may be ineffective at the most distal synapses[20–22]. Recent studies have demonstrated that an alternative postsynaptic signal could be provided by dendritic spikes[23]. Moreover, it was shown that LTP could be induced by only a single burst of dendritic spikes, in concomitance with activation of the NMDARs and L-type voltage-gated Ca^{2+} channels (VGCCs)[24]. These results provide important insight into how *in vivo* activity might lead to LTP at these synapses, although further studies are required to elucidate these mechanisms.

The persistence of E-LTP for hours or days gives rise to L-LTP, which, unlike E-LTP, requires gene transcription and protein synthesis. This has made L-LTP induction an attractive candidate for the molecular analogue of long-term memory (LTM)[25,26]. L-LTP induction is widely believed to depend on both local dendritic protein synthesis[27] and nuclear transcription[28]. PKA, CaMKIV and extracellular signal-regulated kinase (ERK) signalling to the nucleus activates key transcription factors, including cyclic AMP-responsive element-binding protein (CREB), that trigger the synthesis of proteins that underlie L-LTP maintenance[29]. It is also thought that the maintenance of L-LTP is mediated by the structural remodelling of synapses at which LTP occurs. These morphological changes include growth of new dendritic spines and enlargement of pre-existing spines[30], and are mediated by changes in the actin cytoskeleton[31,32].

Signalling cascades activated by TrkB

TrkB activates several well-known intracellular signalling cascades on ligand binding (FIG. 1). The ligands for TrkB are BDNF and neurotrophin 4 (NT4). The binding of these ligands to the full-length TrkB receptor ($TrkB^{TK+}$) (BOX 1) induces ligand–receptor dimerization and autophosphorylation of tyrosine residues in the intracellular kinase domain of the receptor[33]. This leads, in turn, to phosphorylation of tyrosine residues in the juxtamembrane domain or the carboxyl terminus of the receptor, which act as docking sites for adaptor molecules (FIG. 1). Phosphorylation of a tyrosine at position 515 in the juxtamembrane region of $TrkB^{TK+}$ recruits Shc adaptor molecules through their phosphotyrosine-binding (PTB) domains[34]. Another adaptor molecule, fibroblast growth factor receptor substrate 2 (FRS2), competes with Shc adaptor molecules for binding at this site[35,36]. Phosphorylation of a tyrosine at position 816 in the C terminus of $TrkB^{TK+}$ causes phospholipase Cγ (PLCγ) to bind to this site through a Src-homology 2 (SH2) domain and to be phosphorylated. Additional adaptor proteins containing pleckstrin homology (PH) and SH2 domains, such as SH2B and SH2B2, that associate with Trk receptors through direct binding to phosphotyrosine residues in the catalytic domain of the receptor[37] have also been shown to activate TrkB signalling (FIG. 1).

Three main intracellular signalling cascades are activated by the TrkB receptor: the Ras–mitogen-activated protein kinase (MAPK) pathway, the phosphatidylinositol 3-kinase (PI3K)–Akt pathway and the PLCγ–Ca^{2+} pathway[38]. The recruitment and phosphorylation of Shc adaptors leads to the binding of growth factor receptor-bound protein 2 (GRB2) and/or son of sevenless (SOS) and the activation of the Ras–MAPK pathway[39]. FRS2 also contains several phosphorylation-dependent recruitment sites for GRB2, which provides a Shc-independent mechanism for activation of Ras through the GRB2–SOS exchange factor complex[35,40,41]. FRS2 also recruits numerous other signalling proteins, including the adaptor protein CRK, the tyrosine kinase SRC and a protein tyrosine phosphatase, SRC-homology phosphatase 2 (SHP2; also known as PTPN11)[36] (FIG. 1). This complex response to receptor activation is believed to allow sustained activation of the MAPK pathway in response to neurotrophin binding[42].

PI3K does not interact directly with Trk receptors. However, adaptor proteins such as GRB-associated binder-1 (GAB1), insulin-receptor substrate 1 (IRS1) and IRS2, which are recruited to activated TrkB through GRB2 binding, mediate the association and activation of PI3K with TrkB[43,44]. In response to this association, 3-phosphoinositides are generated by PI3K and activate 3-phosphoinositide-dependent protein kinase 1 (PDPK1). Together with these 3-phosphoinositides, PDPK1 activates the protein kinase Akt (also known as protein kinase B), which phosphorylates several proteins[45,46]. Phosphorylation of GAB proteins also leads to the formation of complexes that include SHP2 (REF. 47), which enhances MAPK signalling (FIG. 1).

Finally, phosphorylation of tyrosine 816 of TrkB leads to the recruitment of PLCγ1, which is phosphorylated by the active receptor[38]. Activated PLCγ1 hydrolyses phosphatidylinositol-4,5-bisphosphate ($PtdIns(4,5)P_2$) to generate inositol-1,4,5-trisphosphate ($Ins(1,4,5)P_3$) and diacylglycerol (DAG). $Ins(1,4,5)P_3$ promotes release of Ca^{2+} from internal stores, which results in the activation of enzymes such as Ca^{2+}/calmodulin-dependent protein kinases. DAG stimulates DAG-regulated PKC isoforms[42]. However, evidence that this last pathway is specifically activated by TrkB signalling is still lacking[48] (FIG. 1).

Dendritic spike
An action potential generated in the dendrite of a neuron.

Long-term memory
(LTM). In contrast to short-term memory, LTM has a high capacity for storage of information for potentially unlimited duration.

Adaptor molecules
Molecules containing distinct modular domains, which typically mediate protein–protein interactions, allowing these proteins to form signal transduction complexes.

Phosphotyrosine-binding (PTB) domains
Modular domains within a protein structure. They usually bind to phosphorylated tyrosine residues and are often found in signal transduction proteins.

Src homology 2 (SH2) domains
Modular domains within a protein structure. They usually bind to phosphorylated tyrosine residues and are often found in signal transduction proteins.

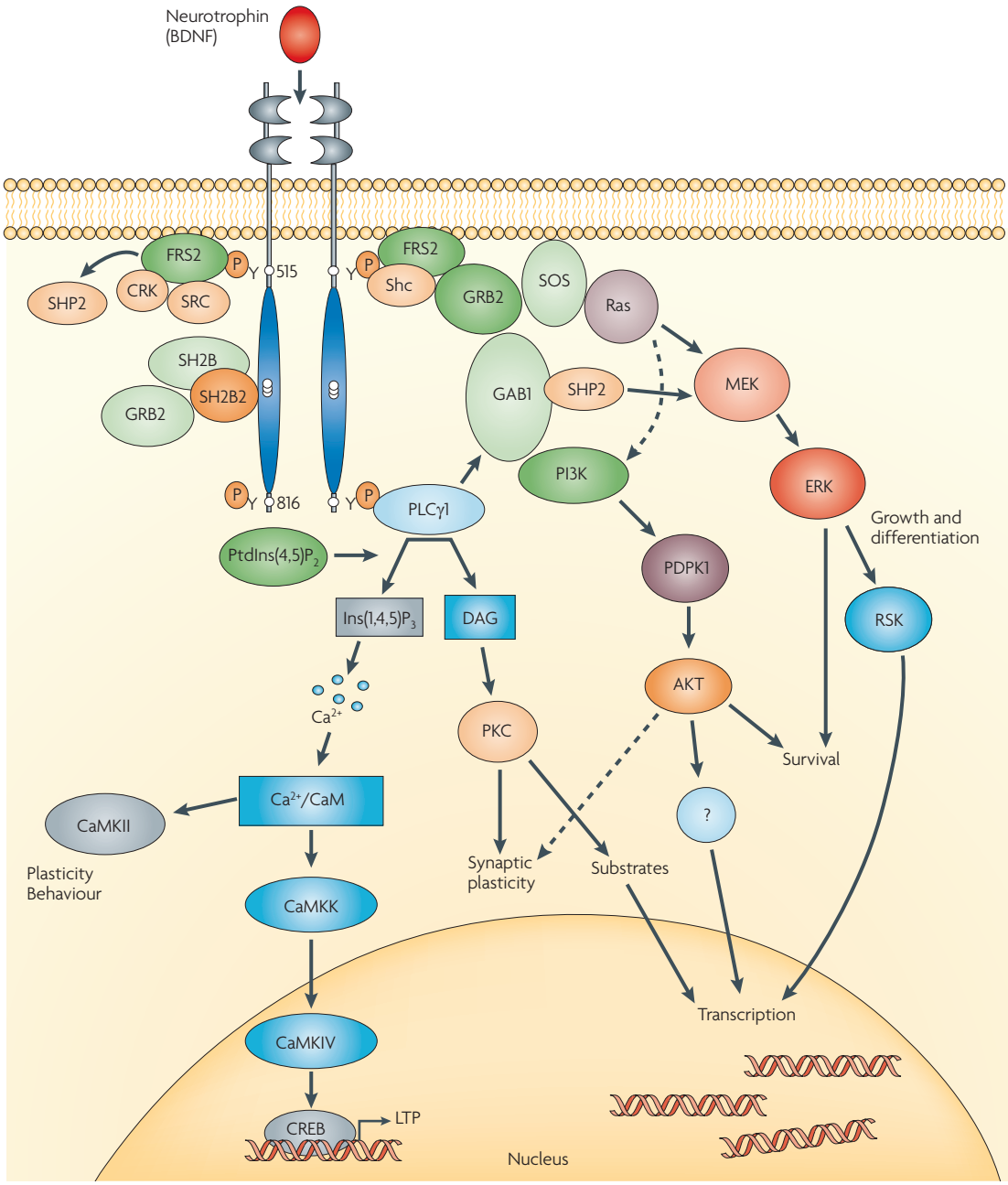
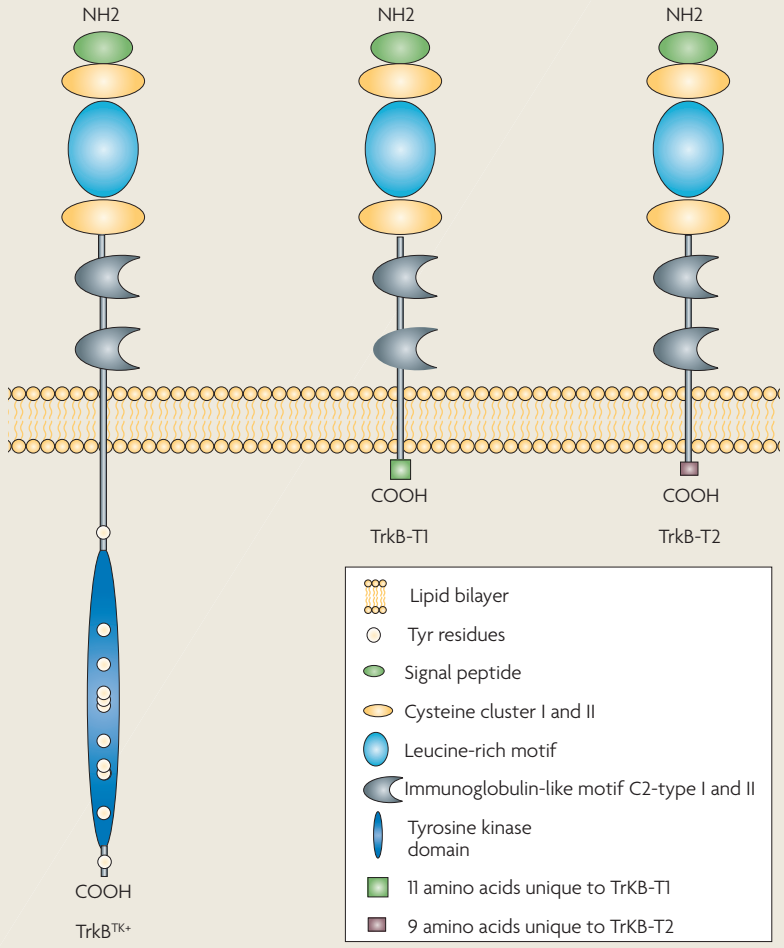


Figure 1 | **Major TrkB-signalling-activated pathways.** The interaction between the receptor tyrosine kinase TrkB and neurotrophins activates three main intracellular signalling pathways. Phosphorylation and recruitment of adaptors to Y515 leads to activation of the Ras–mitogen-activated protein kinase (MAPK) signalling cascade, which promotes neuronal differentiation and growth through MAPK/ERK kinase (MEK) and extracellular signal-regulated kinase (ERK), and to activation of the phosphatidylinositol 3-kinase (PI3K) cascade, which promotes survival and growth of neurons and other cells through Ras or GRB-associated binder 1 (GAB1)[42]. Recruitment and activation of phospholipase Cγ1 (PLCγ1) through phosphorylation of Y816 results in the generation of inositol-1,4,5-trisphosphate ($Ins(1,4,5)P_3$) and diacylglycerol (DAG). Whereas DAG stimulates protein kinase C (PKC) isoforms, $Ins(1,4,5)P_3$ promotes the release of Ca^{2+} from internal stores and subsequent activation of Ca^{2+}/calmodulin (Ca^{2+}/CaM)-dependent protein kinases (CaMKII, CaMKK and CaMKIV)[42]. Point mutation of Y816F impairs phosphorylation of CaMKII, CaMKIV and cyclic AMP-responsive element-binding protein (CREB) and synaptic plasticity[72]. Pathways activated through the Shc adaptor protein site (Ras–MAPK and PI3K) are not impaired by Y816F mutation[72]. Each of these signalling pathways also regulates gene transcription and some may be involved in long-term potentiation (LTP)[42]. PLCγ1 is also able to associate with GAB1, which may stabilize the formation of the complex that forms downstream of TrkB on activation[148]. Some additional adaptors, such as the Src homology domain-containing protein SH2B and SH2B2, have been identified that interact with TrkB[37]. BDNF, brain-derived neurotrophic factor; FRS2, fibroblast growth factor receptor substrate 2; GRB2, growth factor receptor-bound protein 2; PDPK1, 3-phosphoinositide-dependent protein kinase 1; $PtdIns(4,5)P_2$, phosphatidylinositol-4,5-bisphosphate; RSK, ribosomal protein S6 kinase; SHP2, SRC-homology phosphatase 2; SOS, son of sevenless.

Box 1 | **TrkB: a receptor tyrosine kinase**

The *TRKB* (also known as *NTRK2*) locus encodes two different classes of receptors (see the figure). The first consists of $TrkB^{TK+}$ (also known as $gp145^{trkB}$), a heavily glycosylated molecule of 821 amino acid residues that contains all of the canonical motifs of tyrosine kinase receptors, including a signal peptide, two cysteine clusters, a leucine-rich motif, two immunoglobulin-like C2-type motifs, a transmembrane region, a tyrosine kinase domain and a short carboxy-terminal tail of 15 amino acids that includes a Tyr residue[120]. The second class of TrkB receptors (designated $TrkB^{TK-}$) consists of two alternatively spliced 'truncated receptors' (TrkB-T1 (also known as $gp95^{trkB}$) and TrkB-T2) that have identical extracellular and transmembrane domains to $TrkB^{TK+}$ but lack the entire kinase catalytic region[121].



Hippocampal synaptic plasticity and learning

In most experiments, LTP has been measured in hippocampal slices, where it can be induced by the application of a brief train of electrical stimuli. For many years, there was little evidence that hippocampus-dependent learning leads to observable LTP at hippocampal synapses *in vivo*. However, an LTP-like increase in hippocampal synaptic responses was recently observed in mice trained in a simple associative learning task[49]. When NMDARs were blocked both the learning and the synaptic potentiation failed to occur, suggesting that the mechanism of potentiation was NMDAR dependent. Another recent study described *in vivo* LTP in the hippocampus of rats in an avoidance learning task[26]. One outstanding question is whether the molecular pathways required for learning are the same as those that generate LTP *in vitro* and *in vivo*. Here, I review the evidence for an involvement of TrkB signalling in LTP *in vitro* and *in vivo* and in learning models.

Associative learning
Any learning process in which a new response becomes associated with a particular stimulus. In animal behaviour it has mainly been limited to learning that occurs through classical and instrumental conditioning.

Conditional mutagenesis
Regional and temporal control of gene inactivation in mice.

BDNF and TrkB in hippocampal LTP

Activity-dependent transcription and release of BDNF. Evidence for the activity-dependent regulation of BDNF transcription and secretion[50,51] as well as the localization of BDNF and TrkB at glutamatergic synapses[52] suggested that these molecules might be synaptic modulators.

Neuronal activity leading to LTP strongly increases BDNF expression in hippocampal neurons in brain slices[53,54]. The activity-dependent release of BDNF from vesicular stores has been demonstrated in dendrites and axon terminals by direct visualization of BDNF tagged with a green fluorescent protein and overexpressed in hippocampal neurons[55]. However, this approach did not provide information on endogenous BDNF secretion. Recently, a new assay using a cell-based fluorescent indicator has enabled the detection of endogenous BDNF secretion in response to stimulation (such as glutamate application) in neurons[56]. The activity-regulated BDNF release involves an increase in intracellular Ca^{2+} concentration, which may arise as a result of Ca^{2+} influx through NMDAR channels or VGCCs or as a result of release from intracellular Ca^{2+} stores[57]. Furthermore, the release of endogenous BDNF from single neurons following the pairing of repetitive postsynaptic spikes with two-photon uncaging of glutamate at single spines has been demonstrated[58]. This protocol produced spine enlargement in CA1 pyramidal neurons, which was strongly dependent on both protein synthesis and BDNF activity. Therefore, physiological synaptic signals can induce the postsynaptic release of endogenous BDNF at the single-cell level.

Acute versus trophic effects of BDNF–TrkB signalling. Because BDNF–TrkB signalling has been shown to have various functions both during development and in the adult nervous system[59], it is important to distinguish between trophic and acute effects of BDNF–TrkB signalling, especially when analysing experiments based on genetic null mutants for *Bdnf* and/or *Trkb* (also known as *Ntrk2*), which are prone to substantial developmental defects[59]. However, this difficulty can be circumvented by the use of conditional mutagenesis. In fact, because many of the genetic experiments that have suggested the involvement of TrkB signalling in LTP were based on analysis of conditional mutants in which *Trkb* is recombined after development is completed (see below), there was little chance for developmental defects to interfere with the LTP phenotype observed[60]. Even in such conditional mutants, there might still be undetected consequences resulting from the prolonged loss of the trophic effect of TrkB–BDNF signalling in the adult. For instance, if trophic support is required to maintain the synaptic machinery in a condition necessary for plasticity to occur, its absence over a long time could impair potentiation. However, in an extensive morphological analysis performed on these mutants[60] such defects were not apparent.

Evidence for a role of BDNF–TrkB in LTP. There is substantial evidence for a role for BDNF and TrkB in both E-LTP and L-LTP. Deletion of *Bdnf* in mice disrupted the normal induction of E-LTP in the CA1 region of hippocampal slices[61]. BDNF seems to be directly involved in the process of LTP because reintroducing BDNF by viral transduction (hippocampal slices were injected with recombinant adenovirus and electrophysiological recordings were obtained after 14 hours) or by supplying exogenous BDNF (to freshly cut hippocampal slices for 12–15 hours before the start of recording) rescued the defect[62–64].

Blocking the binding of BDNF to TrkB strongly reduced the synaptic responses to high-frequency stimulation (HFS) as well as the magnitude of adult hippocampal E-LTP, which suggests that BDNF may regulate hippocampal LTP by enhancing synaptic responses to HFS[65]. However, the effects of BDNF in rat hippocampal slices seem to depend on age: exogenous BDNF (applied for 2.5–4 hours in all cases) did not affect synaptic potentiation in response to HFS in slices taken from mice at postnatal day 8–9 (P8–9), whereas it promoted stable E-LTP in hippocampal slices subjected to HFS at P12–13 (REF. 65). In the absence of BDNF, all neonatal slices show only short-term potentiation in response to HFS. In slices at P17–18, as in adult slices, exogenous BDNF no longer increased LTP by HFS[65], possibly because there are higher levels of endogenous BDNF at this age than at younger ages[66,67]. It has also been suggested that BDNF might facilitate LTP induction by HFS by suppressing an after-hyperpolarization that normally reduces the responses[68]. However, although it seems to be crucial for LTP induction, BDNF is unable to induce synaptic potentiation by itself. One report showed that a brief bath application of BDNF can trigger a sustained potentiation of synaptic efficacy at CA1 synapses in hippocampal slices[69]; however, this finding has not been reproduced by several laboratories[9,63,65].

L-LTP maintenance was significantly impaired in slices pretreated with TrkB antiserum (1.5–2 hours before recording), indicating a direct involvement of BDNF–TrkB signalling in the maintenance of LTP[70]. Conditional deletion of *Trkb* from forebrain principal neurons also provided evidence for the involvement of TrkB in both E-LTP and L-LTP measured in hippocampal slices[60,71,72], as well as in hippocampus-dependent learning tasks[60], and demonstrated that BDNF influences hippocampal synaptic plasticity through TrkB[73]. This suggests that BDNF and TrkB modulate a synapse's ability to undergo LTP.

Particular consideration has been given to the role of BDNF in protein-synthesis-dependent L-LTP, a process also known as synaptic consolidation. The latest experiments suggest that BDNF activates synaptic consolidation by stimulating the synthesis and the rapid dendritic trafficking of mRNA encoded by the immediate early gene activity-regulated cytoskeleton-associated protein (Arc)[74]. In addition, recent findings indicate that synthesis of BDNF during the late protein-synthesis-dependent phase of LTP is crucial for the persistence of memory storage. It has been shown that blocking protein synthesis and BDNF expression in the rat hippocampus during a restricted time window around 12 hours after training on a one-trial associative learning task caused a deficit in the persistence of LTM storage but not in memory formation[75]. These findings suggest that memory formation and memory persistence share some of the same molecular mechanisms, such as a requirement for protein synthesis and BDNF activity; however, whether memory persistence is actually regulated by two opposing mechanisms — one that reinforces the memory trace and another that weakens it — remains to be determined.

It should also be noted that some studies have reported that exogenous BDNF or NT4 can rapidly depolarize neurons in the hippocampus, cortex and cerebellum[76,77]. This action resulted from the rapid gating of Na^+ channels (in particular $Na_V1.9$ channels) by activation of $TrkB^{TK+}$, and was independent of the classical signalling cascades activated by the TrkB receptor[76,77]. These findings suggest that there is a direct interaction between TrkB and Na^+ channels, although the region of the receptor responsible is unknown. The BDNF-elicited depolarization activates VGCCs and the resulting Ca^{2+} influx enhances the effects of the concurrent activation of NMDAR channels that results from the presynaptic release of glutamate, which is not elicited by BDNF[78].

The effect of exogenous BDNF on HFS-induced LTP at medial perforant path–granule cell synapses has also been investigated: locally applied BDNF induced a sharp rise in Ca^{2+} concentrations in the spines and shafts of hippocampal granule cells and triggered LTP when paired with weak HFS[78]. It was proposed that the coupling of BDNF–TrkB to the Na^+ channel $Na_V1.9$ provides the molecular basis for an instructive role of BDNF in LTP induction[77,78]. These findings suggest that exogenous binding of BDNF to TrkB receptors could generate permissive and/or instructive signals to induce LTP; however, it remains to be determined whether the same phenomenon is induced by endogenous BDNF. Furthermore, it will be important to identify the sites of endogenous BDNF release. Moreover, the existence of such BDNF-induced fast Na^+ currents, which have so far been described by only one laboratory, has now become highly controversial. In particular, it has been noted that the kinetics of BDNF release conflict with the much faster activation kinetics of the $Na_V1.9$-mediated currents[55].

TrkB has also been shown to have a role in long-term depression (BOX 2). Furthermore, in addition to the hippocampus, the involvement of the TrkB receptor in LTP and learning has also been described in other brain structures such as the amygdala and the midbrain, with the latter suggesting an important role for the BDNF–TrkB system in addictive behaviours (BOX 3).

Dissecting the signalling cascades mediating TrkB's effects on LTP. Several of the TrkB-mediated signalling pathways described above have been implicated in LTP and learning. For example, CaMKII autophosphorylation has been shown to be essential for LTP[79–83]. The MAPK cascade that leads to activation of

Hyperpolarization
A change in a cell's membrane potential that makes it more negative.

the ERK1–ERK2 pathway has also been suggested to be important for LTP and some forms of learning and memory[84], although the experimental evidence supporting its role is not well substantiated[29]. Results based on a pharmacological approach pointed to a crucial role for ERK in the induction of LTP by exogenous BDNF in the intact adult rat hippocampus[85,86]. Specifically, intrahippocampal infusion of BDNF led to an increase in ERK phosphorylation in the dentate gyrus. Local infusion of MEK (MAPK/ERK kinase) inhibitors during BDNF delivery abolished both LTP and associated ERK activation. It has also been shown that infusion of recombinant BDNF in the CA1 region of the dorsal hippocampus 12 hours after an inhibitory-avoidance training task can reverse the deficit in memory persistence caused by local inhibition of protein synthesis. Pharmacological inhibition of ERK abolished this effect[87]. Moreover, BDNF and TrkB signalling were shown to modulate the subcellular distribution and nuclear translocation of activated MAPK, rather than being the primary upstream activators of MAPK[88]. Activation of the Ca^{2+}/calmodulin-dependent protein kinase and/or ERK signal transduction pathways mediates the activation of transcription factors such as CREB, which induces gene expression and long-lasting synaptic changes[89]. However, both the Ras–MAPK and the Ca^{2+}/calmodulin-dependent protein kinase pathways (in particular the pathway mediated by CaMKIV) were shown to activate CREB in response to stimulation of cortical neurons or hippocampal slices by BDNF[59,90]. It was therefore unclear which of these pathways contributed to the involvement of TrkB in hippocampal LTP and learning.

To genetically dissect the signalling pathways that mediate the involvement of TrkB in hippocampal LTP, transgenic mice carrying mutations in individual phosphorylation sites on the TrkB receptor were generated and compared[72]. *In vitro* electrophysiology revealed that signalling through the TrkB receptor and its PLCγ docking site[72], but not its Shc-binding site[72,91], is important for both the early and the late phase of hippocampal LTP. Moreover, a point mutation at the PLCγ site significantly impaired the Ca^{2+}-dependent signalling pathway, whereas ERK1–ERK2 activation and nuclear translocation were intact[72], implicating a novel pathway to CREB, through the PLCγ binding site, as being responsible for certain forms of hippocampal synaptic plasticity downstream of TrkB (FIG. 1). These results were surprising and in contrast to the results described above that had pointed to a crucial role for ERK in the induction of LTP by BDNF in the intact adult rat hippocampus[85,86]. The discrepancies between the two sets of data could be due to the experimental set-up or to the fact that different hippocampal regions were analysed in the two experiments (the medial perforant path and the CA3–CA1 region). Furthermore, the LTP experiments in the CA3–CA1 region study were performed in adult tissue slices, whereas the signalling capability of the mutant neurons was assessed in dissociated embryonic cultures.

A combination of mouse genetic models, behavioural analysis and *in vivo* recordings was used to determine the involvement of TrkB signalling in the modification of the strength of the CA3–CA1 synapse in conscious mice during associative learning[92]. These studies revealed that these activity-dependent synaptic changes require an intact TrkB–PLCγ docking site but not the TrkB–Shc docking site, and therefore provide *in vivo* evidence that the molecular pathways activated by docking to the TrkB–PLCγ site underlie both LTP triggered at CA3–CA1 synapses and associative learning in conscious mice. It should be noted that the mouse models used in these experiments are based on constitutive point mutations. To avoid concerns about developmental abnormalities, heterozygous point mutants were used. These mice do not have developmental abnormalities likely to affect the behavioural analysis[92].

In these experiments, synaptic potentiation was assessed in a randomly selected population of hippocampal projections. In order for learning to be the cause of the synaptic potentiation observed in these randomly selected neurons, it would need to induce synaptic changes (LTP) in a large percentage of the total synaptic population. However, data collected *in vivo* has shown that learning invokes only small changes in synaptic strength (no more than 120%)[49] in many synapses. Thus, the probability that a single learning episode would cause LTP in a high percentage of synapses has been questioned. However, it is important to note that a 'single' learning episode, such as the classical conditioning of eyelid responses (trace eyeblink conditioning) requires a

Box 2 | **TrkB–BDNF and long-term depression**

Another prevalent form of excitatory synaptic plasticity is long-term depression (LTD)[3,83]. The typical protocol to elicit NMDAR (*N*-methyl-D-aspartate receptor)-dependent LTD involves prolonged repetitive low-frequency stimulation[122] and a modest increase in postsynaptic Ca^{2+} concentration in dendritic spines[123], which leads, among other events, to the activation of protein phosphatases and so to the dissociation of AMPARs (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors) from the postsynaptic density and to their endocytosis. Recent work has shown that LTD causes shrinkage of dendritic spines[124,125], possibly owing to the loss of AMPARs[126]. This supports the idea that activity-dependent trafficking of AMPARs into and out of synapses underlies the structural modifications associated with growth or shrinkage of synapses. There are many additional forms of LTD that are independent of NMDARs, such as those that are dependent on metabotropic glutamate receptors[3].

Brain-derived neurotrophic factor (BDNF) is initially secreted as a precursor, proBDNF, which is proteolytically cleaved to generate mature BDNF. One molecule that may have a role in this conversion is the secreted protein tissue plasminogen activator (tPA)[127]. It was established that the mature BDNF binds the receptor tyrosine kinase TrkB, whereas the precursor form binds the pan-neurotrophin receptor $p75^{NTR}$ (REFS 128,129), and that, through these two different receptors, pro- and mature BDNF elicit opposite cellular responses[130,131]. Although extracellular cleavage of proBDNF was found to be crucial for hippocampal late long-term potentiation (L-LTP)[127], proBDNF–$p75^{NTR}$ binding was shown to facilitate NMDAR-dependent LTD in the CA1 hippocampal region[132,133]. Moreover, $p75^{NTR}$, unlike TrkB, was shown to negatively modulate dendritic complexity and spine density in adult hippocampal pyramidal neurons[134]. However, contrasting results have been obtained regarding the biosynthesis and processing of endogenous BDNF. One laboratory[135] showed that proBDNF is rapidly converted intracellularly to mature BDNF, which is stored and released by excitatory neurons. Another laboratory, using more sensitive tools to quantify endogenous BDNF forms, found that both the pro- and the mature forms are secreted by neurons[136], and concluded that the actions of BDNF were developmentally regulated by secretion of proBDNF or mature BDNF and by local expression of $p75^{NTR}$ and TrkB. The discrepancy between the two laboratories was shown to be due to differences in the experimental set-up[136].

Box 3 | **TrkB in synaptic plasticity of other brain regions**

In addition to the hippocampus, the receptor tyrosine kinase TrkB was found to be involved in the synaptic plasticity of other brain regions. The amygdala is considered to be crucial for the acquisition, storage and expression of fear memory[137–140]. Fear conditioning (FC), a conditioned-learning test, was shown to induce long-term potentiation (LTP) directly in lateral amygdala neurons from fear conditioned rats (as measured *in vitro*) and in the lateral amygdala of freely behaving rats during fear conditioning (measured *in vivo*)[141,142].

The first evidence for brain-derived neurotrophic factor (BDNF) and TrkB involvement in amygdala-dependent learning came from Pavlovian fear conditioned rats in which BDNF expression and activation of the TrkB receptor were elevated in the amygdala after fear conditioning[143]. Intra-amygdala infusion of a lentiviral vector expressing a dominant-negative TrkB isoform (TrkB.T1) showed that TrkB plays an essential part in the acquisition of Pavlovian fear conditioning triggered in the amygdala nuclei[143]. However, these experiments did not identify the molecular pathways involved downstream of the TrkB receptor. Recently, a study used pharmacological approaches to show that BDNF is required for the acquisition of fear learning through recruitment of the Shc adaptor protein to TrkB and activation of mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K)[144]. This study did not examine phospholipase Cγ (PLCγ) site activation. It will be important to confirm these conclusions using genetic manipulations in combination with biochemical analysis.

BDNF–TrkB signalling was also shown to be involved in the synaptic plasticity of a brain area that is involved in processing reward information, the nucleus accumbens–ventral tegmental area. It was suggested that changes in BDNF and signalling pathways activated downstream alter the structural plasticity of neurons within the nucleus accumbens–ventral tegmental area circuit and promote the development and persistence of addictive behaviours[145–147].

total of 600—1,000 trials in mice. Therefore, although it is possible that not all synapses show increased strength during learning, there could still be a reasonable percentage in which such effects do occur[49]. It is also possible that, rather than increasing the strength of all synapses, learning may involve smaller, more general changes in a synapse's functional properties. Future work may determine whether learning involves other mechanisms such as homeostatic changes, and whether other forms of TrkB-dependent learning are based on similar molecular mechanisms.

TrkB and glutamate neurotransmission

Many of the effects of BDNF on synaptic plasticity are thought to occur through its modulation of ion channels after TrkB-mediated activation of intracellular signalling cascades. How does TrkB signalling interact with the molecules most closely associated with LTP and learning, the synaptic glutamate receptors? Here, I discuss the crosstalk between TrkB receptor signalling and the pathways underlying synaptic plasticity at glutamatergic synapses.

Distribution of TrkB at glutamatergic synapses. TrkB receptors have been found in the axons, nerve terminals and dendritic spines (and to a lesser extent the cell bodies) of glutamatergic pyramidal and granule cells in the rat hippocampus[52], as well as in the dendritic spines of neurons in the rat cerebral cortex[93]. Subcellular fractionation revealed that TrkB receptors are present in a third of the glutamatergic nerve terminals of the rat hippocampus, where they are evenly distributed between the presynaptic active zone and the postsynaptic density[94].

Modulation of glutamate release. The role of BDNF as a modulator of synaptic transmission through presynaptic modifications of transmitter release has been documented in several earlier reviews[73,95]. BDNF enhances glutamate release in synaptosomes[96,97]. Similarly, BDNF increases the frequency, but not the amplitude, of spontaneous synaptic currents (miniature excitatory postsynaptic currents, mEPSCs) in brain slices and in dissociated cultures of hippocampal neurons[98–102], suggesting a presynaptic locus for BDNF's effects (but see below for further discussion of this issue). BDNF has been shown to modulate quantal neurotransmitter release in organotypic slice cultures of rat hippocampus by modulating the distribution of synaptic vesicle pools within presynaptic terminals[102]. BDNF induces modulation of a rapidly recycling pool of vesicles and increases the probability of transmitter release, without affecting the number of independent release sites or the quantal amplitude, at excitatory hippocampal CA3–CA1 synapses[103]. These effects have been shown to be mediated by TrkB, which is localized to the presynaptic sites[104]. Virus-mediated expression of a form of TrkB with a truncated C terminus that acts as a dominant-negative receptor[105] in presynaptic embryonic hippocampal neurons in culture abolished the BDNF-induced synaptic potentiation[104]. The mechanisms by which TrkB receptors facilitate presynaptic glutamate release remain mostly unknown. However, recent work suggests that synapsin[106] and a myosin VI complex[107] may contribute to the presynaptic effect of BDNF.

Despite the results indicating an effect of BDNF and TrkB on glutamate release, a more detailed analysis has revealed that the effect of BDNF on cultured hippocampal neurons is more complex than previously thought. It was shown that among the glutamatergic synapses, 30% were potentiated by BDNF, 10% were inhibited by BDNF and the remaining 60% showed no response to BDNF[99]. To understand these results, we will need to clarify issues such as the heterogeneity of the cultures and whether reduced or absent expression or localization of TrkB at the site of the synapse in these neurons might have contributed to their lack of response. Nevertheless, the limited effects of BDNF on glutamatergic synapses represent a potential caveat for the hypothesis that the effects of TrkB are mediated by alterations in glutamatergic transmission. Indeed, whether BDNF enhances basal synaptic transmission at CA1 synapses in acute hippocampal slices remains controversial. Although initial experiments showed that bath application of BDNF enhances basal synaptic transmission at excitatory CA1 synapses[69,108], other studies indicated that BDNF does not affect basal excitatory transmission[63,65,109–111]. In some studies, no enhancements in synaptic transmission were also obtained by blocking TrkB receptor activity using TrkB-Fc (a BDNF scavenger)[65] or the K252a tyrosine kinase inhibitor[110]. One study in particular could not reproduce the enhancement of synaptic transmission by BDNF, despite using the same experimental conditions as the earlier studies[69,108], but reported a small decrease in inhibitory postsynaptic currents, which suggests that BDNF modulates neuronal excitability by inhibiting

Pavlovian fear conditioning
(FC). A simple form of associative learning that is considered a model system in which to examine the neurobiological basis of learning and memory in the mammalian brain. In this learning paradigm an initially neutral conditioned stimulus (CS), such as a tone, elicits defensive responses on association with an aversive unconditioned stimulus (US), such as a mild electric footshock.

Trace eyeblink conditioning
A form of classical conditioning extensively used to study neural structures and mechanisms that underlie learning and memory. It is based on a relatively simple procedure that often consists of pairing an auditory (or visual) stimulus with an eyeblink-eliciting unconditioned stimulus (such as a mild puff of air to the cornea or a mild shock).

Synaptosome
A subcellular fraction obtained from homogenization of brain tissues that is rich in chemical synapses. Used in biochemical studies.

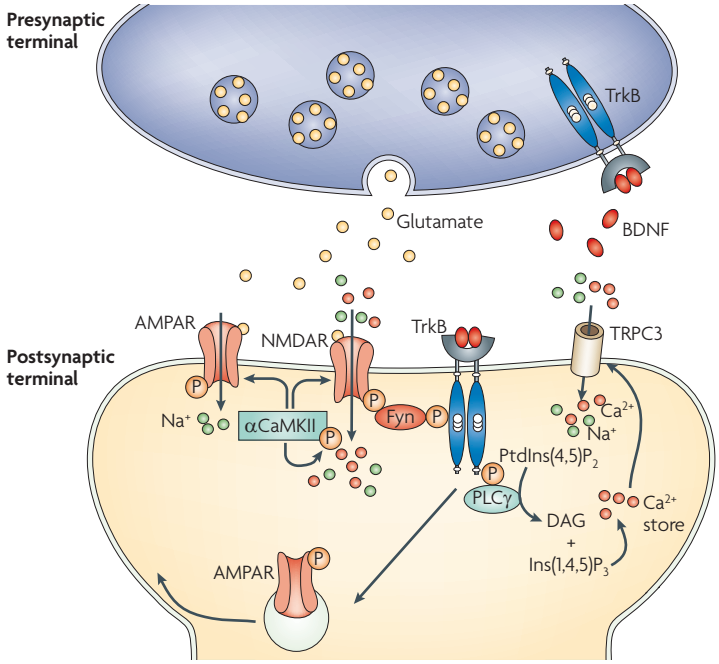


Figure 2 | **Interactions between TrkB signalling and glutamate receptors.** Brain-derived neurotrophic factor (BDNF) and the receptor tyrosine kinase TrkB modulate synaptic transmission through presynaptic modifications of transmitter release[73,95]. In addition, postsynaptic activation of TrkB receptors causes them to interact with glutamate receptors. In particular, the protein tyrosine kinase Fyn, when activated by TrkB, interacts with NMDARs (*N*-methyl-D-aspartate receptors) and increases the open probability of the NMDAR ion channel[114]. Moreover, BDNF–TrkB can induce cation influx through canonical transient receptor potential (TRPC) channels[149,150]. In this case, activation of TrkB and phospholipase Cγ (PLCγ) leads to inositol 1,4,5-trisphosphate ($Ins(1,4,5)P_3$)-dependent Ca^{2+} store depletion, which activates influx of Ca^{2+} and Na^+ through TRPC3, altering membrane potentials that might, in turn, facilitate synaptic Ca^{2+} entry through voltage-gated channels or NMDARs. Ca^{2+} influx through NMDARs activates α-Ca^{2+}/calmodulin-dependent protein kinase II (αCaMKII), which, in turn, contributes to the induction and expression of long-term potentiation through positive regulation of NMDARs and AMPARs (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors), respectively. In addition, BDNF–TrkB modulates AMPAR expression and trafficking[118]. The latter seems to depend on Ca^{2+} mobilization from $Ins(1,4,5)P_3$-sensitive internal stores[119]. DAG, diacylglycerol; $PtdIns(4,5)P_2$, phosphatidylinositol-4,5-bisphosphate.

Open probability
The probability of an individual ion channel protein being in the open state under a given condition, observed as the fraction of the time that an ionic current is flowing. The value can be between zero and one.

Spatial memory formation
A type of learning that is dependent on an intact hippocampus. The primary method of studying spatial learning has been to put a rodent in a maze in which the rodent learns where a particular resource is and how to get to it from the starting location by developing a strategy based on a set of distal visual cues.

transmission mediated by GABA (γ-aminobutyric acid)[111]. The reason for these discrepancies is not clear, but they could be a result of limited penetration of BDNF into the slice, or of differences in a number of experimental variables. As such, this issue cannot yet be resolved.

Modulation of glutamate receptors. Bath application of exogenous BDNF has been shown to increase the firing rate of cultured hippocampal neurons within 2–3 minutes[112]. This effect was selectively blocked by intracellular injection of the tyrosine kinase inhibitor K252a in postsynaptic neurons, suggesting that it was mediated by TrkB activation. One caveat that should be noted is that K252a is membrane permeant and so could have diffused from the injected postsynaptic cell and affected tyrosine kinases in adjacent presynaptic membranes. However, TrkB activation in rat hippocampal neuron cultures has also been shown to increase tyrosine phopshorylation of the NMDAR subunit NR2B[113], which, in turn, caused an increase in NMDAR open probability[114]. Later, evidence was provided for a direct link between TrkB and NMDAR phosphorylation by the tyrosine kinase Fyn[115]. These data identified a postsynaptic signalling cascade that is likely to contribute to hippocampal spatial memory formation (FIG. 2). BDNF was also recently reported to modulate the expression and trafficking of the NMDARs in cultured hippocampal neurons[116]. Because these findings have been extensively reviewed elsewhere[17,117] they are not addressed in detail here.

It is widely accepted that the trafficking of AMPA receptors to the synaptic plasma membrane has an essential role in LTP[13]. BDNF has been shown to modulate AMPA receptor expression and trafficking. Cultured hippocampal neurons stimulated with BDNF were shown to upregulate the expression of the AMPA receptor subunits GluR1 and GluR2 to the same extent; however, BDNF selectively increased the amount of GluR1 associated with the plasma membrane in hippocampal slices[118]. BDNF promoted the synaptic delivery of GluR1 by mechanisms that presumably involved TrkB (as K252a prevented synaptic delivery induced by BDNF)[118] and the mobilization of Ca^{2+} from $Ins(1,4,5)P_3$-sensitive internal stores[119] (FIG. 2). Although there is as yet no direct evidence for BDNF regulation of AMPA trafficking during LTP, and although the mechanisms by which BDNF exerts these functions remain to be determined, these findings suggest that interactions between BDNF–TrkB and the synaptic machinery underlie its effects on LTP and learning.

Concluding remarks

The role of TrkB signalling in certain forms of hippocampal synaptic plasticity is becoming well established, and recent experiments have begun to elucidate the sigalling pathways involved in associative learning and LTP at the CA3–CA1 synapse. It will be essential to elucidate the signalling pathways downstream of TrkB that are required for other forms of synaptic plasticity using a similar combination of *in vivo* methods.

The balance between inhibition and excitation is crucial to brain function. As TrkB is expressed in both excitatory and inhibitory neurons, further work is needed to dissect its contribution to learning and LTP in different neuronal populations. Although we know a lot about the role of TrkB in excitatory neurons, it will be important to generate new genetic tools to allow for cell type-specific ablation of TrkB receptors in inhibitory neurons.

Neuronal diversity may also have a major role in the activation of specific signalling pathways through TrkB receptors, because different neuronal types may express different subsets of adaptor protein. The development of new genetic tools that allow spatial and temporal examination of protein complexes in defined populations of neurons, ideally during or after a particular learning task, is clearly important.

One goal of much recent work on learning and synaptic plasticity has been to devise mechanisms to enhance learning. As we learn more about the TrkB signalling pathways involved in LTP and learning it may be possible to apply this knowledge to advance learning in patient populations in which learning is impaired (see Supplementary information S1 (box)).

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Acknowledgements
I thank members of the laboratory for helpful discussions and comments. This work was supported in part by grants from the European Union (EU FP6 MEMORIES, 037831; EU FP6 StemStroke, 037526).

DATABASES

Entrez Gene: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene
BDNF | CaMKII | CREB | ERK | NT4 | PLCγ | TrkB
OMIM: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM
UniProtKB: http://ca.expasy.org/sprot

FURTHER INFORMATION

Liliana Minichiello's homepage: http://www.embl.it/research/unit/minichiello/index.html

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