

# The neurotrophin hypothesis for synaptic plasticity

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**The neurotrophin hypothesis proposes that neurotrophins participate in activity-induced modification of synaptic transmission. Increasingly, evidence indicates that the synthesis, secretion and actions of neurotrophins on synaptic transmission are regulated by electrical activity and that neurotrophins themselves can acutely modify synaptic efficacy. Neurotrophins appear to exert either a permissive or instructive role on activity-dependent synaptic potentiation and depression, which depends on the particular synaptic connections and developmental stages. The characteristics of synaptic changes that are induced by neurotrophins suggest that this family of proteins is crucial for providing a molecular background in which activity-dependent plasticity can occur at selective synaptic sites within the neural network.**

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**D**URING DEVELOPMENT, particular sets of genes are expressed at specific times and in specific contexts and the functions of gene products are determined by the context in which they are expressed. The neurotrophin (NT) family of molecules is an interesting set of gene products that have multiple functions at different stages of development and at different locations in the nervous system. In addition to their classical roles in neuronal differentiation and survival, NTs have also been implicated in axon pathfinding<sup>1</sup> and synaptic plasticity<sup>2</sup>. The discoveries that expression of NTs in the brain is regulated by neuronal activity<sup>3–5</sup> and that NTs acutely potentiate synaptic transmission<sup>6–8</sup>, paved the way for an expanding field of research that focuses on the role of NTs in synaptic plasticity of developing and adult brains. In this review, we discuss experimental findings in this field in the context of the NT hypothesis for synaptic plasticity.

## The neurotrophin hypothesis

The NT hypothesis proposes that repetitive neuronal activity enhances the expression, secretion and/or actions of NTs at the synapse to modify synaptic transmission and connectivity (Fig. 1), and thus provides a connection between neuronal activity and synaptic plasticity. NTs can play either an instructive or permissive role in activity-dependent synaptic modification of developing and adult brains. In the instructive role, modification is a consequence of NTs acting at the synapse to directly modify presynaptic transmitter release, postsynaptic sensitivity or synaptic morphology, thus leading to a persistent synaptic modification. In the permissive role, modification is induced by other factors that are associated with neuronal activity, whereas NTs carry out housekeeping functions that are necessary for the modification of the synapse.

According to the NT hypothesis, NTs can be secreted locally or from the entire neuron, pre- or postsynaptically, and can act in an autocrine or paracrine fashion. In general, observations support a model in which NTs are secreted locally from the dendrites and act retrogradely at presynaptic terminals to

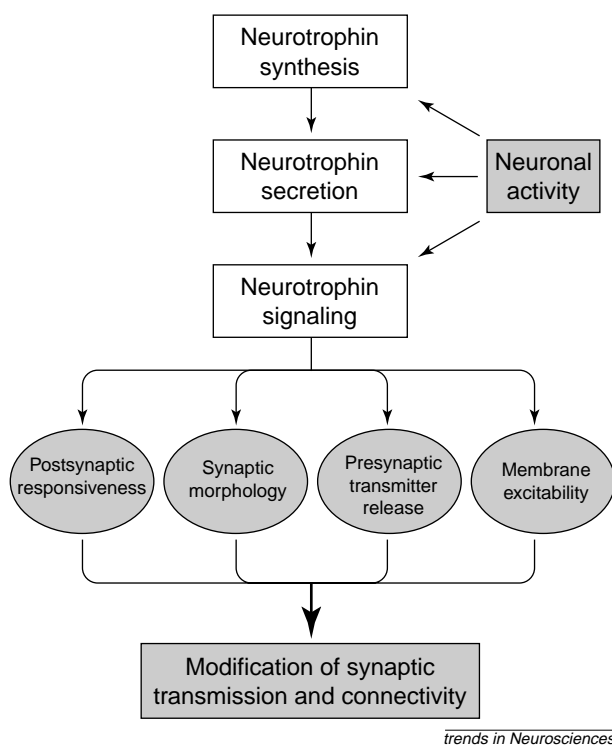
induce long-lasting modifications. Different types of neuronal activity, such as correlated spiking, theta burst and tetanic activity are known to induce persistent synaptic modifications. The nature and the time course of the modifications that are induced by different activities might vary and NTs could be involved at different stages or aspects of synaptic changes.

## Neuronal activity regulates neurotrophin expression and secretion

It is well known that mRNAs encoding various NTs and their respective trk receptors are selectively expressed in different regions of the brain<sup>9</sup>. The notion that the expression of these proteins is linked to activity-dependent plasticity was prompted by the finding that transcription of NT genes is regulated by neuronal activity. For example, epileptogenic activation of glutamatergic synapses increased the expression of mRNAs encoding nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) in slices of rat hippocampus<sup>3–5</sup>, and increasing synaptic activity by reducing AMPA receptor inactivation with ampakines induced a transient elevation in mRNA levels encoding BDNF and trkB in the hippocampus and entorhinal cortex<sup>10</sup>. Conversely, reduction of electrical activity by blockade of glutamate receptors or stimulation of the GABAergic system reduced mRNA levels encoding BDNF and NGF in the hippocampus<sup>11</sup>. These studies demonstrate that an increase or decrease of neuronal activity can enhance or reduce NT expression. Consistent with these observations, light-induced physiological activity enhanced the expression of *BDNF* mRNA in the visual cortex<sup>12</sup> and, in the peripheral system, expression of *NT-4* in skeletal muscle was also elevated by electrical activity<sup>13</sup>.

In hippocampal slices, or cultures overexpressing NGF, depolarization with high KCl or glutamate elicited NGF secretion<sup>14</sup>. Similarly, in neuronal cell lines or cultured hippocampal neurons overexpressing BDNF, membrane depolarization in response to KCl induced a Ca<sup>2+</sup>-dependent release of BDNF (Ref. 15). Experiments using overexpression of mRNAs for the

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**Fig. 1.** The neurotrophin hypothesis for plasticity of synaptic transmission. Neuronal activity regulates neurotrophins (NTs) at three different levels: synthesis, secretion and signaling. Synaptic transmission and connectivity are modified as a consequence of specific changes in the pre- and postsynaptic neurons. There is experimental evidence to support the existence of all three levels of regulation (see text for details).

precursor proteins pro-BDNF and pro-NGF in cultured neurons showed that NGF is constitutively secreted and BDNF remains in the cytoplasm under resting conditions. However, depolarization triggered the release of BDNF but not NGF, suggesting that whereas the secretion of NGF is constitutive, the secretion of BDNF is activity-dependent<sup>16</sup>. Together, these observations suggest that, in systems that express high levels of NTs, NT release can be elicited by robust neuronal depolarization. In addition, studies using the BDNF scavenger protein trkB-IgG to deplete extracellular NT, have also shown that BDNF secretion occurs under conditions that induce long-term potentiation (LTP) in hippocampal slices<sup>17–19</sup>, suggesting a causal link between NT secretion and activity-dependent synaptic plasticity. It is noteworthy that expression of NT-3 or NT-4 does not seem to be modulated by neuronal activity.

Whether NT secretion can be triggered by synaptic activity has been examined at developing neuromuscular junctions (NMJs) in *Xenopus* nerve-muscle cultures. In cultures overexpressing NT-4, a brief tetanus delivered to the presynaptic neuron induced a potentiation of transmitter release only when the postsynaptic myocyte was overexpressing NT-4. This effect was abolished by trkB-IgG, suggesting that the potentiation was mediated by postsynaptically released NT-4 that, in turn, bound to presynaptic trkB receptors<sup>13</sup>. In addition, constitutive NT-4 secretion from myocytes overexpressing NT-4 also elevated the frequency of spontaneous transmitter release from presynaptic nerve terminals, suggesting that the target-derived NT-4 regulated presynaptic function in a trophic manner<sup>13</sup>. Activity-dependent secretion of endogenous NT-3 from the myocyte was also required for maintaining the quantal size of synaptic currents in these cultures<sup>20</sup>. Furthermore,

chronic depolarization or repetitive electrical stimulation of *Xenopus* cultures elevated endogenous NT-3 mRNA production in myocytes, and conditioned medium containing secreted factors increased the frequency of spontaneous transmitter release<sup>21</sup>. Constitutive secretion of NTs at synapses might be triggered by subthreshold depolarization (in the absence of action potentials) and could, therefore, also be activity-dependent. Taken together, these observations support a model in which NTs secreted from the postsynaptic cell in response to physiological activity 'instruct' the presynaptic terminal to increase transmitter release.

In central synapses, experiments carried out under pathological conditions have also been revealing. Increased expression of BDNF mRNA induced by epileptogenic activity<sup>3,5</sup> is accompanied by BDNF release: kindling increased phosphorylation of trkB receptors in hippocampal mossy fibers<sup>22</sup>, and kindling epileptogenesis was abolished by sequestering BDNF using trkB-IgG (Ref. 23). Thus, kindling induces BDNF secretion, which could in turn result in the development of hyper-excitability. In this case, whether BDNF is secreted by the pre- or postsynaptic cell is unclear. Secretion of NTs is also subjected to positive feedback regulation, in which NTs can trigger NT secretion in the absence of other stimuli. Hippocampal neurons overexpressing NTs secreted BDNF in response to NT-3 or NT-4 (but not to NGF), an effect mediated by trk receptors<sup>24</sup>. Similar effects were found in PC12 cells overexpressing different NTs, although secretion appeared to be mediated by the low-affinity receptor p75 (Ref. 25). These studies have shown that NTs can be released in response to stimuli other than electrical activity. Together with NT secretion elicited by neuronal activity, this positive feedback might enhance NT effects at the synapse by acting in an autocrine manner. It remains to be determined whether NT-induced NT release operates under physiological conditions.

In summary, the evidence so far strongly supports the notion that expression and secretion of BDNF and NGF are upregulated by electrical activity (Fig. 2a), but also raises further questions. In particular, the precise patterns of physiological activity that regulate NT expression and secretion need to be determined. Is postsynaptic spiking required to elicit NT secretion? Can spontaneous transmitter release (independent of action potentials) be effective in triggering postsynaptic NT secretion? What cellular mechanisms link electrical activity, NT expression and NT secretion? Are the expression and plasmalemma-insertion of trk receptors also regulated by activity?

### Pre- and postsynaptic secretion of neurotrophins

An important question concerning the function of NTs in synaptic plasticity is whether they are released from pre- or postsynaptic cells. Neurotrophins could be transported anterogradely from the soma to presynaptic terminals, released as a consequence of neuronal spiking, and received by the postsynaptic neuron. Conversely, neuronal or synaptic activity could lead to secretion of NTs from dendrites, and the secreted NTs might act as retrograde factors on the presynaptic neuron. Evidence now exists to support both pre- and postsynaptic secretion of NTs. Presynaptic secretion is suggested by the finding that exogenous NT-3 injected into the retina is internalized by the retinal ganglion cells, anterogradely transported to and released from axonal terminals and

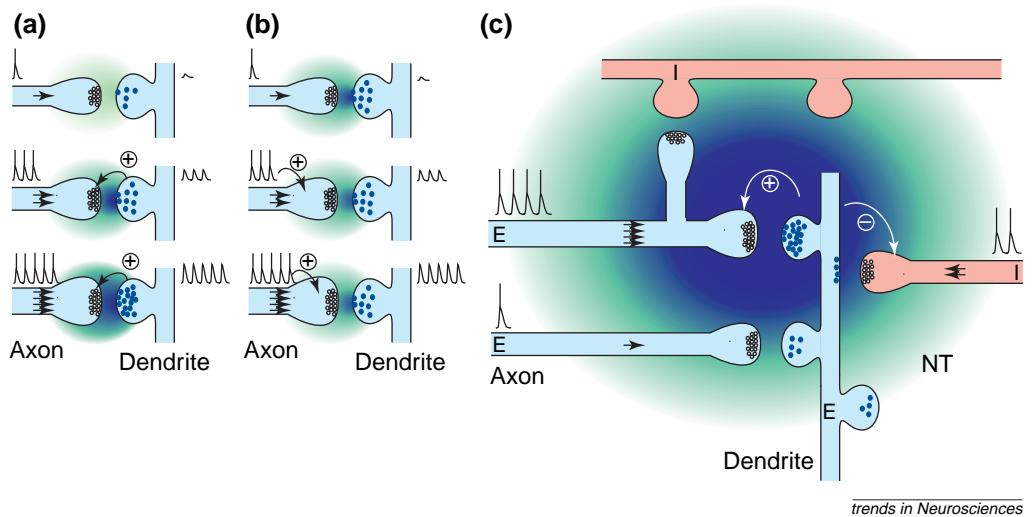
then taken up by second-order neurons in the visual pathway<sup>26</sup>. In the hippocampus, *BDNF* mRNA was found in the granule layer of the dentate gyrus, and the mossy fibers displayed striking BDNF immunoreactivity, suggesting that anterograde transport of the protein had occurred<sup>27,28</sup>. Furthermore, the level of BDNF in mossy fibers was increased following kindling<sup>28</sup> and electroconvulsive seizures<sup>29</sup>, and epileptogenic activity-induced *trkB* receptor activation in the CA3 region<sup>22</sup>, suggesting that activity-induced BDNF secretion from mossy fiber terminals had occurred. Anterograde transport and presynaptic accumulation of BDNF in cortical neurons has also been suggested by anatomical studies of rat neostriatum<sup>30</sup>.

Studies of *Xenopus* nerve–muscle cultures have provided strong evidence for postsynaptic NT secretion. For example, activity-induced synaptic potentiation in nerve–muscle pairs was found only in those pairs in which the postsynaptic muscle, but not the presynaptic neuron, overexpressed NT-4 (Ref. 13). Observations on the trophic function of endogenous NT-3 in this culture system<sup>20,21</sup> are also consistent with postsynaptic secretion of NT-3. Furthermore, the somatodendritic (as opposed to axonal) localization of BDNF in hippocampal cultured neurons and depolarization-induced secretion of this NT (Ref. 15) suggest that BDNF might be postsynaptically secreted by hippocampal neurons.

At the NMJ, electrical activity increases the expression and secretion of NTs at the postsynaptic cell and NT actions are exerted primarily at the presynaptic terminal, supporting a model of retrograde action. It remains to be determined if expression and secretion of NT at central synapses follows a uniform pattern or if different synaptic connections and neuronal types display particular characteristics.

### Neurotrophins modulate synaptic efficacy

For NTs to play an instructive role in activity-dependent synaptic modification, NT secretion should, by itself, promote synaptic modifications. Thus, exogenous application of NTs should be sufficient to elicit the effects associated with activity. Lohof *et al.*<sup>8</sup> were the first to show that exogenous NTs can modify synaptic efficacy in *Xenopus* nerve–muscle cultures. Acute treatment of these cultures with BDNF or NT-3 increased the frequency of spontaneous quantal transmitter release (without changing the quantal size) and the amplitude of evoked postsynaptic responses, suggesting that NTs enhanced the presynaptic transmitter release. Subsequently, the acute effects of NTs have been extensively studied in culture and slice preparations, as well as in the intact brain (reviewed in Refs 31–33). Studies in the central nervous system have been concentrated in the visual cortex and hippocampus. The main questions addressed



**Fig. 2. Modulation of the neurotrophin cascade by activity.** (a) and (b) represent different aspects of activity-dependent regulation. (a) Postsynaptic expression and secretion of neurotrophins (NTs) are regulated by activity. The amount of NT secreted (denoted by the intensity of the blue/green gradient) increases in proportion with the level of synaptic activity. Secreted NTs, in turn, promote the potentiation of transmitter release. The size of the nerve terminal and postsynaptic responses reflects the degree of synaptic potentiation. Blue dots at dendrites represent NT-containing granules, the number of which increases with activity. (b) The actions of NTs at the presynaptic terminal are enhanced by presynaptic spiking. This mechanism might allow small amounts of released NTs to act synergistically with presynaptic activity to enhance transmission. (c) A model integrating the various aspects of NT-induced synaptic modulation. Expression, secretion and actions of NTs are all enhanced by activity. Active excitatory inputs to glutamatergic target neurons (E) are potentiated (+). Inactive inputs, in addition to neighboring glutamatergic connections onto GABAergic neurons (I) within the range of NT action, remain unaltered and inhibitory inputs are depressed (-). Presynaptic secretion of NTs would also be compatible with these models.

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are whether NTs acutely modify synaptic transmission and whether the effects are long lasting. As discussed below, different systems show diverse responsiveness to NTs and some discrepancies have yet to be clarified. *Studies of cultured neurons*

In cultures of hippocampal neurons, the application of BDNF, NT-3 or NT-4 induced a rapid potentiation of glutamate-mediated synaptic transmission<sup>7,34–37</sup>, whereas in cortical neurons, NT-3 has been reported to depress GABA-ergic transmission<sup>38</sup>. Synaptic potentiation lasted for at least 30 min after the removal of exogenous BDNF (Refs 35,37) and was more pronounced for connections with low initial strength, high variability and significant paired-pulse facilitation<sup>34,35</sup>, all of which are characteristics of immature synapses. In recordings of autaptic connections, BDNF increased the frequency of miniature excitatory postsynaptic currents (mEPSCs) but not the amplitude of EPSCs (Ref. 39), consistent with strong (i.e. mature) connections used in these studies, which are less susceptible to BDNF. Overall, evidence from cultured neurons indicates that acute treatments of NTs facilitate excitatory, but reduce inhibitory, transmission. These opposite actions of NTs on excitatory and inhibitory transmission are surprising, because modulation appears to occur at the level of vesicular release, yet there is no evidence that the machinery involved in the vesicular release of GABA or glutamate is different.

Chronic effects on synaptic transmission appear to be different to acute actions and require lower concentrations of NTs. For instance, endogenous secretion of BDNF as a result of chronic activity in cortical cultures decreased the postsynaptic responsiveness of glutamatergic neurons to excitatory inputs, whereas exogenous BDNF increased the responsiveness of GABAergic interneurons<sup>40</sup>. By contrast to the rapid effects of NTs (discussed below), the actions of chronically

released BDNF appear to be purely postsynaptic, as reflected by the modification of both AMPA and NMDA receptor densities<sup>41</sup>. Chronic blockade of neuronal activity also increased membrane excitability in glutamatergic and GABAergic neurons, an effect that was prevented by BDNF (Ref. 42). The latter finding suggests that neuronal excitability is decreased by activity-dependent secretion of BDNF. In contrast to these findings in cortical cultures, chronic application of BDNF to cultured hippocampal neurons forming autaptic connections resulted in an increased amplitude of mEPSCs and EPSCs (Ref. 39). The reason for the discrepancy between the results obtained from cortical and hippocampal neurons is unknown, although it might be attributed to differences among the cell types or between synapses and autapses. Therefore, chronically released BDNF in cortical neurons instructs a postsynaptic modification. Although these modifications are different from the acute effects of NTs, these observations are in agreement with the hypothesis that activity-dependent NT synthesis and secretion modifies synaptic transmission. Whether these modifications are persistent remains to be investigated.

#### Studies of brain slices

Do the observations of NT action at synapses in cell culture apply to mature synapses in the adult brain? Early studies performed in rat hippocampal slices showed that perfusion with BDNF and NT-3 induced a striking potentiation of glutamatergic transmission in Schaffer collateral–CA1 synapses (SC–CA1) within minutes<sup>6,19,43</sup>. By contrast, others have reported that basal synaptic transmission at these connections is not acutely affected by exogenous NTs (Refs 18,44–47), although infusion of BDNF *in vivo* did induce long-lasting potentiation of perforant path–dentate gyrus connections<sup>48</sup>. Interestingly, BDNF depresses GABAergic transmission in the CA1 region of the hippocampus<sup>44,47</sup>, an effect that would enhance excitability as a consequence of decreased inhibition. Overall, evidence from studies of hippocampal slices favors the notion that exogenous NTs do not affect basal glutamate-mediated transmission, but do depress GABA-mediated transmission (Fig. 2c). Recently, it was reported that rapid application of BDNF or NT-4 to central neurons induced a fast depolarization<sup>49</sup> that mimics the response induced by glutamate. This suggests the striking possibility that NTs might act as excitatory transmitters if secreted rapidly at the synapse. By contrast to hippocampal slices, application of BDNF or NGF to slices of visual cortex did produce a rapid potentiation of excitatory synaptic transmission<sup>50,51</sup>. Therefore, it is likely that there are cell type-specific responses to NTs, in addition to the region-specific expression of NTs and trk receptors in the brain. The discrepancy between the results obtained from hippocampal cultures and slices might be attributed to the state of synapse maturation, a parameter that is known to affect the susceptibility of synapses to NTs (Refs 34,35). In summary, the available evidence suggests, first, that NTs potentiate glutamatergic transmission at immature hippocampal synapses and adult cortical connections and, second, that NTs depress GABAergic transmission. Therefore, NTs probably have an instructive or permissive role in synaptic modification that depends on the particular synaptic connections and their state of maturation.

#### Pre- and postsynaptic modification by neurotrophins

The question of whether potentiation occurs pre- or postsynaptically has drawn the field of LTP into a long-lasting debate that has contributed substantially to the understanding of central synaptic transmission<sup>52</sup>. Will this be the case for NT-induced synaptic modification? Currently, most available evidence suggests presynaptic modifications following acute NT treatments. In *Xenopus* NMJs, BDNF and NT-3 increased the frequency but not the amplitude of mEPSCs (Refs 8,13,53,54). Similarly, in hippocampal pyramidal neurons, potentiation of evoked synaptic transmission by BDNF or NT-4 was accompanied by an increase in the frequency but not the amplitude of mEPSCs (Refs 35–37), a reduction in paired-pulse facilitation<sup>6,35,37</sup> and the coefficient of variation<sup>35,37</sup>, in addition to potentiation of NMDA receptor-mediated EPSCs (Ref. 37). Consistent with presynaptic modification, overexpression of dominant-negative trkB receptors in presynaptic (but not postsynaptic) neurons abolished the transient potentiation induced by BDNF (Ref. 36). The BDNF-induced depression of GABAergic synapses in hippocampal slices has also been attributed to presynaptic modifications<sup>44</sup>. The mechanism responsible for NT-induced presynaptic changes in transmitter release is largely unknown, although a recent report indicated that phosphorylation of synapsin I might be involved<sup>55</sup>. It would be of interest to determine whether changes in synapsin I phosphorylation are opposite at glutamate versus GABA release sites.

There is little evidence to support a postsynaptic action of BDNF. In cultures of cortical neurons, BDNF appears to enhance the responses of NMDA but not of AMPA receptors to locally applied agonists<sup>56</sup>. Because glutamate-mediated synaptic transmission is carried out mainly through AMPA receptors, it is unlikely that this modulation contributes to the potentiation of evoked responses by NTs. At the *Xenopus* neuromuscular synapse, NT-4 secreted by the muscle cell produced an autocrine effect, lengthening the mean burst duration of postsynaptic acetylcholine channels resulting in a slower decay of endplate currents<sup>13</sup>. In the latter case, the postsynaptic effect constitutes a minor contribution to the overall synaptic potentiation induced by NT-4 secretion. Taken together, these data strongly support the notion that NT-induced modification of synaptic transmission is expressed predominantly as a change in presynaptic transmitter release. Because the expression of LTP at SC–CA1 hippocampal synapses is largely postsynaptic<sup>52</sup> it should be noted that acute potentiation by NTs cannot account for activity-induced LTP in this region.

#### Target specificity of neurotrophin-induced potentiation

Activity-dependent plasticity of synaptic transmission is determined by the phenotype of pre- and postsynaptic neurons. In the hippocampus, the same pattern of stimulation that potentiates glutamatergic transmission onto glutamatergic neurons fails to do so when the postsynaptic neuron is GABAergic<sup>57–59</sup>. In addition, the identity of the postsynaptic target cell in neocortical slices determines whether a synapse undergoes paired-pulse facilitation or depression – two forms of short-term presynaptic plasticity<sup>60</sup>. Interestingly, potentiation of presynaptic glutamate release by NTs has also been shown to be specific for those connections that impinge upon glutamatergic target neurons<sup>37</sup>, suggesting that retrograde modulation occurs during

development. This potentiation was not global, but instead was localized to terminals that contacted glutamatergic target neurons. Perhaps the presence of a glutamatergic dendrite during synaptogenesis results in an NT-responsive presynaptic terminal. As discussed below, because BDNF has a permissive function in LTP at the CA1 region of the hippocampus<sup>18,19,45,46,61,62</sup> the actions of NTs might provide a mechanism by which the induction of LTP becomes target-specific (Fig. 2).

### Role of neurotrophins in LTP and LTD

Regardless of whether or not NTs affect basal synaptic transmission, there is solid evidence implicating NTs in activity-induced LTP and LTD at central synapses. For example, the induction of LTP at SC-CA1 synapses by tetanic stimulation is impaired in hippocampal slices from BDNF knockout mice<sup>46,61</sup>, but can be rescued either by re-expression of BDNF in the slice via viral infection<sup>62</sup>, or by infusion of recombinant BDNF for a few hours<sup>46</sup>. These results strongly suggest that BDNF is involved in LTP. In addition, in normal hippocampal slices, induction of LTP by theta burst stimulation (TBS), but not by tetanic stimulation, was impaired if endogenous BDNF was sequestered using either trkB-IgG (Refs 18,19) or antibodies against BDNF (Ref. 17). BDNF was also required for maintaining the late phase of LTP induced by tetanus<sup>19</sup>. The differential effects of depleting BDNF on LTP induced by different stimulation protocols (TBS versus tetanus) suggest that different cellular mechanisms underlie the induction and maintenance of these two types of LTP, and that BDNF might have a differential involvement in these mechanisms.

Does NT play an instructive role in LTP by inducing synaptic potentiation or a permissive role by maintaining housekeeping functions that are necessary for the induction and maintenance of LTP? Based on the effects of NTs on synaptic efficacy, the possibility that LTP at central synapses is due to direct synaptic action of NTs (an instructive role) cannot be ruled out. However, in the particular case of LTP at hippocampal CA1 synapses, the evidence supports a permissive role for NTs. This permissive role is illustrated well by the finding that BDNF pre-incubation, which had no effect on basal synaptic transmission, facilitated the induction of LTP in young hippocampal slices by sustaining presynaptic transmitter release during high-frequency stimulation<sup>18,45</sup>. Consistently, recent observations in BDNF knockout mice suggested that the number of docked vesicles at CA1 synapses might be regulated by BDNF (Ref. 63).

Electrophysiological recordings made in slices from visual cortex have implicated both NGF and BDNF in synaptic plasticity during the critical period for the formation of ocular dominance columns (ODCs). A high concentration of BDNF produced an acute potentiation of basal excitatory synaptic transmission<sup>51</sup>, and low concentrations of BDNF facilitated tetanus-induced LTP but prevented LTD induced by low-frequency stimulation<sup>50,64,65</sup>. Moreover, sequestration of BDNF using trkB-IgG facilitated the induction of LTD, suggesting that endogenous release of BDNF might prevent the depression of synaptic transmission induced by low-frequency activity. The susceptibility to LTP in the visual cortex (Ref. 66) coincides with the critical period of plasticity<sup>67</sup>. In a recent study, LTP during the critical period in the visual cortex was blocked by NGF and also by antagonists of muscarinic receptors<sup>68</sup>. After the

critical period, LTP was restored by sequestering NGF using trkA-IgG or by activating muscarinic receptors, suggesting that NGF might end the critical period of plasticity by modulating cholinergic transmission. BDNF can also induce the maturation of GABA-mediated transmission, which in turn prevents LTP in the visual cortex<sup>69</sup>. This is consistent with the finding that chronic BDNF increases excitatory transmission onto GABAergic neurons in cortical cultures, shifting the balance from excitation to inhibition<sup>40</sup>. Blockade of GABA<sub>A</sub> receptors also restores LTP after the critical period. Therefore, it appears that both NGF and BDNF 'cooperate' to finalize the critical period. These observations support a permissive role (or rather, a 'non-permissive' role) of NTs in synaptic plasticity in the visual cortex.

The influence of visual inputs on the formation of ODCs in the primary visual cortex during the critical period<sup>70</sup> has been a classical model for activity-dependent modification of connectivity in the developing nervous system. There is now substantial evidence that NTs are involved in development of ODCs (reviewed in Refs 32,71). One attractive hypothesis is that activity-dependent refinement of thalamocortical projections is caused by NT-dependent synaptic modification. Specifically, it has been proposed that either thalamocortical axons compete for limited amounts of target-derived NTs in the visual cortex or that only active nerve terminals are receptive to the NTs and can thus be stabilized. It is possible that the NT-induced potentiation in the visual cortex directly contributes to the stabilization of thalamocortical connections. In such a case, does activity in the presynaptic nerve terminal confer the responsiveness of the synapse to NTs? There is now evidence that the synaptic action of NTs might be regulated by electrical activity (described below).

### Activity-dependent actions of neurotrophins

NTs were shown to increase the length and complexity of the dendritic trees in cortical neurons<sup>72</sup>; however, this effect could be abolished if spiking, synaptic transmission, or L-type Ca<sup>2+</sup> channels were blocked<sup>73</sup>. Similarly, the ocular dominance shift induced by monocular deprivation can be prevented by NGF only in the presence of neuronal activity<sup>74</sup>. These observations suggest that NT-induced morphological changes require neuronal activity, but how neuronal activity affects NT-dependent morphological changes is unknown. Recent studies of the synaptic action of NTs showed that neuronal activity can enhance NT-induced potentiation of synaptic transmission. For example, synaptic potentiation at *Xenopus* NMJs in response to the application of exogenous BDNF is greatly facilitated by stimulation of the presynaptic neuron<sup>53</sup>, an effect that can be abolished by inhibition of cAMP signaling<sup>75</sup>. It appears that presynaptic depolarization elevates the concentration of intracellular cAMP, which in turn facilitates the transduction of NT signaling. In retinal ganglion cells, neuronal depolarization together with elevation of intracellular cAMP increased the number of trkB receptors in the plasma membrane<sup>76</sup>, a mechanism that might account for the synergistic relationship between NTs and activity at the synapse. Synergism might also occur in the cytoplasmic transduction cascades triggered by NTs and electrical activity. Both BDNF and synaptic activity have been reported to activate the Ca<sup>2+</sup>-calmodulin-dependent

pathway that leads to CREB phosphorylation<sup>77,78</sup>, suggesting that there is crosstalk between two separate transduction pathways. Synergism between synaptic activity and NT actions could also provide a mechanism by which low concentrations of locally released NTs could be sufficient to elicit a persistent modification at the synapse, thereby facilitating an instructive action (Fig. 2b). Furthermore, active inputs will be selectively strengthened by endogenously released NTs (Fig. 2c).

### Concluding remarks

Overall, experimental observations support the NT hypothesis as described at the outset of this review. The evidence is summarized in the model illustrated in Fig. 2c, where: (1) synthesis and secretion of NTs are increased by neuronal activity; (2) NTs are secreted postsynaptically; (3) the action of NTs on presynaptic terminals is spatially restricted; (4) active glutamatergic terminals impinging onto glutamate-containing (but not GABA-containing) neurons are potentiated; and (5) GABAergic terminals are depressed. A crucial aspect of this model, which remains to be addressed experimentally, is the spatial and temporal range of action of secreted NTs. This would determine how far the NT effect would spread, and to what extent adjacent synapses that have uncorrelated activity would be affected. Furthermore, consistent with the rapid morphogenic effects of NTs in initiating axonal and dendritic sprouting<sup>72,79</sup>, secreted NTs might induce changes in synaptic morphology that form an integral part of persistent synaptic modifications.

The ubiquitous presence of NT in the adult nervous system<sup>9</sup> clearly argues for multiple functional roles of this family of proteins throughout the life of an organism. Given the diversity of synaptic organization and distribution of NTs and trk receptors in the nervous system, whether NT plays an instructive or permissive role probably depends on the type of synapse, the stage of neural development and the pattern of neuronal activity. Most of our current knowledge, which forms the basis of the NT hypothesis of synaptic plasticity, is derived from studies of *in vitro* preparations. A crucial test of the hypothesis will be to determine whether the activity-dependent expression, secretion and actions of NTs occur *in vivo* under physiological conditions.

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## BOOK REVIEWS

### Dendrites

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Successive generations of neuroscientists have fallen under the spell of neuronal dendrites. It is as if the branching patterns express an exotic cellular personality unique to their owners, extending their arms and beckoning with their undulating hands and fingertips to entice the beholder to try to follow them in their dance to the unheard rhythms of the neural symphony.

Such, at least, is the hold that dendrites have exerted over the present reviewer, and such appears to be the hold that they have exerted over the editors and contributors to this book. The editors come to their task with impeccable credentials, tracing their lineage from the laboratory of Bert Sakmann to their graduate mentors Julian Jack, Stephen Redman and Daniel Johnston, who themselves are steeped in

the methods of Wilfrid Rall, the founder of the biophysical and computational analysis of dendritic function in the 1950s and 1960s. Among many who could have been chosen, they have assembled a representative cast of authors, largely the new generation, which communicates a fresh enthusiasm for the subject.

Since the 1960s it has been realized that understanding how these highly branched structures contribute to neuronal information processing requires analysis at all levels of cellular organization and function. Dendrites, thus, constitute one of the great