Neurotrophin regulation of synaptic transmission

Erin M Schuman

Examples of signaling molecules that are devoted to neuronal development at the exclusion of other functions are scarce. It may then come as no surprise to learn that a family of molecules that promote neuronal survival, differentiation and outgrowth also regulate synaptic transmission at both developing and mature synapses. Indeed, many studies over the past five years have shown that neurotrophins, including nerve growth factor (NGF), neurotrophin-3 (NT-3), NT-4/5 and brain-derived neurotrophic factor (BDNF), have both rapid and long-latency influences on synaptic strength. New research has highlighted the enormous range of neurotrophin actions at both developing and mature synapses, demonstrating that transmission can be enhanced or reduced at excitatory and inhibitory synapses by either pre- or postsynaptic mechanisms.

Addresses
Howard Hughes Medical Institute, Division of Biology 216-76, Caltech, Pasadena, California 91125, USA; e-mail: schumane@cco.caltech.edu

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Abbreviations

BDNF	brain-derived neurotrophic factor
E	embryonic day
GABA	γ-aminobutyric acid
IgG	immunoglobulin G
LTP	long-term potentitation
mEPSC	miniature excitatory postsynaptic current
NGF	nerve growth factor
NMDA	*N*-methyl-D-aspartate
NT	neurotrophin

Introduction

The earliest demonstration of fast actions of neurotrophins on synaptic transmission was by Lohof and Poo [1]. They showed that the addition of brain-derived neurotrophic factor (BDNF) or neurotrophin-3 (NT-3) to developing frog neuromuscular synapses in culture causes a rapid, but reversible, increase in the frequency of miniature excitatory postsynaptic currents (mEPSCs). Many studies since have shown that BDNF and other neurotrophins can facilitate synaptic function, in nerve–muscle synapses [1–3,4•], cultured hippocampal neurons [3,4•,5–7,8•], hippocampal slices [9–15], the *in vivo* hippocampus [16•], and visual cortical slices [17,18]. A simple catalog of neurotrophin actions such as this can be misleading. There are important points in the details of these experiments and in the different results obtained, sometimes in the same experimental preparation. In this review, I will focus on the common emergent themes and highlight unresolved issues.

Similarities and differences between developing and adult synapses

It appears that neurotrophins can influence synaptic transmission at both developing and adult synapses. In one of the earliest tissue ages examined, McKay, Segal and colleagues [19•] have shown that neurotrophins can speed up the development of both excitatory and inhibitory synaptic transmission in cultured hippocampal neurons. Embryonic day 16 (E16) hippocampal cultures have little spontaneous or evoked synaptic activity; the addition of BDNF for 3 days induces the formation of both excitatory and inhibitory synapses, whereas the addition of NT-3 affects only excitatory synapses. This study has a morphological equivalent in another recent paper examining the ontogeny of hippocampal afferents and axonal and synaptic structure in TrkB and TrkC knock-out mice [20]. Neurotrophins exert their effects through Trk receptors. Both knock-out mice showed a reduced number of axon collaterals, varicosities and synaptic contacts.

Other studies have shown that BDNF can enhance either evoked or spontaneous excitatory synaptic transmission in slightly older (E18) hippocampal neuron cultures, where initial synaptic contacts have already been established [5–7,8•]. BDNF is also important in regulating the balance and absolute level of both excitatory and inhibitory synaptic input in developing visual cortical cultures [21]. In addition, TrkB ligands may play a role in the visual cortex in the development of ocular dominance columns [22,23], in sculpting the dendritic morphology of pyramidal neurons [24] and in enhancing synaptic transmission [17,18]. Consistent with the persistent expression of both the neurotrophins and their receptors [25], neurotrophins can also modulate synaptic transmission in the adult hippocampus [9,12,13,15,16•,26•]. These studies are reviewed in greater detail below.

Fast actions of neurotrophins

There are many examples of relatively fast modulation of inhibitory transmission by neurotrophins. These include an NT-3-induced decrease in inhibitory transmission seen in cultured hippocampal neurons [27] and a BDNF-induced decrease in inhibition in hippocampal slices [28,29]. Can neurotrophins such as BDNF also produce similarly rapid actions on excitatory synaptic transmission? In cultured nerve–muscle synapses [1–3,4•] and cultured hippocampal synapses [5–7,8•] the answer is a resounding 'yes'. In other experimental preparations, the reports are mixed. We [9,12,13,26•] and others [15,16•] have observed relatively fast (<1 h) actions of BDNF in the hippocampus. Two groups have also observed similar effects in visual cortical slices [17,18]. Other groups have failed to observe these rapid actions of BDNF in either the hippocampus [11,14,28,29] or visual cortex [30]. One explanation for this discrepancy is the rate of neurotrophin application [12]; BDNF is a sticky molecule [31] that does not penetrate tissue easily [32,33]. Two groups [11,14] who reported a lack of rapid action of BDNF on synaptic transmission introduced the factor into the tissue at an extremely slow rate

(i.e. 3–10 ml/h). (Indeed, in these studies, an incubation period of 2.5–8 h was required to see any biological actions of BDNF.) A parametric study of different perfusion rates has shown that similarly slow BDNF application rates never result in synaptic enhancement [13]. Fast perfusion rates may be required to present BDNF in a rapid, concerted fashion to available TrkB receptors to induce sufficient increases in downstream signaling molecules (e.g. Ca^{2+} [2,7,34]). It has also been shown that TrkB signaling becomes dramatically desensitized shortly after binding BDNF [35]. Thus, the effect of slow delivery of BDNF is two-fold: first, insufficient initial binding of BDNF to TrkB leads to insufficient generation of downstream signaling molecules (e.g. Ca^{2+}), and second, it decreases the probability of future BDNF–TrkB signaling events because the response becomes desensitized. Perfusion rates cannot account for all of the variability, however, because two studies [28,29] have used relatively rapid perfusion rates (>100 ml/h) and still have not observed any significant effect on excitatory synaptic transmission.

Another hypothesis, generated by a study of hippocampal microcultures, is that BDNF may act more reliably at synapses where paired-pulse facilitation (a presynaptic phenomena) can be elicited [36]. Greater paired-pulse facilitation is usually readily observed at synapses with initially low probabilities of release (see e.g. [37]). Thus, heterogeneity in release probabilities might lead to differences in neurotrophin action. Truth be told, the application of a neurotrophin by superfusion is a poor mimic of natural release mechanisms, in both the kinetics of neurotrophin delivery to Trk receptors and the absolute amount of neurotrophin available to the receptor. Thus, even if all studies agreed that neurotrophins have fast actions when applied at high concentrations extracellularly, this would not indicate that endogenously released neurotrophins cause similar changes.

Normal versus plastic synaptic transmission

Do neurotrophins participate in influencing normal synaptic transmission or are they linked exclusively to episodes of plasticity? The question itself may be inappropriate given that synapses in a living brain are never in a truly steady state: they have natural histories of plasticity that are as dynamic and varied as those we impose on them experimentally. Nonetheless, we can ask whether blocking neurotrophin actions, using either a genetic or immunochemical approach, influences normal synaptic transmission. Two different studies of BDNF knock-out mice bear directly on this issue. Both studies examined the relationship between stimulus strength and postsynaptic response — the steepness or shallowness of this relationship can tell you how faithfully the synapses are functioning. One study [10] found a deficit in long-term potentiation (LTP) but no deficit in normal synaptic transmission. Another study [11], using a different BDNF mutant mouse, found that hippocampal slices from homozygous BDNF mutant animals showed reduced synaptic transmission and LTP relative to heterozygote and wild-type mice. This reduction in normal synaptic transmission could reflect either a developmental abnormality or an acute effect of the loss of BDNF. The acute blockade of TrkB function in another study [26•] helps to distinguish between these possibilities. In that study, treatment of slices with a function-blocking TrkB antibody, which abolishes TrkB function, led to no deficits in normal synaptic transmission, suggesting that TrkB ligands do not tonically influence synaptic transmission in the adult hippocampal slice. In developing nerve–muscle synapse co-cultures, however, the over-expression of NT-4 caused a tonic elevation of mEPSC frequency, implying a continuous enhancement of presynaptic efficacy by NT-4 [3]. In addition, in developing visual cortical cultures, application of TrkB–IgG for 24 h increased mEPSC amplitude [21], suggesting that endogenously released TrkB ligands usually decrease excitatory transmission. Blocking action potential activity in these cultures had similar effects on the mEPSC amplitude, however, suggesting that the tonic actions of TrkB ligands on synaptic transmission are activity dependent. Indeed, this study illustrates that activity-dependent processes shape normal synaptic function, reinforcing the idea that it is inappropriate to think of either activity-dependence or plasticity as special aspects of synaptic transmission.

Presynaptic and postsynaptic actions of neurotrophins

Abundant evidence indicates that neurotrophins can modulate synaptic transmission by presynaptic as well as postsynaptic mechanisms. Evidence for a presynaptic change comes from a study in visual cortical slices where BDNF increased the frequency of spontaneous synaptic events and decreased the likelihood of synaptic failures [18]. In developing nerve–muscle synapses [2] and hippocampal slices [9,38], several studies found that the application of BDNF influenced paired-pulse facilitation. More direct support for a presynaptic locus of action comes from studies in cultured neurons. Neurotrophins increased the frequency, but not the amplitude, of mEPSCs in hippocampal neurons [7,36], as has been observed at the developing frog neuromuscular junction *in vitro* [1,3]. In addition, adenovirus-mediated expression of a truncated (dominant-negative) TrkB receptor in presynaptic, but not postsynaptic, neurons blocked BDNF's facilitation of both evoked and spontaneous synaptic transmission [8•].

On the other hand, there is ample evidence supporting a postsynaptic action of BDNF and other neurotrophins. In developing *Xenopus* nerve–muscle synapses, overexpression of NT-4 in the muscle results in an increase in the mean burst duration of acetylcholine channels, as well as an increase in neurotransmitter release [3]. Additional evidence includes the observation that a receptor tyrosine kinase inhibitor injected into a (postsynaptic) cultured hippocampal neuron prevents BDNF-induced increases in firing rate and concomitant increase in spontaneous

synaptic currents [6]. In addition, BDNF can increase the phosphorylation of the NR1 subunit of the *N*-methyl-D-aspartate (NMDA) receptor in hippocampal synaptic fractions [39]. Moreover, Levine *et al.* [40•] have reported that an NMDA receptor antagonist prevented the BDNF-induced increases in spontaneous synaptic currents. In hippocampal slices, there is also a requirement for presumed postsynaptic protein synthesis in BDNF- and NT-3-induced synaptic potentiation [9]. Finally, in developing visual cortical cultures, BDNF probably acts by postsynaptic mechanisms to decrease the amplitude of EPSCs [21]. The differences described above cannot by explained solely by differences in Trk receptor localization because Trk receptors are often found on both the pre- and postsynaptic sides of a given synapse in the hippocampus or cortex. Similarly, there does not appear to be a clear correlation between the age or type of tissue and the presumed site of action of neurotrophins. Determining the localization of both synaptic and extrasynaptic Trk receptors, as well as the nature of signaling components to which they are coupled, will help clarify these issues.

Activity-dependent release and activity-dependent action – both or neither?

Are neurotrophins released in an activity-dependent manner or do they merely act in an activity-dependent manner? No experiment has conclusively distinguished between these possibilities. *In vitro* studies provide clear evidence that the neurotrophins can be secreted both constitutively and following depolarization of neurons [3,41,42]; this secretion originates primarily from the somatic or dendritic compartments. Despite these data, in experiments using either genetic or pharmacological disruption of neurotrophin signaling, we cannot ascertain whether neurotrophins are released by plasticity-inducing stimuli or a constitutively available source.

A study examining the role of neurotrophins in LTP demonstrated that the particular activity patterns used to induce LTP are important determinants of TrkB dependence [26•]. LTP induced by prolonged 100 Hz stimulation was not affected by function-blocking TrkB antibodies, whereas LTP induced with an equivalent number of stimuli delivered as a theta-burst (i.e. bursts delivered at 7–10 Hz) was inhibited [26•]. Although this observation suggests that the specific timing of activity patterns is important in promoting neurotrophin release, the possibility of activity-dependent action cannot be ruled out. Another study found that bath-applied BDNF potentiates postsynaptic responses, but only at high (100 Hz) stimulation frequencies [34]. The activity-dependence seen in this experiment suggests that an individual axon *in vivo* must fire at 100 Hz in order for BDNF to facilitate transmission. Perhaps the most compelling case for activity-dependent release is that blocking activity in visual cortical cultures with tetrodotoxin scales up the quantal amplitude of excitatory events; this increase can be blocked by the co-application of BDNF or mimicked by the application of a TrkB–IgG [21].

Activity-dependent processes are usually invoked to explain how diffusible messengers can selectively influence some, but not all, of the synapses in a given area. A study of developing nerve–muscles synapses suggests that NT-4 is restricted to a spatial synaptic territory of less than 60 μm [4•], indicating that spatially restricted secretion/diffusion alone can provide local synaptic modifications.

Developing circuits in most regions of the vertebrate nervous system exihit highly regular episodes of spontaneous activity, as described in the review by O'Donovan (see pp 94–104 in this issue). It will be interesting to determine the extent to which such activity regulates neurotrophin release and action, and to determine the consequences of this on circuit formation. Neurotrophins may also play a role in the plasticity of these early circuits — for example, when glutamate-mediated transmission is blocked in the spinal cord, GABA becomes capable of driving spontaneous activity; such plasticity (see e.g. Figure 1b in the O'Donovan review) could be attributable to neurotrophin-mediated alterations in synaptic strength, as reviewed here.

As is the case for many other molecules that appear to participate in synaptic plasticity, the easy experiments (i.e. applying agonists and antagonists) have been done. We lack a basic understanding of neurotrophin dynamics, however, because we cannot visualize neurotrophins in real time in intact tissue. Quantitative information about the amount of neurotrophin released and the duration of neurotrophin signaling *in vivo* is needed to achieve a real understanding of neurotrophin's contribution to plasticity.

In vivo actions?

Does the abundant evidence that neurotrophins can affect synaptic transmission *in vitro* imply that neurotrophins act similarly in the intact brain? Clive Bramham and colleagues [16•] have recently shown that local infusion of BDNF into the intact adult rat hippocampus causes a long-lasting enhancement of synaptic transmission, similar to that observed (by some) in slices of hippocampus [9,13,15] and visual cortex [17,18]. A recent study of water-maze learning in mice carrying a deletion in one copy of the BDNF gene has shown that these mutant mice have a modest learning deficit associated with the acquisition, rather than the retention, of memory for this task [43]. This deficit was greater in aged BDNF mutant mice. Another study has shown that intracerebroventricular infusion of NGF, NT-3, or NT-4/5 can improve age-related declines in performance in the water-maze task [44]. Perhaps surprisingly, BDNF infusion did not improve performance, although it is unclear how effectively it can diffuse out of the cerebral ventricles [32,33]. Potential additional support for BDNF–TrkB's involvement in learning comes from a recent analysis of BDNF levels in the ataxic mutant mouse *stargazer* [45]. BDNF protein levels are reduced by 70% in the cerebellum of these mutant mice; furthermore, *stargazer* mice fail to learn the conditioned association between a tone and a

shock (which usually results in an eye-blink elicited by the tone alone). It remains to be seen whether exogenous BDNF can rescue the *stargazer* phenotype. The use of conditional neurotrophin knock-out animals in the future may permit a broader analysis of the contributions of neurotrophins to behavior.

Conclusions

The plasticity of a chemical synapse — its ability to change over timescales ranging from seconds to days — is perhaps its most important feature. As more multifunctional and persistent signaling molecules are discovered, it will be important to distinguish the actions of neurotrophins from a (depressingly) long list of other molecules that modulate synaptic strength. Pushing our understanding of neurotrophin actions in the intact brain beyond a superficial level will require an understanding of the quantity, conditions and dynamics of release in situations where synaptic circuits are minimally perturbed (e.g. slices or *in vivo*). In addition, the conditions for neurotrophin action are important. Is the concept of activity-dependent action applicable for the neurotrophins, or are we forcing an analogy with other molecules? Given the restricted spatial domain over which some neurotrophins act [4•], a requirement for activity-dependent actions may not provide any additional benefit. Recent technical advances may well allow us to visualize neurotrophin release directly, providing answers to some of these questions.

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