REVIEW

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Regulation of Synaptic Function by Neurotrophic Factors in Vertebrates and Invertebrates: Implications for Development and Learning

Abstract

Recent studies have demonstrated that neurotrophic factors contribute to the molecular events involved in synaptic plasticity, both during vertebrate development and in the mature nervous system. Although it is well established that many of the cellular and molecular mechanisms underlying synaptic plasticity are conserved between invertebrates and vertebrates, there are, as yet, very few neurotrophic factors identified in invertebrate species. Nonetheless, vertebrate neurotrophins can influence invertebrate neuronal growth and plasticity. In addition, homologs of neurotrophic factor receptors have been identified in several invertebrate species. These studies may indicate that the roles of neurotrophins in both developmental and adult plasticity are highly conserved across diverse phyla.

Introduction

A recurrent theme in the analysis of both development and learning is that these two forms of plasticity in the nervous system may share some common mechanistic features (Hebb 1949; Wolpaw et al. 1991; Kandel and O'Dell 1992; Chen and Tonegawa 1997; Carew et al. 1998). For example, parallels between development and learning can be found in the marine mollusc *Aplysia*, where neuronal differentiation and neurite growth in developing animals and synaptic plasticity underlying behavioral sensitization in adults are all regulated by a common modulatory neurotransmitter, serotonin (Marcus et al. 1994). Furthermore, among vertebrate species well characterized examples of synaptic plasticity, such as long-term potentiation (LTP) and long-term depression (LTD), occur in neuronal structures known to undergo activity-dependent synaptic modification in development and learning (Kirkwood and Bear 1994a,b; Crair and Malenka 1995). The search for molecular agents of synaptic change has revealed the importance of the NMDA receptor in both early and adult plasticity (Cline et al. 1987; Bear and Kirkwood 1993; Kuno 1995; Carew et al. 1998). Likewise, other types of molecules, such as cell adhesion molecules and voltage-gated ion channels, have been implicated in both types of plasticity. Recent studies have revealed the neurotrophins, a family of protein growth factors important for neural development, as a new molecular component in multiple forms of

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plasticity (Kang and Schuman 1995, 1996; Korte et al. 1995; Patterson et al. 1996).

The first neurotrophin was identified by Hamburger and Levi-Montalcini (Levi-Montalcini and Hamburger 1953; Levi-Montalcini et al. 1954) who observed that tumors implanted in developing chick embryos had remarkable effects on the growth of peripheral sensory and sympathetic neurons. The neurons became much larger and had extensive neuritic projections, even perforating blood vessels in a trajectory toward tumor explants placed on the outer embryonic membranes. The trophic activity of the tumor was isolated through a series of serendipitous events (Levi-Montalcini and Cohen 1956) and dubbed nerve growth factor (NGF), opening new areas of cellular investigation that led to the isolation and characterization of numerous families of growth factors. The NGF family of growth factors, the neurotrophins, consists of NGF, brain-derived neurotrophic factor (BDNF; Barde et al. 1982), neurotrophin-3 (NT-3; Ernfors et al. 1990; Hohn et al. 1990; Kaisho et al. 1990; Maisonnier et al. 1990; Rosenthal et al. 1990), NT-4/5 (Berkemeier et al. 1991; Hallbook et al. 1991), NT-6 (Gotz et al. 1994), NT-7 (Lai et al. 1998; Nilsson et al. 1998), and a newly cloned member from lamprey considered to be the ancestral form of neurotrophins (Hallbook et al. 1998). All the neurotrophins bind with high affinity to members of a family of receptor tyrosine kinases, the Trk family. The events leading to signal transduction include (1) binding of neurotrophin to the appropriate Trk receptor (in general, NGF binds to TrkA, BDNF and NT4 to TrkB, and NT3 to TrkC); (2) receptor homodimerization; (3) autophosphorylation of the tyrosine kinase domains of the bound receptors; and then (4) activation of various intracellular signaling molecules that are associated with the receptor (for reviews, see Meakin and Shooter 1992; Schlessinger and Ulrich 1992; Barbacid 1993; Kaplan and Stephens 1994). There is a second receptor (p75) that binds each neurotrophin with similar, but not identical, binding properties. The p75 neurotrophin receptor was formerly thought to be a low-affinity binding protein that interacted with the signal-producing Trk receptors to enable high-affinity binding. Although p75 can modulate Trk receptor activity (Greene and Kaplan 1995), reports published in the past few years reveal unique functions of p75 that may be independent of Trk receptors (Carter et al. 1996a, 1996b; Chao et al. 1998; Dobrowsky and Carter 1998; Frade and Barde 1998). To date, studies of neurotrophin involvement in plasticity have focused on the role of Trk receptors; however, interesting new work in an invertebrate species (discussed below) may shed light on the neuronal function of p75 (Fainzilber et al. 1996).

One theme that emerged, in part, from the early work on the role of NGF in neural development is the “neurotrophic hypothesis” (Purves 1988). Neurons have trophic requirements, either for survival or for maintenance of some aspect of differentiation, that are satisfied by contact with an appropriate target or by contact from appropriate afferent cells. For example, many populations of neurons undergo developmental periods of naturally occurring cell death in which postmitotic, differentiated neurons are eliminated as a result of competition for target-derived factors (Prestige 1967a,b; Rogers and Cowan 1973; Hamburger 1975; Oppenheim and Ch-Wang 1977; Chu-Wang and Oppenheim 1978; Hamburger et al. 1981). Successful (surviving) cells are those that obtain the necessary factor (or factors) and retrogradely

transport it (or some signal generated by its binding) to the soma where the cellular changes required for survival occur. NGF was recognized quickly as a potential target-derived survival factor when studies of peripheral ganglia showed that NGF could indeed promote cell survival in these populations. For example, sympathetic ganglion (SG) neurons require NGF for their survival during embryonic development; a requirement that is fulfilled by tissues receiving sympathetic innervation (Levi-Montalcini and Booker 1960; Korsching and Thoenen 1983). NGF applied exogenously during this phase of development enhances SG cell survival, whereas induced NGF autoimmunity or genetic elimination of NGF using transgenic technology results in loss of virtually all SG neurons (Gorin and Johnson 1980; Crowley et al. 1994). Finally, target-derived NGF must be transported retrogradely, along with rapidly propagated tyrosine phosphorylated signaling molecules, from neuronal processes to the cell body (Purves 1976; Heumann et al. 1981; Seeley et al. 1983; Senger and Campenot 1997).

Although the traditional neurotrophic hypothesis continues to guide research on the effects of neurotrophic factors, newer studies hint at other mechanisms of neurotrophic factor action, such as anterograde transport and presynaptic release of neurotrophins (discussed below), that are likely to be involved in synaptic plasticity. The goal of this review is to present some of the primary evidence for the participation of neurotrophins in synaptic plasticity. Much of this evidence comes from electrophysiological studies of long-term synaptic changes in two systems: mammalian cortical system and invertebrate central neurons. We will not offer a comprehensive review of neurotrophins in cortical plasticity as there are a number of recent reviews on the topic (Thoenen 1995; Bonhoeffer 1996; Nawa et al. 1997; Schuman 1997a,b; Shieh and Ghosh 1997; Carew et al. 1998). Rather, we will focus briefly on possible neurotrophic influences contributing to the cellular mechanisms in hippocampal LTP, and then move on to discuss recent findings suggesting that similar mechanisms may be operating in invertebrate species.

Synaptic Plasticity in the Hippocampus

Perhaps the first hint that neurotrophins might play a role in LTP came when the third member of the NGF family, NT-3, was cloned from hippocampus (Ernfors et al. 1990; Hohn et al. 1990; Kaisho et al. 1990; Maisonpierre et al. 1990; Rosenthal et al. 1990). After studies demonstrating increased neurotrophin expression as a result of induced seizures (Gall and Isackson 1989; Zafra et al. 1990), Patterson and colleagues (1992) later showed that LTP induction also increased expression of the mRNAs for both NT-3 and BDNF (see also, Castren et al. 1993; Dragunow et al. 1993, 1997). This led to a series of studies that directly examined the role of neurotrophins in hippocampal LTP (Kang and Schuman 1995; Korte et al. 1995; Patterson et al. 1996). Hippocampal slices treated with BDNF or NT-3, but not NGF, show persistent increases in EPSP amplitude, which are similar to tetanically induced LTP (Kang and Schuman 1995). Furthermore, LTP induced by either theta burst or tetanic stimulation is blocked by pretreating slices with the TrkB-IgG fusion protein, a protein that removes BDNF from extracellular fluids (Figurov et al. 1996; Kang et al. 1997), suggesting that endogenous BDNF is involved in the induction of LTP. This work has been complemented by the generation of two strains of BDNF knockout mice that show no LTP after

tetanic stimulation; a phenotype that can be rescued by either application of exogenous BDNF or transfection with a BDNF-containing adenovirus (Korte et al. 1995, 1996; Patterson et al. 1996; but, for conflicting results with an NT-3 knockout, see Kokaia et al. 1998). As with some other aspects of LTP, there are inconsistencies between laboratories. Frerking and colleagues (1998) have reported recently that BDNF treatment of hippocampal slices produces a minor decrease in inhibitory neurotransmission (Tanaka et al. 1997), but has no effect on the field EPSP or any measure of excitatory transmission. However, Gottschalk and colleagues (1998) have found that in neonatal animals (normally incapable of expressing LTP), LTP is induced at previously active synapses when BDNF is present in the bath. Thus, some of the differences in the effects of BDNF on mature hippocampal slices may stem from differences in levels of constitutive activity.

In spite of the inconsistencies described above, a model has emerged for neurotrophin-mediated long-term plasticity in the hippocampus that includes both pre- and postsynaptic mechanisms. Modulation of paired pulse facilitation has been observed in many studies of neurotrophin-induced LTP (Kang and Schuman 1995; Korte et al. 1995; Patterson et al. 1996; Gottschalk et al. 1998; but see, Kokaia et al. 1998), indicating a presynaptic locus of action. In support of a presynaptic mechanism, cultured hippocampal neurons, which form synapses *in vitro*, show increased mEPSC frequency, but not amplitude, in response to brief treatment with BDNF (Li et al. 1998b). The mEPSC increase is calcium dependent and does not include any modulation of postsynaptic glutamate-induced currents, strongly supporting a presynaptic mechanism. In similar cultures, neurons transfected with a function-blocking, truncated form of TrkB show no BDNF-induced facilitation when presynaptic, but not postsynaptic, cells express the construct (Li et al. 1998a). Furthermore, BDNF attenuates synaptic depression in hippocampal slices from immature (neonatal) animals (Figurov et al. 1996; Gottschalk et al. 1998) by a mechanism that includes recruiting synaptic vesicles to the active zone (Pozzo-Miller et al. 1998). BDNF has been shown to modulate both expression levels and phosphorylation of some synaptic vesicle associated proteins (Jovanovic et al. 1996; Pozzo-Miller et al. 1998) and, thus, may be involved in vesicle distribution at nerve terminals and increased neurotransmitter release. In fact, when cultured embryonic hippocampal cells are treated chronically with BDNF or NT-3 they show increased excitatory synaptic transmission, as measured by increased frequency of miniature postsynaptic currents (mEPSCs), without a concomitant increase in synaptic profiles, synaptic vesicle protein concentration, or number of dendritic spines (Vicario-Abejon et al. 1998). This argues strongly for the neurotrophins playing a role in a final stage of maturation of the vesicle release mechanism. Interestingly, cultured spinal motor neurons also show enhanced transmitter release after BDNF application suggesting that a similar effect may be exerted on the release machinery of these cells (Lohof et al. 1993; Stoop and Poo 1996).

Evidence that postsynaptic mechanisms may also be involved comes from a number of different areas. First, Kang and Schuman (1996) showed that dendritic protein translation was necessary for BDNF-induced LTP, suggesting that a local postsynaptic change contributes to the induction of this form of LTP. Second, depolarization of hippocampal neurons results in rapid, Na^+ -dependent dendritic release of neurotrophins (Blochl

and Thoenen 1995; Canossa et al. 1997). Thus, as they do in development, neurotrophins may act like target-derived neurotrophic factors in the induction of LTP, that is, activity-induced postsynaptic release of factors alters the presynaptic innervating cell, in this case by increasing neurotransmitter output. In addition, when hippocampal postsynaptic densities are incubated with BDNF and [32 P]ATP, they show a rapid, transient phosphorylation of the NR2B subunit of the NMDA receptor (Lin et al. 1998). Tyrosine phosphorylation of postsynaptic NR2B has been implicated previously in the maintenance of LTP (Rostas et al. 1996). Finally, NMDA receptors on cultured hippocampal and striatal neurons show increased channel open probability when they are exposed to BDNF in the absence of glycine (Jarvis et al. 1997). This effect is independent of TrkB activation suggesting that BDNF may be capable of directly modulating NMDA receptor activity in a manner analogous to glycine. These data suggest either (1) that dendritically released BDNF acts in an autocrine fashion to potentiate the post-synaptic response or by a paracrine mechanism to facilitate presynaptic release, or (2) that BDNF is also released by the presynaptic terminals, in which case it is acting in both autocrine and paracrine fashion. Of course, these two possibilities are not mutually exclusive. Ample evidence for presynaptic release of neurotrophins is found in the developing avian visual system (von Bartheld et al. 1996), in cortical neurons transiently transfected with a BDNF-GFP construct (Haubensak et al. 1998), in the sorting of BDNF precursor to the regulated secretory pathway (Mowla et al. 1999), and in the localization of some neurotrophins to dense core (noradrenergic) vesicles in PC12 cells (Moller et al. 1998).

Are there structural changes in the vertebrate nervous system that account for more permanent changes in synaptic efficacy, (i.e., changes that last the lifetime of the organism)? Permanent synaptic change in learning is generally thought to include growth of synaptic contacts—either the formation of new synapses or an extension of the area of previously existing contacts. Neurotrophins are ideally suited to mediate such changes. The developmental literature, as already described, focuses largely on morphological changes in cells exposed chronically to growth factors (McAllister et al. 1999). In addition, a large literature reflecting the neurotrophic effects (i.e., promotion of directed neurite outgrowth) of growth factors also exists. Direct effects on neurite outgrowth can be demonstrated by applying gradients of neurotrophins to one side of the growing processes of cultured neurons (Song et al. 1997; Gundersen and Barrett 1979, 1980). Upon application, the neurites rapidly change their direction of growth toward the source of neurotrophin. Other studies have shown rapid and reversible changes in growth cone morphology in PC12 cells exposed to NGF (Seeley and Greene 1983). Originally, it seemed these effects were physiologically irrelevant because, in developing systems, NGF is not present in target tissues until after innervation by NGF-dependent neurons; thus, NGF is not present at the appropriate time to attract neurites (Davies et al. 1987). However, the ability to induce and direct neurite growth and morphological changes within the highly localized regions of synaptic input zones may provide a mechanism for producing long-lasting functional synaptic change in the mature system at specific loci where neurotrophins and their receptors are being expressed. Interestingly, it has been suggested recently that BDNF may regulate spine formation in the hippocampus in conjunction

with estrogen levels (Murphy et al. 1998). Likewise, there is evidence in the hippocampus that LTP is associated with new growth, including increased dendritic spine density and increased numbers of synaptic contacts on spines (Chang et al. 1991; Durand et al. 1996, but see Sorra and Harris 1998; Maletic-Savatic et al. 1999). However, because most studies of LTP measure the summed responses of populations of neurons, until recently (Engert and Bonhoeffer 1999) it has been difficult to assess directly both electrophysiological and anatomical changes in a single cell. Studies of local microscopic changes at identified synapses are possible in invertebrates and have learnt much to our current understanding of cellular morphological changes associated with learning. As in the past, such models may be useful in elucidating the precise cellular and molecular mechanisms of neurotrophin-mediated plasticity.

Cellular and Molecular Mechanisms of Synaptic Plasticity in Invertebrates

A number of invertebrate models have been developed to study synaptic plasticity in both adult and developing organisms. Examples include the developing *Drosophila* neuromuscular (Keshishian et al. 1996) and visual (Barth et al. 1997) systems, visual and olfactory learning in honey bees (Hammer and Menzel 1995), in vitro growth and regeneration of *Lymnaea* neurons (Bulloch and Ridgway 1989), and classic conditioning of rotationally evoked behaviors in *Hermissenda* (Lederhendler and Alkon 1986; Crow 1988). In addition, genetic dissection of learning in *Drosophila* and studies of identified synapses in the marine mollusc *Aplysia* have both contributed to an understanding of the cellular and molecular mechanisms of learning and its underlying synaptic plasticity (Carew 1996; Dubnau and Tully 1998). In *Aplysia*, the defensive withdrawal reflexes (e.g., of the gill and siphon, or the tail) exhibit several forms of learning, including sensitization, a nonassociative form of learning characterized by enhanced reflex responsiveness after a noxious stimulus such as tail shock. Tail shock in *Aplysia* releases serotonin (5-HT) in the CNS and, accordingly, sensitization of withdrawal reflexes has been correlated with serotonergic enhancement of the synaptic connections between the sensory neurons (SNs) and motor neurons (MNs) that contribute to the reflexive behaviors (Byrne and Kandel 1996). Both behavioral sensitization and 5HT-induced synaptic facilitation exhibit distinct temporal phases (Pinsker et al. 1973; Hawkins et al. 1983). For example, a single pulse of 5-HT to the SNs and MNs induces short-term facilitation (STF) lasting up to 15 min (Schacher et al. 1990). Exposure to four or five spaced pulses of 5-HT produces two additional persistent forms of facilitation of the tail sensorimotor connections: intermediate-term and long-term facilitation (Montarolo et al. 1986; Emptage and Carew 1993; Ghirardi et al. 1995; Mauelshagen et al. 1996). Intermediate-term facilitation (ITF) is evident for up to 3 hr after 5-HT application, whereas long-term facilitation (LTF) commences ~10 hr and can last for >24 hr after treatment.

Distinct biochemical mechanisms underlie each of the different temporal forms of synaptic facilitation described above. STF is believed to be mediated by the activation of protein kinase A (PKA) and protein kinase C (PKC) in a state- and time-dependent manner in the presynaptic sensory neuron (Byrne and Kandel 1996). PKA and PKC modulate specific potassium conductances ultimately giving rise to an increase in transmitter release. There is also evidence suggesting that PKA and PKC can modify

synaptic proteins involved with vesicular release machinery, further modifying transmitter release during subsequent activity. It is not currently known whether any neurotrophic factors can modify transmitter release in *Aplysia* sensory neurons. However, insulin has been shown to modulate release of neuropeptides from bag cell neurons, neuroendocrine cells that regulate reproductive behaviors (Jonas et al. 1997).

Cellular mechanisms mediating ITF are not yet well understood; however, evidence suggests that it is dependent on protein translation, but not transcription (Ghirardi et al. 1995). In addition, translationally dependent PKA and PKC activity has been shown to be persistently elevated after 5-HT stimulation sufficient to induce ITF, suggesting that either, or both, may play a role in the production of this form of facilitation (Sossin et al. 1994; Sossin 1997; Muller and Carew 1998).

Considerable work has focused on the characterization of molecules involved in establishing LTF. Like STF, current evidence suggests a presynaptic mechanism for the induction of LTF in response to 5-HT treatment. Application of 5-HT sufficient to produce LTF causes a substantial increase in cAMP concentration leading to nuclear translocation of the catalytic subunit of PKA in sensory neurons (Bacskai et al. 1993). Nuclear PKA phosphorylates cyclic AMP response element binding protein (ApCREB1), which acts as a transcription factor capable of initiating new gene expression (Kaang et al. 1993). ApCREB-mediated transcription is essential for 5-HT-induced LTF (Dash et al. 1990). In addition, another transcription factor, ApCREB2, interacts with ApCREB1 preventing it from initiating transcription. Injection of antibodies to ApCREB2 into sensory neuron nuclei allows LTF to be induced with a single pulse of 5-HT, which would normally only produce STF (Bartsch et al. 1995, 1998). These results suggest that the repeated stimulation necessary for the normal induction of LTF provides a signal that relieves the ApCREB2 block from CREB1-mediated transcription. ApCREB2 does not contain PKA phosphorylation sites but does possess sites for PKC and mitogen-activated protein (MAP) kinase suggesting that the repeated pulses may be accessing a signaling cascade that leads to translocation or nuclear activation of PKC or MAP kinase. Evidence supporting this hypothesis comes from studies showing that *Aplysia* MAP kinase translocates into the nucleus of sensory neurons in response to repeated applications of 5-HT and phosphorylates ApC/EBP (Martin et al. 1997; Michael et al. 1998). Moreover, injection of antibodies against MAP kinase in the sensory neuron blocks the induction of LTF by spaced 5-HT treatment. Interestingly, although multiple exposures of 5-HT are sufficient to remove ApCREB2, other external signals, such as neurotrophins, are transduced through the MAP kinase signaling cascade (Nakamura et al. 1996; Yoon et al. 1997), and regulate CREB phosphorylation (Riccio et al. 1997; Shieh et al. 1998). It is inviting to think that a growth factor-induced signal could provide the necessary derepression of ApCREB1 required for the production of LTF. Finally, growth leading to the formation of new synaptic connections is known to occur at the sensory neuron synapses after LTF (Glanzman et al. 1990, 1991; Bailey and Chen 1991). The process includes endocytosis of ApCAM, thus breaking cell-cell contacts and allowing new growth to occur (Bailey et al. 1992, 1997; Mayford et al. 1992; Hu et al. 1993). Interestingly, NGF treatment of PC12 cells increases the formation of

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coated pits (Connolly et al. 1984), suggesting that neurotrophins may mediate this type of structural change.

Various growth factors have been found in invertebrate species (see Table 1), some of which are homologs of previously identified vertebrate molecules (Muskavitch and Hoffmann 1990). However, some invertebrates possess completely unique gene products that can be functionally defined as growth factors. Table 1 shows selected examples of both novel and homologous invertebrate molecules. Interestingly, although the neurotrophins (i.e., members of the NGF family) have not been found in invertebrates (for example, see Ruvkun and Hobert 1998), growth factors, including neurotrophins, have been reported to have effects on cells, neuronal as well as non-neuronal, from many invertebrate species. Table 2 provides several examples of the effects of vertebrate growth factors on invertebrate cells. In addition, some invertebrate species possess Trk-like molecules (M. Giusetto, S. Patterson, K. Martin, and E. Kandel, pers. comm.; Moreno et al. 1998; van Kesteren et al. 1998). These examples will be discussed in more detail below. Interestingly, it should be noted here that the recently published *Caenorhabditis elegans* genome does not possess any Trk or neurotrophin molecules (Ruvkun and Hobert 1998). The presence of Trk or neurotrophin homologs in some, but not all, invertebrates may provide important clues for understanding the evolution of complex nervous systems as has been suggested by Barde (1994).

Evidence for responsiveness to vertebrate growth factors among invertebrates comes from work on cultured molluscan neurons. It has been well established that *Helisoma* and *Lymnaea* neurons respond with altered outgrowth and synaptogenesis to media conditioned with excised neural tissue from the same species (Wong et al. 1981, 1984; Magoski and Bulloch 1998). As part of identifying specific trophic agents in the

Table 1: Selected examples of invertebrate growth factors

Organism	Growth factor	Reference
<i>Drosophila</i>	EGF	Rutledge et al. (1992)
	FGF	Sutherland et al. (1996)
	TGFβ	Wharton et al. (1991)
	activin	Kutty et al. (1998)
<i>Sarcophaga</i>	insect-derived growth factor (IDGF)	Homma et al. (1996)
<i>Aplysia</i>	bone morphogenic protein	Liu, et al. (1997)
	molluscan-derived growth factor (MDGF) ^a	D.-B.G. Akalal and G.T. Nagle (GenBank accession no. AF117336)
<i>Strongylocentrotus</i>	TGFβ	Stenzel et al. (1994)
<i>Lymnaea</i>	insulin-like peptide	Smit et al. (1998)
	EGF	Nagle et al. (1998)
	CRNF	Fainzilber et al. (1996)
<i>Asterias</i>	IL-1, IL-2	Legac et al. (1996)

^aHomolog of IDGF.

Table 2: *Biological effects of vertebrate growth factors in invertebrate organisms*

Organism	Growth factor ^a	Effect	Reference ^b
<i>Neuronal</i>			
<i>Drosophila</i>	mNGF	increase neurite outgrowth	1
<i>Lymnaea</i>	mNGF	increase neurite outgrowth	2
		increase $I_{Ca^{2+}}$	3
		promotes synaptogenesis	4
	CNTF	promotes regeneration	4
	EGF	neurite growth	5
<i>Aplysia</i>	bovine	increase Ca^{2+} ;	6
	insulin	neuropeptide secretion;	6
		increase neuronal	7
		excitability; PKC	8
		regulation	
	hTNF α	increase I_{Cl^-}	9
	hIL-2	increase I_{Cl^-}	9
	hTGF β	long-term synaptic	10
		facilitation	
	hBDNF	long-term synaptic	11
		facilitation, filopodial	12
		dephosphorylation,	13
		neurite growth	
	hCNTF	neurite growth	13
	mNGF	neurite growth	13
<i>Loligo</i>	hNGF	reduced EPSP	14
<i>Non-neuronal</i>			
<i>Haliothis</i>	EGF, insulin	hemocyte proliferation	15
<i>Mytilus</i>	IL-1 and TNF	immunocyte motility	16
	TGF β ,	hemocyte regulation	17–21
	PDGF-AB,		
	IL-1 α,β ,		
	TNF α,β		
Echinoderms and tunicates	IL-1	stimulate phagocytosis	22

^a(m) Mouse; (h) human.^b(1) Hayashi et al. (1992); (2) Ridgway et al. (1991); (3) Wildering et al. (1995); (4) Syed et al. (1996); (5) Hermann et al. (1998); (6) Jonas et al. (1997); (7) Jonas et al. (1996); (8) Sossin et al. (1996); (9) Sawada et al. (1991); (10) Zhang et al. (1997); (11) McKay and Carew (1996); (12) Ranpura et al. (1997); (13) Gruenbaum and Carew (1999); (14) Moreno et al. (1998); (15) Lebel et al. (1996); (16) Hughes et al. (1990); (17) Franchini et al. (1996); (18) Ottaviani et al. (1997a); (19) Ottaviani et al. (1997b); (20) Ottaviani et al. (1998); (21) Kletsas et al. (1998); (22) Beck et al. (1993).

invertebrate CNS, various purified vertebrate growth factors have been used to replace conditioned media. These studies have shown that epidermal growth factor (EGF), ciliary neurotrophic factor (CNTF), and NGF promote neurite outgrowth (Ridgway et al. 1991; Syed et al. 1996; Hermann et al. 1998). Further studies in this system have shown that NGF can rapidly modulate the activity of cultured *Lymnaea* neurons by activating voltage-dependent calcium channels (Wildering et al. 1995).

These studies suggest that the CNS of *Lymnaea* possesses multiple growth-promoting activities with specific roles in cellular regulation. Furthermore, an EGF homolog has been identified recently in *Lymnaea* (Nagle et al. 1998). However, despite the presence of a Trk receptor (van Kesteren et al. 1998) in the same species, no neurotrophin homolog has been found.

Recent studies in *Aplysia* have shown that neurotrophic factors may play some role in mediating long-term synaptic plasticity. Byrne and colleagues have shown that treatment with transforming growth factor-beta (TGF- β) increases synaptic efficacy over 24 to 48 hr in cells mediating the tail withdrawal reflex (Zhang et al. 1997). Their data suggest that TGF- β and 5-HT share the same pathway in inducing LTF, as coapplication of TGF- β and 5-HT revealed no additive or synergistic effects. Moreover, serotonin-mediated LTF was blocked with TGF- β receptor-blocking peptides indicating that an endogenous TGF- β like molecule operates during synaptic modulation. These results provide convincing evidence that there is some form of growth factor in *Aplysia* that may mediate serotonin-induced synaptic modification.

In addition to the effects of TGF- β , human BDNF applied to isolated pleural-pedal ganglia can increase the EPSP from tail sensory neurons to tail motor neurons 18–24 hr after treatment (McKay and Carew 1996). Although the effect of BDNF was not as robust as that seen with either TGF- β or 5-HT (40% of preparations exposed to BDNF showed modest LTF), the control preparations, treated with cytochrome c (a protein with physical characteristics similar to BDNF but no known neurotrophic activity), never showed any facilitation. These results indicate that *Aplysia* neurons are capable of responding to BDNF and may possess some BDNF-like molecule. However, the level of conservation may be so low that functional responses to human BDNF are limited, as has been shown with avian neurons, which exhibit altered receptor-ligand interactions with mammalian neurotrophins (Davies et al. 1993). In addition, the high salt concentrations in the artificial seawater used as the medium for *Aplysia* neurons may render some vertebrate neurotrophins partially inactive. However, a recent report (M. Giusetto, S. Patterson, K. Martin, and E. Kandel, pers. comm.) suggests that an endogenous molecule may bind an *Aplysia* Trk homolog at the BDNF binding site. Serotonin-induced LTF is inhibited in cultured *Aplysia* neurons by treatment with a TrkB receptor body, which scavenges endogenous BDNF in vertebrate systems. Furthermore, TrkB antibodies recognize a 140-kD protein on Western blots of *Aplysia* nervous tissue. Thus, as in *Lymnaea*, *Aplysia* appear to possess a Trk homolog.

Regardless of the limited extent of BDNF-induced LTF, there is information in these studies to guide thinking about invertebrate neurotrophin-like molecules. For example, neither BDNF nor TGF- β had any short-term effect on synaptic transmission from the SNs. Likewise, neither molecule altered neuronal excitability or the characteristics of the action potential. Thus, neither molecule acts like a conventional neurotransmitter or neuromodulator, but instead they appear to have long-term effects on the cells. One possibility is that TGF- β and BDNF promote new growth of either the SN or the MN component of the synapse. A variety of growth-related effects are known to be associated with LTF at the SN–MN synapse of *Aplysia*, including increased area of synaptic contact, increased sensory neuron branching and the presence of

increased numbers of varicosities (sites of synaptic contact) along sensory projections (Bailey and Chen 1988, 1991). Interestingly, one of the effects of MAP kinase activation is to promote uptake of *Aplysia* cell adhesion molecule (ApCAM) at presynaptic terminals (Bailey et al. 1997). The uptake of ApCAM is considered a prelude to the growth of synaptic areas after repeated 5-HT application in LTF induction (Mayford et al. 1992; Bailey et al. 1997). Thus, an important issue to be addressed in future experiments will be the characterization of the effects of growth factors on ApCAM and MAP kinase.

More evidence for neurotrophin-mediated growth of *Aplysia* neurons comes from recent work showing that BDNF can regulate phosphorylation events among cytoskeletal elements in *Aplysia* growth cones (Ranpura et al. 1997). Immunocytochemical localization of phosphotyrosine on cultures of sensory neurons has revealed a decrease in tyrosine phosphorylation at the filopodial tips of cells treated with BDNF. Analysis of the time course in BDNF-treated cells revealed that dephosphorylation begins after 12–15 hr and persists up to 30 hr. 5-HT treatment also induces a late stage dephosphorylation of the tips beginning sometime after 15 hr. The slightly later onset may reflect 5-HT-induced release of a BDNF-like molecule from *Aplysia* cells. Reduced phosphotyrosine immunolocalization at filopodial tips was first described in bag cell neurons by Wu and Goldberg (1993) where it was shown to be coupled tightly to the actin cytoskeleton and induced by treatment with hemolymph (Wu and Goldberg 1993; Wu et al. 1996). Although the functional implications in situ have yet to be elucidated, tyrosine phosphorylation may play some role in growth or remodeling of local connections. This may be a mechanism by which growth factors promote long-term facilitation.

A final line of evidence indicating that neurotrophins can induce structural modifications of *Aplysia* neurons has been provided by Gruenbaum and Carew (1999) who show that specific growth factors (BDNF, CNTF, and NGF) can differentially modulate substrate specific growth patterns in bag cell neurons. These results, taken together with work described above examining synaptic facilitation, indicate that *Aplysia* neurons express functional receptors that can interact in highly specific ways with vertebrate growth factors. If there are functional receptors for vertebrate neurotrophins, then there must be some functional and/or structural homolog of neurotrophins.

Are There Invertebrate Neurotrophins?

Although most animals can alter their behavioral repertoire in response to experience, there exist many differences in the nature of behavioral responses and the environmental contingencies that bring about behavioral change. As we have reviewed thus far, many of the cellular mechanisms underlying plasticity are remarkably well conserved (Carew and Sahley 1986). In particular, the evidence for neurotrophic factor involvement in both vertebrate and invertebrate plasticity argues for some mechanistic overlap at the receptor and signaling levels. As Table 2 demonstrates, vertebrate growth factors can regulate both neuronal and non-neuronal invertebrate cells with the same broad spectrum of activities as seen in vertebrates. The challenge now is to identify homologs of both growth factors and their receptors. An important step in this direction has been taken by Liu and colleagues (1997), who have isolated a TGF- β

binding protein from *Aplysia*. This protein may activate some native TGF- β ; however, neither the native molecule, nor any TGF- β receptor have yet been identified. As is clear in Table 2, there are still relatively few identified homologs of vertebrate growth factors generally, and no true homologs of NGF or other members of the NGF family.

The absence of NGF homologs in the invertebrate phyla does not diminish the weight of the empirical evidence demonstrating the cellular effects of vertebrate neurotrophins. There are a number of possible explanations for the discrepancy. For example, neurotrophins may bind to some receptor in invertebrates that is not like the vertebrate NGF receptors. One possibility may be an NMDA-like receptor. The neurotrophins have been shown to modulate the activity of vertebrate NMDA receptors in a manner analogous to glycine (Jarvis et al. 1997). Second, invertebrates may possess homologs of the receptors for members of the NGF family. Two invertebrate Trk homologs have been cloned, the *Drosophila* Trk (Pulido et al. 1992), a distant relative with a number of properties not found in other Trks, and *Lymnaea* Trk (LTrk; van Kesteren et al. 1998). In addition, there are reports of cross-reactivity of vertebrate anti-Trk antibodies with squid neurons (Moreno et al. 1998), and, as already described, with *Aplysia* neurons (M. Giusetto, S. Patterson, K. Martin, and E. Kandel, pers. comm.). Although still controversial, the existence of Trk homologs in arthropods and molluscs hints at a longer evolutionary history for Trk-mediated events than has previously been suggested (Barde 1994). In another recent report, a molluscan growth factor, cysteine-rich neurotrophic factor (CRNF), was isolated from *Lymnaea* hemolymph based on its ability to bind the mammalian neurotrophin receptor p75 (Fainzilber et al. 1996), again suggesting that neurotrophin receptors may be present in lower phyla.

If neurotrophin receptors are present in invertebrates, what ligands bind to them? One possible ligand may be CRNF. Currently, studies are under way to determine whether other molluscs possess CRNF or some homolog thereof. But, CRNF is not necessarily the only invertebrate neurotrophin. Both EGF and insulin have been isolated from *Lymnaea* (see Table 1) demonstrating the presence of homologs of some growth factors in the molluscan phylum. More important, functional protein homology can be present at the level of three-dimensional structure even in the absence of obvious amino acid sequence homology. For example, the three-dimensional structure of a sulfide-binding form of hemoglobin from a bivalve mollusc is almost identical to the oxygen-binding myoglobin of the sperm whale, although these two proteins have only ~20% amino acid homology (Rizzi et al. 1994; Gerhart and Kirschner 1997). Likewise, upon crystallization of the cytoplasmic tyrosine kinase cbl, a functional SH2 phosphotyrosine-binding motif was discovered that was not predicted from the amino acid sequence (Meng et al. 1999). Coagulen, a recently crystallized protein from horseshoe crab, possesses an NGF-type cysteine knot structural motif that was once thought to be present only in a few vertebrate proteins, primarily growth factors (Bergner et al. 1997). Although coagulen itself is not a growth factor, two of the vertebrate proteins with similar motifs are BDNF and TGF- β , both shown to induce long-term synaptic facilitation in *Aplysia*. Furthermore, it has been suggested recently, based on molecular modeling, that a biologically active proteolytic fragment of the *Drosophila* protein Spatzle (involved in dorsoventral patterning of the embryo) possesses

three-dimensional structural elements seen in vertebrate NGF (DeLotto and DeLotto 1998). Thus, it seems possible that functional neurotrophin homologs may exist that are inaccessible using techniques requiring sequence homology, such as PCR or low-stringency screening. Although there may be no highly conserved structural homologs of some of the neurotrophins in invertebrates, there may be several functional homologs that activate similar receptors.

Concluding Remarks

In conclusion, studying the mechanisms of action of neurotrophic factors provides an excellent opportunity to explore links between development and learning. As we have illustrated in this review, evidence continues to demonstrate, in both vertebrate and invertebrate phyla, that neurotrophins may play a significant role not only in shaping the architecture of the developing nervous system, but also in regulating learning-related changes in the adult brain.

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