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Neurotrophins and neuronal differentiation in the central nervous system

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Abstract. The central nervous system requires the proper formation of exquisitely precise circuits to function properly. These neuronal circuits are assembled during development by the formation of synaptic connections between hundreds of thousands of differentiating neurons. For these circuits to form correctly, neurons must elaborate precisely patterned axonal and dendritic arbors. Although the cellular and molecular mechanisms that guide neuronal differentiation and formation of connections remain mostly unknown, the neurotrophins have emerged recently as attractive candidates for regulating neuronal differentiation in the developing brain. The experiments reviewed here provide strong support for a bifunctional role for the neurotrophins in axonal and dendritic growth and are consistent with the exciting possibility that the neurotrophins might mediate activity-dependent synaptic plasticity.

Key words. BDNF; NT-3; dendrite; axon; synaptic plasticity; activity-dependent development; synaptogenesis; cortex.

Introduction

During development, neurons in the central nervous system (CNS) differentiate from immature cells with few processes into elaborate, richly interconnected components of a network capable of complex information processing. The exquisite precision of the thousands of connections within the cerebral cortex, in particular, is established during a critical period of development, when immature neural connections are remodeled by experience to generate adult patterns of connectivity [reviewed in ref. 1]. Although the development of the cerebral cortex has been well described anatomically, the cellular and molecular mechanisms that guide neuronal differentiation and formation of connections remain mostly unknown. In recent years, the neurotrophins have emerged as attractive candidates for regulating neuronal differentiation in the developing brain [reviewed in ref. 2].

The neurotrophins comprise a family of at least four structurally related proteins – nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and neurotrophin-4 (NT-4) – that exert their effects through both a low-affinity neurotrophin receptor, $p75^{NTR}$, and high-affinity tyrosine kinase receptors (Trk receptors) [for reviews see refs. 3, 4]. NGF activates TrkA, BDNF and NT-4 activate TrkB, and NT-3 activates TrkC most strongly, although it can also bind TrkA and TrkB under some specific cellular contexts [reviewed in ref. 2]. Both the neurotrophins and their receptors are most highly expressed in the developing nervous system during times of active neuronal growth and differentiation [reviewed in ref. 2].

The neurotrophins were first described as target-derived trophic factors required for the survival of specific neuronal populations; limited availability of the neurotrophins serves to match the number of innervating axons to the size of target cell populations [reviewed in ref. 5]. In addition to this trophic function, the neurotrophins also have potent effects in stimulating neurite outgrowth [reviewed in ref. 2]. More recently, neurotrophins have been proposed to regulate structural and synaptic plasticity by releasing retrograde factors from target neurons to modulate the strength or number of synaptic connections [reviewed in refs. 2, 6, 7].

Axonal growth

The neurotrophins are potent regulators of axonal growth in both the peripheral nervous system (PNS) and the

CNS. In fact, NGF was isolated because of its dramatic effects on neurite growth: addition of an NGF-secreting sarcoma to a chick sensory ganglion explant stimulates rapid growth of a dramatic halo of neurites [8]. Since this first report, each neurotrophin has been demonstrated to stimulate neurite outgrowth of specific populations of neurons in the PNS in vitro and in vivo [reviewed in refs 9, 10]. Exploration of the nature of these neurotrophin effects on axon pathfinding in the CNS is just beginning.

Neurotrophins are believed to exert both tropic and trophic influences on axonal growth. In vitro experiments demonstrate that gradients of neurotrophins can mediate chemotropic axon guidance [11–15]. In support of such a role, all of the neurotrophins have been demonstrated to exert chemotropic effects on growth cones of specific populations of dorsal root ganglion neurons in vitro. Interestingly, depending on the neuronal and neurotrophin type, these effects can be either attractive or repulsive [16]. However, despite the compelling nature of the in vitro data, there is little evidence for a chemotropic role for the neurotrophins in vivo. Specifically, the phenotypes of neurotrophin knockout mice [reviewed in ref. 10] do not manifest the clear deficits in axon pathfinding that are expected for genuine chemotropic molecules [see, for example, ref. 17].

Independent of their potential effects on axon guidance, that neurotrophins potently influence the complexity of axonal arbors both in vitro and in vivo in the CNS, particularly in the visual system. Application of BDNF, NT-3, and NT-4, but not NGF, enhances axonal arborization of retinal axons co-cultured with optic tecta from the chick [18]. Furthermore, in vivo infusion of BDNF, but not other neurotrophins, into the optic tectum of *Xenopus* tadpoles dramatically increases branching and complexity of retinal ganglion cell axons within 2 h [19]; these effects are long-lasting, persisting for at least 24 h. Conversely, blocking BDNF with antibodies infused into *Xenopus* optic tectum prevents axon growth and reduces axon complexity [19].

Like other axon guidance molecules [reviewed in ref. 20], the effects of neurotrophins on axons are complex and cell type specific. Recently, neurotrophins have also been demonstrated to dramatically *decrease* axon growth and branching in several systems. For example, acutely applied BDNF rapidly induces axonal growth cone collapse and neurite retraction of embryonic *Xenopus* spinal neurons in culture [21]. BDNF also inhibits axonal growth of cultured sympathetic neurons by antagonizing NGF binding to $p75^{NTR}$; thus, innervation of sympathetic targets may be determined by a balance of positively and negatively acting target-derived neurotrophins [22]. In the CNS, the neurotrophins have been implicated in the complex axon guidance decisions that underlie development of vertical connections in the visual cortex. Specifically, endogenous NT-3 may serve as a bifunctional axon guidance molecule in the rodent visual cortex. In in vitro assays, NT-3 is attractive for axons from neurons in layer 6, while it is repulsive for axons from neurons in layers 2/3 [23]. Such bifunctionality may contribute to the highly specified axon branching patterns characteristic of vertical connections in the cerebral cortex, although as yet there is no evidence to support such a role in vivo.

To better understand the ability of neurotrophins to act in a bifunctional manner, attention in this field has turned to investigating the effects of ligand/receptor interactions and the resulting signal transduction cascades that determine a neuron's response to a particular neurotrophin. In a series of elegant experiments, Poo and colleagues [14] have clearly demonstrated that the levels of cyclic nucleotides in an axonal growth cone can change the response to a single neurotrophin from attractive to repulsive. Cultured *Xenopus* spinal neurons are usually attracted and turn toward a gradient of BDNF. However, this same BDNF gradient repulses these axons when the cultures are treated with a competitive analog of cAMP or a specific inhibitor of protein kinase A [14]. In fact, levels of cAMP or cGMP can mediate the bifunctional effects of many axon guidance molecules on *Xenopus* neurons in vitro [24]. Thus, a neuron could possibly respond to the same extracellular signal with different cellular responses at different times based on modulation of intracellular levels of cAMP by other environmental factors. However, even though these results are compelling and attractive, it is important to keep in mind that these manipulations of cyclic nucleotides are large-scale, non-physiological manipulations and that there is not yet any evidence for such a function for cyclic nucleotides in vivo.

The bifunctional effects of the neurotrophins on axon guidance could alternatively/also be mediated by the small GTPases of the Rho family [25]. These GTPases have recently received much attention for their possible roles in rapid, activity-dependent changes in dendritic growth [reviewed in ref. 26]. Recently, a direct, physical interaction between $p75^{NTR}$ and the RhoA GTPase has suggested a molecular basis for the neurite-promoting effects of the neurotrophins [27]. Because the Rho proteins control actin cytoskeleton organization, this interaction provides a potential link between neurotrophins and the actin cytoskeleton [25]. Specifically, inactivation of RhoA is required for the effects of NGF mediated by $p75^{NTR}$ in enhancing the growth of ciliary neurons [27], implying that the actin cytoskeleton of growth cones can be rapidly remodeled in response to neurotrophins encountered during axonal pathfinding.

In the future, two major issues must be elucidated to understand the role of neurotrophins in axonal growth in more depth. First, do neurotrophins act as long-range diffusible chemotropic signals to guide axons to their targets in vivo or do they function simply to modulate the location and complexity of terminal branching? Second, what

are the cellular and molecular mechanisms that underlie the ability of neurotrophins to exert bifunctional effects on axon guidance? Elucidation of the roles of the different Trk receptors, their interactions with $p75^{NTR}$, and the signal transduction cascades that ultimately control the actin cytoskeleton should increase our understanding of these phenomena.

Dendritic growth

Dendritic growth is crucial for the proper functioning of the brain, as dendritic form determines the number, pattern, and types of synapses received by each neuron. Neurotrophins play a central role in sculpting dendrites both in the PNS and CNS [reviewed in ref. 28]. Neurotrophins were first demonstrated to regulate dendritic growth in the PNS in an elegant series of experiments by Snider and colleagues [29–33]. In these experiments, neonatal and adult rats were treated systemically with NGF for 1–2 weeks. This NGF treatment dramatically increased the complexity of dendritic arbors of sympathetic ganglion cells, whereas injections of NGF antiserum in adult rats decreased dendritic growth of sympathetic neurons [31–33].

In the CNS, the neurotrophins also regulate dendritic growth of many different types of neurons in several different brain regions [reviewed in ref. 2]. In particular, the neurotrophins potently regulate dendritic growth of pyramidal neurons in the developing visual cortex. When applied to organotypic cortical slices for only 36 h, each of the four neurotrophins rapidly increases the length and complexity of dendrites of cortical pyramidal neurons [34]. Neurons in each of the six cortical layers respond to specific neurotrophins with distinct effects on basal and apical dendrites [34]. Within a single cortical layer, each neurotrophin elicits a unique pattern of changes in dendritic morphology [34]. Moreover, pyramidal neurons transfected to overexpress BDNF retract their existing dendritic spines and sprout more dendrites [35]. Time-lapse imaging shows that the dendrites of these cells are much more dynamic than non-transfected control dendrites, suggesting that BDNF induces structural instability and increases plasticity in both dendrites and spines [35]. The spectrum of neurotrophin effects and the laminar specificity of these actions imply that neurotrophins act instructively to guide development of particular patterns of dendritic arborizations in the cerebral cortex.

An important criticism of these and similar experiments that rely on applying relatively high levels of exogenous neurotrophins to tissue is that any result revealed by these manipulations may not reflect the normal levels or spatial distribution of endogenous signaling molecules. However, endogenous neurotrophins have also been shown to influence dendritic growth, by blocking endogenous factor with Trk receptor-bodies (immunoadhesins) [36]. Results from these experiments clearly demonstrate that endogenous neurotrophins powerfully influence the complexity of dendritic arbors of pyramidal neurons in the developing visual cortex [37]. Consistent with the results from adding exogenous neurotrophin, endogenous BDNF is required for growth and maintenance of dendritic arbors of layer 4 neurons, while endogenous NT-3 is required for growth and maintenance of dendritic arbors of layer 6 neurons.

Blocking endogenous neurotrophins also revealed an extra level of regulation not apparent from experiments in which exogenous neurotrophins were manipulated. In the original series of experiments, endogenous neurotrophins were found not only to enhance dendritic growth but also to limit growth and even cause dendritic retraction, depending on the layer-specific location of the neurons examined [37]. Moreover, endogenous TrkB ligands and NT-3 appear to oppose each other in regulating dendritic growth. In layer 4, NT-3 inhibits dendritic growth caused by BDNF, while in layer 6, BDNF limits dendritic growth enhanced by NT-3 [37]. Thus, in addition to their bifunctional effects on axon guidance, neurotrophins also have bifunctional effects on dendritic growth. In fact, bifunctional effects of the neurotrophins were first demonstrated in experiments studying dendritic growth, and were later observed in axon guidance [37]. The opposing roles of the TrkB ligands and NT-3 suggests that the colocalization of TrkB and TrkC in single cortical neurons [see ref. 4 for a review] may not represent simple redundancy, but rather a tightly controlled push-pull system for regulating dendritic growth. These antagonistic roles for BDNF and NT-3 provide a potential mechanism by which dendritic growth and dendritic retraction can be dynamically and locally regulated by intercellular interactions.

A recent report using an alternative method for manipulating endogenous BDNF [38] suggests functions for this factor that are similar to the original report [37] but contain some potentially important differences; the reasons for these discrepancies have yet to be resolved and are probably due to the different experimental approaches. By manipulating levels of TrkB isoforms through overexpressing full-length TrkB and a truncated TrkB receptor (T1) in slices of ferret visual cortex, the specific complement of neurotrophin receptors was shown to determine the effects of a particular neurotrophin on dendritic growth [38]. Overexpression of TrkB increased dendritic branching, overexpression of T1 increased growth of existing dendrites, and overexpression of TrkC minimally increased proximal dendritic growth of layer 6 neurons [38]. Thus, these results appear to indicate that BDNF and NT-3 may not act in opposition to regulate dendritic growth in layer 6, as previously suggested [37]. One explanation for this discrepancy is that the previously reported opposing effects of the TrkB ligands and NT-3 in-

volve indirect effects of the Trk receptor-bodies on nonpyramidal cells. However, it is also possible that nonspecific effects of massive overexpression and transport of the Trk receptors may have influenced these more recent results. Future experiments should clarify this matter. Although these proposed functions for the neurotrophins in regulating dendritic growth are intriguing, one should keep in mind that the bulk of these studies used in vitro assays; to date, there is no evidence supporting these roles in vivo.

In recent years, the neurotrophins have received much attention as potential molecular mediators of the effects of synaptic activity on dendritic morphology. In support of this model, experiments manipulating both activity and neurotrophin levels in visual cortical slices indicate that neurotrophins preferentially affect active neurons [39]. Inhibition of either spontaneous electrical activity, synaptic transmission, or L-type calcium channels, completely prevents the large increase in dendritic growth elicited by exogenous BDNF. These results indicate that neurons must be active in order to respond to the growth-promoting effects of BDNF [39]. Such a requirement for conjoint neurotrophin signaling and synaptic activity suggests a potential mechanism for selectively enhancing the growth of dendrites receiving inputs primarily from active neurons in the developing nervous system.

In addition to their complex and bifunctional effects in the developing visual cortex, neurotrophins also influence dendritic growth of neurons in the developing retina and cerebellum. Local addition of BDNF in vivo reduces the complexity of dendritic arbors of *Xenopus* retinal ganglion cells, while neutralization of endogenous BDNF levels with locally applied function-blocking antibodies increases dendritic arbor complexity [40]. In the developing cerebellum, BDNF is required for the proper development of Purkinje cell dendrites; these dendritic arbors do not grow and branch properly in homozygous BDNF knockout mice [41, 42]. Interestingly, changing BDNF levels postnatally dramatically increases the number of dendritic spines but does not alter Purkinje cell dendrites [43, 44].

Endogenous neurotrophins also have important functions for maintaining the dendritic form of more mature cortical pyramidal neurons. This was recently demonstrated using a targeted genetic knockout approach in which endogenous TrkB was deleted only from those neurons that express CamKII, primarily cortical pyramidal neurons in the cortex [45]. In homozygous mice, the TrkB gene is depleted in cortical neurons by the fourth postnatal week. These mice exhibit massive neuronal loss in the cerebral cortex and dramatic dendritic retraction of cortical pyramidal neurons. Consistent with a role for endogenous BDNF in stimulating growth of pyramidal neuron dendrites, cortical neurons from these knockout mice have reduced dendritic arbors. Importantly, these results implicate neurotrophins in dendritic maintenance and indicate a possible role for neurotrophins in the etiology and/or treatment of neurodegenerative diseases [45].

Synapse formation and maintenance

In addition to regulating the size of presynaptic terminal arbors, or the extent of postsynaptic dendrites, target-derived neurotrophins have been widely hypothesized to regulate overall synapse number through modulating synapse formation and/or stabilization. There are a number of observations that are consistent with a role for neurotrophins in both synapse formation and maturation, but there is not yet any direct evidence that neurotrophins are involved. Consistent with this hypothesis, synaptic density is increased 2.5-fold in the superior cervical ganglion of transgenic mice overexpressing BDNF, and is decreased in BDNF knockout mice [46]. Mice lacking TrkB and TrkC also show decreased density of synapses in addition to reduced axonal arborizations [47]. However, these effects of BDNF on synapse number could result from direct effects of this factor on neuronal survival or morphology that indirectly influence the number of neural connections. Similarly, chronic treatment of *Xenopus* nerve-muscle cultures with BDNF and NT-3, but not NGF, increases the number of synapses exhibiting mature properties of synaptic transmission and morphology [48]. Furthermore, treatment of cultured rat spinal motor neurons with BDNF, NT-3, and NT-4 upregulates neuregulin expression, which in turn promotes the maturation of neuromuscular synapses [49]. Finally, and perhaps most compelling, BDNF knockout mice show presynaptic structural defects, including a decrease in the number of docked synaptic vesicles and reduced expression of the synaptic vesicle proteins synaptophysin and synaptobrevin [50].

Activity-dependent plasticity

In the last few years, much attention has focused on the neurotrophins as regulators of synaptic plasticity and development [reviewed in ref. 2]. Structural changes in axonal and dendritic arbors are obviously required for synaptic refinement in the developing cortex and these morphological changes necessarily alter the locations and numbers of synapses [51]. Activity-dependent development has been most extensively studied in the visual system where activity-driven structural changes result in eye-specific layers in the visual thalamus and ocular dominance columns in visual cortex [reviewed in refs 51, 52]. Although considerable progress has been made in identifying the specific structural changes that occur in response to altered experience, the detailed mechanisms

by which activity is translated into structural changes remain poorly understood.

The neurotrophins are attractive candidates for molecular mediators of the effects of activity in altering axonal, dendritic, and synaptic form, particularly in the visual system, for several reasons. First, neurotrophins and their receptors are present in the developing visual cortex during the period of ocular dominance column formation [53, 54]. Second, expression of the neurotrophins, particularly BDNF, is rapidly regulated by activity within the visual system, especially during the time of activity-dependent synaptic refinement [55–57]. Third, the neurotrophins themselves rapidly regulate synaptic transmission in the developing visual cortex [58–62] and appear to play an integral role in long-term plasticity in the visual cortex [63–65]. BDNF may also be critical for the synaptic scaling that occurs with short-term, global manipulations of activity [66, 67]. Fourth, in addition to their effects on synaptic activity, the neurotrophins also regulate axonal and dendritic growth in the developing visual cortex (as described above). Finally, infusion of excess neurotrophins, as well as blockade of their function, can alter normal ocular dominance column formation [68, 69] and can prevent the physiological consequences of monocular deprivation [70–72]. Thus a consensus is emerging that neurotrophins are important for activity-dependent plasticity in the developing visual cortex at some level. However, there is considerable controversy about the synapse specificity and cellular mechanisms of the neurotrophin effects [reviewed in ref. 2].

Concluding remarks

Although there is strong evidence that the neurotrophins are potent regulators of axonal and dendritic growth, support for their potential role in mediating activity-dependent plasticity is more indirect and circumstantial. Because the neurotrophins mediate both short-term effects on synaptic strength and possibly longer-term effects on the existence of connections, they are in an attractive position to control activity-dependent plasticity. However, direct proof for such a role remains elusive. Much of the controversy surrounding the role of neurotrophins in activity-dependent development and plasticity stems from inherent difficulties in interpreting the results from experiments published to date. Although these experiments have been seminal in forming our current theories on the role of neurotrophins in development, results from global manipulation of these factors in intact tissue are quite difficult to interpret. In addition, basic facts, such as the precise cellular localization of the neurotrophins and their receptors, and the effects of activity on this localization, must be clarified for the field to advance. Ultimately, the specific effects of the neurotrophins, and their interactions with synaptic activity at individual synapses must also be elucidated. Given the rapid pace of discoveries in the field of neurotrophin research, we will hopefully have answers to these questions in the near future.

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