Neurotrophins: **New roles for a seasoned cast**

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Recent studies suggest that endogenous neurotrophins play a central role in the patterning of cortical connections and in cortical synaptic physiology. Do these effects of neurotrophins reflect independent cellular events, or are they manifestations of a single cellular mechanism central to developmental plasticity?

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Much of our understanding of the activity-dependent development of the cortex has been derived from studies of thalamic projections to the visual cortex. Axons from the lateral geniculate nucleus (LGN) of the thalamus are initially intermixed within layer 4 of the visual cortex. A process of eye-specific axon segregation leads to the formation of ocular dominance columns, which include groups of neurons that respond preferentially to stimulation of one eye (Figure 1). Monocular deprivation during a restricted period in development — called the critical period — leads to a shift in ocular dominance columns in favor of the non-deprived eye [1]. The formation of ocular dominance columns can be prevented by intraocular injection of tetrodotoxin, a sodium channel blocker, suggesting that the process requires action potential activity [2]. It has also been shown that blockade of the *N*-methyl-D-aspartate (NMDA) class of glutamate receptors in the cortex prevents ocular dominance plasticity, indicating a role for synaptic transmission in this process [3]. There has been much interest over the past few years in identifying the molecular mechanisms that mediate these activity-dependent changes in the developing cortex.

One class of molecules that has been suggested to play a role in the development of thalamocortical projections is the neurotrophin family of growth factors. Neurotrophins are small, secreted proteins that have been found to play important roles in various aspects of nervous system development. Members of this family, which includes nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and neurotrophin-4/5 (NT-4/5), were initially identified as factors that promote the survival of various classes of neurons. As discussed below, a number of recent studies have provided evidence that neurotrophins can also exert marked influences on cellular events that may be central to cortical plasticity.

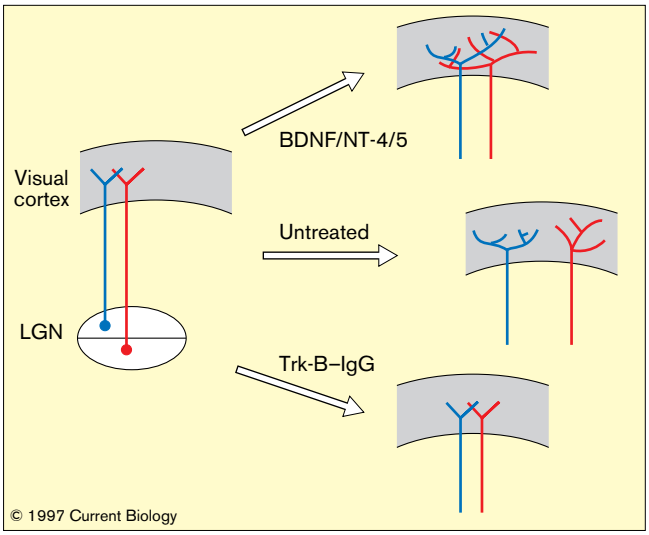
Neurotrophins and thalamocortical patterning

A long-standing hypothesis concerning the patterning of axonal projections holds that developing axons require target-derived factors for their survival, and that ingrowing axons compete for limiting amounts of such target-derived trophic factors. It has also been proposed that, during thalamocortical development, more active thalamic afferents have a competitive advantage. One class of molecules that may serve as target-derived trophic factors are the neurotrophins. A prediction of this possibility is that an excess of target-derived neurotrophins should eliminate competition among thalamic afferents and, indeed, Cabelli *et al.* [4] have shown that infusion of BDNF or NT-4/5 into the visual cortex of kittens during the critical period prevents the segregation of geniculocortical axons into ocular dominance columns.

Although this observation indicates that exogenously applied neurotrophins can influence the patterning of thalamic axons in the cortex, it does not show whether endogenous neurotrophins have a similar function. Cabelli *et al.* [5] have recently addressed this question by infusing neurotrophin 'receptor-bodies' into the visual cortex during the critical period. Receptor-bodies are fusion proteins consisting of the ligand-binding domain of a receptor — in this case one of the neurotrophin receptors, Trk-A, Trk-B or Trk-C — fused to the Fc portion of human immunoglobulin G (IgG). They found that infusion of Trk-B–IgG, but not Trk-A–IgG or Trk-C–IgG, into the visual cortex of kittens blocked the segregation of LGN axons into ocular dominance columns. This observation suggests that a Trk-B ligand, most likely BDNF or NT-4/5, participates in the eye-specific segregation of geniculocortical axons (Figure 1).

These elegant experiments suggest that endogenous neurotrophins play an important role in the patterning of thalamocortical projections, but the specific cellular function of the neurotrophins in this process is not easily inferred. One possibility is that BDNF or NT-4/5 acts principally to regulate the growth of thalamic axons within layer 4. Neurotrophin infusion may lead to an increased growth of thalamic axons within layer 4, and Trk-B–IgG infusions may arrest the ingrowing axons in an immature, unsegregated state. Alternatively, BDNF or NT-4/5 may play a central role in activity-dependent synaptic plasticity and may mediate the stabilization or growth of appropriate synaptic contacts. Infusion of neurotrophins may lead to the stabilization of inappropriate synapses, and the sequestration of neurotrophins by Trk-B–IgG receptor-bodies might prevent all forms of activity-dependent

Figure 1



Diagrammatic representation of the effects of neurotrophin perturbation on ocular dominance column formation. Infusion of BDNF, NT-4/5 or Trk-B–IgG prevents the formation of ocular dominance columns, but the effects of these perturbations on individual LGN axons may be distinct, as shown here. See text for details.

rearrangements from taking place. Both of these potential mechanisms are consistent with the results of the neurotrophin perturbation experiments. Moreover, as discussed below, emerging evidence suggests that neurotrophins can also have major effects on the dendritic development of postsynaptic cortical neurons, which could indirectly influence the elaboration of presynaptic axon terminals.

Neurotrophins and dendritic growth

In a recent series of experiments, McAllister and colleagues [6,7] have made some interesting observations regarding the influence of neurotrophins on dendritic development in cortical slice cultures. In their initial study [6], the authors reported that cells in different layers of the cortex respond differentially to neurotrophin stimulation. For example, BDNF promotes the growth of dendrites of layer 4 and 5 neurons, but suppresses the development of basal dendrites in layer 6. They also noted that cells in a given layer respond distinctly to stimulation by different neurotrophins. Layer 4 neurons, which respond positively to BDNF stimulation, are virtually unaffected by NT-3 stimulation. These findings indicate that neurotrophins can have marked layer-specific effects on the dendritic development of cortical neurons.

These observations have recently been extended to include an analysis of the role of endogenous neurotrophins in the regulation of dendritic growth. By using receptor-bodies to inhibit the function of endogenous neurotrophins, McAllister *et al.* [7] found that treatment of cortical slices with Trk-B–IgG or Trk-C–IgG had opposite effects on the same population of neurons. Whereas Trk-B–IgG treatment inhibited dendritic growth of layer 4 neurons, Trk-C–IgG treatment promoted it, suggesting that the endogenous Trk-B ligands, BDNF and NT-4/5, and the Trk-C ligand, NT-3, have opposing effects on the dendritic growth of layer 4 neurons.

This result is particularly striking, as stimulation of both Trk-B and Trk-C receptors leads to the activation of the Ras–mitogen activated protein (MAP) kinase signal transduction cascade, and therefore would be expected to have similar cellular consequences. The distinct effects of inhibiting BDNF and NT-3 strongly suggest that there are important differences in the Trk-B and Trk-C signaling pathways that remain to be identified. Although it is not yet clear whether neurotrophins can influence dendritic growth during the critical period, given the findings of the slice culture experiments that possibility must be taken into account in interpreting the results of neurotrophin or Trk-B–IgG infusion experiments described above.

Neurotrophins and synaptic plasticity

The cellular effects of neurotrophins on thalamic axons and cortical dendrites are seen over the course of days, and therefore do not reveal whether these factors can have acute effects on the physiology or function of cortical neurons. In the past few years, this possibility has received much attention from experiments that have examined the role of neurotrophins in synaptic plasticity. In 1995, Kang and Schuman [8] reported that acute treatment of adult hippocampal slices with BDNF or NT-3 led to a rapid enhancement of synaptic transmission, and that this form of synaptic enhancement did not occlude long-term potentiation (LTP), a form of synaptic plasticity that has been extensively investigated in the hippocampus and neocortex as a cellular model of learning and memory.

This observation generated a great deal of excitement, as well as some level of controversy, in part because some subsequent reports were not entirely consistent with this finding. For example, Figurov *et al.* [9] reported that BDNF promoted the induction of LTP in young, but not adult, hippocampal slices. Moreover, they found that, in the absence of activity, BDNF did not affect the efficacy of basal synaptic transmission. Although these differences have generally been attributed to variations in the details of the experimental procedure, they underscore the point that there is not yet universal agreement on the specific role of neurotrophins in the modulation of synaptic transmission.

A second line of evidence that supports a role for BDNF in synaptic plasticity has come from analysis of mice with a targeted disruption of the BDNF gene. Two different groups have reported that LTP is impaired in BDNF null mice [10,11]. Importantly, this defect can be rescued by

BDNF provided either by retroviral infection of hippocampal slices [12] or by bath application of BDNF [11], suggesting that the defect is likely to be related to an acute requirement for BDNF rather than being a developmental consequence of the absence of BDNF. It is also noteworthy that the heterozygous animals also show defective LTP, suggesting that the levels of BDNF may be an important determinant of synaptic plasticity.

Recent observations suggest that, as in the hippocampus, plasticity in the cortex can also be modulated by neurotrophins. Two findings in this regard are particularly noteworthy. Akaneya *et al*. [13] have reported that application of recombinant BDNF can prevent the induction of long-term depression (LTD) in layer *2*/3 of cortex in response to low frequency stimulation of layer 4. More recently, the same group [14] found that treatment with BDNF — but not NT-3 or NGF — could lead to an enhancement of field potentials recorded in layer *2*/3 following layer 4 stimulation. They also found that bath application of Trk-B–IgG or K252a (a Trk receptor family inhibitor) could prevent the induction of LTP in these slices, suggesting that endogenous BDNF may be required for certain forms of synaptic plasticity in cortical slices. Although these findings require further investigation, they suggest that neurotrophins can have rapid and pronounced effects on cortical synaptic physiology.

Perspectives

The recent evidence that neurotrophins modulate both synaptic plasticity and cortical development has renewed interest in the possibility that synaptic plasticity and activity-dependent ocular dominance plasticity may share common underlying mechanisms. One interpretation of these findings is that neurotrophins directly contribute to synaptic plasticity, and that these synaptic changes in turn are responsible for the activity-dependent remodeling of thalamocortical axons that is the basis of ocular dominance column segregation.

This model is appealing, because it unifies the mechanism underlying two forms of activity-dependent plasticity. Recent studies in the rat somatosensory [15] and visual [16] cortex, which show that LTP can be induced during a time that coincides with the critical period and that the two events have similar pharmacological responses, provide indirect support for this possibility. It should be noted, however, that such correlations do not prove that synaptic plasticity and activity-dependent reorganization of thalamic axons are causally related events, and further work is necessary before such a conclusion can be drawn.

With regard to the effects of neurotrophins on the activity-dependent reorganization of thalamic afferents, there are several important issues that remain to be addressed. It will be of particular interest to explore how BDNF or NT-4/5 might contribute to the growth or stabilization of appropriate thalamic axons. One possibility is that, in the postsynaptic neuron, the neurotrophin is transported to active synapses, leading to specific stabilization of those synapses. Another possibility is that BDNF or NT-4/5 is released by the postsynaptic neuron in a relatively non-specific way and acts as a permissive signal for activity-dependent synaptic plasticity. A third possibility is that active thalamic axons are more effective in responding to target-derived neurotrophins, even if the factors are not released in a synapse-specific manner. These possible modes of action by which neurotrophins might affect synaptic physiology and afferent growth are not mutually exclusive, and additional experiments are required to determine whether one or more of these mechanisms are indeed involved.

Another issue that needs to be addressed is the electrophysiological response of cortical neurons *in vivo* under conditions of neurotrophin or Trk-B–IgG infusion. Given the extensive evidence that inhibition of neuronal activity can prevent ocular segregation, it is important to determine whether perturbation of neurotrophins has acute effects on synaptic physiology *in vivo*. It would also be interesting to know whether the effects of monocular deprivation on the patterning of thalamic afferents can be rescued by providing exogenous neurotrophins. Monocular deprivation typically leads to the retraction of thalamic axons receiving inputs from the deprived eye. If this is because of their inability to access target-derived BDNF or NT-4/5, then infusion of these neurotrophins should rescue this defect. A failure to rescue would be more consistent with the possibility that BDNF acts as a permissive factor for ocular dominance plasticity. The answers to these questions will be critical as we try to understand the specific function of neurotrophins in cortical plasticity.

The observations from recent neurotrophin perturbation experiments have provided important evidence in support of a role for these factors in cortical development. Despite this progress, we are still far from understanding the mechanisms by which neurotrophins affect various cellular events in the cortex, and from knowing whether they are manifestations of a single neurotrophin-regulated cellular event. It will be of interest to see which of the many current hypotheses survive more rigorous investigations, which are sure to come in short order.

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