Previews

Spatially Restricted Actions of BDNF

In this issue of *Neuron*, Zhang and Poo present evidence for localized BDNF-induced synaptic potentiation that is accompanied by spatially restricted calcium influx and requires local axonal protein synthesis. These results are consistent with a synapse-specific role for BDNF and provide a potentially novel way to think about cellular mechanisms for potentiation of neurotransmitter release.

The neurotrophins were first discovered based on their ability to promote the differentiation and survival of cultured neurons from the peripheral nervous system. These findings led to the formation of the "neurotrophin hypothesis," that neurotrophins are produced in limited amounts within postsynaptic targets and act to match the size of innervating neuronal populations with their targets during development (reviewed in Levi-Montalcini, 1987). Since this original discovery, a large number of studies have demonstrated strong effects of neurotrophins in enhancing both acute and long-term synaptic efficacy. The neurotrophin hypothesis has therefore been revised to include a critical role for the neurotrophins in the survival of individual synaptic connections, as opposed to the whole neuron (reviewed in McAllister et al., 1999). In this revised hypothesis, neurotrophins are secreted in an activity-dependent manner from postsynaptic neurons and act to mediate activity-dependent synaptic refinement. Correlated pre- and postsynaptic activity stimulates the secretion of neurotrophins, resulting in strengthening and maintenance of active synapses. Synapses that are not coincidentally active with their postsynaptic partner do not receive neurotrophins and are weakened, and perhaps eventually eliminated (reviewed in Snider and Lichtman, 1996; Poo, 2001).

This revised neurotrophin hypothesis assumes that neurotrophins are secreted and act exclusively at active synapses. Indeed, it is well established that synaptic activity can potently regulate the expression, secretion, and function of neurotrophins (reviewed in McAllister et al., 1999; Poo, 2001). In turn, neurotrophins influence both acute and long-term electrophysiological and structural synaptic plasticity. However, the synapse specificity of these effects of synaptic activity on neurotrophins and vice versa is unresolved. It is unclear whether neurotrophins are synthesized exclusively at active synapses and whether the secretion and function of neurotrophins are restricted to that single active synapse.

There are, in broad terms, two issues that will determine the specificity of neurotrophin action–the precise location of secretion and binding of the neurotrophin and the spatial extent of the resulting intracellular signaling. First, the site of neurotrophin secretion and its ability to diffuse away from that site will determine the distance over which neurotrophins influence nearby neurons.

There is increasing evidence that neurotrophin function is controlled temporally by regulated, activity-dependent secretion (reviewed in Poo, 2001). It has been assumed that neurotrophins are secreted at the synapse mostly because neurotrophins exert such rapid and profound effects on synaptic transmission; yet, this remains unknown. Because neurotrophins are highly basic, "sticky" molecules, it is likely that they cannot diffuse far from their site of secretion. Second, the precise localization of neurotrophin receptors is also unclear. Although Trk receptors can be located at synapses, a number of studies have demonstrated a diffuse distribution of neurotrophin receptors on dendrites and axons of neurons (reviewed in Poo, 2001; McAllister, 2002); thus, it is possible that neurotrophins may act on extrasynaptic receptors at an unknown distance from the synapse. It is also possible that the distribution and membrane insertion of these receptors at active synapses changes dynamically with activity levels (reviewed in Poo, 2001; McAllister, 2002). Finally, once the neurotrophin has bound its receptor, an additional factor in the specificity of its effects is the extent of diffusion of its intracellular signal transduction cascades (reviewed in Poo, 2001). The extent of intracellular spread of neurotrophin signaling may also be regulated by synaptic activity. Activity may modulate the ability of local portions of neurons (or specific synapses) to respond to neurotrophin signaling by modifying local signal transduction cascades (reviewed in McAllister et al., 1999; Poo, 2001).

Although local application of neurotrophins clearly induces localized changes in neuronal morphology (Campenot, 1977; reviewed in Poo, 2001), the distance over which neurotrophins exert their effects is unknown. Evidence that neurotrophins may exert their effects specifically at synapses was first provided several years ago by two reports from Mu-ming Poo's laboratory. Using *Xenopus* nerve-muscle cultures, these authors found that neuromuscular synapses formed on myocytes overexpressing neurotrophin-4 (NT-4) exhibit enhanced synaptic transmission, as compared to those formed on control myocytes (Wang and Poo, 1997). Moreover, NT-4 secreted from NT-4-overexpressing myocytes does not modulate synapses on myocytes at distances greater than 50 μm. Finally, the intracellular changes leading to enhanced neurotransmitter release in the presynaptic neurons are also restricted to a distance of about 60 μm (Wang et al., 1998). In contrast to the localized presynaptic action of NT-4, activity-induced long-term depression at these synapses can spread presynaptically long distances (up to 400 μm) to neighboring synapses formed by the same axon on other myocytes (Cash et al., 1996).

In this issue of *Neuron*, Zhang and Poo provide compelling evidence that the action of brain-derived neurotrophic factor (BDNF) is also restricted to a limited distance from the site of BDNF application. Using *Xenopus* nerve-muscle cultures, the authors demonstrate that contact of a BDNF-coated bead with a presynaptic axon leads to potentiation of neurotransmitter release within

minutes from a newly formed synapse between an axon and muscle cell. This synaptic potentiation occurs only if the bead, multiple beads, or a pipette secreting BDNF is placed within 60 μm of the synapse. These results indicate that a localized source of BDNF can potentiate synaptic transmission only in a defined nearby area. Furthermore, this localized BDNF-induced potentiation may be mediated by spatially restricted calcium signaling, as there is a gradual and persistent elevation of intracellular calcium in the axon that extends for a distance of about 40 μm from the bead.

These data provide some of the first evidence that the effects of BDNF are restricted to a limited area near a source of BDNF. The implication of these results is that BDNF, when secreted from a synapse in response to activity, would only exert its effects on synaptic efficacy locally. The key to the significance of this result is in the definition and relevance of "local" effects. The ability of BDNF to exert effects for 60 μm within an axon at a neuromuscular junction may be functionally relevant in that there are probably no other synapses made within this distance. In contrast, however, 60 μm is not an input-specific distance, i.e., local, for an axon from a neuron in the central nervous system (CNS) that may have tens to hundreds of synapses within that distance (depending on axonal branching density and neuron type). However, even if the results reported in Zhang and Poo (2002, this issue) extrapolate to the CNS, this may not be inconsistent with some forms of synaptic plasticity. A number of reports have shown that changes in synaptic efficacy, including long-term potentiation (LTP) and depression (LTD) in the hippocampus, are not restricted to the active synapse but can spread over relatively large distances (reviewed in Schuman, 1997). This spread of LTP is believed to be mediated by intracellular signaling in the presynaptic neuron and could conceivably be mediated by calcium influx from synaptic neurotrophin signaling (reported in this paper). Future studies similar to those reported here but performed in CNS neurons are critical to clarify this issue.

In addition to local intracellular calcium-dependent TrkB signaling, Zhang and Poo (2002, this issue) demonstrate that the spatial restriction of BDNF-induced potentiation of synaptic transmission may also be achieved by local protein synthesis in the axon. This surprising result is consistent with a previous report showing that neurotrophin-induced LTP in hippocampal slices is dependent on local protein synthesis near potentiated synapses–i.e., in the axons, dendrites, or both (Kang and Schuman, 1996). In this issue of *Neuron*, Zhang and Poo demonstrate that acute BDNF-induced synaptic potentiation in their *Xenopus* nerve-muscle cultures is blocked after a 2 hr, but not a 45 min, preincubation with protein synthesis inhibitors. This protein synthesis must occur locally in the axon, as the same result is obtained even when axons are severed from the cell bodies or a protein synthesis inhibitor is injected into the postsynaptic myocyte. Although de novo induction of protein synthesis by BDNF is not required for potentiation of neurotransmitter release (since there was no effect of a 45 min incubation of protein synthesis inhibitors on BDNF-induced potentiation), ongoing local axonal protein synthesis of a critical presynaptic protein must be required for potentiation since the longer preincubation blocked the BDNF effect.

The nature of the critical presynaptic component that is translated locally within the axon and is required for BDNF-induced synaptic potentiation is unknown. It is possible that this protein could be the TrkB receptors themselves. If these receptors are rapidly turned over on a time scale of hours, then blocking protein synthesis may lead to a dramatic decrease in TrkB receptor numbers in the axonal membrane and an inability to respond to BDNF after 2 hr of blockade. Consistent with this hypothesis, prolonged inhibition of protein synthesis also abolished BDNF-induced calcium influx (Zhang and Poo, 2002). Alternatively, local protein synthesis may influence the expression of presynaptic proteins important for modulating exocytosis and/or components of the cytoskeleton critical for modulation of synaptic transmission. Future studies identifying the proteins synthesized in the axon will be important not only for our understanding of BDNF function, but also for understanding cellular mechanisms of synaptic plasticity in general.

In conclusion, this study provides important information on the spatial specificity of BDNF effects in enhancing neurotransmitter release. Future work will likely focus on whether similar spatial specificity is found in postsynaptic dendrites and in neurons in the mammalian CNS. In addition, studies determining whether neurotrophins are secreted from focal areas at or near the synapse are also critical for our understanding synapse specificity of neurotrophin action.

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Selected Reading

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