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Neurotrophic Factors and Synaptic Plasticity

Minireview

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Models of activity-dependent synaptic plasticity, whether in the context of development or of learning and memory, have long postulated the existence of extracellular signaling molecules that enhance and stabilize active synapses. In recent years, neurotrophic factors have emerged as attractive candidates for such signaling molecules. The work of several laboratories has shown that neurotrophins fulfill the two major criteria for any such mediators of synaptic plasticity: their production is regulated by neuronal activity, and neurotrophic factors, in turn, have potent effects on the signaling properties of target neurons. Neurotrophic factors represent a new and exciting class of molecules for a signaling role in synaptic plasticity because of their strong regulation of gene expression and neuronal morphology; neurotrophic factors could consequently regulate neuronal excitability and synaptic function over a much longer time scale than conventional neuromodulators.

The neurotrophic factors that have been most studied in this regard are the neurotrophins, which are much better known for their promotion of neuronal survival and differentiation. Nerve growth factor (NGF) remains the archetypical neurotrophin; in addition, the neurotrophin family now includes brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), NT-4/5, and NT-6 (reviewed in Lindsay et al., 1994; Götz et al., 1994). Responsiveness to particular neurotrophins is mediated through receptors specific for each factor. These receptors, members of the *trk* family of protooncogenes, are receptor tyrosine kinases related to other peptide factor receptors such as insulin and epidermal growth factor (EGF) receptors. Although cross-activation can occur, in neurons TrkA is primarily a receptor for NGF, TrkB a receptor for BDNF and NT-4/5, and TrkC a receptor for NT-3.

Regulation of Neurotrophins by Neuronal Activity

Regulation of neurotrophin mRNA levels by activity was first discovered in the hippocampus, where high basal levels of neurotrophins are expressed. NGF and BDNF mRNA levels, but not those for NT-3, are rapidly and strongly regulated by epileptiform activity in the hippocampus; even a single epileptiform afterdischarge is sufficient to increase levels of NGF and BDNF mRNA substantially (e.g., Ernfors et al., 1991; Isackson et al., 1991). Changes in BDNF mRNA levels are particularly dramatic, increasing by over 6-fold in dentate granule cells within 30 min after stimulation of seizure activity (Ernfors et al., 1991). These increases in NGF and BDNF mRNAs are transient, returning to control levels after 24 hr (Isackson et al., 1991; Ernfors et al., 1991). Importantly, conditions inducing long-term potentiation (LTP) in the hippocampus have also been shown to increase BDNF and NT-3 mRNAs (Patterson et al., 1992). However, it will be essential to determine how ongoing levels of endogenous activity during normal development and function contribute to the regulation of neurotrophin gene expression.

This tight linkage between electrical activity and neurotrophin mRNA levels is particularly evident in dissociated neuronal cultures. Depolarization of cultured hippocampal neurons by high potassium or by glutamate receptor activation strongly induces mRNAs for NGF and BDNF, while GABAergic transmission reduces these mRNA levels (e.g., Lu et al., 1991; Zafra et al., 1991). As observed in vivo, these responses to changing levels of electrical activity are rapid: levels of BDNF mRNA increase by over 10-fold within 3 hr after stimulation by kainate, an agonist of non-N-methyl-D-aspartate-type glutamate receptors. Similar regulation of BDNF mRNA occurs in cultured cerebellar granule cells, a process that appears to involve both ionotropic and metabotropic glutamate receptors (Bessho et al., 1993; Lindholm et al., 1993). The signal transduction mechanisms through which this regulation occurs are unknown and remain an important area for future study.

Short-Term Neurotrophic Regulation of Neuronal Signaling

In turn, neurotrophins have strong effects on synaptic transmission and the intrinsic excitability of target neurons, both in the short term (minutes to hours) and the long term (days or more). Short-term effects of neurotrophins on cellular functions such as electrical signaling can be predicted from the nature of neurotrophin signal transduction itself. Within minutes, neurotrophin binding to Trk receptors triggers multiple signal transduction pathways, such as those involving phospholipase C-γ1, protein kinase A, and protein kinase C that are known to have strong posttranslational regulatory effects on neuronal signaling proteins such as ion channels and neurotransmitter receptors (reviewed in Kaplan and Stephens, 1994).

Direct evidence for short-term modulation of synaptic transmission was provided by Lohof et al. (1993), who found strong effects of BDNF and NT-3 on synaptic transmission at developing Xenopus neuromuscular synapses in culture. In these cultures, acute application of BDNF and NT-3, but not NGF, increases the frequency of spontaneous synaptic transmission but not the size of postsynaptic currents. These effects are large (>6-fold for NT-3), begin within 5 min of neurotrophin application, and are dependent on the continued presence of the neurotrophin. Ciliary neurotrophic factor (CNTF) also has a potentiating effect at these synapses, but while CNTF requires a somatic signaling step, BDNF still does not; it is able to potentiate neurotransmitter release in isolated motor neuron terminals (Stoop and Poo, 1995).

There is now evidence that similar mechanisms may operate in the mammalian CNS. Kang and Schuman (1995) found that BDNF and NT-3, but not NGF, potentiate glutamatergic transmission at Schaffer collateral–CA1 synapses in adult rat hippocampal slices. The effects of BDNF

and NT-3 are rapid, increasing synaptic efficacy by 2- to 3-fold within 1 hr of neurotrophin application. In contrast to what is observed for Xenopus neuromuscular junctions, however, synaptic enhancement remains stable for at least 2 hr after the washout of neurotrophins. Synaptic potentiation by BDNF and NT-4/5 has also been studied in dissociated cultures of embryonic hippocampal neurons, where both pre- and postsynaptic effects of these TrkB ligands on glutamatergic transmission have been reported (Lessmann et al., 1994; Levine et al., 1995). Finally, hippocampal LTP appears to be impaired in both homo- and heterozygous mice deficient for the BDNF gene (Korte et al., 1995).

Long-Term Neurotrophic Regulation of Neuronal Signaling

While the effects described above presumably arise from posttranslational modifications of neuronal signaling proteins, the consolidation of these short-term effects into long-term changes likely requires changes at the level of gene expression and neuronal morphology/connectivity. The maintenance of mammalian LTP beyond the first few hours after induction, for example, is dependent on a critical period of transcription (Nguyen et al., 1994). Longer-term regulation of neuronal signaling by neurotrophins could also involve changes in neuronal form and connectivity; the long-term regulatory effects of NGF on the morphology of both developing and adult PNS neurons are well known (reviewed in Purves et al., 1988). Similar but more complex morphoregulatory effects of neurotrophins have now been found in neocortex (McAllister et al., 1995). Importantly, these effects are specific for each neurotrophin and for neurons in each cortical layer, suggesting that neurotrophins have distinct functional roles in regulating neuronal form and connectivity in the CNS.

With respect to long-term regulation of excitability, NGF remains the most extensively studied neurotrophin. Most of this work has been done using PC12 cells, the classic model neuronal cell line, on which studies on NGF action have been carried out over the last two decades. The dramatic effect of NGF on the excitability of PC12 cells was appreciated from the outset (Dichter et al., 1977) and involves increases in functional levels of ion channels such as voltage-gated sodium, calcium, and potassium channels, and neurotransmitter receptors such as nicotinic acetylcholine receptors. For sodium channels and nicotinic acetylcholine receptors, this regulation involves gene regulatory mechanisms (e.g., Mandel et al., 1988; Henderson et al., 1994, and references therein). NGF and other neurotrophic factors such as CNTF also regulate functional ion channel expression in other neuronal cell lines (e.g., Lesser and Lo, 1995). Neurotrophic factor regulation of ion channels in these cell lines lasts at least several weeks; similar regulation of ion channels and neurotransmitter receptors in vivo could potentially persist for the life of the neuron.

Synaptic Plasticity in Development

Despite the long-term regulatory effects of neurotrophic factors on the signaling properties described above, direct evidence for such effects on synaptic plasticity in vivo is only just emerging. Muscle-derived NT-4/5, for example, is regulated by electrical muscle activity, which is normally stimulated by synaptic transmission at the neuromuscular junction. In turn, exogenous NT-4/5 promotes sprouting of motor neuron terminals. These observations together suggest that NT-4/5 could be an activity-dependent retrograde factor that stabilizes and/or enhances active neuromuscular junctions (Funakoshi et al., 1995).

In the developing visual system, neurotrophins have effects on the synaptic organization of axonal projections from the lateral geniculate nucleus (LGN) to primary visual cortex, in particular on the formation of ocular dominance columns. Infusion of BDNF or NT-4/5, but not NGF or NT-3, prevents the formation of ocular dominance columns as determined by anatomical techniques (Cabelli et al., 1995). This finding is consistent with the idea that LGN projections compete in visual cortex for a factor that is produced in limiting supply by cortical neurons. Provision of excess BDNF or NT-4/5, in this model, would eliminate such competition by allowing all projecting neurons in the LGN to gain access to sufficient amounts of factor. In contrast to this anatomical evidence, in which exogenous NGF was not found to affect the development of ocular dominance columns, electrophysiological experiments have shown effects of NGF infusion on both ocular dominance column development and plasticity (e.g., Carmignoto et al., 1993; Gu et al., 1994).

Additional evidence for competition among LGN neurons for neurotrophins produced in visual cortex has come from monocular deprivation experiments during the critical period of visual system development. LGN neurons that normally receive input from the deprived eye become less active as a result of monocular deprivation and eventually undergo shrinkage of their cell bodies and axonal projections to visual cortex. These neurons do not, however, undergo cell death. Local provision in visual cortex of exogenous NT-4/5, but not NGF, BDNF, or NT-3, rescues inactive LGN neurons from the atrophic effects of monocular deprivation (Riddle et al., 1995). Similar rescue effects have also been reported for NGF when provided intraventricularly (e.g., Carmignoto et al., 1993). It is important to note, however, that some or all of the actions of these neurotrophins on LGN neurons may occur indirectly through effects on their postsynaptic targets, the visual cortical neurons, rather than by direct effects on LGN neurons themselves. Indeed, the apparently different results for particular neurotrophins on ocular dominance column development described above may have resulted from neurotrophins having a mixture of direct and indirect effects in this system.

These findings regarding the effects of neurotrophins on synaptic plasticity parallel more traditional views of trophic action, in which the survival of neurons, particularly during development, is dependent on the acquisition of trophic factors produced in limiting amounts by target cells. The notable difference here is that synaptic plasticity, rather than neuronal survival, is being regulated by trophic interactions, furthering the already blurred distinction between the regulation of neuronal survival and neuronal function by neurotrophic factors. Ghosh et al. (1994) have shown, for example, that neuronal activity involving voltage-gated

calcium channels promotes survival of cortical neurons in vitro by stimulating autocrine production of BDNF. Because cortical neurons survive in BDNF knockout mice (reviewed in Snider, 1994), such autocrine BDNF in cortex likely has other functions, including the regulation of neuronal signaling through effects on intrinsic excitability, synaptic transmission, and connectivity.

Conclusions

These findings together point to a central role for neurotrophic factors in the long-term regulation of synaptic plasticity. Reciprocal regulation between neurotrophic factors and electrical/synaptic activity provides a way in which active synapses and circuits can be selectively strengthened. Most importantly, by regulating gene expression and neuronal morphology, neurotrophic factors could have effects on neuronal signaling that persist long after the electrical events that first stimulate their production; short-term effects of neurotrophins may serve to bridge the temporal gap between the initiation and expression of these long-term changes. Many important questions remain, however. Prominent among these is where and how neurotrophins are released from neurons and whether such release is dependent on electrical activity. Evidence for activity-dependent release of NGF has recently been reported (Blöchl and Thoenen, 1995), but the subcellular release sites for NGF and other neurotrophic factors and the activity-dependent and -independent mechanisms by which they are released remain wholly unknown. Given the wide range of neurotrophic factors, their localization, and their modes of action, it would be surprising if their release mechanisms and their effects on synaptic plasticity were not equally diverse.

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