Role of Neurotrophins in Synapse Formation

Phyllis Dan Ph.D.

The neurotrophins ("neuro" means nerve and "trophe" means nutrient) are a family of soluble, basic growth factors which regulate neuronal development, maintenance, survival and death in the central and peripheral nervous systems. They include NGF, the first member of the family to be discovered, BDNF, NT3 and NT4/5. Their actions are mediated by two types of receptors: the Trk family, which matches each neurotrophin to its own receptor, and p75NTR which is a universal neurotrophin receptor.

The neurotrophins have been shown to affect dendritic and axonal growth, efficacy of synaptic transmission, maturation of synaptic contacts, density of synaptic innervation, and development of ocular dominance columns in the visual cortex. BDNF specifically has emerged as a central player in this arena and has been shown to be essential in establishing neuronal connectivity, modulation of axon and dendritic branching, increasing synaptic transmission efficacy, and influencing synaptic and network maturation.

Synapses are asymmetric communication junctions formed between two neurons, or at the neuromuscular junction, between a neuron and a muscle cell. Chemical synapses enable cell to cell communication via secretion of neurotransmitter, whereas in the less abundant electrical synapses, signals are transmitted through gap junctions. Synapse assembly begins when axons approach their targets and establish contact with dendritic arbors or soma of their target neuron.

Neurotrophins and Formation of Functional Synapses

In order to postulate a connection between neurotrophins and formation of functional synapses, one of the first things to investigate is the effect of neurotrophins on the number of synapses. It has been shown that synaptic density is increased 2.5-fold in the superior cervical ganglion of transgenic mice overexpressing BDNF and is decreased in synapses. It has been shown that synaptic vesicles, and a dramatic and specific downregulation of presynaptic proteins. This points to a role for neurotrophins in the development and maturation of synaptic structure by regulating the levels of some presynaptic proteins.

After establishing that neurotrophins affect the number and stability of synapses, it must be established that these are functional synapses, according to the electrophysiological criterion. The first direct evidence that the presence of neurotrophins was required for formation of functional synapses was shown in Lymnaea neurons. It was shown that when juxtaposed in cell culture, excitatory synapse formation between a variety of presynaptic and postsynaptic neurons depends on extrinsic trophic factors, and that the effect was mediated by receptor tyrosine kinases, leaving no doubt that the neurotrophins are involved, although specific neurotrophins were not identified.

At central glutamatergic synapses, BDNF promotes the transition of immature, electrically "silent" synapses into mature synapses. The precise mechanisms of neurotrophin actions being elucidated. The formation of the synapse is a complicated process with multiple possibilities for regulation at the biochemical and topographical levels. One of the points to be clarified is the precise location of the neurotrophin effect. The clustering of neurotransmitter containing vesicles at the presynaptic side of the synapse occurs during synapse formation. BDNF specifically increased the number of synaptic vesicles docked at the presynaptic terminal of the active zone of CA1 pyramidal neurons in hippocampal slices. On the other hand, in Lymnaea neurons, the modulation of postsynaptic nicotinic acetylcholine receptors was sufficient to account for the trophic factor induced excitatory synaptogenesis. Therefore, it seems that the action of neurotrophins can be both at the presynaptic or postsynaptic side of the synapse, since there is experimental evidence for both views. The effect of electrical activity on synaptogenesis is complex. According to the classic Hebb's rule excitatory synapses that successfully stimulate a postsynaptic neuron, or are active when the postsynaptic neuron is depolarized are selectively stabilized. However, it has been shown that neurotrophins promote the development of excitatory and inhibitory synapses in the presence of Tetrodotoxin (which blocks voltage-gated Na+ channels) indicating that neurotrophins do not require action potential invasion of the presynaptic terminal to promote the maturation of these synapses.
Conclusion

It is clear that the neurotrophin family, acting through their specific Trk receptors are essential for the formation and maturity of synapses in the central and peripheral nervous systems. The precise mechanisms of their complex actions are being investigated in in vivo and in vitro models even at the level of the single cell. As we continue to unravel the multifaceted effects of this family of proteins we come closer to a full understanding of the marvelous workings of the nervous system.

Related Products

![Image]

Antibodies

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<tr>
<td><strong>Anti-enNGF</strong></td>
<td>WB, IH* ** M, R, H</td>
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<td>Anti-NT3</td>
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<td><strong>Anti-rat P75</strong></td>
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<td><strong>Anti-rat P75</strong> (homogeneous conjugate)</td>
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![Image]

Immunohistochemical staining of the rat diagonal band nucleus, demonstrating partial co-localization of NGF receptor (green fluorescence) and nitric oxide synthase (red fluorescence). NGF receptor was stained using mouse Anti-rat P75 antibody (#AN-170) and rabbit anti-NOS (Sigma).

Contributed by Shai Shoham Ph.D. Herzog Hospital, Jerusalem.

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Voltage-Gated Na+ Channel Blockers

### Technical Information

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<tr>
<th>Compound</th>
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<td>&gt;98%</td>
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<tr>
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<td>T-550</td>
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### References