TABLE 2. Molecules with neurotrophic activity in vivo and/or with neurons in culture, and the Trk receptors of neurotrophin tyrosine kinase with which they interact.

Neurotrophic Factor	Biology	Cells Influenced:	Potential In:	Receptor
Nerve growth factor (NGF)	2 x 118 aa	Sympathetic neurons, cholinergic basal forebrain neurons	Alzheimer's, peripheral neuropathies	Trk A
Brain-derived neurotrophic factor (BDNF)	119 aa; pI 9.9; localized in CNS	Retinal ganglia, dopaminergic neurons, cholinergic neurons, embryonic spinal motor neurons, cortical neurons	ALS, Parkinsonism, Huntington's	Trk B
Neurotrophin-3 (NT-3)	119 aa; pI 9.5; expressed in embryogenesis	Various, including dorsal root Parkinsonism, and nodose ganglia neurons neuropathies	peripheral	Trk A, Trk B, Trk C
Neurotrophin-4/5 (NT-4/5), mammalian form		Various motor neurons, various CNS neurons	ALS, Alzheimer's, Parkinson's, Huntington's	Trk B
Neurotrophin-6 (NT-6) (from *Xiphophorus* fish)	143 aa, pI 10.8	To be fully characterized. Spectrum of sensitive neurons appear similar to those of NGF.		?
Ciliary neurotrophic factor (CNTF)	200 aa; acidic cytoplasmic protein; released from damaged cells	Ciliary neurons; spinal motor neurons	ALS, peripheral neuropathies	Trimer, consisting of CNTFRα, LIFR ß, and GP13
Glial cell line-derived neurotrophic factor (GDNF)	Homodimeric glycosylated polypeptide; 34-45 kDa	Dopaminergic, developing motor neurons, spinal sensorimotor neurons	Parkinsonism, ALS	?

reevaluated both because recent studies of many of the molecules listed above have shown both that neurotrophic factor synthesis is not restricted to target cells and that some factors affect nonneuronal cells. NGF, for example, is synthesized by mast cells[4] and may influence cells of the immune system.

Furthermore, some neurotrophins appear to display paracrine or autocrine effects.[5] Sensory neurons of the dorsal root ganglion (DRG), for example, lose their dependence on exogenous growth factor (S54) upon maturation.[6] The mature cells express both BDNF and its receptor, suggesting an autocrine role for the neurotrophin. Several neuronal populations are believed to express specific neurotrophins and their receptors.[6]

A better understanding of the physiological significance of neurotrophic factors regarding neuronal function may also be obtained by studying "knock-outs"—animals in which the genes coding for specific neurotrophic factors (or their receptors) have been deleted.[7]

Neurotrophic Biopharmaceuticals: The Reality

One of the first clinical targets for neurotrophic factors was amyotrophic lateral sclerosis (ALS, also

How Nerve Cells Grow

The nervous system consists of three cell types: neuronal, (neuro)glial, and endothelial cells. The neurons constitute the communicative elements, while the glial cells serve various supportive roles. The central nervous system (CNS), which integrates all neuronal activities, consists of the brain and spinal cord, while the additional vertebral neuronal elements constitute the peripheral nervous system (PNS).

The cytoskeleton of neuronal cells provides the axon—which may be several meters long in large mammals—with mechanical support and plays a critical role in the transport of materials from the cell body toward the synapse (anterograde transport) and away from it (reterograde transport). The axons of most mature neurons are covered with a myelin sheath, formed by specific glial cells (oligodendrocytes in the CNS and Schwann cells in the PNS). Sensory neurons are those leading from a stimulus-detecting receptor cell, while motor neurons are those normally carrying a nerve impulse to an effector cell, often a muscle cell.

Axonal growth toward its target tissue appears to be mediated by specific guidance molecules leading toward the target tissue for which specific receptors exist on the surface of the axonal growth cone. Such guidance molecules include surface glycoproteins (cell adhesion molecules), which provide direct cell-cell and other guidance, and soluble (diffusable) chemoattractants.

If the developing axon fails to innervate the target tissue, the neuronal cell dies; furthermore, many (excess) neurons also die upon innervation. Electrical activity is important in determining which neurons survive but so is competition between neurons for soluble target-derived factors such as neurotrophic factors. These are required to develop, guide, and maintain the innervating neuron.

General Reading

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