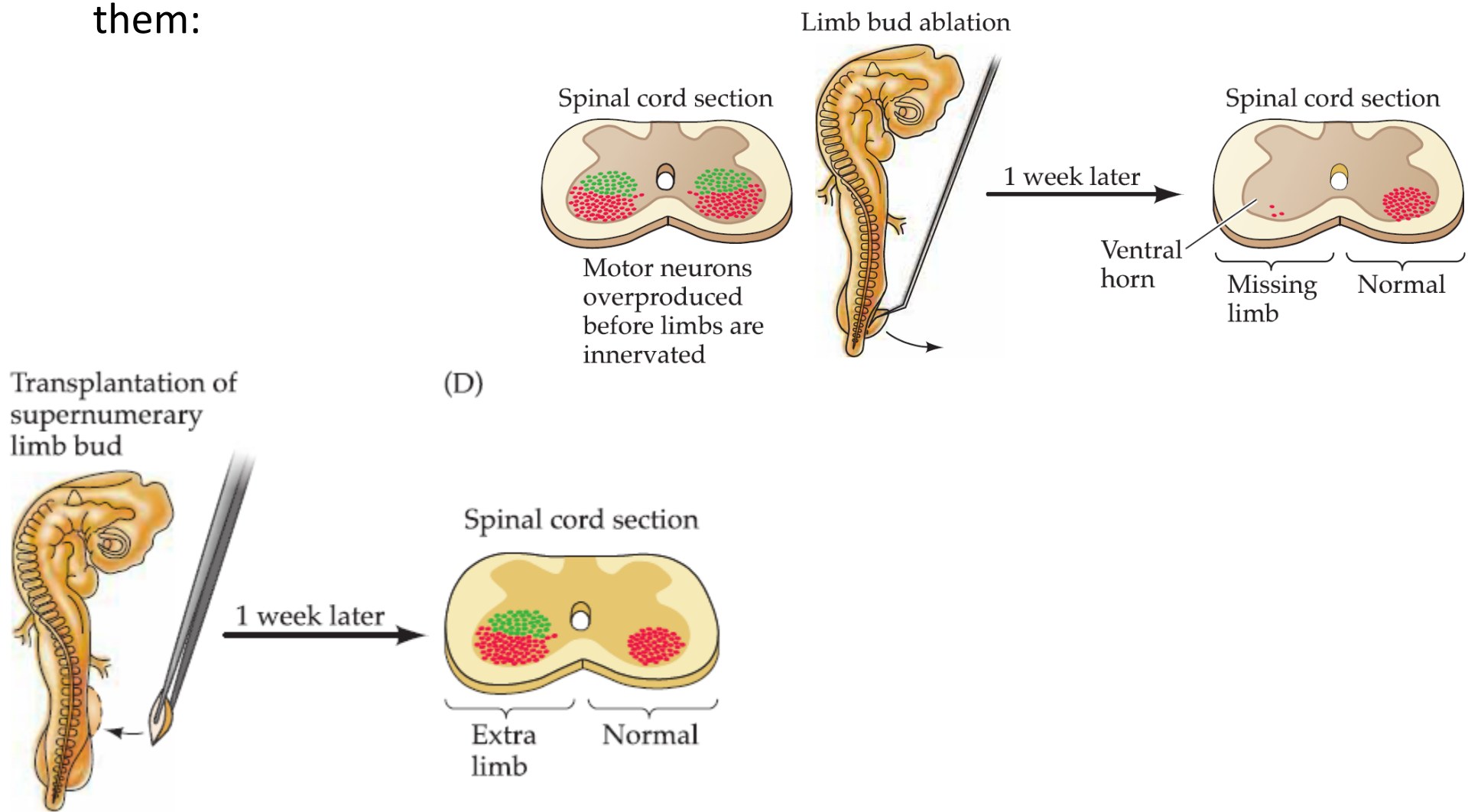
Regulation of neuronal connections by trophic interactions

- **Trophic interaction** (Greek *trophe,* meaning, "nourishment"): long-term dependency between neurons and their targets.
  - Once synaptic contacts are established and the initial distribution of synapses is set, neurons become dependent on the presence of their targets for continued survival as well as the further growth and differentiation of axons and dendrites.
  - In the absence of synaptic partners, the axons and dendrites of developing neurons typically atrophy and often die.
- **Neurotrophic factors** (also called **neurotrophins**): signaling molecules provided by target cells.
  - expression is limited to neurons and a few non-neural neuronal targets such as muscles.
- Why do developing neurons depend so strongly on their targets?
  - production of an initial surplus of nerve cells (on the order of two- or threefold); the final population is subsequently established by the death of those neurons that fail to interact successfully with their intended targets.

Target-derived trophic support regulates survival of related neurons

- The pioneering neuroembryologists Viktor Hamburger and Rita Levi-Montalcini carried a series of studies and showed that targets play a major role in determining the size of the neuronal populations that innervate them:

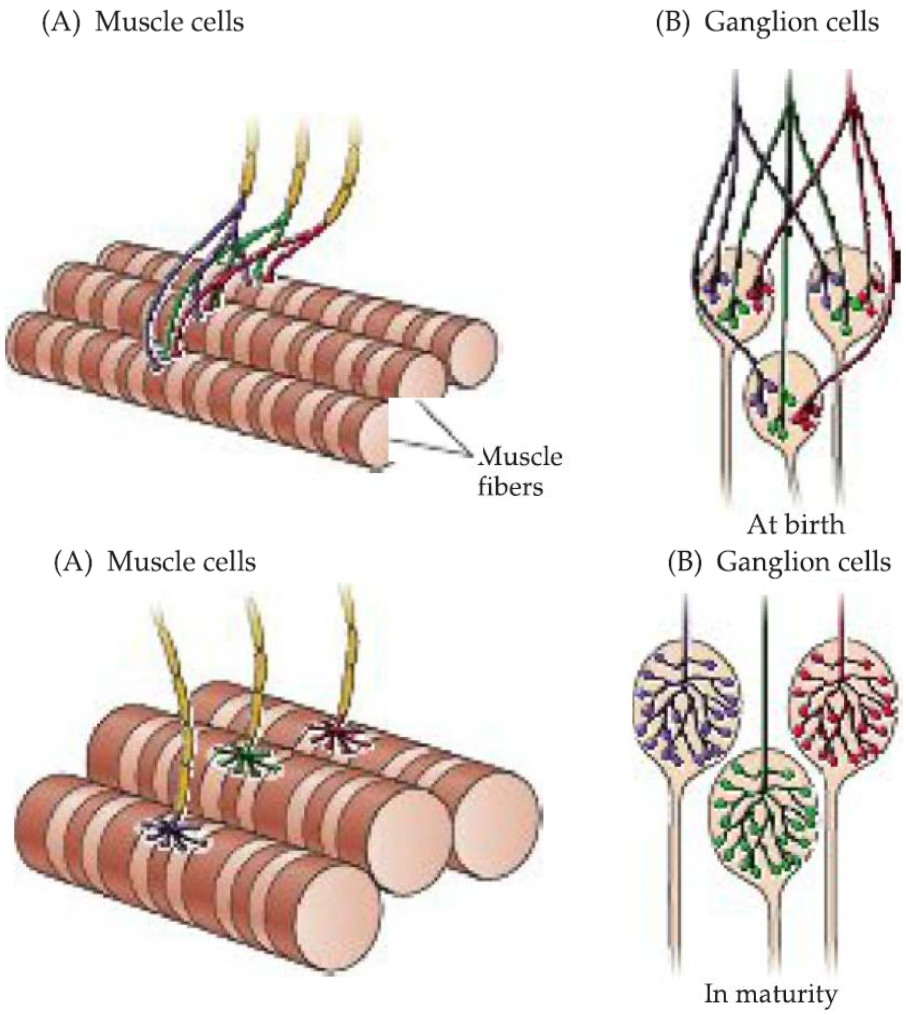


Competitive interactions and formation of neuronal connections: Synaptic refinement

- Once the size of a neuronal population is established by trophic regulation, trophic interactions continue to modulate formation of synaptic connections.

- Many fundamental ideas about the ongoing modification of developing brain circuitry have come from simpler, more accessible parts of the nervous system, most notably the vertebrate **neuromuscular junction** and **autonomic ganglion cells**.

- Adult skeletal muscle fibers and neurons in some classes of autonomic ganglia (parasympathetic neurons) are each innervated by a single axon.
  - Initially, however, each of these target cells is innervated by axons from several neurons---**polyneuronal innervation**.
  - inputs are gradually lost during early postnatal development until only one remains---**synapse elimination**.
    - overall number of synaptic contacts in the peripheral nervous system increases steadily during the course of development.
  - Patterns of electrical activity in the pre- and postsynaptic partners are thought to influence this competition for target space and neurotrophic support.
    - acetylcholine receptors (AChR): curare
    - presynaptic action potentials: TTX

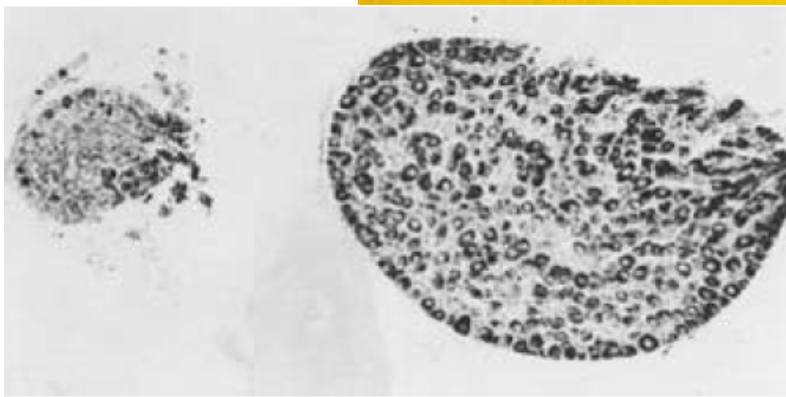


- Convergence: every target cell is innervated-and continues to be innervated-by the right number of inputs and synapses.
- Divergence: every innervating axon contacts the right number of target cells with an appropriate number of synaptic endings.
  - This regulation of convergence (the number of inputs to a target cell) and divergence (the number of connections made by a neuron) in the developing nervous system is another key consequence of trophic interactions among neurons and their targets.

Molecular basis of trophic interactions

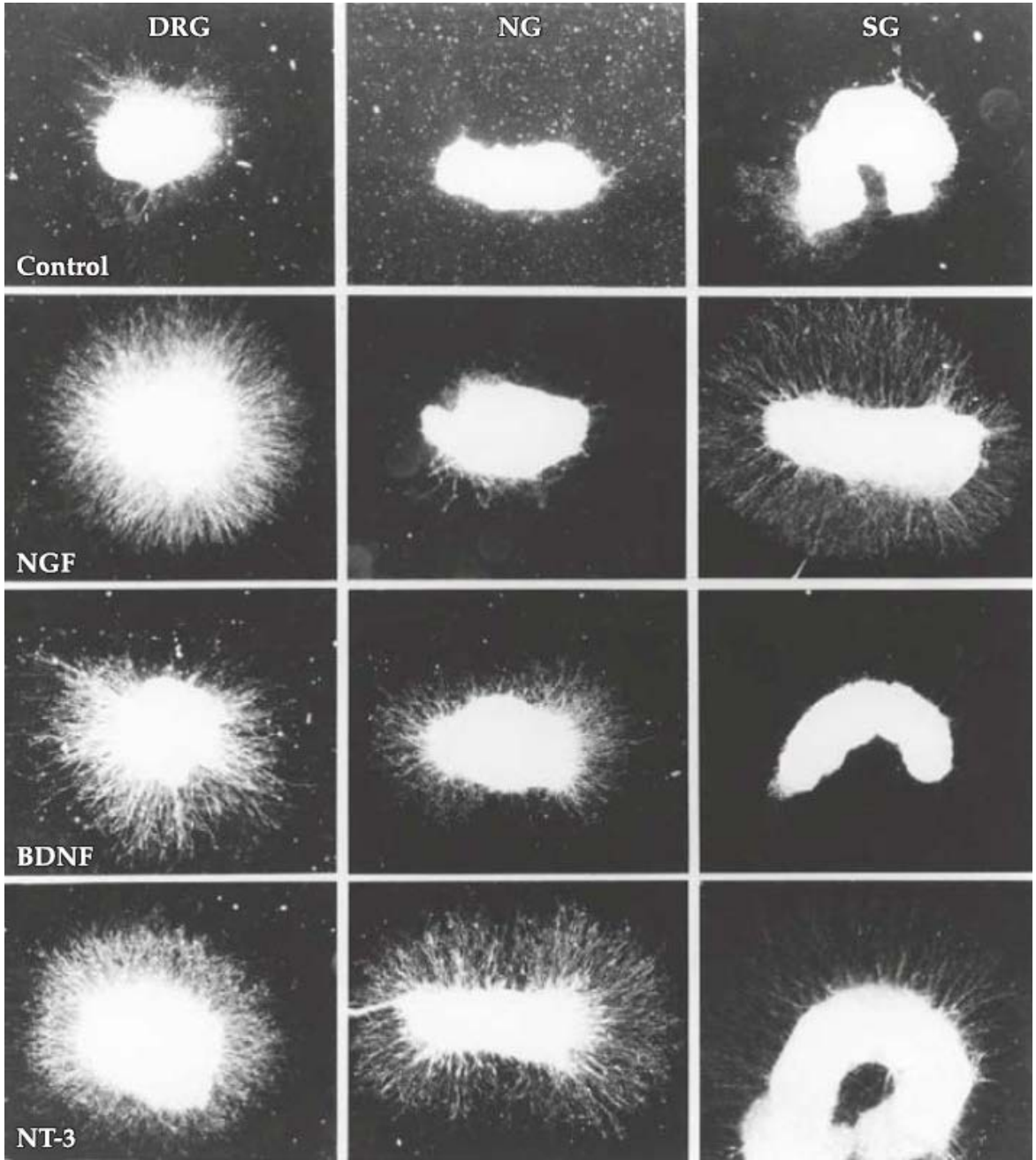
- Trophic interactions regulate three essential steps in the formation of mature neural circuits:
  - Survival of a subset of neurons from a considerably larger population.
  - Formation and maintenance of appropriate numbers of connections.
  - Elaboration of axonal and dendritic branches to support these connections.

- Neurotrophic protein: **NGF** as a model system
  - NGF was discovered by **Levi-Montalcini** as an "activity" that elicited robust growth of neuronal processes both in the animal and in cell culture.
  - Purified as a **protein** from a rich biological source, the salivary glands of the male mouse.



- **Neurotrophins**: NGF, BDNF, NT-3, NT-4/5

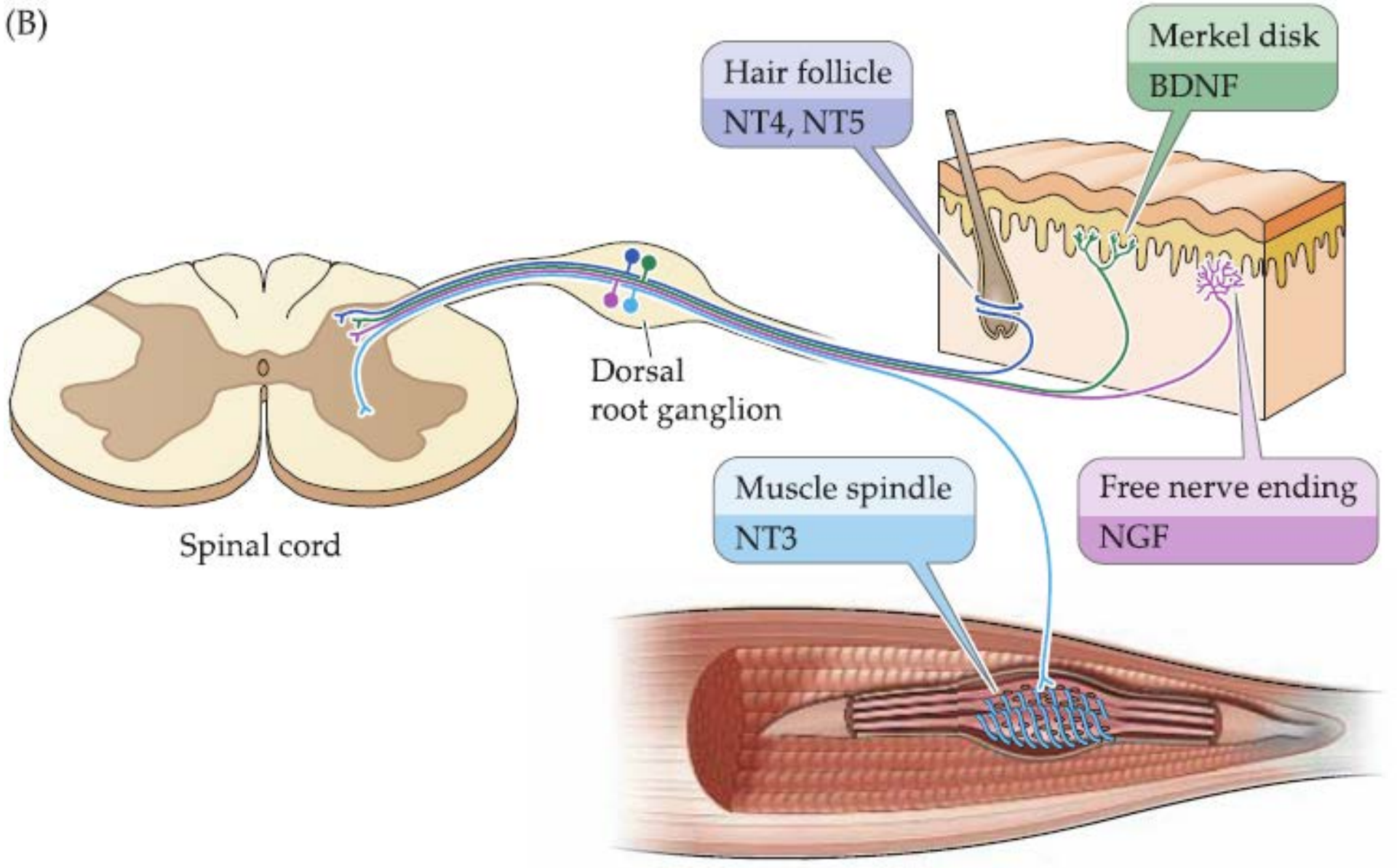
Neurotrophins have distinct effects on different target neurons



NG: nodose ganglia

SG: sympathetic ganglia

Different neurotrophins are selectively available in different targets

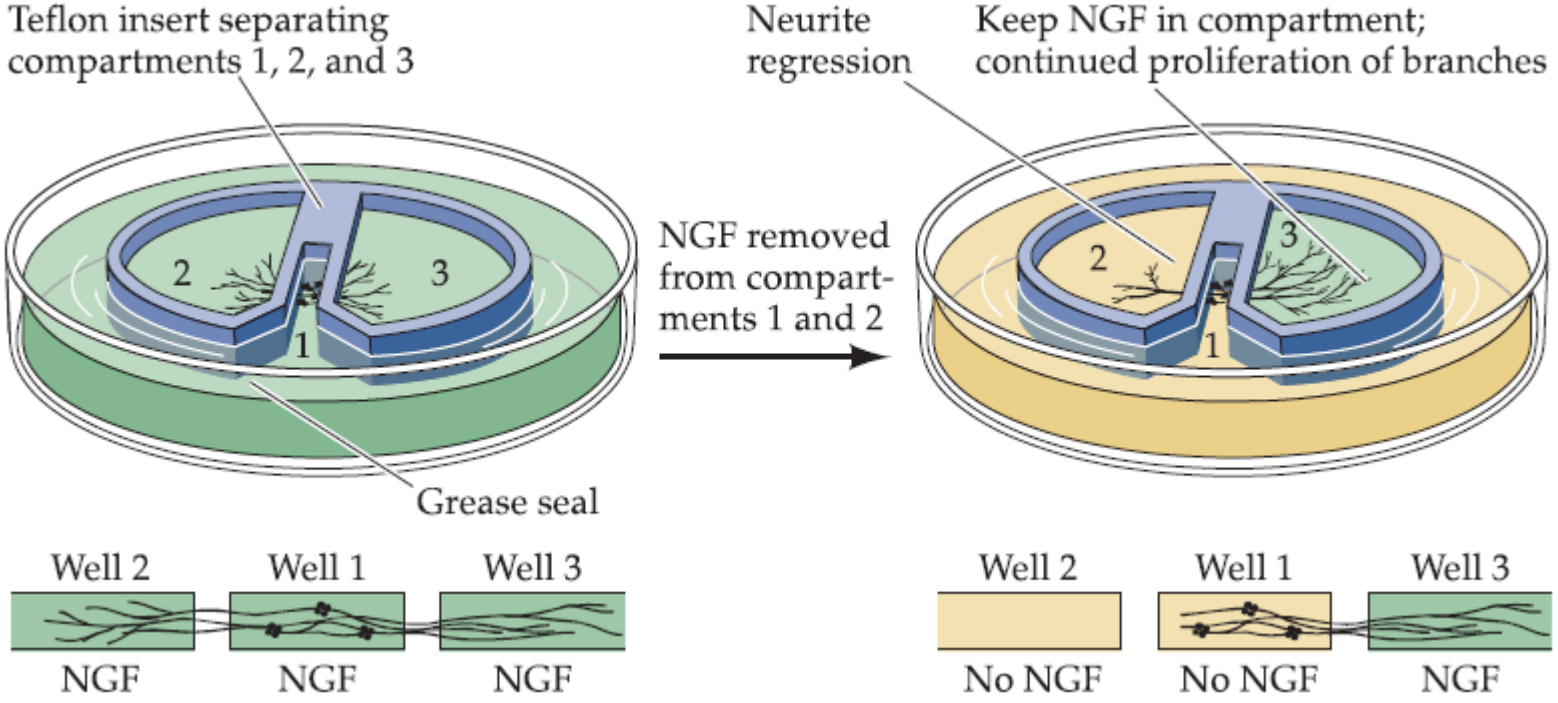


Secreted molecules with neurotrophic influences

- **CNTF (ciliary neurotrophic factor)**: cytokine in inflammation and immune responses
- **LIF (leukemia inhibitory factor)**: cytokine
- **GDNF (glial-derived neurotrophic factors)** and related proteins: kidney development and spermatogenesis

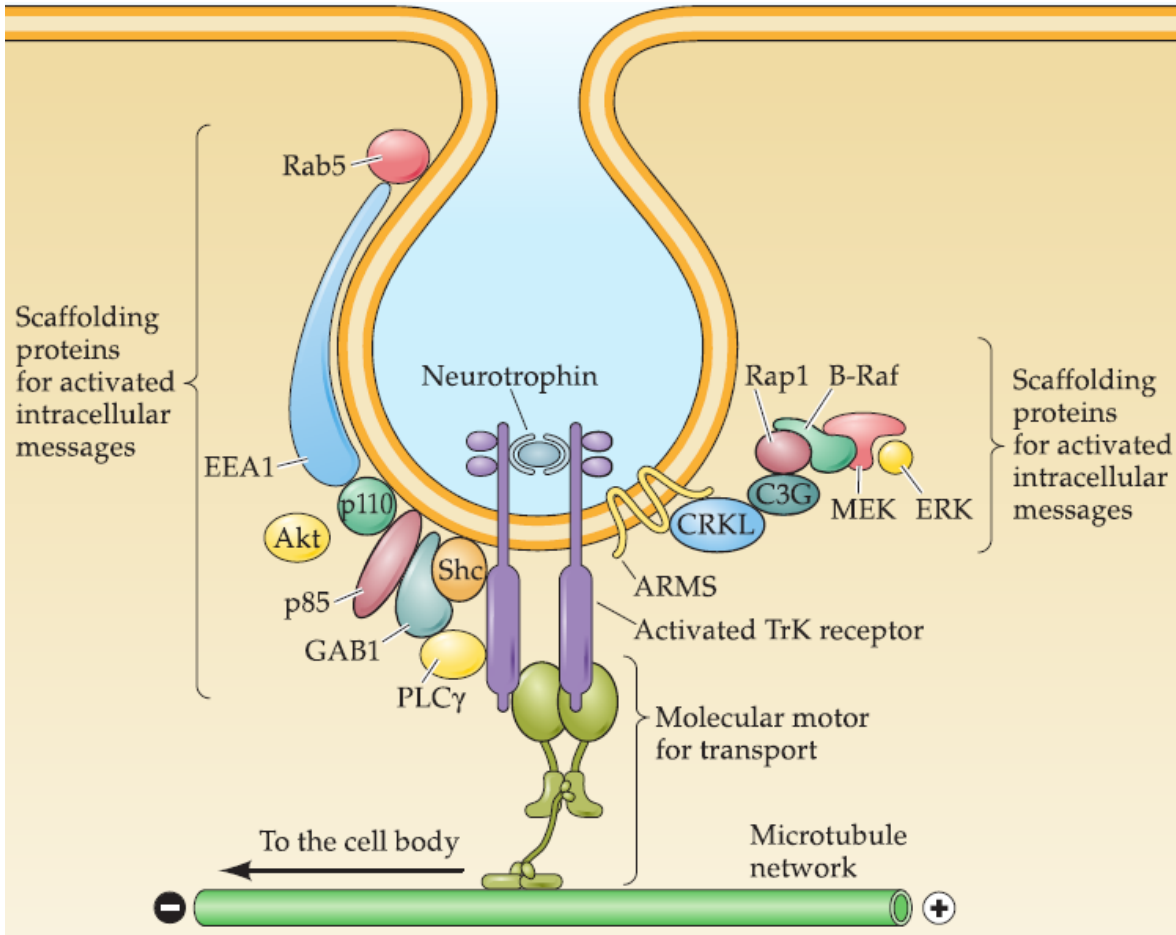
Neurotrophin signaling

- Neurotrophic factors are key regulators for three distinct cellular mechanisms:
  - neural process growth/retraction
  - synapse stabilization/elimination
  - cell survival/death
- NGF acts locally to stimulate neurite growth:
  - relaying the neurotrophic signal from the axon terminal to the cell body



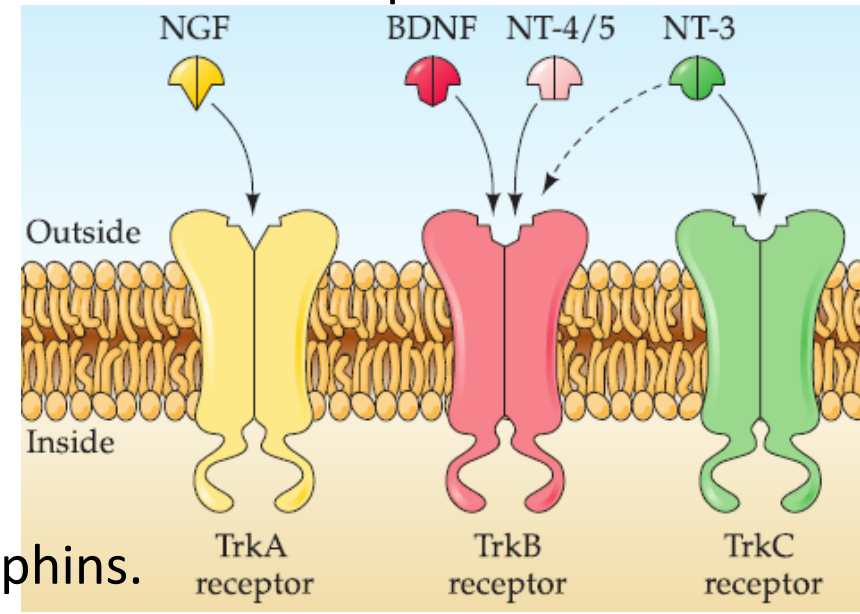
Neurotrophin signaling

- Neurotrophins bound to their transmembrane receptors (primarily the Trk subset of receptors) are selectively internalized by assembling a signaling endosome that includes ligand/receptor complex with several scaffolding proteins that bind one of three Intracellular effectors.
- This signaling endosome can also bind molecular motors that engage the microtubule cytoskeleton.
- This signaling endosome is transported back to the cell body to activate downstream targets, including modifying gene expression.

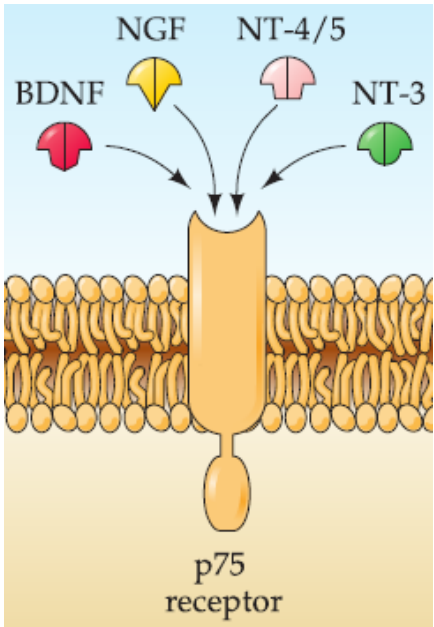


Neurotrophin receptors and their specificity

- Tyrosine kinase (Trk) receptors: a single transmembrane protein with a cytoplasmic tyrosine kinase domain.
  - TrkA: NGF.
  - TrkB: BDNF and NT-4/5.
  - TrkC: NT-3
    - some degree of cross-activation between factors and receptors: NT-3 to TrkB.
  - Trk receptors have high affinity for processed ligands.



- p75 receptors: activated by all neurotrophins.
  - p75 receptor has high affinity for unprocessed neurotrophins but low affinity for the processed ligands.
- All neurotrophins are secreted in an unprocessed form that undergoes subsequent proteolytic cleavage.
- Trk and p75 receptors are expressed only in subsets of neurons, and neurotrophins are available from different classes of targets.
  - selective binding between ligand and receptor likely accounts for some of the specificity of neurotrophic interactions.



Neurotrophin signaling