Neurotrophins act on receptor tyrosine kinase

- Nerve growth factor (NGF)  Trk A receptor
- Brain derived neurotrophic factor (BDNF)  Trk B receptor
- NT4/5  Trk B receptor
- NT3  Trk C receptor

Diagram:
- Untreated Dorsal Root Ganglia
- NGF-Treated Dorsal Root Ganglia
- Lack of trophic factor
  - Activation of cellular proteases
  - Cleavage of DNA
  - Phagocytosis by neighboring cells
  - Apoptosis
NGF induces neuronal differentiation by local action

1. Stimulates neurite outgrowth
2. Supports cell survival
3. Action of NGF: 1 and 2 are independent
RTK and MAP kinase (MAPK) pathway

RTK activation leads to MAP kinase activation through Ras/Raf/MEK/MAPK protein phosphorylation cascade

Ras: a small GTP binding protein (activated by GDP-GTP exchange)
Raf: a serine/threonine protein kinase
MEK: a Dual kinase that phosphorylates and activates MAPK
MAPK: activated by phosphorylation
  phosphorylates target in the cytoplasm and the nucleus
MAP kinase pathway and neuronal differentiation in PC12 cells

Mitogen Activated Protein Kinase
Also called ERK: Extracellular Response Kinase

Several isoforms: p42, p44

Regulated by both tyrosine and serine phosphorylation
Thr-183 and Tyr-185 for p42 ERK

Figure 14-8. A role for the ras/raf/MEK pathway in neurite outgrowth. Injection of activated ras protein, or introduction of DNA for activated raf or MEK enzymes, which leads to the synthesis of the activated proteins within PC12 cells, causes the extension of neurites.
Role for p75NTR (low affinity neurotrophin receptor)

1. Modulation of Trk receptors
2. Trk-independent action
   Stimulation of apoptosis of neurons

Signaling mechanisms of p75NTR. p75NTR can induce apoptosis, cell migration, and aspects of cell differentiation on its own when highly activated (a), suppress Trk signaling and induce apoptosis when highly activated in the presence of low levels of Trk activity (b), and enhance Trk signaling and Trk-mediated cell differentiation when co-activated with Trk (c). Ceramide, NFkB and JNK are signaling proteins that are activated by p75NTR in certain cellular environments, while Ras, PI3-kinase (PI3-K) and SNT are signaling proteins that are activated by TrkA.

Cooperative action of trophic factors for motor neuron survival
A variety of factors have been identified for the survival of embryonic motor neurons

Motor neuron: Acidic fibroblast growth factor (aFGF)
Astrocyte: Basic fibroblast growth factor (bFGF)
Schwann Cell: Ciliary Neurotrophic Factor (CNTF)
Glial cell line-derived neurotrophic factor (GDNF)
Muscle: Brain derived neurotrophic factor (BDNF)
GDNF