Growth and cytokine signals and their receptors

Important:

1. These signals are different from neurotransmitters or neuropeptides.

2. Receptors for these signals are different from:
   - ionotropic receptors (ligand gated channels) (such as nicotinic acetylcholine receptors, NMDA receptors etc)
   - or G-protein coupled receptors (such as muscarinic acetylcholine receptors, adrenergic receptors etc)

3. Some of them mediate cell growth, neuronal differentiation and survival.

   Neurotrophins and their receptors
   - Nerve Growth Factor (NGF)
   - Brain Derived Neurotrophic Factor (BDNF)
   - Neurotrophin 3, 4/5, 6

   Cytokines and their receptors
   - Ciliary Neurotrophic Factor (CNTF)

4. Cytokine receptors-receptor tyrosine kinases
   - receptor components
   - plus non-receptor tyrosine kinase
Receptor activation by neurotrophins and cytokines
Receptor tyrosine kinases
- phosphorylate **tyrosine (Y)** but not serine (S) or threonine (T)
- Major ligands in the brain: neurotrophins (NGF, BDNF, NT3, NT4/5)
- Neurotrophins play roles in neural development, differentiation and survival.

![Diagram of neurotrophin receptors](image)

**Figure 14-5.** Neurotrophin receptors. Neurotrophins such as NGF bind full-length and truncated Trk receptors, as well as the low-affinity neurotrophin receptor p75. There is some cross-talk between different neurotrophins and their Trk receptors.

**Figure 14-6.** Sites of neurotrophin action. After binding to Trk receptors in the plasma membrane, neurotrophins can act locally, or they can be ferried back to the nucleus by retrograde transport.

Note: Second messenger regulated protein kinases (PKA, PKG, PKC, CaMKs) are serine/threonine kinase.
Receptor Tyrosine Kinase (RTK) signal transduction

Ligand binding
⇒ Dimerization of the receptors
⇒ Autophosphorylation of tyrosine residues in the receptors
⇒ Attachment of proteins to that contain SH2 domain
  Specific interaction between phosphorylated tyrosine and SH2 domain containing molecules

**P-Y ─── SH2 domain**

SH2 domain (Src Homology 2: Src is a non-receptor tyrosine kinase)

*SH2 domain containing signaling molecules*
  PI3 kinase
  GTPase activation protein
  Src tyrosine kinase
  SHPTP-1, 2: a protein phosphatase
  Phospholipase C-γ
  Shc (adapter protein)
⇒ Induction of cellular responses
Neuronal Differentiation of PC12 cells by Nerve Growth Factor (NGF)

Phenotype change: Adrenal Chromaffin Cell-ike to Sympathetic Neuron like cells

9.1 Phase-contrast photomicrographs of PC12 cells cultured without NGF (A) or with NGF for 9 (B and D) or 14 (C) days. Magnification: (A) × 250; (B) × 625; (C) × 390; (D) × 195.
Trk A signal transduction pathways

- TrkA: A neurotrophin receptor
  - High affinity to NGF, a neurotrophin
  - Receptor tyrosine kinase

Ras: A GTP binding protein (A small GTPase)
GDP $\rightarrow$ GTP exchange
A close look at Trk A receptor

1. Ligand binding domain (NGF binding site)
2. Transmembrane domain
3. Cytoplasmic domain
   Kinase domain (tyrosine kinase activity)
   Autophosphorylation sites (tyrosine residues)
   Shc/PI3-K (Y490)
   PLC-γ (Y-785)
   SNT site (SNT tyrosine phosphorylation)