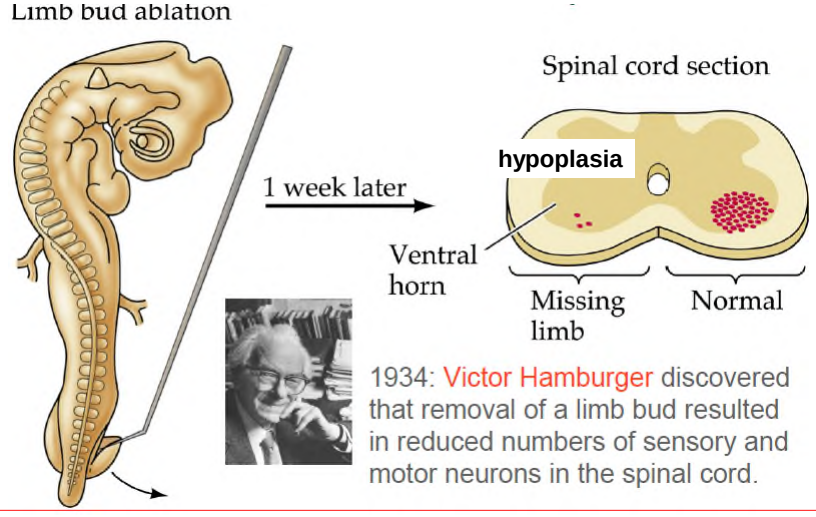
Lessons 16-17

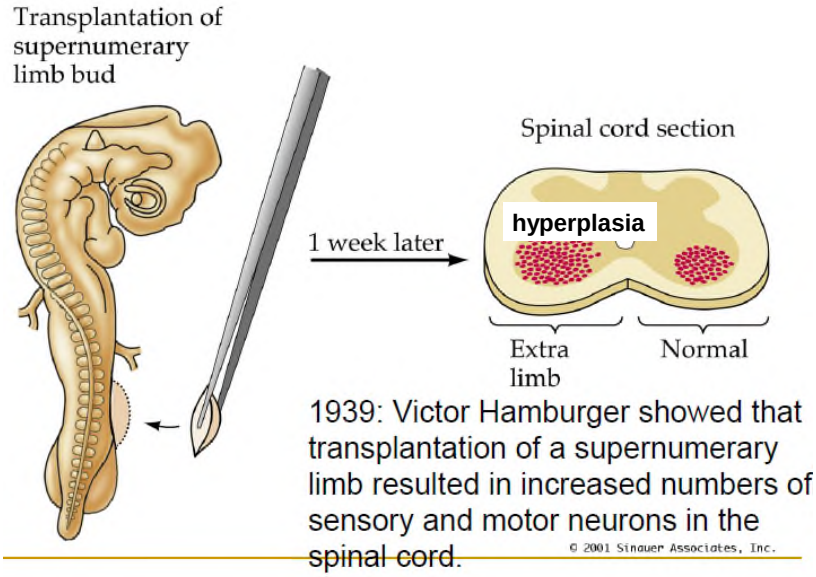
Neurotrophic Factors and their signaling

First experiment by Viktor Hamburger (1934)



[e]very structure within the growing limb, muscle as well as sensory organs, send[s] stimuli to the central nervous system. Each part of the peripheral field controls directly its own nervous center, i.e., the limb muscles affect the lateral motor centers, the sensory fields control the ganglia.

Second experiment by Viktor Hamburger (1939)



1939: Victor Hamburger showed that transplantation of a supernumerary limb resulted in increased numbers of sensory and motor neurons in the spinal cord.

The Neurotrophic factor hypothesis

*Based on his limb-bud experiments, V. Hamburger **hypothesized** that the targets of innervating neurons provide signals that recruit undifferentiated cells to develop into sensory or motor neurons.*

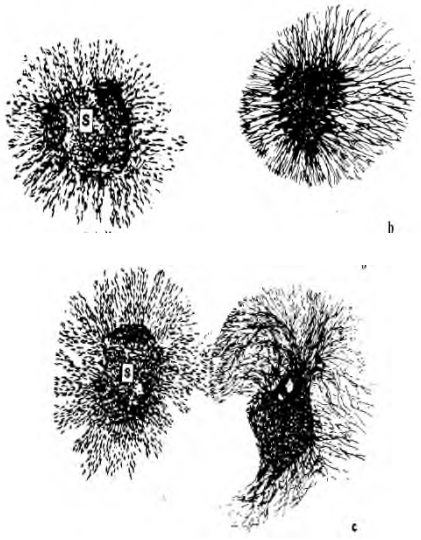
(but he was wrong)

1942, Levi-Montalcini and Levi proposed that target derived signals **maintain survival of differentiating neurons**. In 1949, Hamburger and Levi-Montalcini repeated the limb bud experiments and found that their results supported the **neurotrophic hypothesis**.

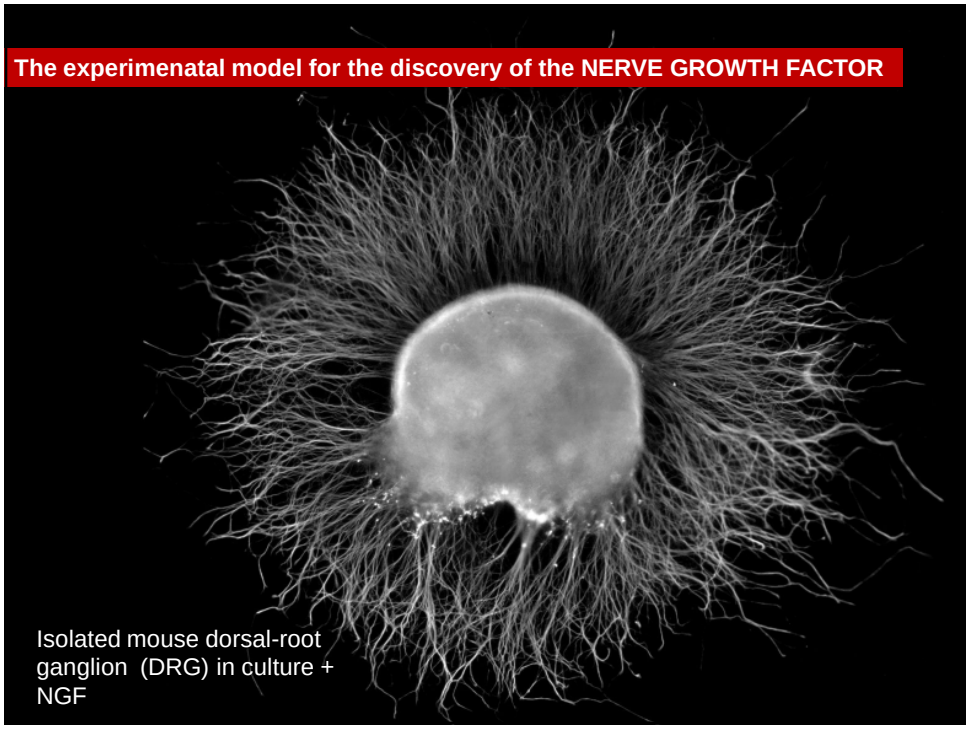
Hamburger, V. and Levi-Montalcini, R. (1949) J. Exp. Zool. 111: 457-502.

The discovery of the Nerve Growth Factor

In December 1952, working on the identification of the development of the nervous system at embryonic stage in chick embryos, Rita Levi-Montalcini identified a «diffusible factor» able to induce nerve fibres sprouting.

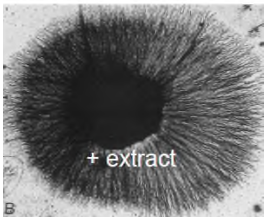


The experimenatal model for the discovery of the NERVE GROWTH FACTOR



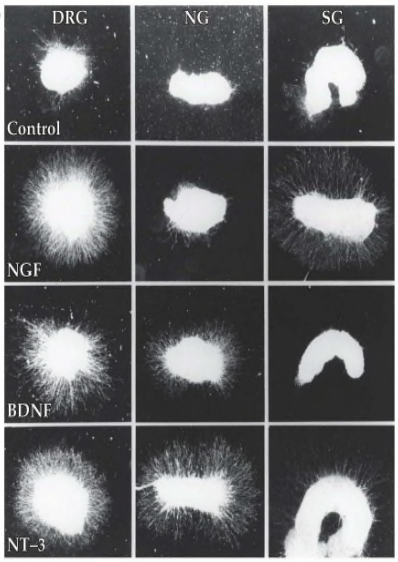
Isolated mouse dorsal-root ganglion (DRG) in culture + NGF

Different Neurons have Different Requirements for Neurotrophic Factors



1960: NGF purified

1969: NGF purified to homogeneity



DRG = Dorsal Root Granglion, NG = Nodose Ganglion, SG = Sympatethic ganglion

The neurotrophins family, besides NGF

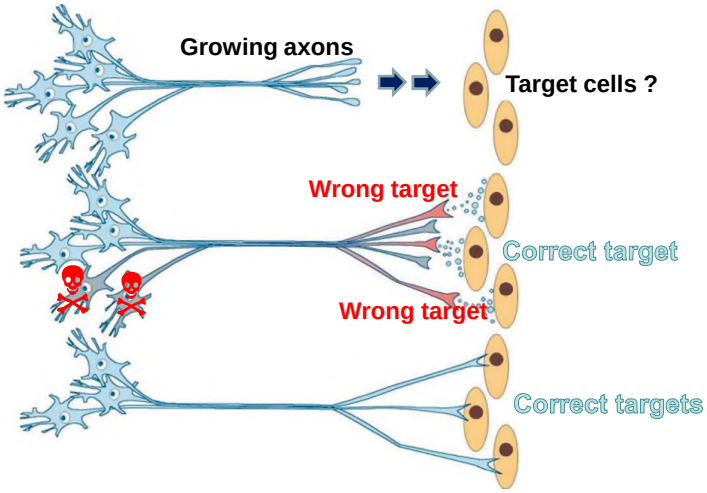
BDNF -brain-derived neurotrophic factor (BDNF), isolated by Barde et al. at the Max Planck in Munich (1982). BDNF is 55% homologous to NGF

NT3 – Discovered by primer sequences constructed from sequences in the conserved regions (Maisonpierre et al., 1990; Hohn et al., 1990; Rosenthal et al., 1990; Ernfors et al., 1990; Jones and Reichardt,1990). 58% homologous to BDNF and 57% homologous to NGF.

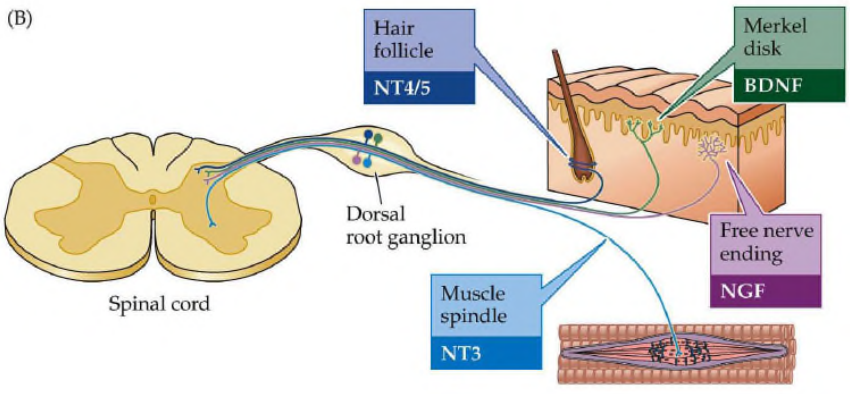
Hallböök et al, 1991) and 1992).

Chao, Nat Rev Neurosci, 2003

Neurotrophins “classical” trophic role on neuronal survival.



Knock-out mice have highlighted the role of neurotrophins in survival of different neuronal types



What is a growth factor ?
What is a trophic factor ?

DEFINITION

Growth factors include substances that stimulate cells to divide (hyperplasia) or increase in size (hypertrophy). Many growth factors are now known to exist

Trophic factors include those substances that have effects on cell differentiation, cell survival, expression of a specific cellular phenotype (e.g. a cell becomes an inhibitory or an excitatory neuron), cellular morphological plasticity, as well as cell hypertrophy including, for example, the induction of neurite extention (also considered a "trophic" action). Importantly, some growth factors may also act as trophic factors and viceversa and each growth/trophic factor may have a specific combination of cellular effects.

Families of growth and trophic factors

Family	Specific examples
Neurotrophin	Nerve growth factor (NGF)
	Brain-derived ticurotrophie factor (BDNF)
	Neurotrophin 3 (NT-3)
EGF	Epidermal growth factor (EGF)
	Transforming growth factor alpha (TGFα)
	Vaccinia virus growth factor
	Amphiregulin (AR)
	Schwannoma-derived growth factor (SDGF)
FGF	Acidic fibroblast growth factor (aFGF)
	Basic fibrobiast growth factor (bFGF)
	INT-2, FGF-5, FGF-6, KGF, HST/KGF
Insulin-like	Insulin
	Insulin-like growth factors (somatomedins)
	Relaxin
Others	Growth hormone (GH)
	Platelet-derived growth factor (PDGF)
	Mast cell growth factor (MGS)
	Colony stimulating factors
	Ciliary neurotrophie factor (CNTF)
	Glial maturation factor
	Protease ne}ân 1, II
	Sweat gland factor
	Cholinergic neuronal differentiation factor (CDF)
	Muscle-derived growth factors (MDGF)
	Striatal-derived neuronotrophic factor
	Transforming growth factor beta (TGFβ)/inhibirVactivin family
	Membrane-associated neurotransmitter stimulating factor (MANS)
	Thrombin
	Entactin
	Erythropoietin
	Neurite inducing factor
	Stem cell factor (SCF)
	Interleukin 1,3,6
	Glial-derived nexin
	Heparin-binding NF
Extracelluiar matrix/adhesion factors	Laminin
	Fibronectin
	Purpurin
	Apolipoproteins
	Gangliosides
Nonpeptide hormones	Steroid
	T3/T4

Neurotrophic factors

Neurotrophic factors are endogenous soluble proteins regulating survival, growth, morphological and synaptic* plasticity, or synthesis of proteins for differentiated functions of neurons or glial cells.

(* synaptic plasticity = regulation of the transmission activity at the level of the synapse)

List of characterized proteins exhibiting neurotrophic activities

Growth factor	References
Nerve growth factor (NGF)	Thoenen et al., 1987
	Whittemore and Sciger, 1987
	Hefti et al., 1989
Brain-derived neurotrophic factor (BDNF)	Barde et al., 1982
	Leibrock et al., 1989
Neurotrophin-3 (NT-3)	Ernfors et al., 1990
	Hohn et al., 1990
	Maisonpierre et al., 1990
	Rosenthal et al., 1990
Neurotrophin-4 (NT-4)	Hallbrook et al., 1991
Neurotrophin-5 (NT-S)	Berkerneier et al., 1991
Ciliary neurotrophic factor (CNTF)	Lin et al., 1989
	Stöckli et al., 1989
Heparin-binding neurotrophic factor (HBNF)	Kovesdi et al., 1990
Growth factors vith neurotrophic activity	
Basic fibroblast growth factor (bFGF)	Morrison et al., 1986
	Walicke, 1988
Acidic fibroblast growth factor (aFGF)	Walicke, 1988
Insulin-like growth factors (IGFs), insulin	Aizenman et al., 1986
	Baskin et al., 1987
Epidermal growth factor (EGF)	Fallon et al., 1984
	Morrison et al., 1987
Transforming growth factor cc (TGFcc)	Deryncl,, 1988
	Fallon et al., 1990
Interleukin 1	Spranger et al., 1990
Interleukin 3	Kamegai, 1990
Interleukin 6	Harna et al., 1989
Protease nexin 1 and II	Monard, 1987
	Oltersdorf et al., 1989
	Whitson et al., 1989
Cholinergic neuronal differentiation factor	Yarnarnori et al., 1989

Which cell synthesizes the neurotrophic factors ?

Neurotrophic factors are produced by all cells of the nervous system, including neurons, glial cells, ependimal cells, blood vessels endothelial cells and cells from innervated tissues such as muscles, epidermis, etc…

How are neurotrophic factors released from cells ?

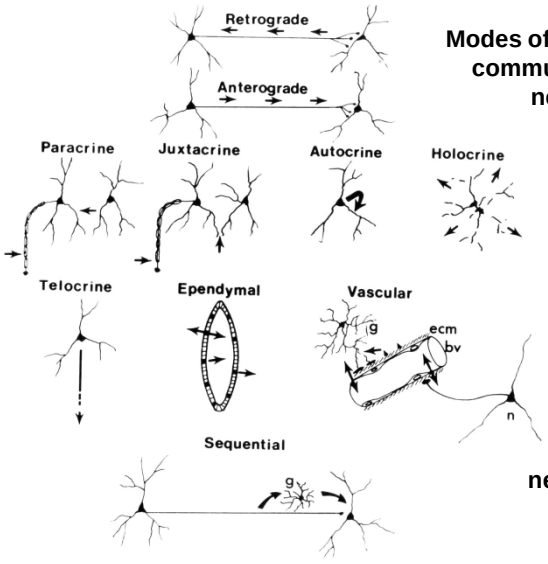


FIGURE 2

Modes of secretion and intercellular communication mechanisms of neurotrophic activity.

Abbreviations: g, glial; n, neuronal; bv, blood vessel; ecm, extracellular matrix.

What cellular actions have neurotrophins ?

- Neurotrophins will be taken as example because they were the first neurotrophic factors to be discovered and because they have a large number of cellular effects. In particular neurotrophins have a:

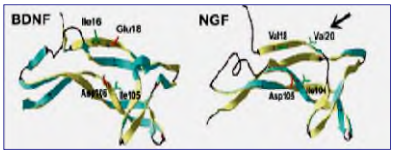
- 1) Trophic action as cell survival factors
- 2) Trophic action by stimulating growth of cellular processes (axons and dendrites = neurites, i.e. they promote *neuritogenesis*)
- 3) Trophic action on the cellular phenotype
- 4) Trophic/growth action on cellular dimensions
- 5) Trophic action on morphological plasticity
- 6) Trophic action on synaptic plasticity
- 7) Trophic action on cellular differentiation

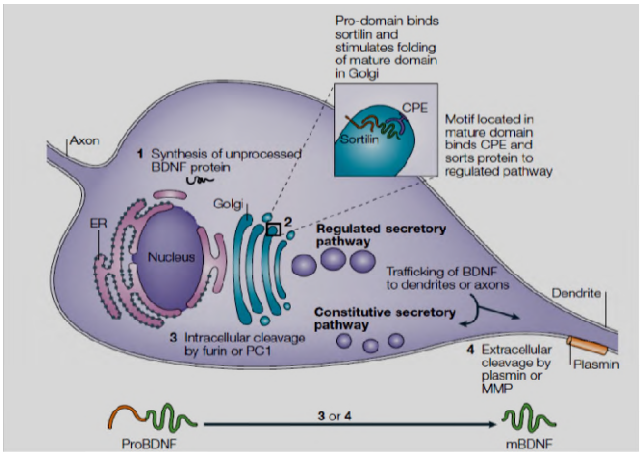
Neurotrophic Factors signalling

Regulation of neurotrophin signalling

1) Synthesis and sorting in the regulated secretory pathway
2) Proteolytic processing (intra or extra cellular)
3) Interaction with the receptor(s)
4) Initiation of the appropriate signaling cascade
5) Localization of the signals and activation of effectors in the compartment

1) Synthesis and sorting of BDNF in the regulated secretory pathway

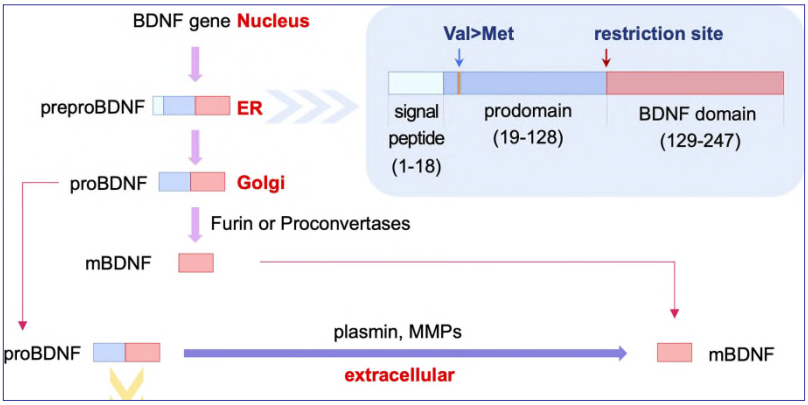




Synthesized in the ER (1), proBDNF binds to intracellular **sortilin** in the Golgi to facilitate proper folding of the mature domain (2). A motif in the mature domain of BDNF binds to **carboxypeptidase E (CPE)**. In the absence of this motif, BDNF is sorted into the constitutive pathway.
proBDNF can be released by neurons. Extracellular proteases, such as metalloproteinases and plasmin, can subsequently cleave the pro-region to yield mature BDNF (4).

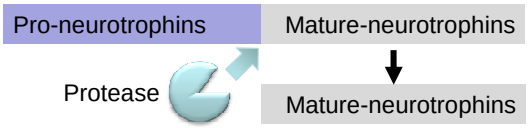
Bai Lu et al, Nat Rev Neurosci, 2005

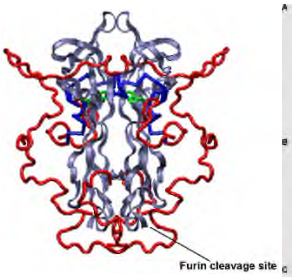
2) Processing of proBDNF.

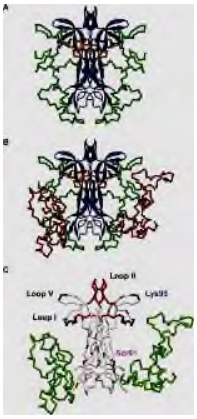


The BDNF gene produces preproBDNF protein in the ER, which is processed to proBDNF in the Golgi. ProBDNF may be cleaved into mBDNF intracellularly by furin or proconvertases, or extracellularly by plasmin or MMPs.

2) Processing of neurotrophins

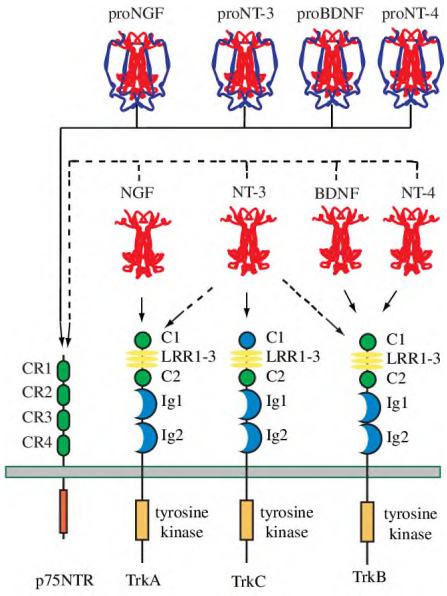






Precursors pro-peptides with IUD (**Intrinsically Unstructured Domain**)

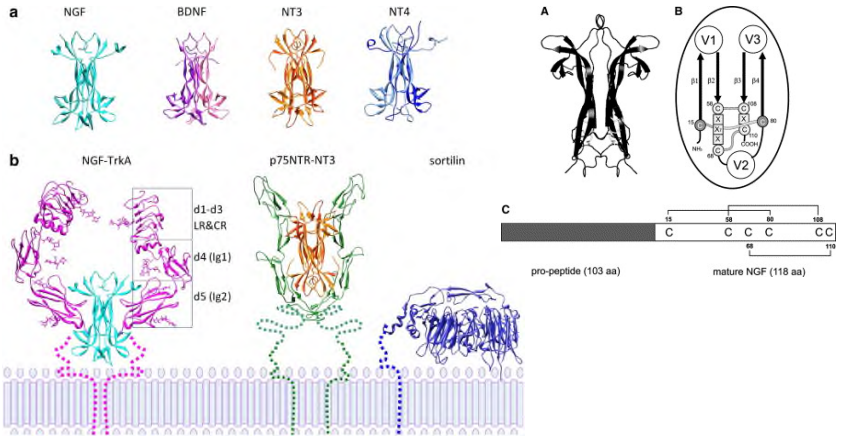
3) Interaction with the receptors



3) Interaction with the receptors

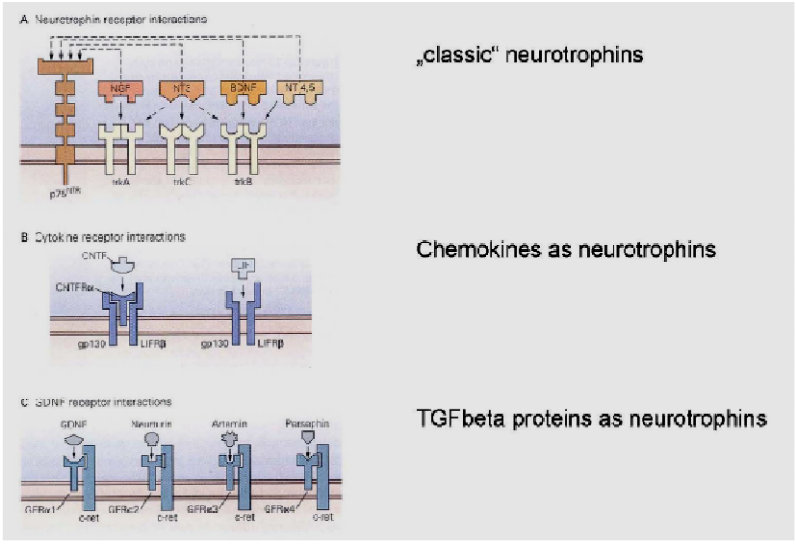
Pro and mature-NT bind as dimers to p75- and Trk-receptors.

Trk receptor dimerization leads to trans-autophosphorylation and to the activation of intracellular signalling cascades mediating differentiation and survival.



3) Interaction with the receptors

The receptors of other neurotrophic factors can also dimerize



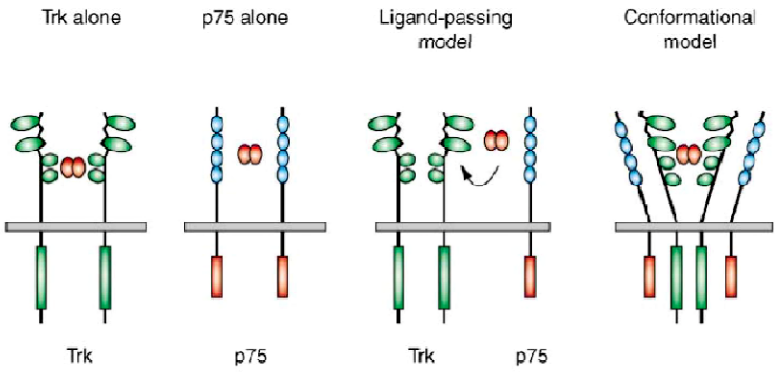
„classic" neurotrophins

Chemokines as neurotrophins

TGFbeta proteins as neurotrophins

3) Models for Trk and p75^{NTR} interaction

The p75 receptor can bind to each NT, and also acts as a co-receptor for Trk receptors



Chao and Bothwell (2002) Neuron

3) Models for Trk and p75^{NTR} interaction: how were they discovered?

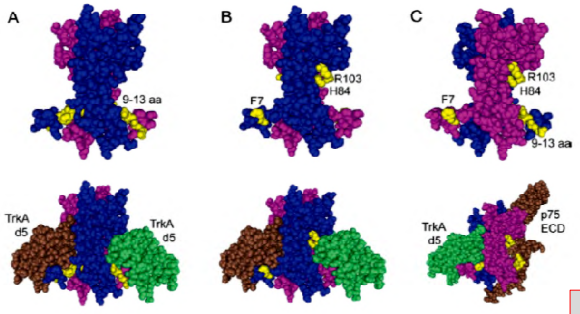


Fig. 1.
Design rationale for an NGF heteromutein capable of forming a TrkA-NGF-p75 complex but not a TrkA-NGF-TrkA complex. **A:** The 9–13 amino acids on the N-terminus of NGF are highlighted in yellow on each protomer (pink, blue) of NGF dimer (upper structure). These amino acids are deleted in the mutein Δ9/13 that is unable to bind TrkA. The lower structure shows the interaction of residues 9–13 with TrkA d5 domain (brown, green). **B:** The F7, H84, and R103 amino acids are highlighted in the NGF dimer (upper structure), and their interaction with TrkA d5 domains (brown, green) is shown in the lower structure. F7A/H84A/R103A (7-84-103) mutein is an NGF mutein binding weakly to TrkA. **C:** A dimer of NGF in which 9–13 amino acids are highlighted on one protomer (pink) and F7, H84, and R103 are highlighted on the other protomer (blue) of NGF shows that, if these highlighted residues are mutated or deleted, it would abolish TrkA binding on one side (upper structure). Therefore, a heterodimer of Δ9/13 mutein and the 7-84-103 mutein would lose TrkA binding on one side but still have the ability to form a heteroreceptor complex (p75 ECD, brown; TrkA d5, green; lower structure). PDB IDs for NGFTrkA(d5) complex and NGF-p75 complex are 1WWW and 1SG1, respectively.

Δ9/13 NGF mutein, a deletion of N-terminal residues 9–13 = **no TrkA binding or activity**

7-84-103 NGF mutein, mutated at residues F7, H84, and R103 to alanine, **has 200-fold reduced binding to TrkA and is signal selective for survival over neuritogenesis**

The two muteins form a heteromutein, which can bind TrkA on only one side at the NGF protomer–protomer interface. The heteromutein Htm1 has the ability to bind normally to p75, in the absence of TrkA homodimerization Htm1 induces cell survival at half-reduced efficiency than wt-NGF.

3) Models for Trk and p75^{NTR} interaction: how were they discovered?

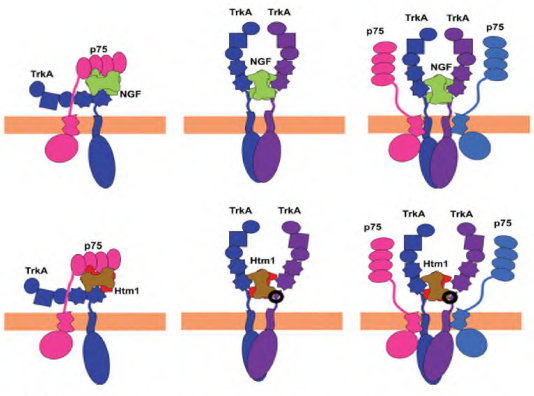
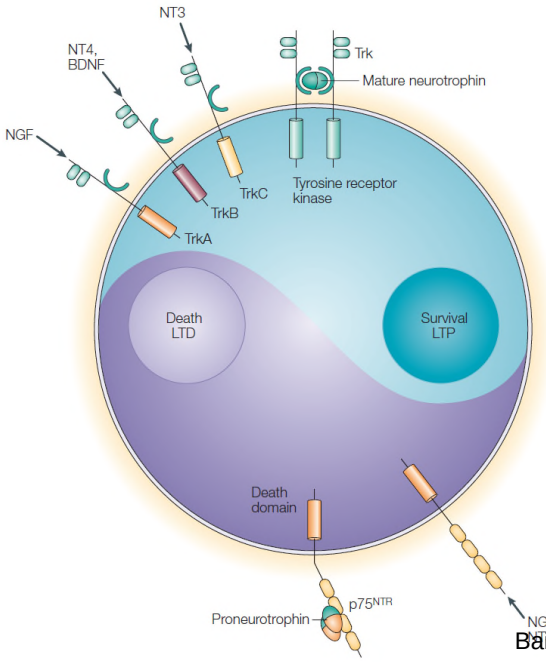


Fig. 10.
Model of ligand passing and TrkA presentation for NGF binding. Upper row: NGF. Lower row: Htm1. Left column: Putative complex of NGF or Htm1 with TrkA and p75 that represents an intermediate in the ligand-passing model. Note the antiparallel orientation of the two receptors resulting from the binding mode of each ligand relative to the membrane (Barker, 2007). The formation of this complex would be preceded by the binding of NGF or Htm1 to the p75 receptor. Middle column: NGF or Htm1 binding to a homodimeric TrkA receptor. The binding pathway for NGF or Htm1 to form this complex can occur by directly binding to TrkA or via the two-step ligand-passing process, which involves formation of the complex shown in the left column. Right column: Putative heteroreceptor complex of undefined stoichiometry in the Trk presentation model. This complex represents the TrkA presentation model. A pre-existing TrkA-p75 heteroreceptor complex can bind to NGF with greater affinity than TrkA alone. In the lower middle and lower right models, the area in the circle designates additional modes of interaction among Htm1 loop L-I, L-II, and L-IV residues and the extracellular, juxtamembrane region of TrkA to explain the cellular and signaling data (see Discussion).

2012

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3674885/pdf/nihms-463239.pdf

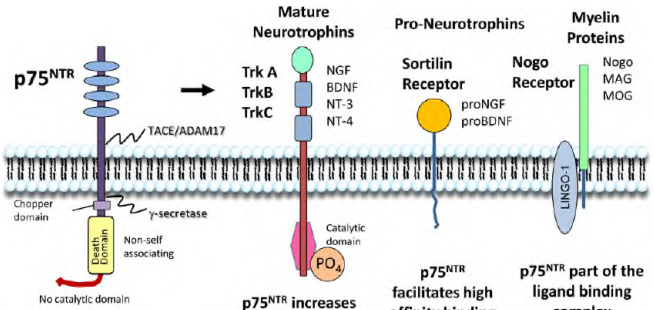
Neurotrophin receptors: what functions have they?



THE YIN AND YANG HYPOTHESIS OF NEUROTROPHIN ACTION

Bai Lu et al, Nat Rev Neurosci, 2005

Neurotrophin receptors: what functions have they?



Increases in response to injury

Effects of $p75^{NTR}$ will depend on how it partners with each of three different receptors as well as the cell type expressing the receptors

$p75^{NTR}$ increases neurotrophin affinity

- Survival
- Growth
- Differentiation
- Synaptic plasticity
- Neural progenitor proliferation and differentiation
- Immune response regulation

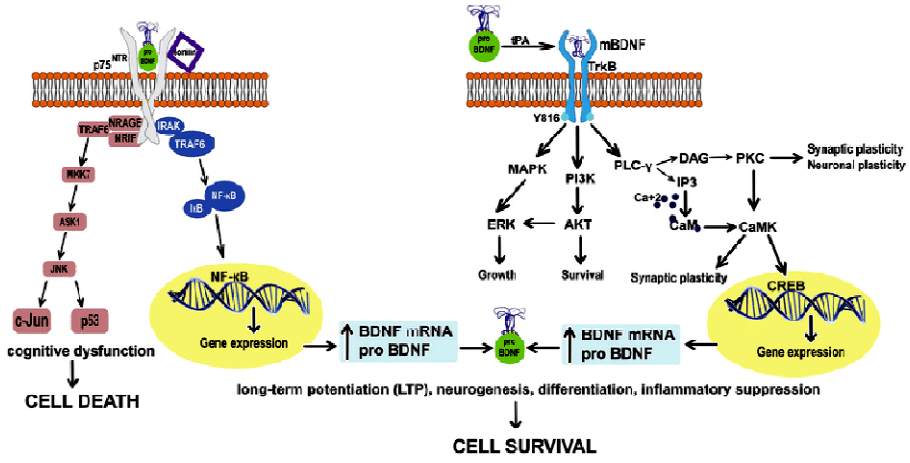
$p75^{NTR}$ facilitates high affinity binding of pro-neurotrophins

- Apoptosis
- Facilitates retrograde neurotrophin signaling?

$p75^{NTR}$ part of the ligand binding complex

- Growth regulation
- Immune response resolution via macrophage clearance

4) Initiation of the appropriate signaling cascade.



4) Trk receptor signaling

When a neurotrophin binds to a trk receptor, the kinase domain is activated resulting in autophosphorylation.

↓

Autophoshorylation results in further activation of the kinase domain, leading to activation of three potential signaling cascades:

MAPK **PI3K** **PLC-γ**

4) NT signalling transduction pathways mediated by trk receptors

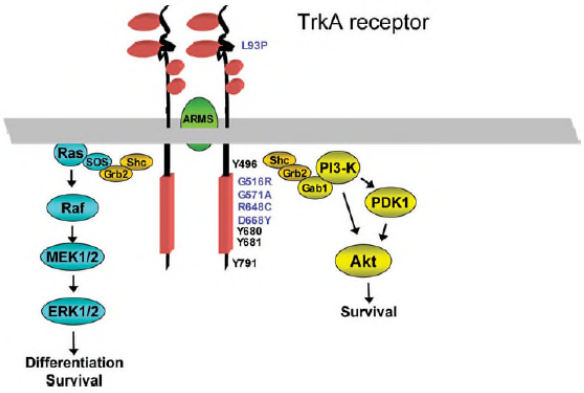
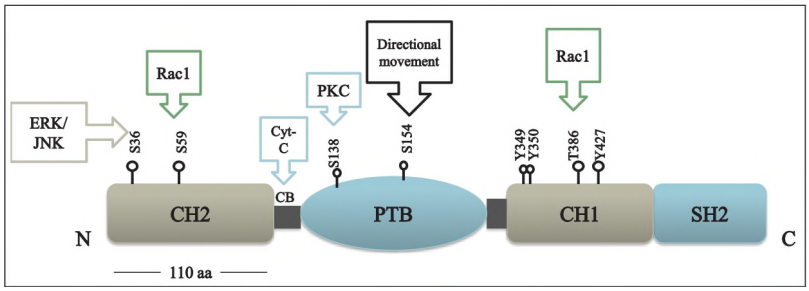


Figure 1 **TrkA receptors mediate differentiation and survival signalling through ERK, PI3K and PLC-γ pathways**
TrkA receptors recruit and increase the phosphorylation of PLC-γ and Shc, which leads to activation of PI3K and ERK. Highlighted residues (blue) are human mutations in TrkA that are associated with patients suffering from congenital insensitivity to pain [33–35]. Grb2, growth factor receptor-bound protein 2; Gab1, Grb2-associated binder-1; PDK1, phosphoinositide-dependent kinase 1; SH2B, Src homology 2-B; SOS, son of sevenless.

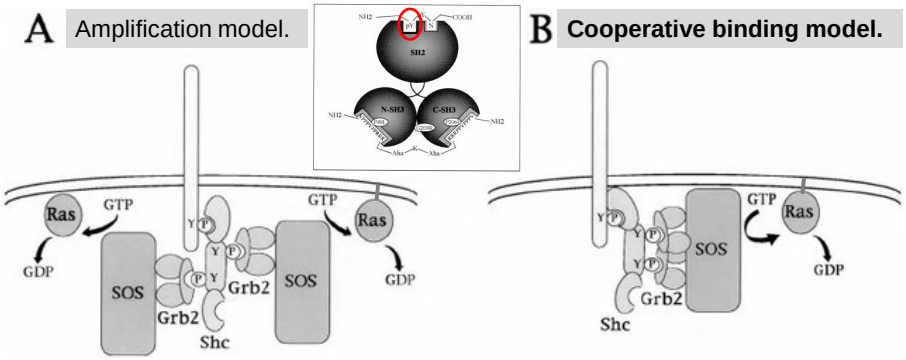
Shc is a multidomain protein able to interact with multiple partners



Schematic representation illustrating the phosphorylation sites on p66ShcA. There are three tyrosine phosphorylation sites and a threonine phosphorylation residue in the CH1 domain. There is one serine phosphorylation site on (Serine 138) the PTB domain as well as two serine phosphorylation sites in the amino terminal CH2 domain. p66ShcA has a unique cytochrome c binding region (CB). Ser36, Ser59, Ser138 and Thr386 are involved in the oxidative stress response, whereas S154 has a role in the directional movement of pancreatic cells. The phosphorylation of tyrosine residues in the CH1 domain are involved in MAPK activation (Adapted from Rajendran et al. 2010)

Published in Journal of molecular signaling 2017
Insights into the Shc Family of Adaptor Proteins
Samrein B. M. Ahmed, S. Prigent

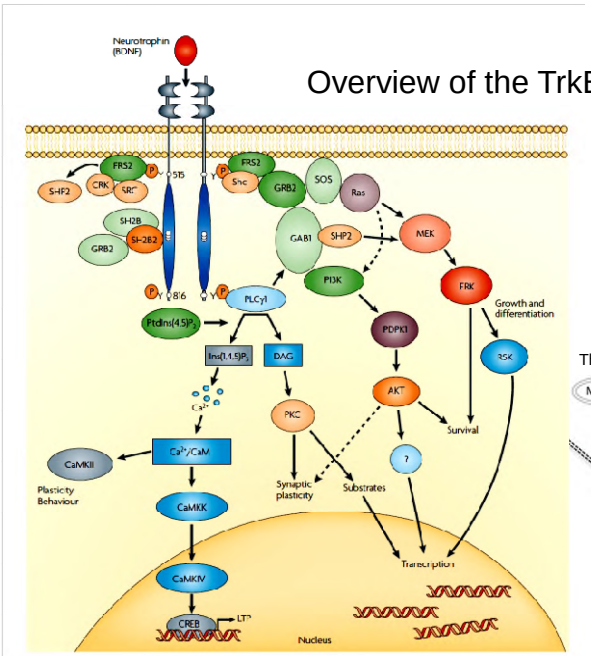
Two models describing Shc-Grb2-SOS interactions.



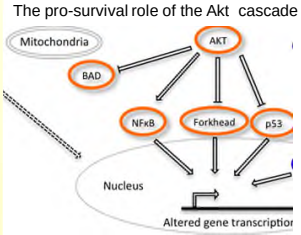
(A) Amplification model. The phosphorylation of two Grb2 binding sites on Shc may allow the recruitment of two SOS molecules, perhaps amplifying the signal and leading to more Ras activation.

B) **Cooperative binding model.** Shc may bind two Grb2 molecules that in turn bind to a single SOS molecule. The multiple protein-protein interactions afforded by such a four-way Shc-Grb2 2 -SOS complex might result in more stable binding than would be provided by the Shc-Grb2-SOS complex depicted in panel A and could explain the enhanced association between Grb2 and SOS that is observed upon BCR stimulation of cells. The identity of the transmembrane protein shown anchoring Shc at the membrane is unknown.

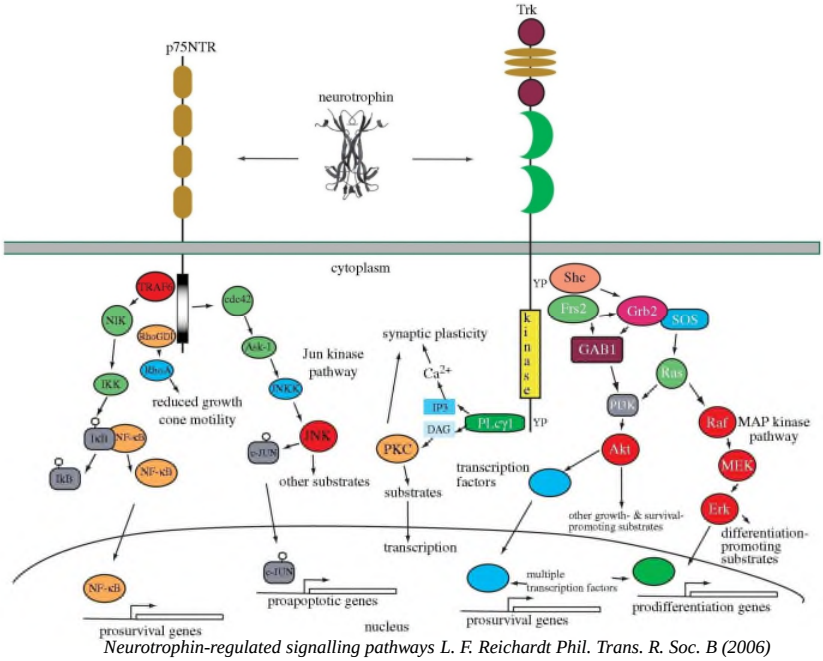
4) NT signalling transduction pathways mediated by trk receptors



The pro-survival role of the Akt cascade

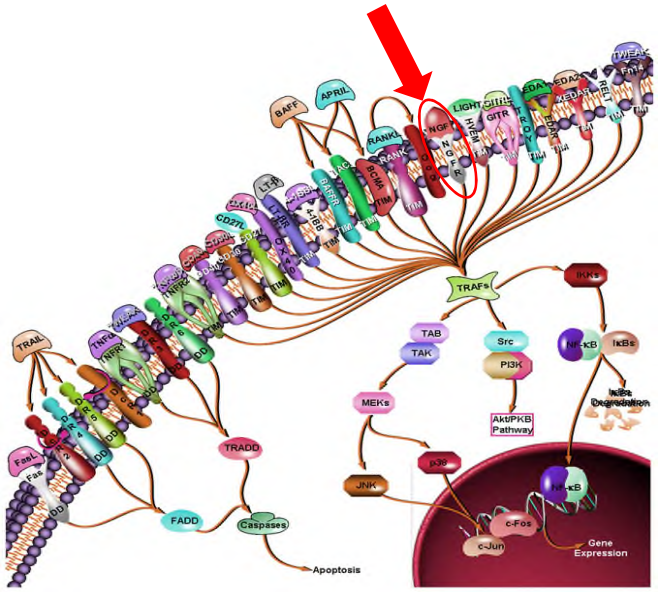


4) Comparison of p75 and Trk signaling

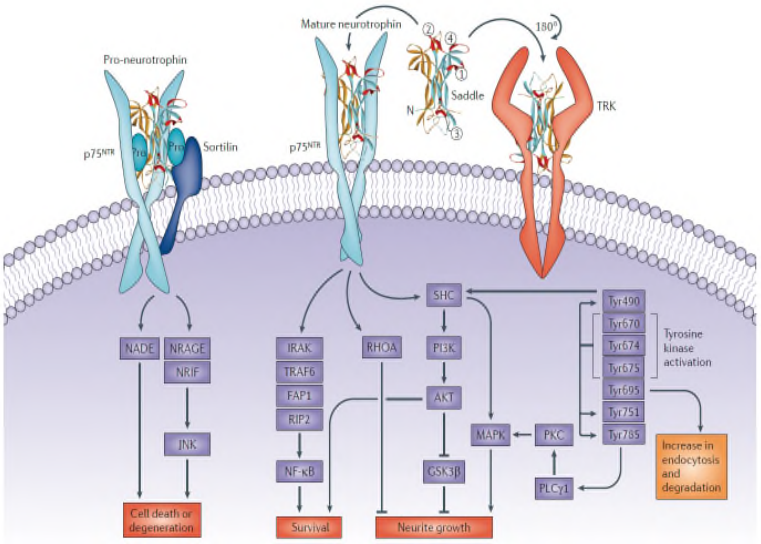


Neurotrophin-regulated signalling pathways L. F. Reichardt Phil. Trans. R. Soc. B (2006)

p75 belongs to the TNF receptors family

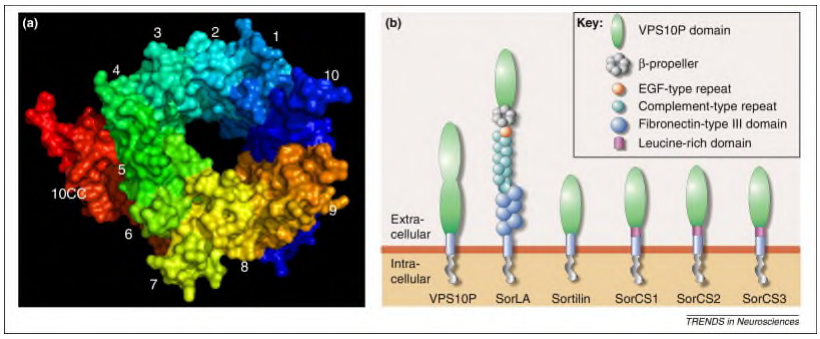


4) Comparison of p75 and Trk signaling



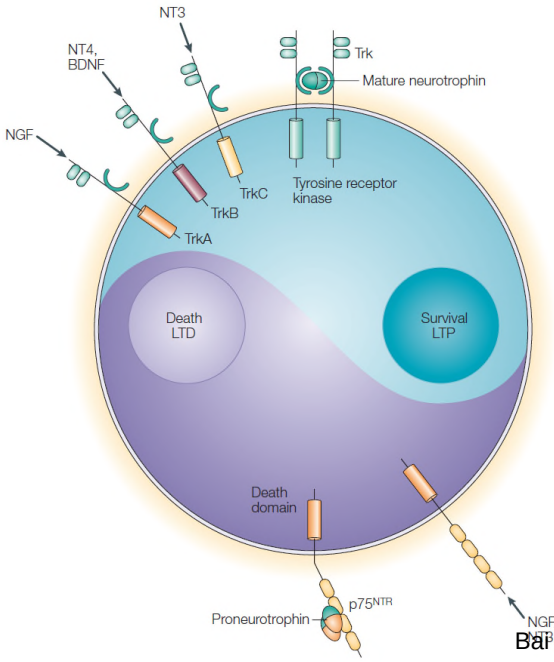
Longo, Massa, Nat Rev Drug Disc, 2013

4) NT signalling transduction pathways mediated by sortilin receptors



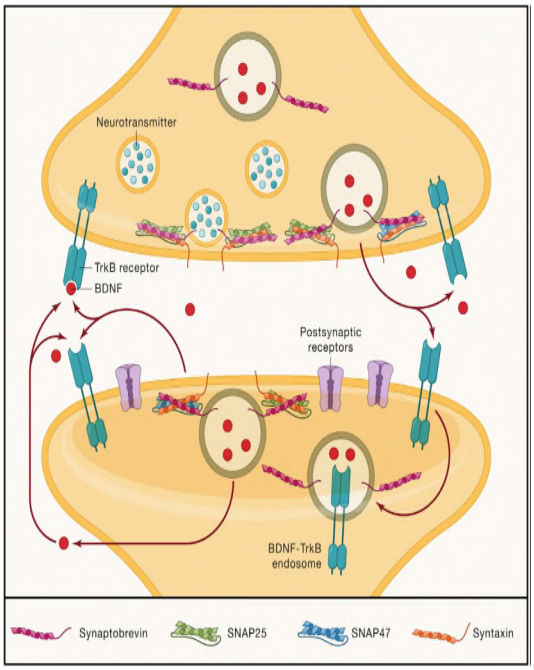
The vacuolar protein sorting 10 protein (VPS10P) domain is a 700-amino-acid module that was first recognized in the *Saccharomyces cerevisiae* protein VPS10P, a sorting receptor that directs the trafficking of lysosomal enzymes from the Golgi to the vacuole

Neurotrophin receptors: what functions have they?



THE YIN AND YANG HYPOTHESIS OF NEUROTROPHIN ACTION

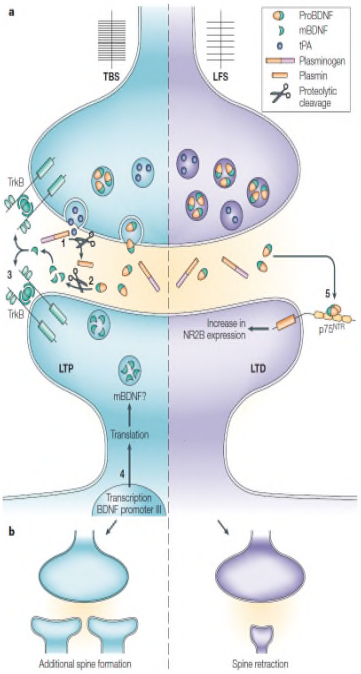
Bai Lu et al, Nat Rev Neurosci, 2005



Pre- and postsynaptic actions of BDNF-TrkB activity

After BDNF is cleaved into its mature form, it can be **trafficked to both presynaptic boutons and postsynaptic dendritic sites**, where it is stored in dense core vesicles.
Upon arrival to the **synapse**, BDNF is **released** with the help with SNARE proteins. Upon release into the extracellular space, BDNF then **acts locally on cis- and transsynaptic TrkB receptors**. Activation of receptors at different locations differentially affects processes such as synaptogenesis to synaptic plasticity.

Wang et al, Cell, 2022

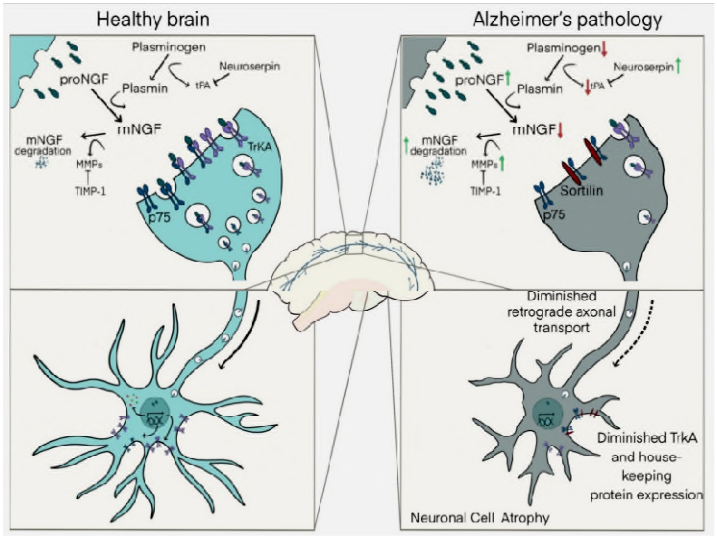


The yin and yang of long-term synaptic regulation by pro- and mature BDNF.

a | In response to theta-burst stimulation (TBS), tissue plasminogen activator (tPA) is secreted into the synaptic cleft and cleaves the extracellular protease plasminogen to yield plasmin (1). Plasmin then cleaves proBDNF, yielding mBDNF (2). mBDNF binds to TrkB and triggers a series of downstream signalling pathways to induce LTP (3). During the maintenance stage of LTP, mBDNF might be generated by intracellular cleavage after postsynaptic transcription and translation (4). By contrast, proBDNF secreted extracellularly remains uncleaved after low-frequency stimulation (LFS). Uncleaved proBDNF binds to the p75NTR) (5) to facilitate the induction of long-term depression (LTD), possibly through the regulation of NMDA receptor NR2B subunit expression. **b** | Morphological alterations in synapses induced by pro- and mature BDNF.

Bai Lu et al, Nat Rev Neurosci, 2005

The NGF pathway and its dysregulation in Alzheimer's and Down syndrome

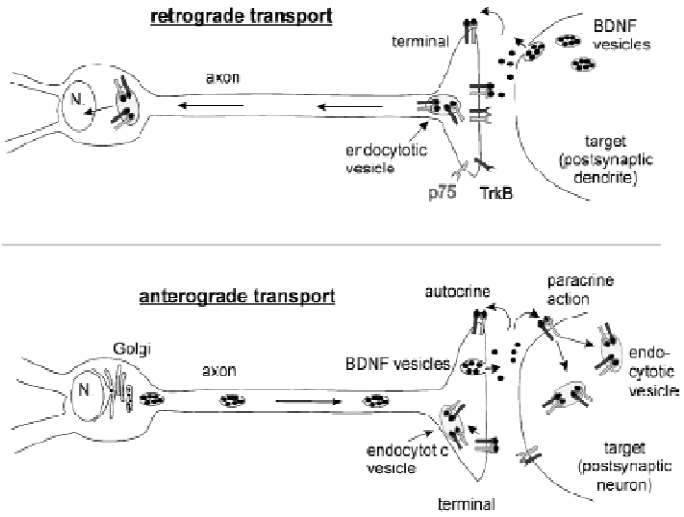


Do Carmo et al, Cells, 2022

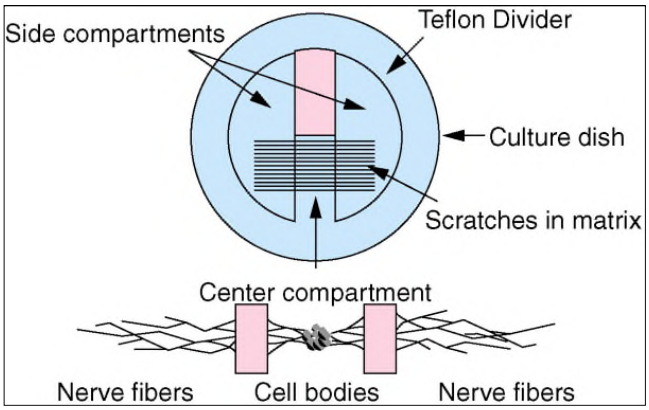
5) A spatial view of NT signalling pathways

Three are the neurotrophin signalling spatial ways in a neuron:
the signalling endosome
the signalling within the axons
the signalling at the cell body

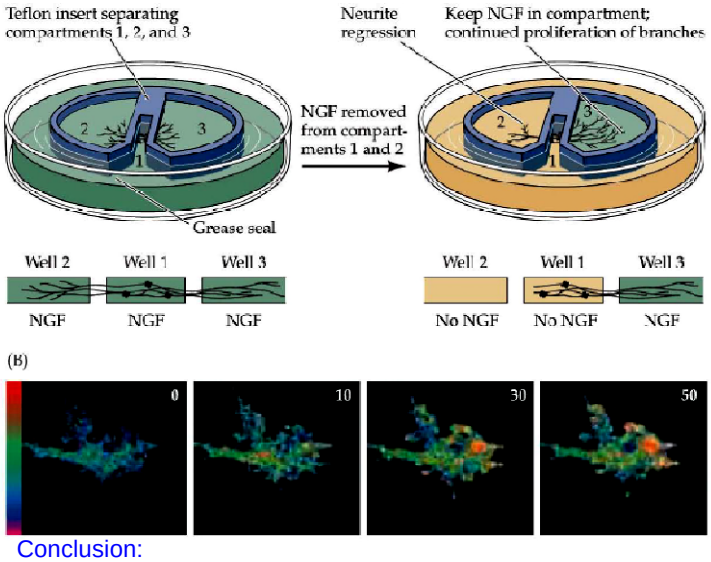
BDNF can be secreted from both axons and dendrites



The experiment of the Campenot's chamber



Neurotrophins influence neurite growth by local effects

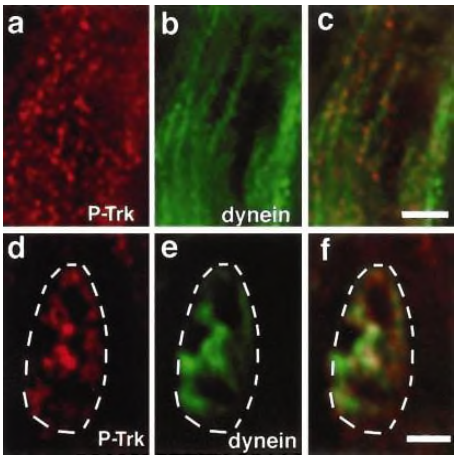


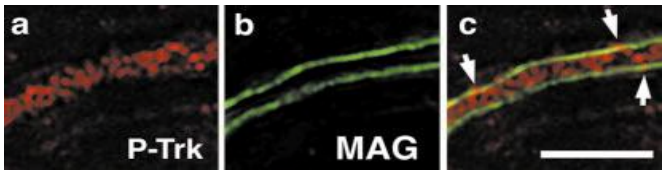
Conclusion:
NGF must be present at growth cones, not cell bodies.
NGF must be transported to the cell body by retrograde transport.

Co-localization of Dynein with p-Trk

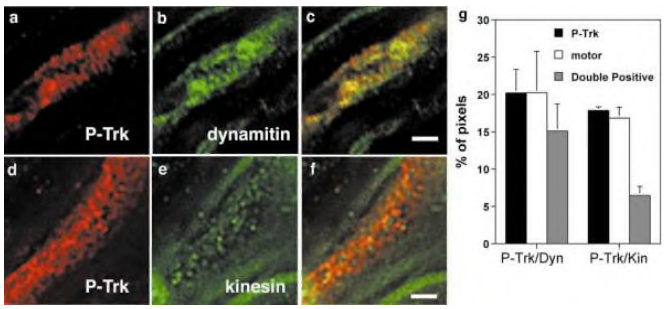
Longitudinal Section

Deconvoluted Cross Section – dashed line is the axon membrane

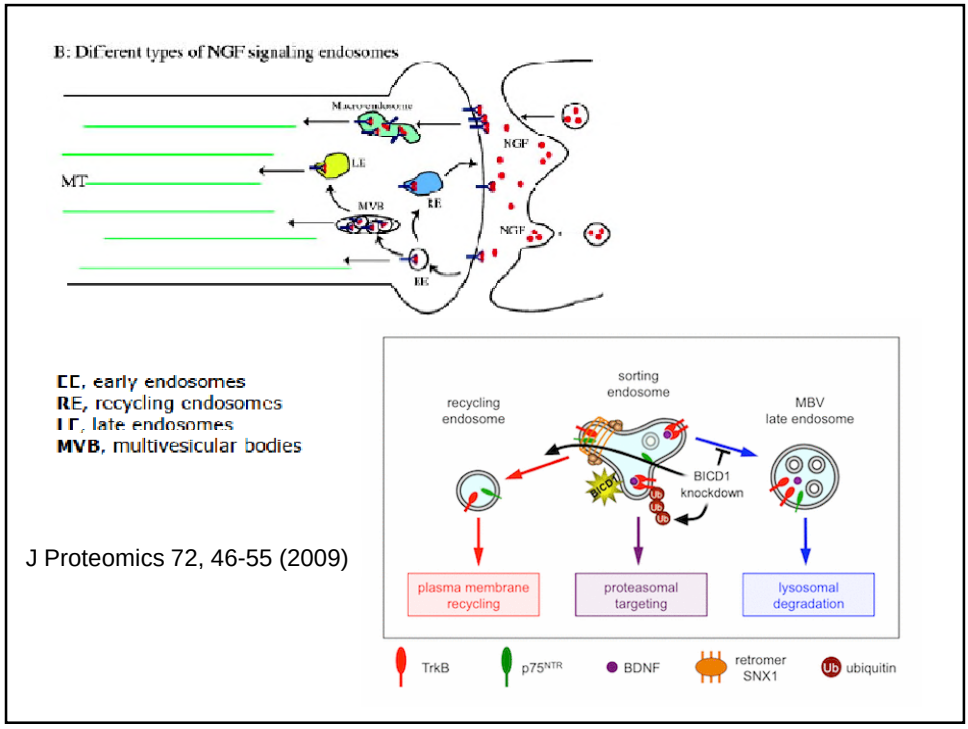


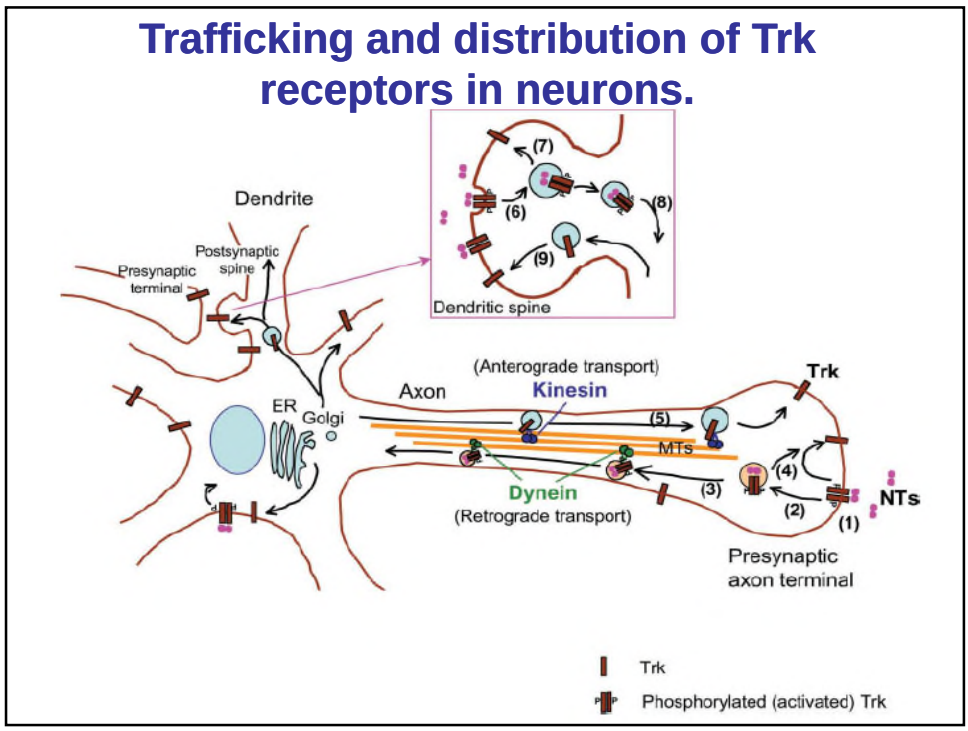


Staining of individual axons of the sciatic nerve
P-Trk (activated Trk) MAG myelin associated glycoprotein)



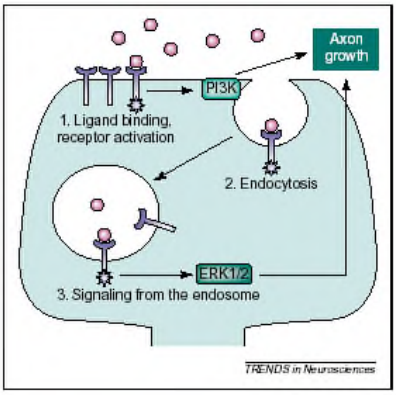
Correlation of Trk with Dynein/ Dynactin
not with Kinesin in sciatic nerves
Dynamitin is the p50 subunit of dynactin (a dynein associated protein)


B: Different types of NGF signaling endosomes
Macroendosome
NGF
LE
MT
RE
MVB
NGF
EE
EE, early endosomes
RE, recycling endosomes
LE, late endosomes
MVB, multivesicular bodies
J Proteomics 72, 46-55 (2009)
recycling endosome
sorting endosome
MBV late endosome
BICD1 knockdown
plasma membrane recycling
proteasomal targeting
lysosomal degradation
TrkB
p75NTR
BDNF
retromer SNX1
ubiquitin

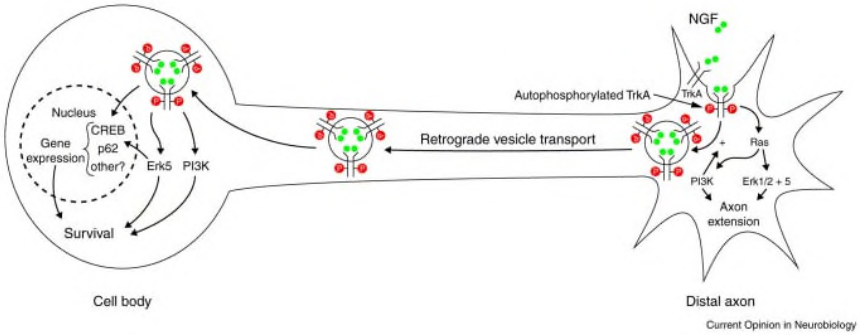

Trafficking and distribution of Trk receptors in neurons.
Dendrite
Postsynaptic spine
Presynaptic terminal
Dendritic spine
(7)
(6)
(8)
(9)
(Anterograde transport)
Kinesin
Axon
Trk
ER
Golgi
(5)
MTs
(4)
(3)
Dynein
(Retrograde transport)
(2)
(1)
NTs
Presynaptic axon terminal
Trk
Phosphorylated (activated) Trk

Activated Trk can signal locally and retrogradely using different signalling pathways

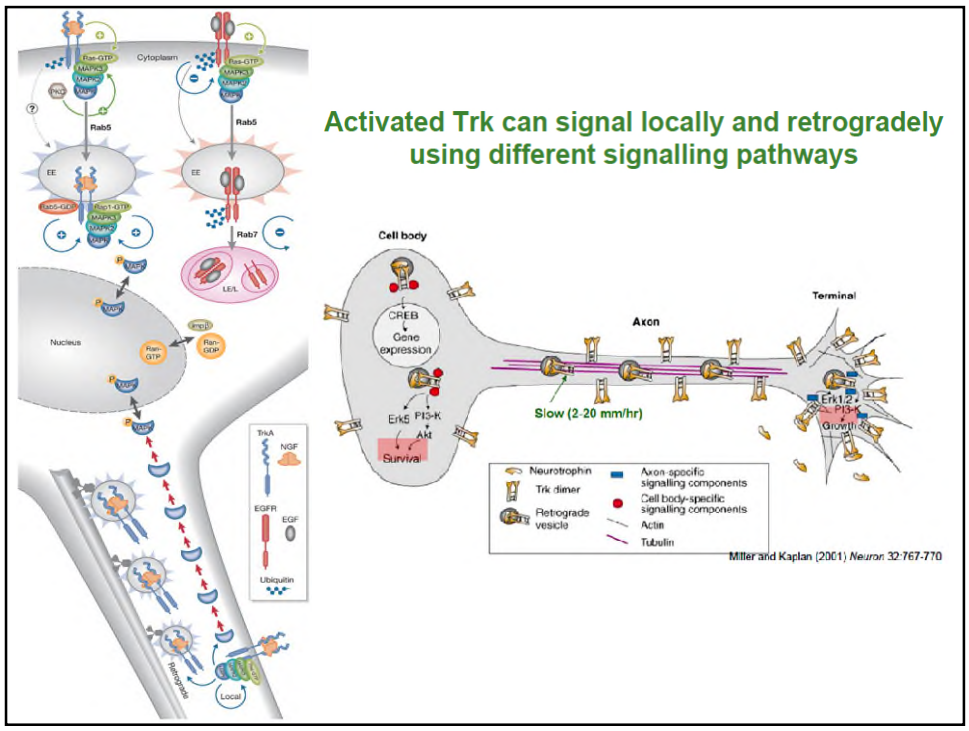
NT (purple spheres) binds to Trks (blue) at the nerve terminal. Location of the PI3 kinase cascade promotes both axon outgrowth and receptor endocytosis. Activated endosomal Trks within the terminal and axon might be primarily responsible for activating the erk172 pathway (from[Heerssen, 2002 #93]).

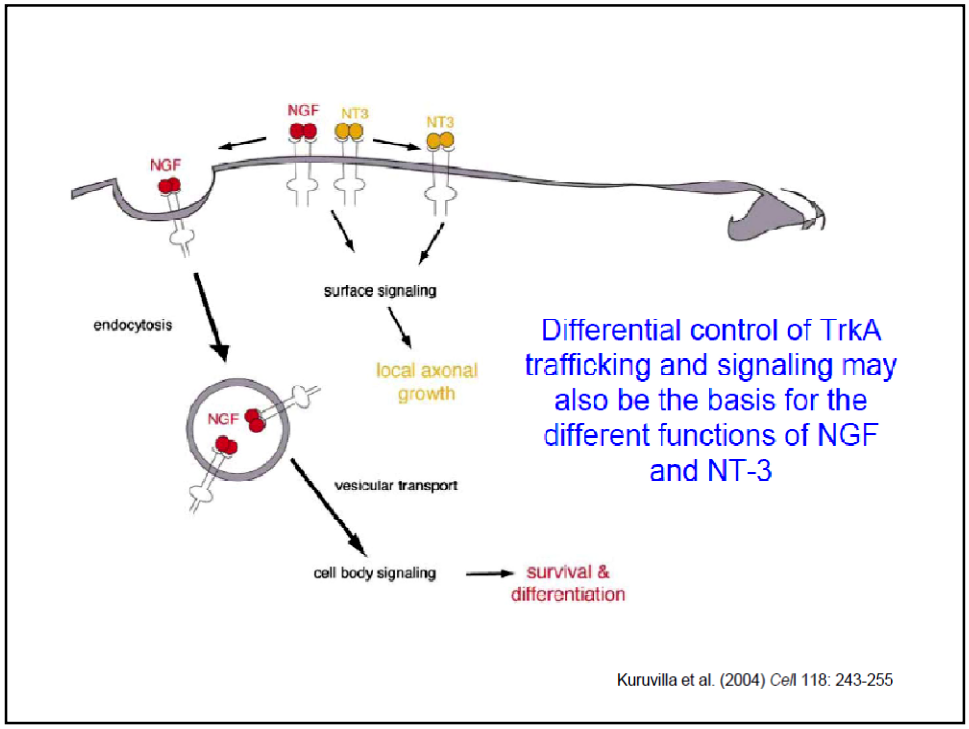


Transport of vesicle with NGF bound to TrkA (nerve growth factor receptor)



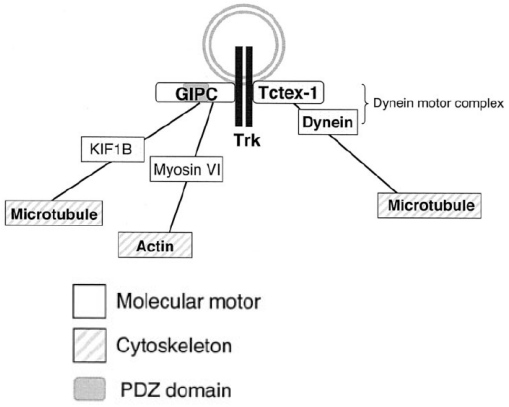
From Rosalind Segal


Activated Trk can signal locally and retrogradely using different signalling pathways
Cytoplasm
Rab5
Rab7
EE
LE/L
Nucleus
Ran-GTP
Ran-GDP
Importin
TrkA
NGF
EGFR
EGF
Ubiquitin
Retrograde
Local
Cell body
CREB
Gene expression
Erk5
PI3-K
Akt
Survival
Axon
Terminal
Slow (2-20 mm/hr)
Erk1,2
PI3-K
Growth
Neurotrophin
Trk dimer
Retrograde vesicle
Axon-specific signalling components
Cell body-specific signalling components
Actin
Tubulin
Miller and Kaplan (2001) Neuron 32:767-770

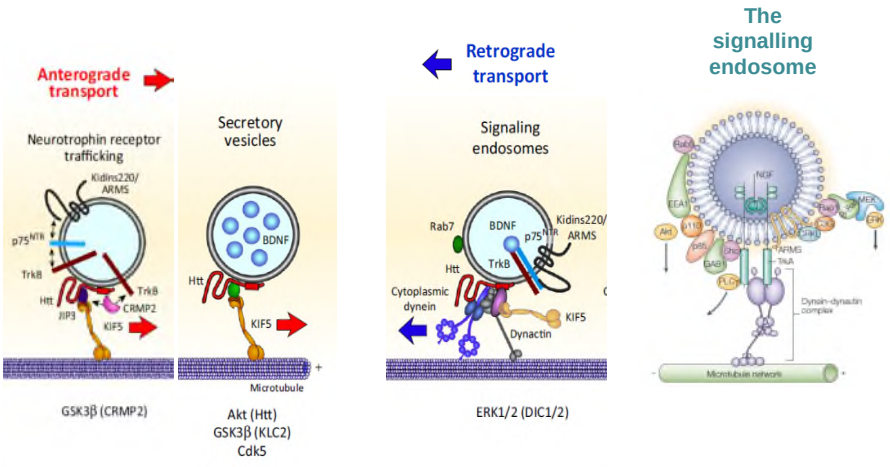

NGF
NT3
NT3
NGF
surface signaling
endocytosis
local axonal growth
NGF
vesicular transport
cell body signaling
survival & differentiation
Differential control of TrkA trafficking and signaling may also be the basis for the different functions of NGF and NT-3
Kuruvilla et al. (2004) Cell 118: 243-255

Model linking Trk-bearing vesicles to motors.

GIPC and Tctex-1 are Trk-interacting proteins that may be involved in Trk trafficking. The interaction of these proteins with Trk has been found by yeast two-hybrid system and coimmunoprecipitation (Lou et al., 2001; Yano et al., 2001). GIPC: a PDZ domain-containing protein; Tctex-1: a dynein light chain subunit. KIF1B and myosin VI were found to bind to GIPC by yeast two-hybrid screen (Bunn et al., 1999). A functional ternary complex of Trk-GIPC-KIF1B (or myosin VI) remains to be shown. The Trk-Tctex-1-dynein motor complex was detected by immunoprecipitation from brain lysate (Yano et al., 2001).



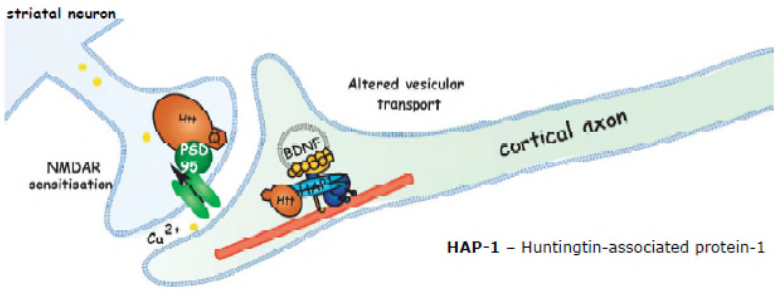
Transport of a vesicle with NGF bound to TrkA (growth factor receptor)



Gibbs, Trends Biochem Sci, 2015

Zweifel et al, Nat Rev Neurosci, 2005

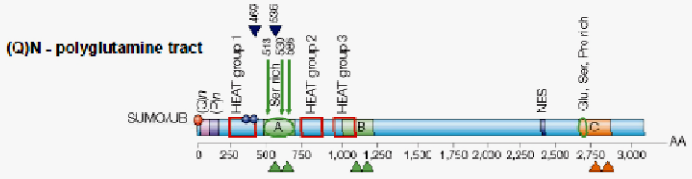
CHANGES IN THE TRANSPORT OF BDNF IN HUNTINGTON'S DISEASE



HAP-1 – Huntingtin-associated protein-1

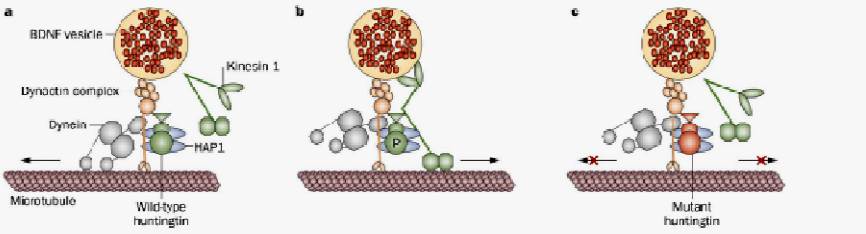
Cell. Mol. Life Sci 63, 1642-2660 (2006)

CHANGES IN THE TRANSPORT OF BDNF IN HUNTINGTON'S DISEASE



Schematic diagram of huntingtin amino acid sequence.

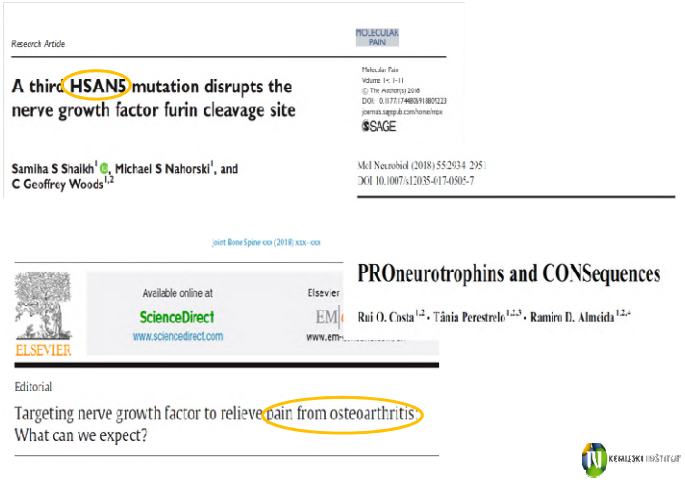
Nature Rev Neurosci 6, 919-930 [2005]



Nature Rev Neurol 5, 311-322 [2009]

Why are neurotrophins still interesting?

Involvement in an a big number of pathways/cellular conditions/pathologies. Pharmacological interest.



Research Article

A third HSAN5 mutation disrupts the nerve growth factor furin cleavage site

Samiha S Shaikh[1], Michael S Nahorski[1], and C Geoffrey Woods[1,2]

Mol Neurobiol (2018) 55:2034–2051
DOI 10.1007/s12035-017-0505-7

Available online at ScienceDirect www.sciencedirect.com

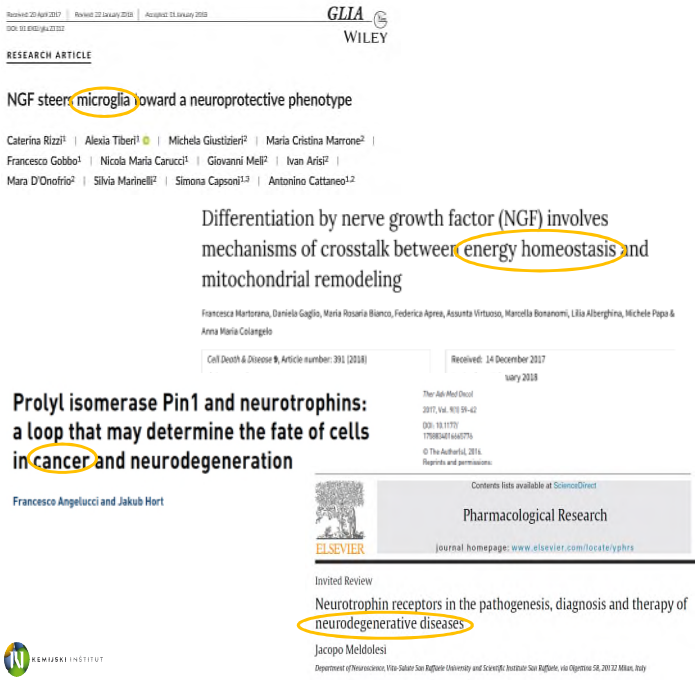
ELSEVIER

Editorial

Targeting nerve growth factor to relieve pain from osteoarthritis: What can we expect?

PROneurotrophins and CONSequences

Rui O. Costa[1,2] · Tânia Perestrelo[1,2,3] · Ramiro D. Almeida[1,2,4]



GLIA
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RESEARCH ARTICLE

NGF steers microglia toward a neuroprotective phenotype

Caterina Rizzi[1] | Alexia Tiberi[1] | Michela Giustizieri[2] | Maria Cristina Marrone[2] | Francesco Gobbo[1] | Nicola Maria Carucci[1] | Giovanni Mell[2] | Ivan Arisi[2] | Mara D'Onofrio[2] | Silvia Marinelli[2] | Simona Capsoni[1,3] | Antonino Cattaneo[1,2]

Differentiation by nerve growth factor (NGF) involves mechanisms of crosstalk between energy homeostasis and mitochondrial remodeling

Francesca Martorana, Daniela Gaglio, Maria Rosaria Bianco, Federica Aprea, Assunta Virtuoso, Marcella Bonanomi, Lilia Alberghina, Michele Papa & Anna Maria Colangelo

Cell Death & Disease 9, Article number: 391 (2018)

Received: 14 December 2017

Prolyl isomerase Pin1 and neurotrophins: a loop that may determine the fate of cells in cancer and neurodegeneration

Francesco Angelucci and Jakub Hort

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Invited Review

Neurotrophin receptors in the pathogenesis, diagnosis and therapy of neurodegenerative diseases

Jacopo Meldolesi

Dev Neurobiol. 2017 April ; 77(4): 405–418. doi:10.1002/dneu.22427.

International Journal of Molecular Sciences

Review

A Review on Ubiquitination of Neurotrophin Receptors: Facts and Perspectives

Julia Sánchez-Sánchez [1] and Juan Carlos Arévalo [2,*]

The Neurotrophin Receptor Signaling Endosome: Where Trafficking Meets Signaling

Kelly Barford[1], Christopher Deppmann[2], and Bettina Winckler[1]

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journal homepage: www.elsevier.com/locate/freeradbiomed

Review Article

Dysregulation of neurotrophin signaling in the pathogenesis of Alzheimer disease and of Alzheimer disease in Down syndrome☆

Xu-Qiao Chen*, Mariko Sawa, William C. Mobley*

Cell. Mol. Life Sci. (2016) 73:1859–1870
DOI 10.1007/s00018-016-2156-7

Cellular and Molecular Life Sciences

REVIEW

Neurotrophin signaling in cancer stem cells

Valérie Chopin[1,2] · Chann Lagadec[1] · Robert-Alain Toillon[1] · Xuefen Le Bourhis[1]

Journal of Medicinal Chemistry

Perspective

pubs.acs.org/jmc

Targeting the Nerve Growth Factor (NGF) Pathway in Drug Discovery. Potential Applications to New Therapies for Chronic Pain

Bryan H. Norman[*,†] and Jeff S. McDermott[‡]