NEUROTROPHIC FACTORS

HISTORY AND HYPOTHESIS

- In 1986 **Levi-Montalcini and Cohen** split the Nobel prize for Physiology or Medicine for their discovery of growth factors

- During development, neurons approaching the same final target vie for limited amounts of target-derived neurotrophic factors. The nervous system moulds itself to maintain only the most competitive and appropriate connections and 'targets of innervation secrete limiting amounts of survival factors to generate a balance between the size of the target organ and the number of innervating neurons'

[*This hypothesis is mainly concerned with peripheral neurons and peripheral target tissues.*]

INTRODUCTION

- Neurotrophins are a unique family of Polypeptide growth factors. They influence :-
  - Proliferation
  - Differentiation
  - Survival
  - Death [neuronal and non-neuronal cells]

INTRODUCTION

- These proteins emerged initially in vertebrate species and do not exist in invertebrates.
- Act to mediate additional higher-order activities, such as learning, memory, and behavior.
- Regulate synaptic connections and synapse structure, neurotransmitter release and potentiation, and pain and synaptic plasticity

THE NEUROTROPHIN FAMILY

- Synthesized as Precursors or Proneurotrophins that are cleaved to release the mature, active proteins
- The neurotrophins Family comprised of :-
  1. NGF
  2. BDNF
  3. NT-3
  4. NT-4
- These proteins, approximately 12 to 14 kDa in size, form stable, noncovalent dimers and are normally expressed at very low levels during development

THE NEUROTROPHIN FAMILY

- NGF
  - In the peripheral nervous system (PNS), it acts on sympathetic neurons as well as sensory neurons involved in nocioception and temperature sensation.
  - In the central nervous system (CNS), NGF promotes the survival and functioning of cholinergic neurons in the basal forebrain.

- BDNF and NT-3 are highly expressed in the CNS
  - In cortical and hippocampal structures they are linked to the survival and functioning of multiple neuronal populations

MECHANISM OF ACTION

1. PRONEUROTROPHINS ARE CLEAVED INTRACELLULARLY BY FURIN OR PROCONVERTASES
2. THE MATURE PROTEINS MEDIATE NEUROTROPHIN ACTIONS BY SELECTIVELY BINDING TO MEMBERS OF THE TROPOMYOSIN–RELATED KINASE (TRK) FAMILY OF RECEPTOR TYROSINE KINASES .
3. ALL MATURE NEUROTROPHINS INTERACT WITH $P75^{NTR}$, WHICH CAN MODULATE THE AFFINITY OF TRK NEUROTROPHIN ASSOCIATIONS.

NEUROTROPHIN RECEPTORS

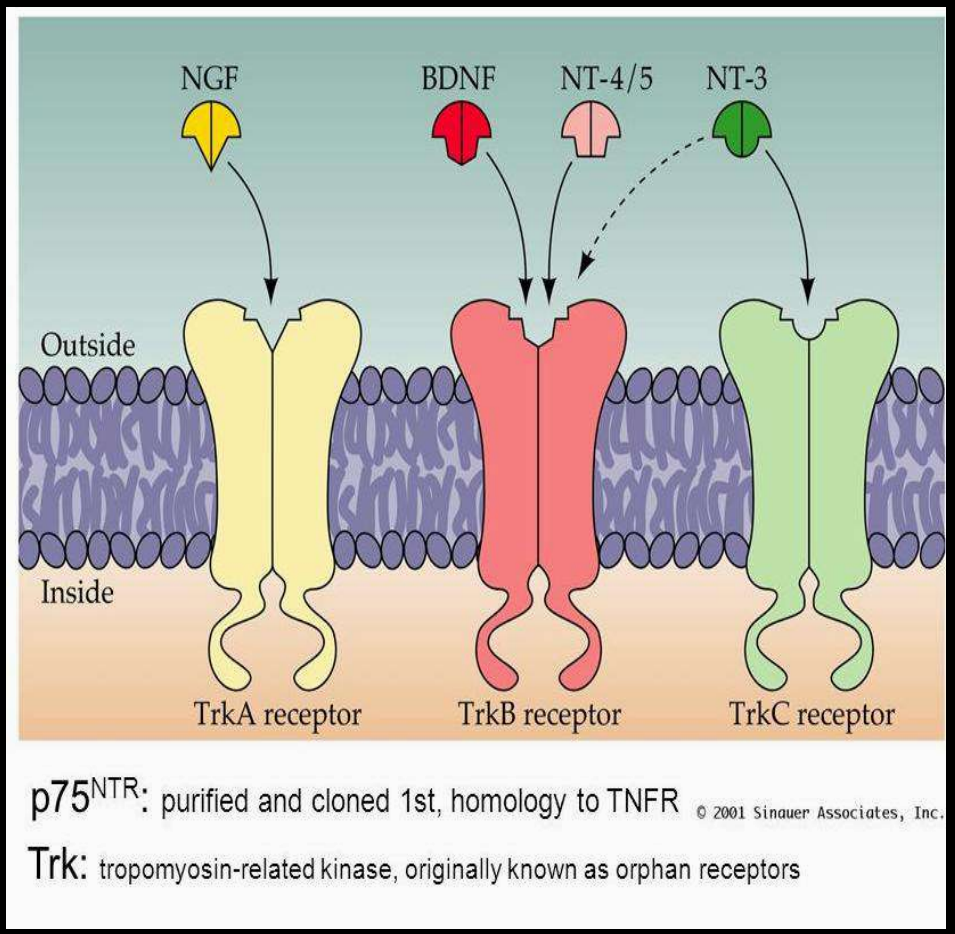
Neurotrohins exert their cellular effects through 2 receptors

1. The Trk receptor tyrosine Kinase - It is a member of the tumor necrosis factor receptor superfamily

2. The p75 neurotrophin receptor ($p75^{NTR}$)

Trk RECEPTOR	$p75^{NTR}$ RECEPTOR
Extracellular ligand-binding region	Extracellular ligand-binding region
A single transmembrane domain	A single transmembrane domain
Intracellular tyrosine kinase domain.	Intracellular portion containing a protein-association region termed the death domain
3 vertebrate *trk* receptor genes, *trkA*, *trkB*, and *trkC*	ALL NEUROTROPHINS bind to the P75 receptor

TRK RECEPTOR



1. NEUROTROPHINS BIND AS DIMERS TO TRK FAMILY MEMBERS LEADING TO RECEPTOR DIMERIZATION AND ACTIVATION OF THE CATALYTIC TYROSINE PROTEIN KINASE DOMAINS
2. THE DIMERIZED TRK RECEPTORS AUTOPHOSPHORYLATE SEVERAL INTRACELLULAR TYROSINE RESIDUES
3. THESE RESIDUES RAPIDLY INITIATE INTRACELLULAR SIGNALING CASCADES

[ACCOMPLISHED BY PHOSPHORYLATED TYROSINES ON RECEPTOR ACTING AS RECOGNITION SITES]

NEUROPHIN RECEPTORS

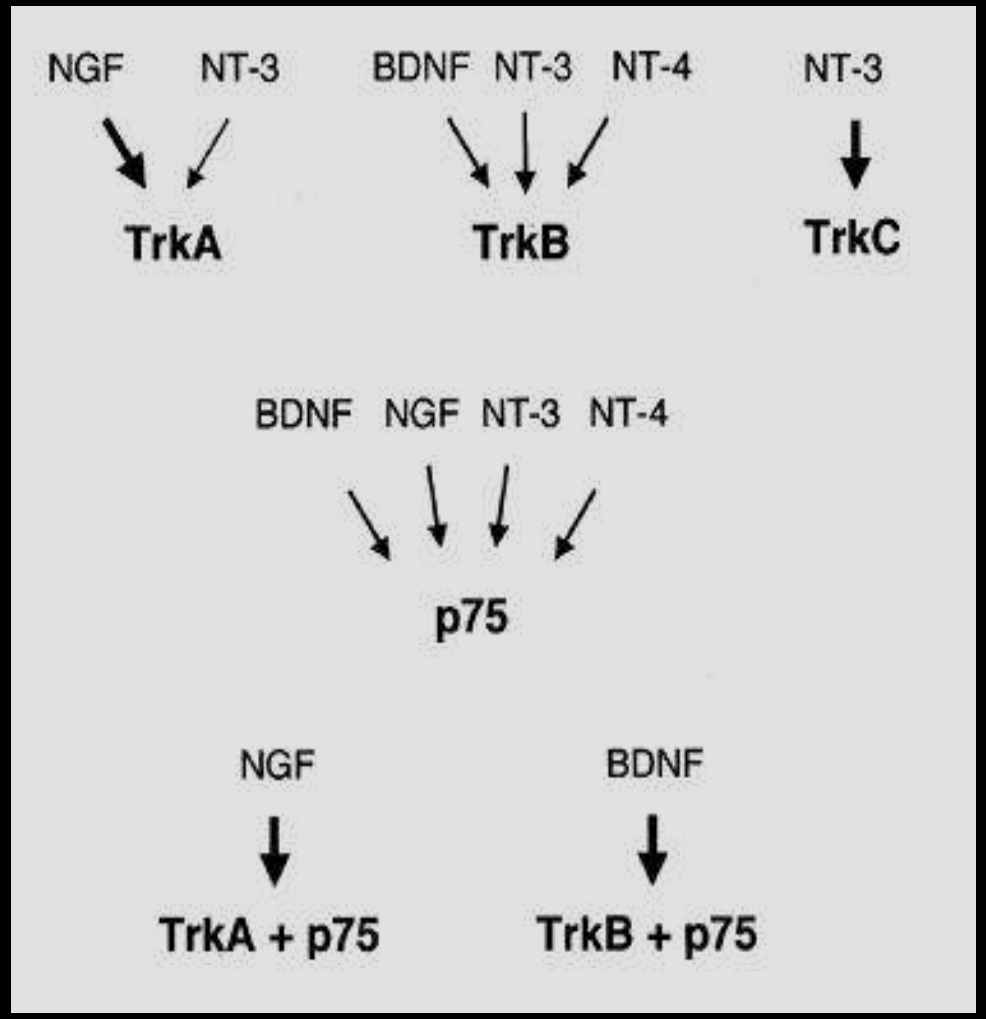
Trk receptors mediate differentiation and survival signaling through

- Increased Mitogen-activated protein kinase (MAPK) activity
- Increase in Phosphatidylinositol-3-kinase (PI3-K)
- Phospholipase C-γ (PLC-γ)
- Trk receptors contain IgG domains for ligand binding and a catalytic tyrosine kinase sequence in the intracellular domain.

NEUROTROPHIN RECEPTORS

P75^{NTR} MEDIATES APOPTOTIC AND CELL MIGRATION RESPONSES THROUGH

- NUCLEAR FACTOR κB (NF-κB)
- C-JUN N-TERMINAL KINASE (JNK) PATHWAYS.
- P75^{NTR} CONTAINS FOUR CYSTEINE-RICH REPEATS; THE INTRACELLULAR DOMAIN CONTAINS A DEATH DOMAIN



- TRK AND P75^{NTR} RECEPTORS HAVE BEEN REFERRED TO AS HIGH- AND LOW-AFFINITY RECEPTORS, RESPECTIVELY.
- P75 AND TRK RECEPTORS DO NOT BIND TO EACH OTHER DIRECTLY, THERE IS EVIDENCE THAT COMPLEXES FORM BETWEEN THE TWO RECEPTORS
- NEUROTROPHINS BIND SELECTIVELY TO SPECIFIC TROPOMYOSIN-RELATED KINASE (TRK) RECEPTORS, AND THIS SPECIFICITY CAN BE ALTERED BY P75^{NTR}

TABLE 21.1 The Neurotrophin Family and Its Receptors

Factor	Receptor: Full-length kinase-containing isoforms[a]	Receptor: Nonkinase forms[b]	Example of responsive neurons[c]
NGF	trkA	p75[d]	Cholinergic forebrain neurons
	($trkA_{I1}$)		Sympathetic ganglia
			DRG nociceptive
BDNF	trkB	$p75^{LNTR}$	Many CNS populations
		$trkB_{T1}$	Vestibular ganglia
		$trkB_{T2}$	Nodose ganglia
			DRG mechanoreceptors
NT-3	trkC	$p75^{LNTR}$	Many CNS populations
	($trkC_{TK+1}$)	$trkC_{TK-1}$	Choclear ganglia
	($trkC_{TK+2}$ $TrkC_{TK+3}$)	$trkC_{TK-2}$	DRG proprioceptive
	trkB and trkA nonpreferred	$trkC_{TK-3}$	
		$trkC_{TK-3}$	
NT-4[e]	trkB	p75	Many CNS populations
		$trkB_{T1}$	Nodose ganglia
		$trkB_{T2}$	Petrosal ganglia
NT-6[f]	trkA	p75	(Found only in fish)

NEUROTROPHIC FACTORS AND DEVELOPMENT

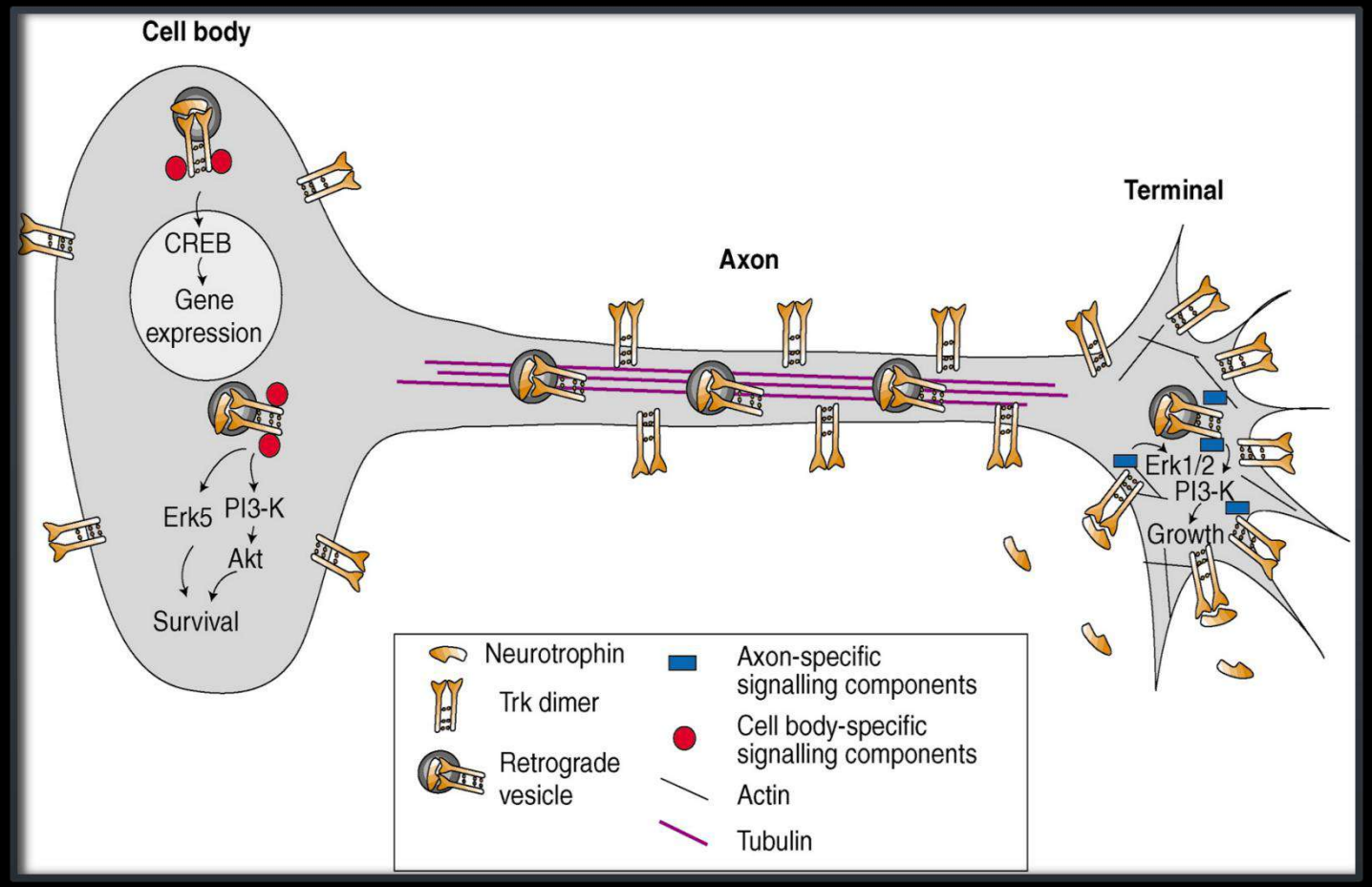
- Neurotrophins are highly expressed during early development and have been shown to be essential for survival of selective populations of neurons during different developmental periods.
- During Development, Neurons release neurotrophins :-
  - Autocrine transmission
  - Anterogradely transported down axons and act on neighboring neurons
- Glial cells can release neurotrophins that act upon neurons in a paracrine fashion.

NEUROTROPHIC FACTORS AND DEVELOPMENT

- In Periphery, neurotrophin retrograde signaling occurs through a pathway that must efficiently transmit information over long distances, at times over a meter.
- Neurotrophins promote cell survival and differentiation during neural development. Paradoxically, they can also induce cell death
- Increases in $p75^{NTR}$ expression are responsible for apoptosis in embryonic retinas and sympathetic neurons during the period of naturally occurring neuronal death.

RETROGRADE TRANSPORT

- EACH NEUROTROPHIN BINDS TO TRANSMEMBRANE RECEPTORS AND UNDERGOES INTERNALIZATION AND TRANSPORT FROM AXON TERMINALS TO NEURONAL CELL BODIES
- A RATE OF TRANSPORT FROM DISTAL TO BODY CELL IS 3 TO 10 MM PER HOUR.
- INTERNALIZATION OF NGF FROM AXON TERMINALS IS NECESSARY FOR PHOSPHORYLATION AND ACTIVATION OF THE CREB TRANSCRIPTION FACTOR



NEUROTROPHINS AND BEHAVIOR

- A recent series of studies on genetically modified mice with reduced levels of BDNF have indicated striking effects upon adult brain function and behavior.
- Reduced Levels of BDNF are associated with :-
  - Enhanced aggressiveness
  - Hyperactivity
  - Hyperphagia
- Lack of BDNF also created defects in memory tasks, consistent with defects in LTP found in the hippocampus

OTHER NEUROTROPHIC FACTORS

Glial-derived neurotrophic factor [GDNF]

- 18-kDa protein, originally isolated from an astrocyte cell line
- Most potent trophic factors for dopaminergic neurons.
- GDNF has been shown to maintain the survival of dopaminergic neurons in the midbrain as well as neurons in the myenteric plexus in the gut.
- Considered a potential therapeutic agent for Parkinson's disease.
- Acts - via ligand - receptor complex Which associates with Ret (a receptor tyrosine kinase)
- Mutations in the Ret receptor and GFRa1 have been associated with Hirschprung's disease

OTHER NEUROTROPHIC FACTORS

Ciliary neurtotrophic factor

- Belongs to a family of cytokines, including leukemia inhibitory factor (LIF) and interleukin-6
- Maintain the survival of ciliary neurons as well as motor neurons
- CNTF has been investigated as a therapeutic agent for motor neuron diseases such as amyotrophic lateral sclerosis (ALS)
- Acts - via ligand-receptor complex Which associates with tyrosine kinase, the Janus kinase (JAK)

SYNAPTIC PLASTICITY

- Recent studies have established that neurotrophic factors play significant roles in influencing synaptic plasticity in the adult brain
- Many neuronal populations are not only dependent upon these neurotrophins for their survival but also for modulating neuronal activity.
- Developmental regulation of synaptic plasticity in the visual system can be illustrated by the formation of ocular dominance columns in layer 4 of the cortex, which can be strongly influenced by exogenous neurotrophins such as BDNF

SYNAPTIC PLASTICITY

- THE EFFECTS UPON THE VISUAL SYSTEM CAN BE OBSERVED USING BLOCKING ANTIBODIES FOR THE NEUROTROPHINS AS WELL AS NEUROTROPHIN ANTAGONISTS
- MODULATION OF SYNAPTIC PLASTICITY IN THE DIFFERENTIATED ADULT BRAIN HAS ALSO BEEN DEMONSTRATED IN THE HIPPOCAMPUS IN A SERIES OF STUDIES
- BDNF PROMOTED THE INDUCTION OF A SYNAPTIC STRENGTHENING, TERMED LTP, IN HIPPOCAMPAL SLICES WHILE BLOCKING AGENTS INTERFERED WITH THE INDUCTION OF LTP
- IN ADDITION, HIPPOCAMPAL PREPARATIONS CONTAINING LITTLE OR NO BDNF GAVE RISE TO THE SAME REDUCTION IN LTP, SUGGESTING THAT THERE WAS A MINIMAL QUANTITY OF BDNF REQUIRED FOR THE MODULATION OF LTP
- SUBSEQUENT ADDITIONS OF EXTRA BDNF TO THESE PREPARATIONS RESTORED LTP.

CLINICAL CORRELATES

- Neurotrophic factors modulate **NEURONAL SURVIVAL AND AXONAL GROWTH** clinical correlates to neurodegenerative disorders and neuronal injury such as :-
  - Alzheimer's disease
  - Parkinson's disease
  - Huntington's disease
  - ALS
  - Spinal cord injury.
- The additional effects of neurotrophic factors on synaptic connections, synaptic plasticity, and neurotransmission Leads to psychiatric disorders such as :-
  - Depression
  - Substance abuse

NEURODEGENERATIVE DISORDERS

1. **Alzheimer's Disease** In the 1980s based on studies cholinergic neurons in the basal forebrain could be rescued with intracerebroventricular NGF, resulting in concomitant improvements in memory function.
2. **Impaired Motor Neuron** The BDNF, NT-3, NT-4, and CNTF could rescue those neurons in an axotomized facial nerve and sciatic nerve.
3. **Motor Neuron Degeneration** BDNF and CNTF could increase the number of motor neurons and improve motor performance.
4. **Huntington's Disease (HD)** is caused by a expansion in the huntington protein resulting in abnormal motor movements, personality changes, cognitive decline, and early death. Decreased BDNF levels in the striatum have been detected.

DEPRESSIVE DISORDERS

- Fundamental dysregulation of synaptic plasticity and neuronal survival in regions of the brain such as the hippocampus.
- MRI studies have shown that patients with depressive or post-traumatic stress disorders exhibit a small decrease in hippocampal volume.
- Exogenously administered BDNF in the hippocampus had antidepressant effects in two animal models of depression
- BDNF has also been shown to have trophic effects on serotonergic and noradrenergic neurons in vitro and in vivo

DEPRESSIVE DISORDER

- Serotonin and norepinephrine reuptake inhibitor antidepressants upregulate CREB and BDNF in a time course that corresponds to therapeutic action (10 to 20 days)

- Conversely, exogenously administered BDNF in the mesolimbic dopamine system appears to have an opposite effect—increasing depression like behavior. In addition, removal of BDNF in this dopamine circuit appears to have antidepressant effects

GENETICS

- The polymorphism of a single nucleotide polymorphism (SNP) leads to a single amino acid change from valine (Val) to methionine (Met) at position 66 in the pro region of the BDNF protein may cause depression, bipolar disorder, and schizophrenia.

- In patients with bipolar disorder, the Val allele appears to confer greater risk for the disease

LIMITATIONS IN THERAPEUTIC POTENTIAL

- Physical delivery of sufficient quantities to target neurons is a major obstacle.
- Small molecules that readily cross the blood – brain barrier to activate neurotrophin receptors or potentiate the actions of neurotrophins is an approach that is in its infancy.
- Neurotrophins have multiple effects on neuronal activity may cause "flooding" of the CNS with neurotrophic factors will likely lead epileptic activity

SUMMARY

- Neurotrophins are Polypeptide growth factors necessary for Cell Survival and its growth.
- Only Found in vertebrate species and are involved in higher-order activities.
- The Major neurotrophins are NGF, BDNF, NT-3, NT-4
- NGF in PNS acts on sympathetic neurons While in CNS acts on cholinergic neurons in the basal forebrain.
- BDNF and NT-3 acts in CNS on cortical and hippocampal structures.
- The Neurotrophins act via Trk receptor and $p75^{NTR}$ and mediate the desired actions.

SUMMARY

- Disturbances in Neurotrophic factors are associated with Depression, Substance abuse, Alzheimer's disease, Parkinson's disease, Huntington's disease, ALS, Spinal cord injury.

- Other Neurotrophic Factors include GDNF (Hirschprung's disease) CNTF (Amyotrophic lateral sclerosis).

- Low Therapeutic Potential because of limitations like Physical delivery, "flooding" of the CNS, approach towards the target receptor.

REFERENCES

- Comprehensive Textbook of Psychiatry Kaplan and Sadock 10th edition
- Davies AM. Neurotrophins: The yin and yang of nerve growth factor. Current Biology. 1997 Jan 1;7(1):R38-40.
- Davies AM. The neurotrophic hypothesis: where does it stand?. Phil. Trans. R. Soc. Lond. B. 1996 Mar 29;351(1338):389-94.
- Landis SC, Roberts JL, Squire LR. Fundamental neuroscience. Zigmond MJ, Bloom FE, editors. San Diego: Academic Press; 1999 Jan 1.