217 - Growth Factors

Giles Plant

Growth and Trophic Factors

Soluble/diffusible factors - polypeptides

Role in:
- Proliferation
- Differentiation (ie Cancer)
- Survival (degenerative diseases)
- Innervation
- Maintenance
- Plasticity, learning and memory
- Regeneration and repair

Retrograde and anterograde transport. Targets.
Paracrine and autocrine functions

Receptors and signal transduction.
Interaction with other neuroactive molecules.

Trophic Factors

• Activities in both the developing and mature nervous systems
• Anatomical and functional plasticity and repair of the damaged system
• Cell death and neurotrophic factors (Hamburger, 1992)

History

• 1934 Hamburger - removal of a target reduces numbers of cells innervating (chick bud)
• 1942 Levi Montalcini and Levi – target derived signals control the survival of differentiating neurons
• 1954 Levi-Montalcini explant experiments using sympathetic ganglia deduced snake venom (used to actually separate nucleic acid and protein fraction) and cell extract from a cancer cell line have the same effect on axonal growth via the same product

Trophic Factors

• The survival of neurons is regulated by survival factors called trophic factors. The neurotrophic hypothesis was formulated by Victor Hamburger and Rita Levi Montalcini based on studies in the developing nervous system. Implanting an extra limb increases the number of motoneurons. Showed that a decreased number of neurons dying was the cause not proliferation. Growth competition!

History 2

• 1956 Cohen examined the mammalian homologue of the snake venom gland-salivary gland. Male mice glands even richer in factor. When antiserum injected into mice all sympathecic motoneurons died
• 1959 Bocchini and Angeletti isolate NGF also known as 2.5S NGF. To purify from target organs would have required a purification factor of 100 million whereas only 100-200 in mouse salivary gland
History 3

• 1982 Barde – isolated new brain factor called “Brain Derived Neurotrophic Factor”
• 1986 Nobel prize to Levi-Montalcini and Cohen for discovery of NGF and EGF

Target-derived neurotrophic factors should be:
“produced and released in limited quantities in the projection areas of the responsive neurons, and regulate the extent of the survival and differentiation of these neurons during embryonic development and the maintenance of their specific function in adulthood”

Hans Thoenen

Examples of growth or trophic factors:
Neurotrophins, Fibroblast growth factors, Cytokines (CNTF, LIF etc), Transforming growth factors (TGFβ, GDNF etc), Insulin-like growth factors

NGF

• Rita Levi-Montalcini and Stanley cohen purified the first trophic factor.
• Nerve growth factor (NGF) for which they received the nobel prize
• BDNF, NT-3 and NT-4 regulate survival of various neurons. The Trk receptors are related receptors for the factors (tyrosine kinase)

CNTF

• Ciliary neurotrophic factor is another protein that acts as a survival factor for motor neurons.
• CNTF acts via receptors CNTFα, GP130 and LIFRβ.

GDNF

• Glial derived neurotrophic factor is a member of the TGFβ family of proteins and is a potent trophic factor for striatal neurons. The functional receptor is heterodimer composed of type 1, type 2 receptors. Activation of SMAD proteins which then translocate to the nucleus to activate gene expression.
## Neurotrophin Receptors

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Full-length kinase-containing isoforms</th>
<th>Neurotrophin forms</th>
<th>Example of responsive neurons</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGF</td>
<td>trkA (trkAa)</td>
<td>p75</td>
<td>Cholinergic and sensory neurons, sympathetic ganglia, DRG neurons, sensory neurons, nociceptors</td>
</tr>
<tr>
<td>BDNF</td>
<td>trkB</td>
<td>p75</td>
<td>Many CNS populations, vestibular ganglia, nodose ganglia, DRG neurons, sensory neurons, nociceptors</td>
</tr>
<tr>
<td>NT-3</td>
<td>trkC</td>
<td>p75</td>
<td>Many CNS populations, C5/7 and C5/C7 sensory neurons, DRG proprioceptive</td>
</tr>
<tr>
<td>NT-4</td>
<td>trkB</td>
<td>p75</td>
<td>Many CNS populations, nodose ganglia, sympathetic ganglia</td>
</tr>
<tr>
<td>NT-6</td>
<td>trkA</td>
<td>p75</td>
<td>Many CNS populations, nodose ganglia, sympathetic ganglia</td>
</tr>
</tbody>
</table>

## NGF Receptors

![NGF Receptors](image1)

## Trks

![Trks](image2)

## Trophic Signals

![Trophic Signals](image3)
Retrograde influences on neuronal viability and phenotype

Fig. 2. Signaling endosomes mediate a retrograde neurotrophic signal. Neurotrophins (purple spheres) released by target neurons (T) bind to and activate Trks (shaded) at the nerve terminals. Activated Trks localize and transport endosomes to form signaling endosomes (white circles). Dynein (white bars) transports Trks containing signaling endosomes retrogradely along microtubules to the cell body. Activated Trks initiate signaling throughout the transport process, both in the axons and at the cell body.

Distinct neuronal influences depend on different neurotrophic factors

Figure 1: Schematic presentation of the regulation of neurotrophin synthesis and release in neurons. Depolarization produced by the release of glutamate (Glu) or acetylcholine (Ach) increases the production of NGF and BDNF mRNAs. Conversely, NGF and BDNF mRNA levels decrease from neural-specific nerve ending-target neuron interactions. Synaptic vesicles in presynaptic terminals contain NGF mRNA and release NGF in response to neurotransmitter (GABA) release. BDNF mRNA is increased by NGF, resulting in increased BDNF synthesis and release. NGF may also induce Tat mRNA, which enhances BDNF production. The release of NGF and protein BDNF in neuronal axons via both a constitutive and a regulated pathway.
Exercise and trophic factor production in the adult brain

CNTF and cyclic AMP

- CNTFRα
- gp 130
- LIFRβ
- Mitogen activated protein kinase (MAPK)
- Phosphotidylinositol-3 kinase (PI-3K)

Procedures - method of surgery

1.5 mm

Fluorogold

Procedures - method of surgery

Injection site

Optic nerve

Peripheral nerve graft

The proportion of surviving retinal ganglion cells that regrew an axon into a peripheral nerve graft


Other Growth Factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>Representative members</th>
<th>Original biologic activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIF</td>
<td>IL-6, LIF, OSM, TL</td>
<td>Bacterial endotoxin production</td>
</tr>
<tr>
<td>M-CSF</td>
<td>CSF-1, CSF-2, CSF-3</td>
<td>Macrophage colony-stimulating activity</td>
</tr>
<tr>
<td>CNTF</td>
<td>CNTF, LIFRα, LIFRβ, gp130, LIFRc</td>
<td>Neuronal survival and differentiation</td>
</tr>
<tr>
<td>BDNF</td>
<td>BDNF, NT-3, NT-4/5</td>
<td>Neurotrophic effects on neurons</td>
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<tr>
<td>NGF</td>
<td>NGF, NGFRα, NGFRβ</td>
<td>Neuronal survival and differentiation</td>
</tr>
<tr>
<td>GDNF</td>
<td>GDNF, RET</td>
<td>Neuroprotection and axon guidance</td>
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<tr>
<td>NT-3</td>
<td>NT-3, NT-4/5, NGF</td>
<td>Neurotrophic effects on neurons</td>
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<tr>
<td>NT-4/5</td>
<td>NT-4/5, NGF</td>
<td>Neurotrophic effects on neurons</td>
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<tr>
<td>FGF-2</td>
<td>FGF-2, FGF-1, FGF-4</td>
<td>Growth factor for endothelial cells</td>
</tr>
<tr>
<td>HGF</td>
<td>HGF, c-Met</td>
<td>Hepatocyte growth factor</td>
</tr>
<tr>
<td>VEGF</td>
<td>VEGF, flk-1, Tie-2</td>
<td>Vascular endothelial growth factor</td>
</tr>
</tbody>
</table>

Biological functions

- cAMP
- Protein kinase A (PKA)

Biological functions

- Mitogen activated protein kinase (MAPK)
- Phosphotidylinositol-3 kinase (PI-3K)