A. Trophic Factors

1. TROPHIC FACTORS AND CELL DEATH
   Experiment: Cell death in the NS-Muscle (Target) removal & grafting
   • Removing muscle/limb → less motor neurons form =

   • Grafting another muscle/limb → more motor neurons form =

   → The survival factor/signal is known as a ________________
   → Injection of trophic factors in place of missing muscle/limb attracted axons and
     allowed cells to survive.

   Effects of Trophic Factors
   • Survival of presynaptic neurons
     →

   • Axonal Pathfinding cue - help attract/guide axons until they reach the target
     →

2. NERVE GROWTH FACTOR (NGF)
   NGF is an example of a trophic factor that activates tyrosine signaling in the cell body. It
   gets picked up at the growth cone of axons and transported back to cell body via
   ___________________________. (Since it is a trophic factor, it is required for cell
   survival & acts as a guidance cue for axons as well)

   Experiment: NGF injection
   -Injection of NGF into brain → caused more axons to grow towards site of injection
   -Injection of α-NGF antibody (receptors cannot interact with NGF) → neurons do not
     extend axons where they normally would & eventually die
   -Neurons with cut axons would not be able to transport trophic factors back to the cell
     body and die → If injected NGF on top of the cell body, the cell could still survive
**Experiment: 3 Chamber Experiment**

- Neurons are placed in central chamber “A”
- With a thin layer of Vaseline underneath (axons are able to grow past it but it forms a seal against NGF)
- No NGF in any chamber → all neurons died

1.) Add NGF to all 3 chambers

2.) Add NGF to central chamber “A” only

3.) Add NGF to chambers “A” and “C”

4.) Add NGF to Chamber “C” only

**Conclusions:**

3. **NGF RECEPTORS**
   
   The NGF receptor is a composite of 2 types of receptors:
   - _______ = High affinity receptor
   - _______ = Low affinity receptor
   
   Need both to form active receptor

   - Other NGF-like trophic factors (BDNF, NT4/5, NT3) also activate other Trk receptors to contribute to cell survival
   - Trk Receptors are in the RTK family → RTK signaling → activate MAPK → change gene expression
   - RTK signaling phosphorylates MAPK or AKT → travel to nucleus → phosphorylate CREB → activate Bcl2 expression (decrease cell death)
<table>
<thead>
<tr>
<th>Trophic Factor</th>
<th>Activated Receptor</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGF</td>
<td>TrkA</td>
<td>Involved in Sympathetic ganglia (reaction to foot/tail pinch)</td>
</tr>
<tr>
<td>BDNF &amp; NT4/5</td>
<td>TrkB</td>
<td>Involved in motor neurons &amp; some sensory neurons (whisker pad sensation &amp; pain)</td>
</tr>
<tr>
<td>NT3</td>
<td>TrkC</td>
<td>Involved in motor neurons &amp; some sensory neurons (propioception)</td>
</tr>
</tbody>
</table>

4. RTK SPECIFICITY

The Big Question: How is RTK signaling made selective? (Why can activation of the same Ras/MAPK pathway have different effects on different cells?)

1.) Different developmental history of cells lead to different responses
   Ex.

2.) Timing & kinetics (Duration/strength of signaling)
   Ex.

**Experiment: Chimeric receptors** (joining different domains of the NGF and EGF receptors)
- Extracellular (outside) domain determines the specificity for the trophic factor
- Intracellular (inside) domain determines the kinetics of signaling

  - EGF (extracellular domain)/NGF (intracellular domain)

  - NGF (extracellular domain)/EGF (intracellular domain)