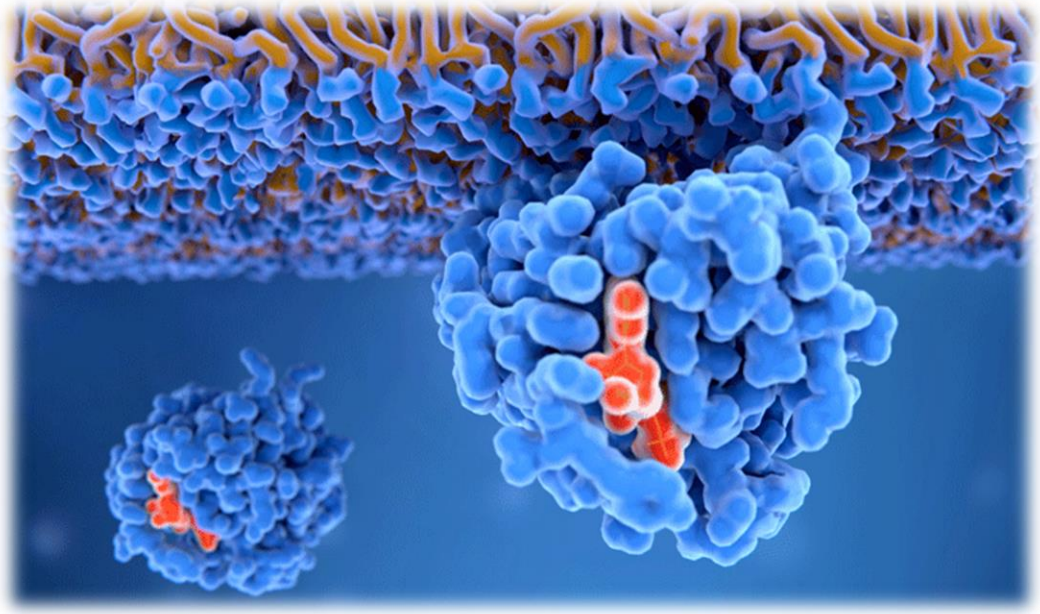

RECEPTORS AND SIGNAL TRANSDUCTION

Cell Biology

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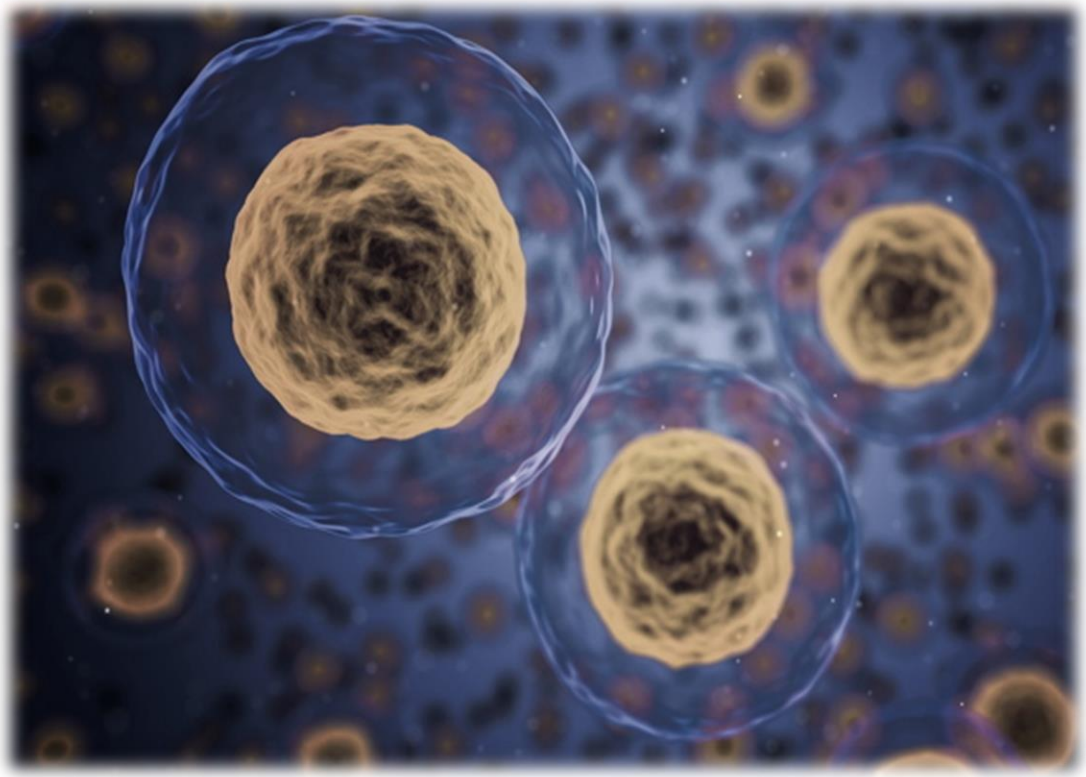
- ✓ Cell-to-cell communication
- ✓ Signal transmission systems
- ✓ All cells can take information and process it



Different Types of Cellular Communication

1) Direct cellular communication with cell-cell contact (Juxtacrine)
   - Cellular connections
   - Cell-to-cell recognition
   - Nanotubes
2) Indirect cellular communication that does not require Cell-Cell contact
   - Chemical signals
     - Autocrine
     - Paracrine
     - Neurotransmitters (Synaptic transmission)
     - Hormones (Endocrine)

Direct cellular communication (Juxtacrine)
that requires physical cell-cell contact

Gap junctions

- ✓ Enable the passage of small molecules (<1.2-2 nm) and ions by providing a connection between the cytoplasm of two cells.
- ✓ Building blocks of macromolecules, cAMP, Ca2 + etc.
- ✓ Provides metabolic and electrical coupling.
- ✓ Allow a large number of cells to function as a single functional unit.

  Ex: Heart muscle, smooth muscle

Cell-to-Cell Recognition

- The cell membrane contains surface carbohydrate molecules (glycolipids, glycoproteins) that generate signals for other cells.
- Recognition of self and non-self cells in the immune system
- Regulation of cellular migration with Ephrin proteins and receptors during embryonic development

Tunnel Formation via Nanotubes

- ✓Filamentous membrane extensions
- ✓Ions, organelles
- ✓Embryonic development, maintenance of homeostasis, spread of infectious agents, drug resistance, etc.

Indirect Cellular Communication
that DOES NOT require physical cell-cell contact

Communication with Chemical Signals

- ✓ Chemical signals are secreted from one cell and target another cell.

- ✓ It often requires **ligand-receptor interaction**.

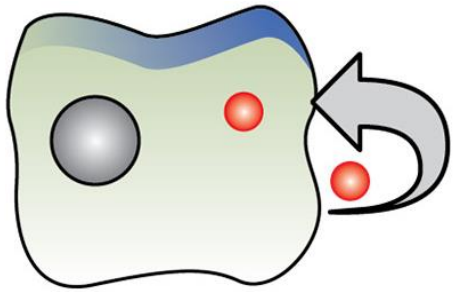
- **Ligands:** Extracellular chemicals that act as signal transduction molecules.
- **Receptors:** Proteins found in the target cell membrane/cytoplasm/nucleus that specifically bind the ligand.

Chemical Communication

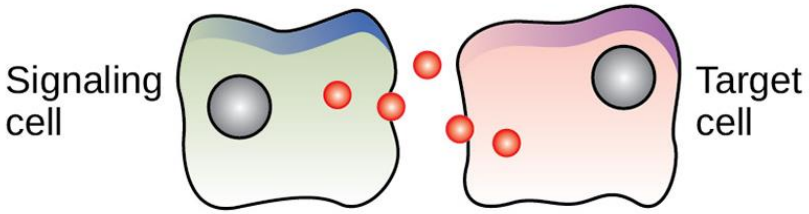
- Local Signaling
  - Autocrine
  - Paracrine
    - Neurotransmitters (Synaptic transmission)
- Long-Distance (Endocrine) Signaling
  - Hormones
  - Neurohormones

Local Signaling

- **Autocrine:** The ligand affects the cell that secretes it.

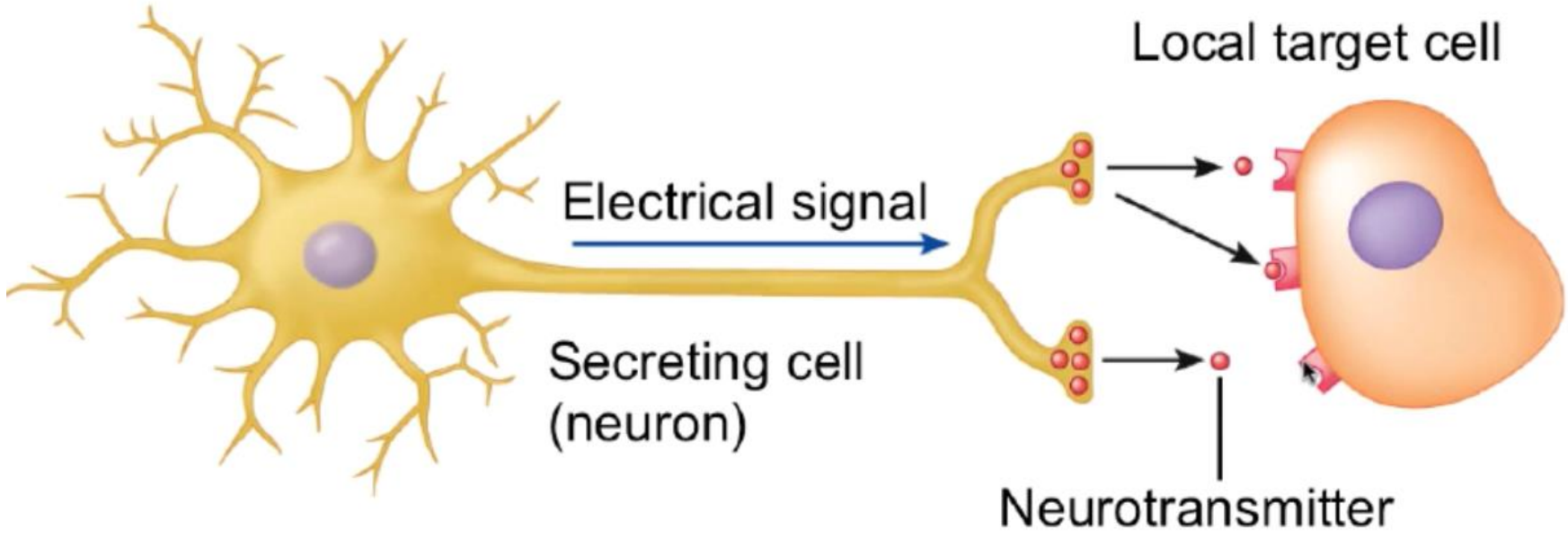


- **Paracrine:** After being secreted, the ligand diffuses and acts on nearby cells.



Neurotransmitters (Synaptic Transmission)

- A special type of paracrine signaling.
- NTs are secreted by neuronal cells and by diffusion they affect nearby the neuron / gland / muscle cell.



Long-Distance (Endocrine) Signaling

Hormones

- Chemical messengers secreted by the **endocrine glands**.
- Act on target cells over long distances through the bloodstream.

Neurohormones:

- Chemicals secreted from **neuronal cells.**
- Act on target cells at long distances through the bloodstream.

Chemical Messengers (Signaling molecules/Ligands)

Amines: Ex. Epinephrine

Peptides and Proteins: Ex. Angiotensin II, Insulin

Steroids: Ex. Aldosterone, Estrogen

Other small molecules: Ex. Amino acids, Nucleotides, Ions, and Gases

RECEPTORS

- Plasma membrane receptors
- Intracellular Receptors / Nuclear Receptors:

Channel coupled receptors:

Ligand-gated ion channels (ionotropic receptors)

- The receptor and channel are the same protein.
- The effect is direct.
- Binding of the ligand causes the channel to open / close.
- The response is fast.
- AMPAR, NMDAR etc.

Enzyme coupled receptors:

Catalytic receptors

- Cytosolic domains have intrinsic enzymatic activity or are directly associated with an enzyme.
- Usually contain one transmembrane segment.
- Binding of the ligand causes conformational change in the receptor, inducing enzymatic activity.
- The effect is direct.
- Activated enzyme causes target response

Enzyme coupled receptors:
Catalytic receptors

5 main types of catalytic receptors in mammalian cells.

- **Receptor tyrosine kinases**
- Tyrosine-kinase-associated receptors (Non-receptor tyrosine kinases)
- Receptor serine / threonine kinases
- Receptor guanylate kinases
- Receptor tyrosine phosphatases

Many extracellular signal proteins (insulin, EGF, FGF, HGF, VEGF, IGF1, MCSF, NGF etc.) show their effects through RTKs.

G-protein Coupled Receptors

- Largest family of cell surface receptors.
- Activated by signals from the extracellular matrix and other cells (hormones, neurotransmitters and local mediators).
- Sight, smell, taste
- ~ 700 in man; only about smell in mouse ~ 1000
- Most of the known drugs act through GPCRs or signaling pathways activated by GPCRs.

Transduction

- Cascades of molecular interactions relay signals from receptors to target molecules in the cell
- A multistep pathway involving many molecules
- Activation of proteins by addition or removal of phosphate groups or release of other small molecules or ions that act as messengers
- Multistep amplifies the signal

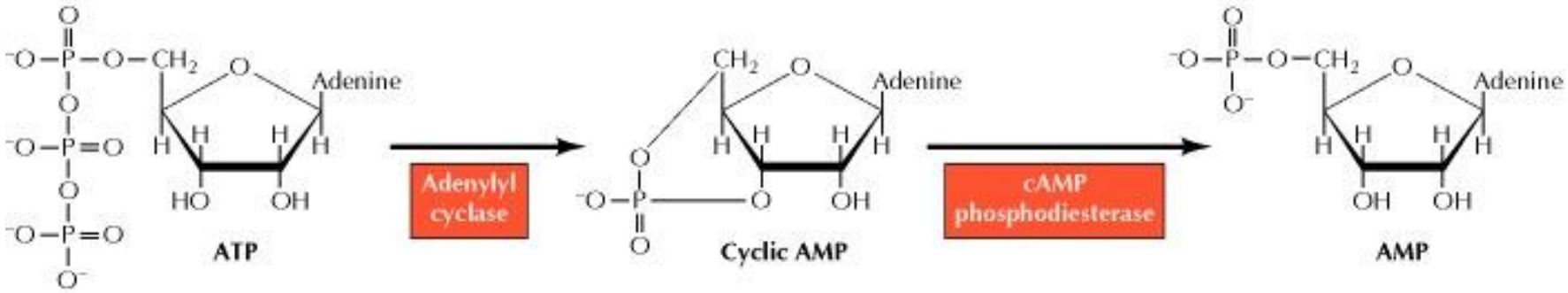
Second messengers

- Signaling molecules with short half-lives.
- Small, non-protein, water-soluble molecules or ions
- Their increased concentration causes rapid changes in the activity of one or more cellular enzymes.
- Participate in G-protein coupled receptor and receptor tyrosine kinase pathways
- Removal or disruption of the second messengers terminates the cellular response.

Important second messengers in the cell

- Cyclic nucleotides
  - **cAMP**
  - cGMP
- Membrane lipid derivatives
  - DAG
  - Phosphatidylinositols: **IP_3** ve PIP_3
  - AA
- **Ca^{2+}**
- NO/CO

cAMP


Adenine
ATP
Adenylyl cyclase
Cyclic AMP
cAMP phosphodiesterase
AMP

Target enzymes of cAMP

cAMP dependent protein kinase: Protein kinase A

- Tetramer: **Inactive**
- Regulatory (2x) and Catalytic (2x) subunits
- cAMP binds to regultory subunits
- Free catalytic subunits: **Active**
- Phosphorylates target proteins at serine amino acids

Ca^{2+}

- Calcium is even more widely used than cAMP as a second messenger
- Increase in the cytosolic concentration of Ca^{2+}
- Most of its effects occur through the Ca^{2+} binding protein «calmodulin».
- Second messenger in both GPCRs and RTKs

✓Protein kinases: **Ca^{2+}/calmodulin-dependent kinases**

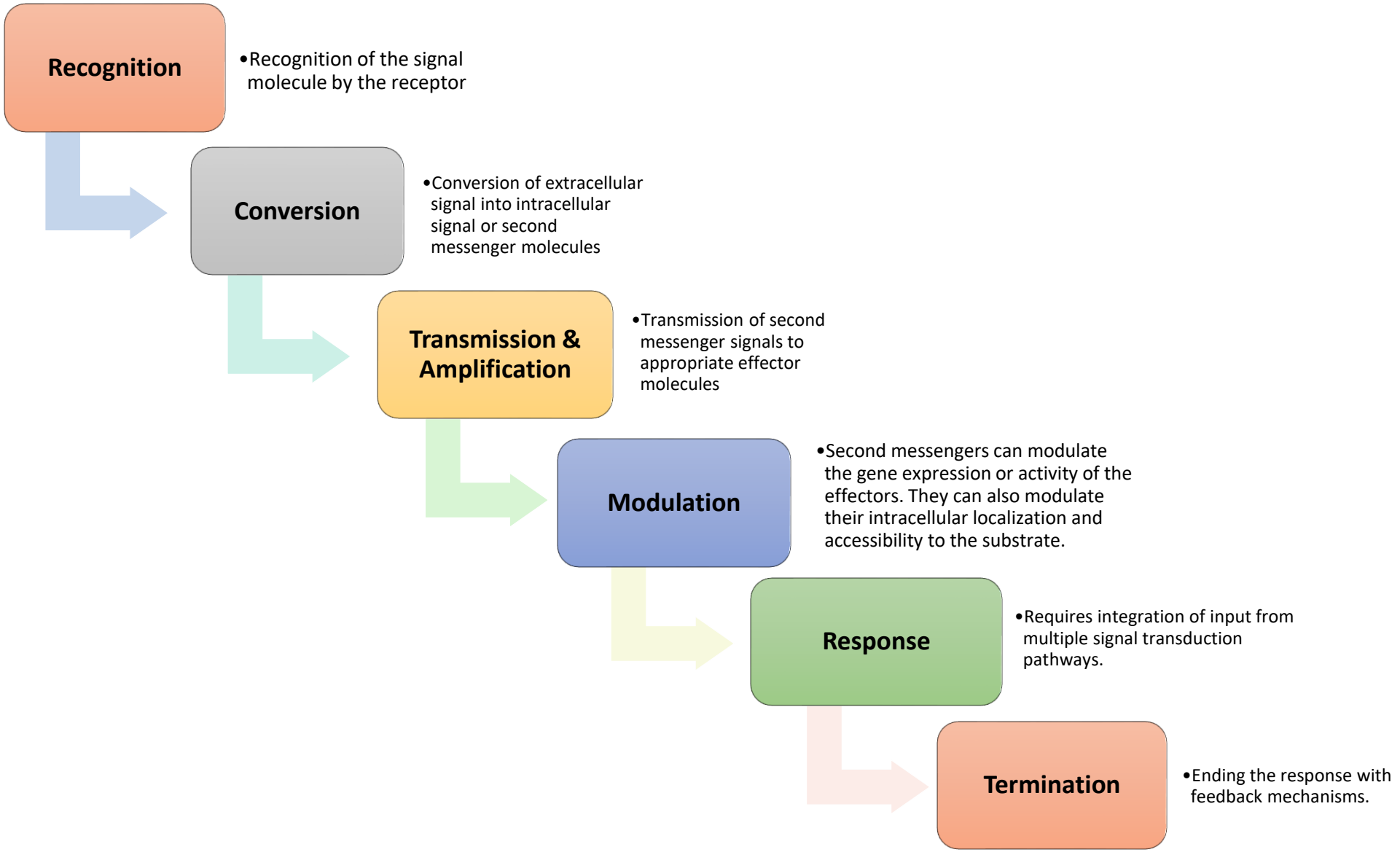
  ✓Ex. Myosisn light-chain kinase

✓Muscle cell contraction, secretion of certain substances, cell division…

The sensitivity of cells to a specific signal can change overtime.

- ✓Adaptation/ Desensitization: Decreased response of the cell to the stimulus because of prolonged exposure

- ✓Allows the cell to respond to changes in concentration of the signaling molecule


Recognition
•Recognition of the signal molecule by the receptor
Conversion
•Conversion of extracellular signal into intracellular signal or second messenger molecules
Transmission & Amplification
•Transmission of second messenger signals to appropriate effector molecules
Modulation
•Second messengers can modulate the gene expression or activity of the effectors. They can also modulate their intracellular localization and accessibility to the substrate.
Response
•Requires integration of input from multiple signal transduction pathways.
Termination
•Ending the response with feedback mechanisms.

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