Signal Transduction

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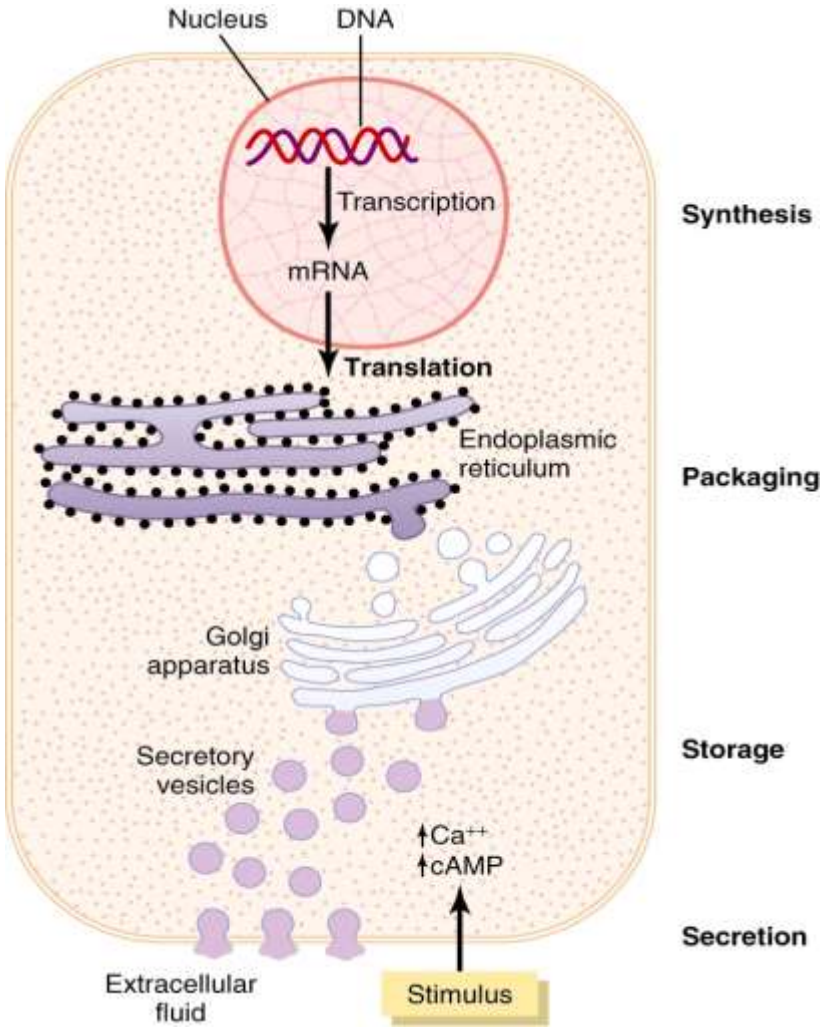
Prohormones and Prehormones

- Prohormone:
  - Precursor is a longer chained polypeptide that is cut and spliced together to make the hormone.
    - Proinsulin – gives insulin
- Preprohormone:
  - Prohormone derived from larger precursor molecule.
    - Preproinsulin.
- Prehormone:
  - Molecules secreted by endocrine glands that are inactive until changed into hormones by target cells.
    - T_4 converted to T_3 (tri-iodothyronin).

Synthesis and secretion of peptide hormones



Chemical classification of hormones

Table 10-4 Chemical Classification and Function of Hormones

Chemical Classification	Examples	Regulated Function
Endocrine Hormones		
Amino acid derivatives	Epinephrine (adrenaline) and norepinephrine (both derived from tyrosine)	Stress responses: regulation of heart rate and blood pressure; release of glucose and fatty acids from storage sites
	Thyroxine (derived from tyrosine)	Regulation of metabolic rate
Peptides	Antidiuretic hormone (vasopressin)	Regulation of body water and blood pressure
	Hypothalamic hormones (releasing factors)	Regulation of tropic hormone release from pituitary gland
Proteins	Anterior pituitary hormones	Regulation of other endocrine systems
Steroids	Sex hormones (androgens and estrogens)	Development and control of reproductive capacity
	Corticosteroids	Stress responses; control of blood electrolytes
Paracrine Hormones		
Amino acid derivative	Histamine	Local responses to stress and injury
Arachidonic acid derivatives	Prostaglandins	Local responses to stress and injury

Peptide & Protein Hormones

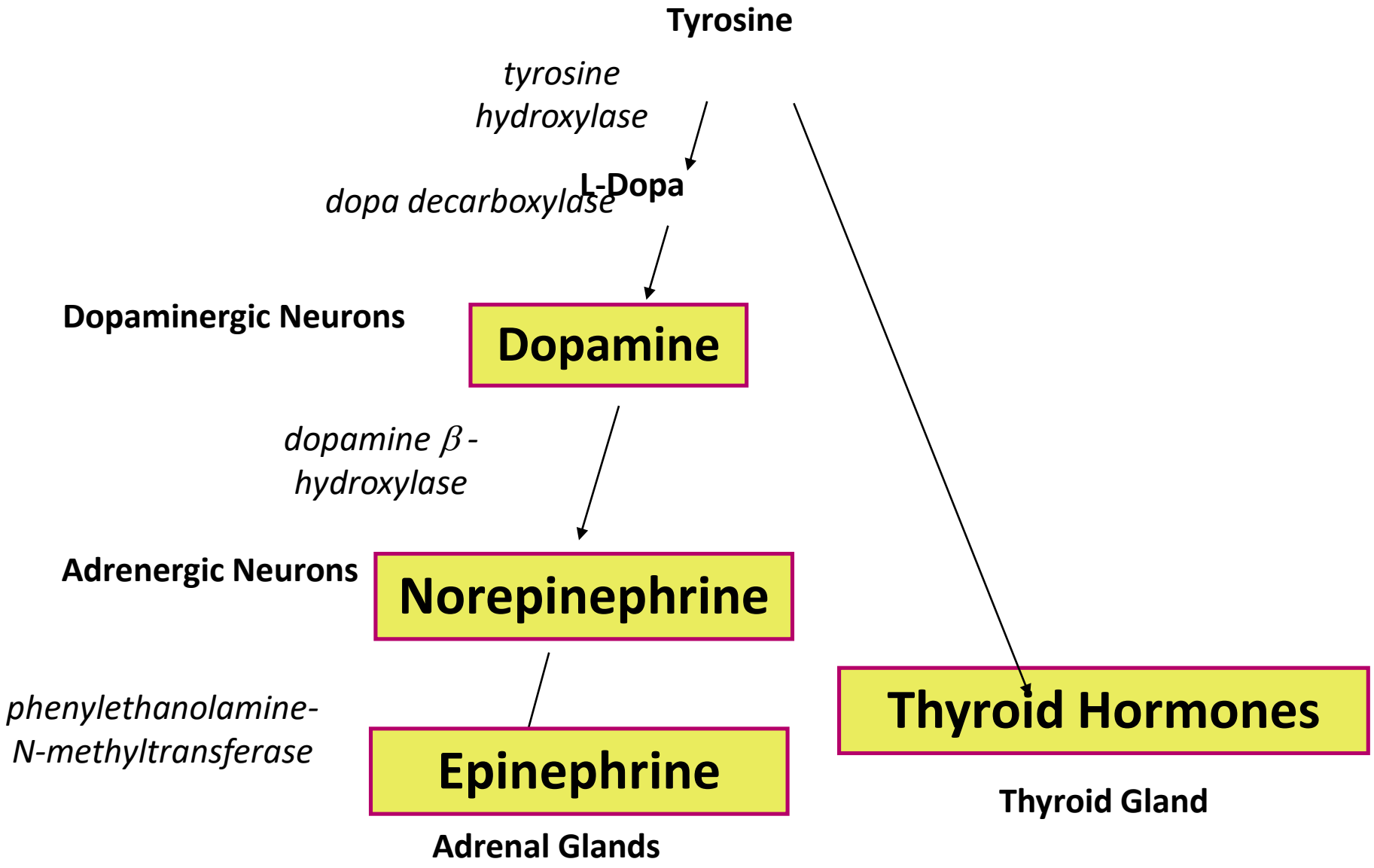
Gland/Tissue	Hormones
Hypothalamus	■ TRH, GnRH, CRH GHRH, Somatostatin,
Anterior pituitary	■ ACTH, TSH, FSH, LH, PRL, GH
Posterior pituitary	■ Oxytocin, ADH
Thyroid	■ Calcitonin
Pancreas	■ Insulin,Glucagon, Somatostatin
Liver	■ Somatomedin C (IGF-1)
Parathyroid	■ PTH

Gland/Tissue	Hormones
Placenta	■ HCG, HCS or HPL
Kidney	■ Renin
Heart	■ ANP
G.I. tract	■ Gastrin, CCK, Secretin, GIP, Somatostatin
Adipocyte	■ Leptin
Adrenal medulla	■ Norepinephrine, epinephrine

Amine Hormones

Gland/Tissue	Hormones
Hypothalamus	■ Dopamine
Thyroid	■ T_3, T_4
Adrenal medulla	■ Epinephrine and Norepinephrine (NE, EPI)

Synthesis of Amine Hormones



Steroid Hormones

Gland/Tissue	Hormones
Adrenal Cortex	■ Cortisol, Aldosterone, Androgens
Testes	■ Testosterone
Ovaries	■ Estrogens, Progesterone
Corpus Luteum	■ Estrogens, Progesterone
Placenta	■ Estrogens, Progesterone
Kidney	■ 1,25-Dihydroxycholecalciferol (calcitriol)

Hormone Activity

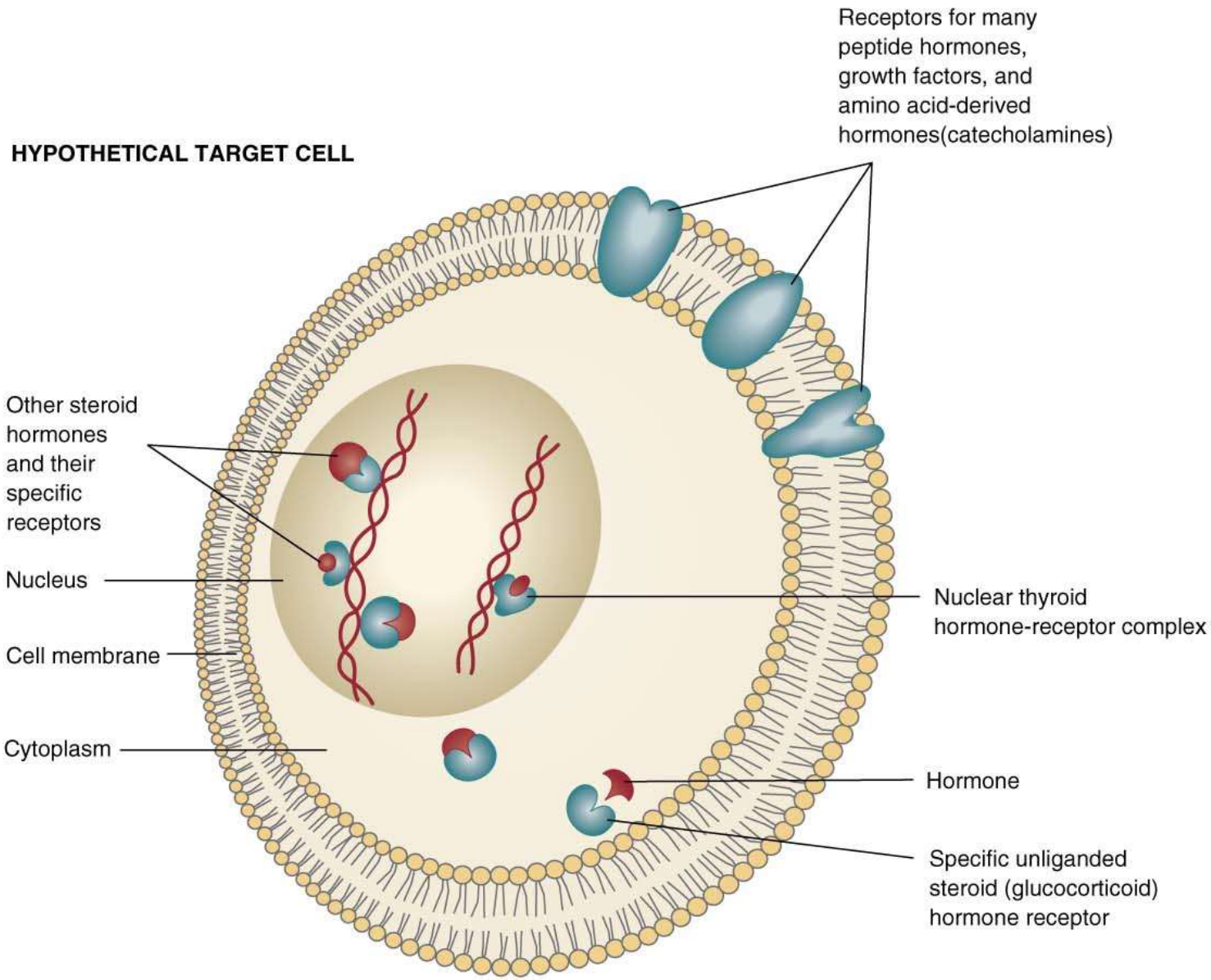
- Hormones affect only specific target tissues with specific receptors
- Receptors are dynamic and constantly synthesized and broken down
  - Down-regulation- decrease in receptor number or esponse
  - Up-regulation- increase in receptor number or activity

Effects of [Hormone] on Tissue Response

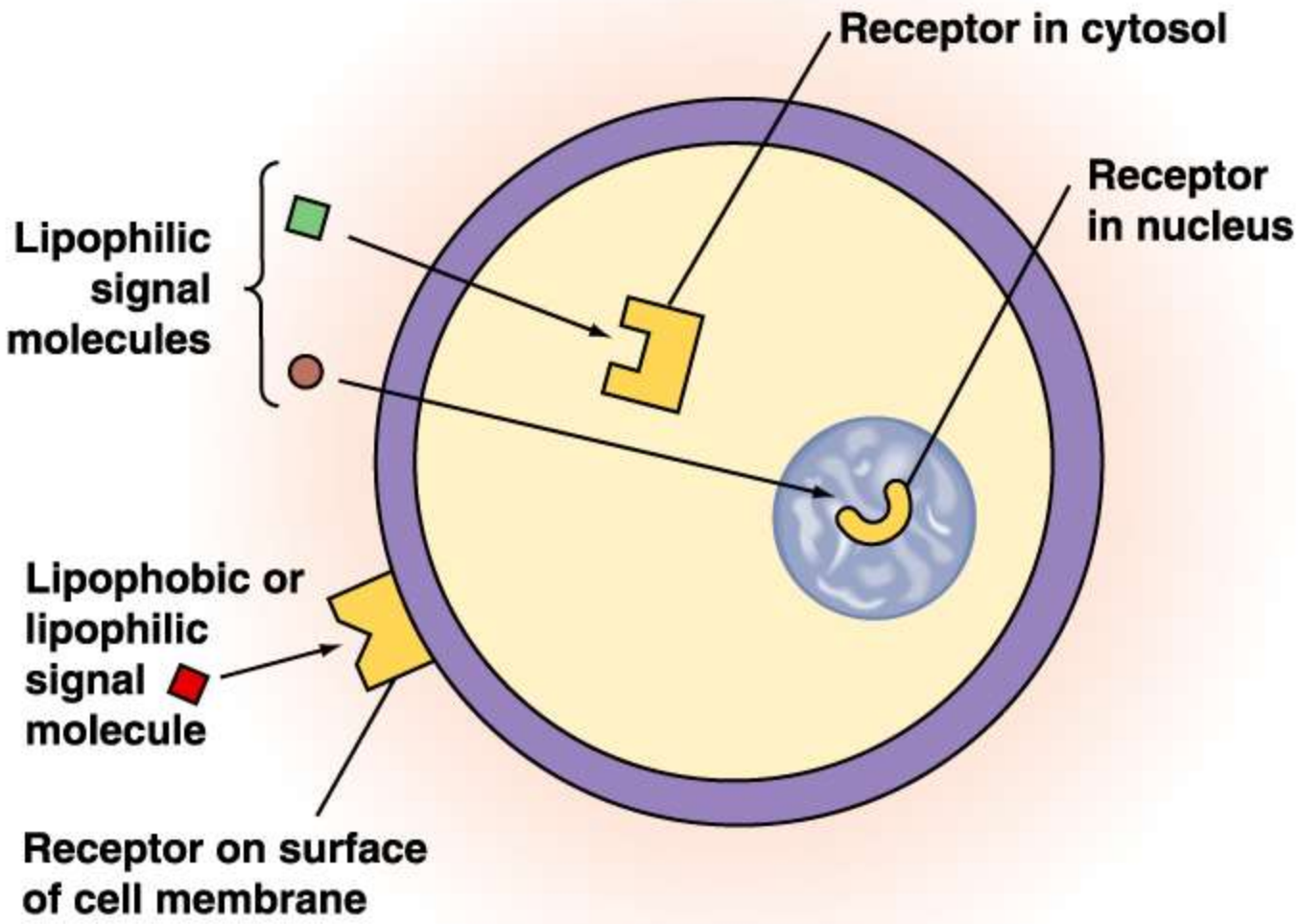
- Priming effect (upregulation):
  - Increase number of receptors formed on target cells in response to particular hormone.
  - Greater response by the target cell.
- Desensitization (downregulation):
  - Prolonged exposure to high [polypeptide hormone].
    - Subsequent exposure to the same [hormone] produces less response.
      - Decrease in number of receptors on target cells.
        - » Insulin in adipose cells.
  - Pulsatile secretion may prevent downregulation.

Effects of hormone concentration on Tissue Response

- [Hormone] in blood reflects the rate of secretion.
- Half-life:
  - Time required for the blood [hormone] to be reduced to ½ reference level.
    - Minutes to days.
- Affinity of receptors to ligands, Kd
- Normal tissue responses are produced only when [hormone] are present within physiological range.
- Varying [hormone] within normal, physiological range can affect the responsiveness of target cells.



. Diagram showing the different locations of classes of hormone receptors expressed by a target cell.



Mechanisms of Hormone Action

- Hormones of same chemical class have similar mechanisms of action.
  - Similarities include:
    - Location of cellular receptor proteins depends on the chemical nature of the hormone.
    - Events that occur in the target cells.
- To respond to a hormone:
  - Target cell must have specific receptors for that hormone (specificity).
    - Hormones exhibit:
      - Affinity (bind to receptors with high bond strength).
      - Saturation (low capacity of receptors).

Mechanisms of Hormone Action

- Response depends on both hormone and target cell
- Lipid-soluble hormones bind to receptors inside target cells
- Water-soluble hormones bind to receptors on the plasma membrane
  - Activates second messenger system
  - Amplification of original small signal
- Responsiveness of target cell depends on
  - Hormone's concentration
  - Abundance of target cell receptors

Receptor

Receptors are specific membrane proteins, which are able to recognize and bind to corresponding ligand molecules, become activated, and transduce signal to next signaling molecules.

Glycoprotein or Lipoprotein

Receptors

- Specificity: The "specificity" of a ligand for a receptor is a description of how favorable the binding of the ligand for the receptor is compared with its possible binding to other types of receptors that may also be present.

- Affinity: "Affinity" simply refers to how strong the binding is (as judged by K association or K dissociation and ΔGo). "High affinity" refers to very strong binding (large negative ΔGo and a

ligand

A small molecule that binds specifically to a larger one; for example, a hormone is the ligand for its specific protein receptor.

- **Membrane receptors**

  Membrane Glycoprotein

- **Intracellular receptors**

  Cytosol or nuclei

  DNA binding protein

- **Receptors superfamilies:**
- Ionotropic receptors (ligand-gated channels)
- Metabotropic receptors (G protein-coupled receptors)
- Tyrosine Kinase

Comparison of Ionotropic and Metabotropic Receptors

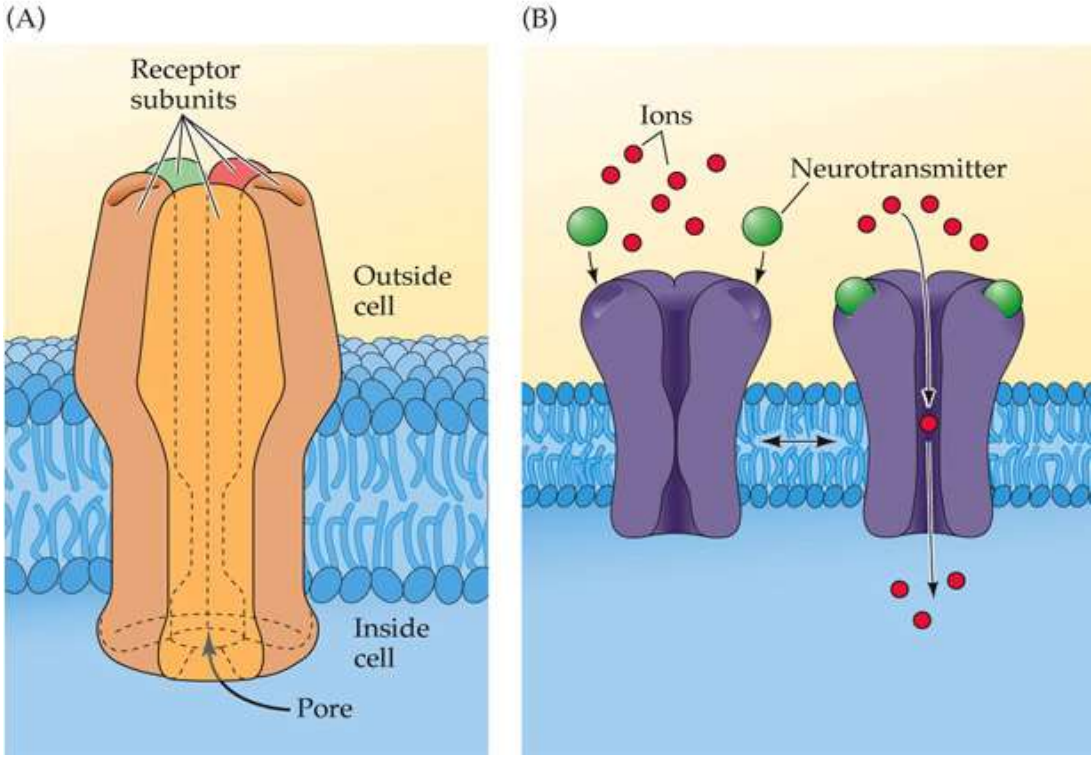
Characteristics	Ionotropic receptors	Metabotropic receptors
Structure	4 or 5 subunits that assemble in the cell membrane	1 subunit
Mechanism of action	Contain an intrinsic ion channel that opens in response to neuro-transmitter or drug binding	Activate G proteins in response to neurotrans-mitter or drug binding
Coupled to second messengers?	No	Yes
Speed of action	Fast	Slower

Almost all neurotransmitters discovered so far have more than one kind of receptor -- called **receptor subtypes.**

Ionotropic Receptors

Work very fast; important role in fast neurotransmission

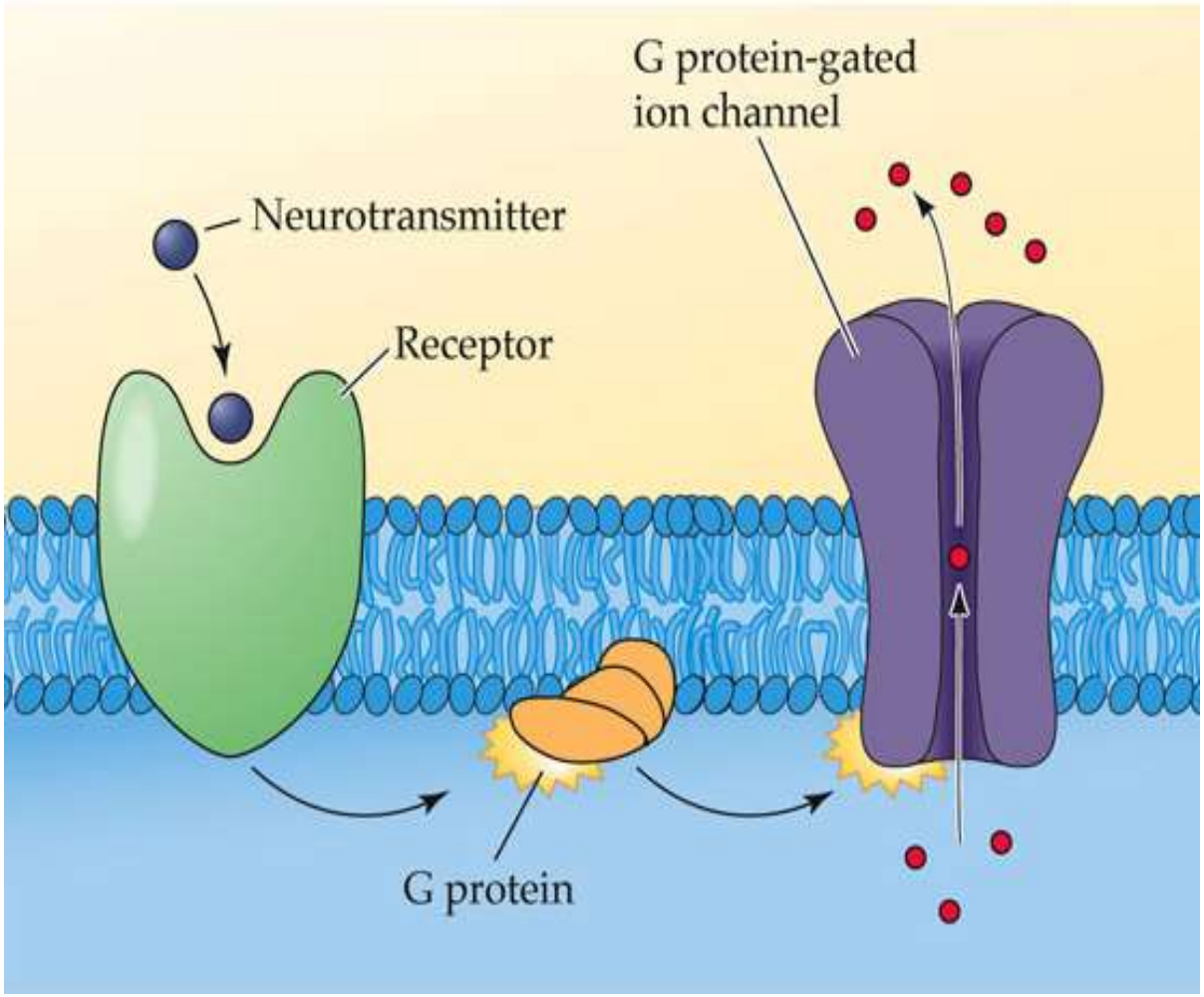
1. Each is made of several subunits (together form the complete receptor)
2. At center of receptors is channel or pore to allow flow of ions
3. At rest - receptor channels are closed
4. When neurotransmitter binds -- channel immediately opens
5. When ligand leaves binding site -- channel quickly closes



Metabotropic Receptors…

Work by activating other proteins called **G proteins**

1. Each is made of several transmembrane regions
2. Stimulate or inhibit the opening of ion channels in the cell membrane
3. Work more slowly than ionotrophic receptors but lasts longer

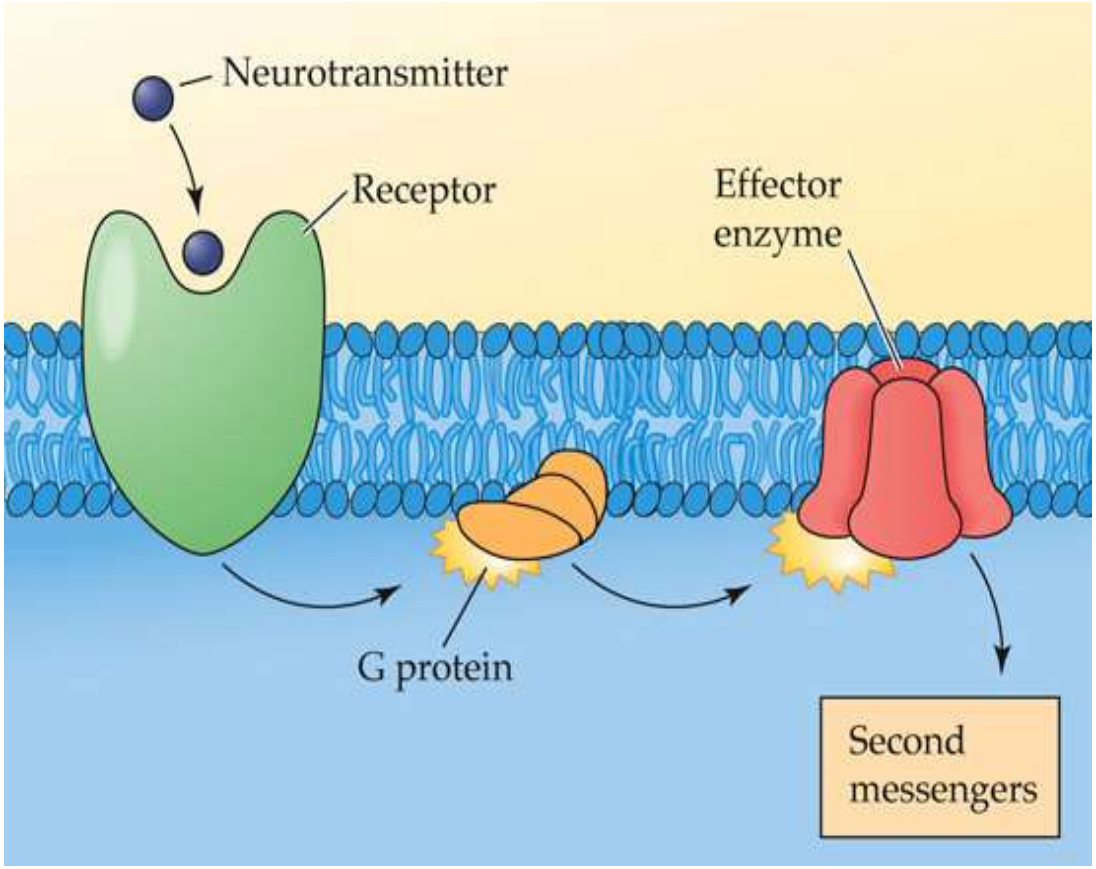


Metabotropic Receptors…

1. Stimulate or inhibit certain effector enzymes
2. Most effector enzymes controlled by G proteins are involved in synthesis of second messengers.

   *First messenger: ligand.

   *Second messenger: effector enzyme



Signaling Overview

3. Three major classes of surface receptors for signaling :

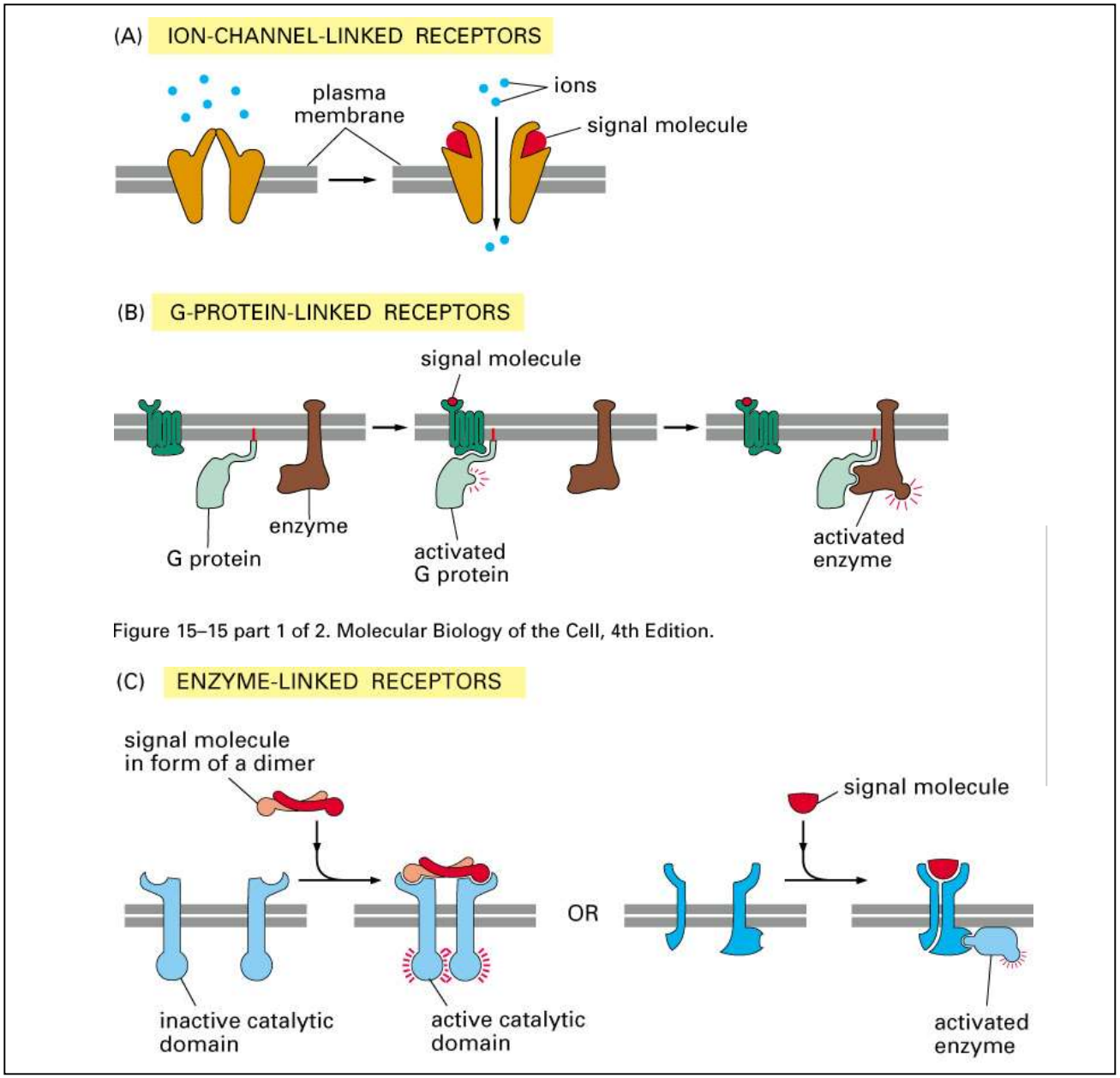
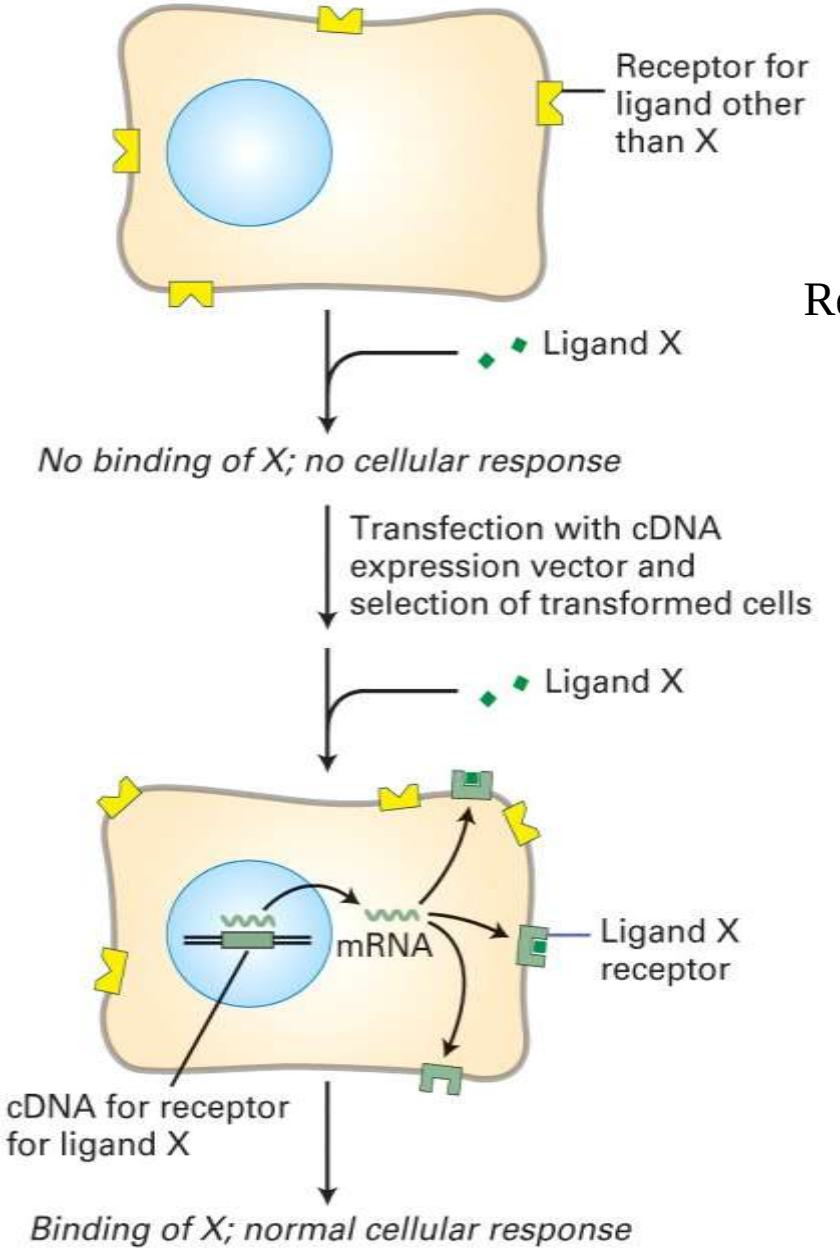


Figure 15–15 part 1 of 2. Molecular Biology of the Cell, 4th Edition.



Receptors determine response

No receptor - no response

3. Three major classes of surface receptors for signaling, cont.:

A. Ion Channels:

B. G protein-coupled receptors (GPRs): largest family of cell surface receptors; present in all eukaryotes; ex: adrenergic receptors, opioid receptors.

1. Overview:

a. 7 trans-membrane spanning domains

b. Act as receptors for many different ligands including NT, H

c. Large amount of receptor diversity, but common mechanism of action

d. Transmit signals to intracellular targets via G proteins

e. Targets are plasma membrane bound enzymes or ion channels

2. Mechanism of Activation of GPRs:

a. Binding of ligand to extracellular domain of GPRs induces conformational change that allows cytosolic domain of the receptor to bind to inactive G protein at inner face of PM.

b. This interaction activates the G protein, which dissociates from the receptor

c. Activated G protein α subunit can now bind GTP instead of GDP, causing dissociation into activated α vs. βγ subunits. Each of these can go on to activate target proteins.

C. Enzyme-linked receptors:

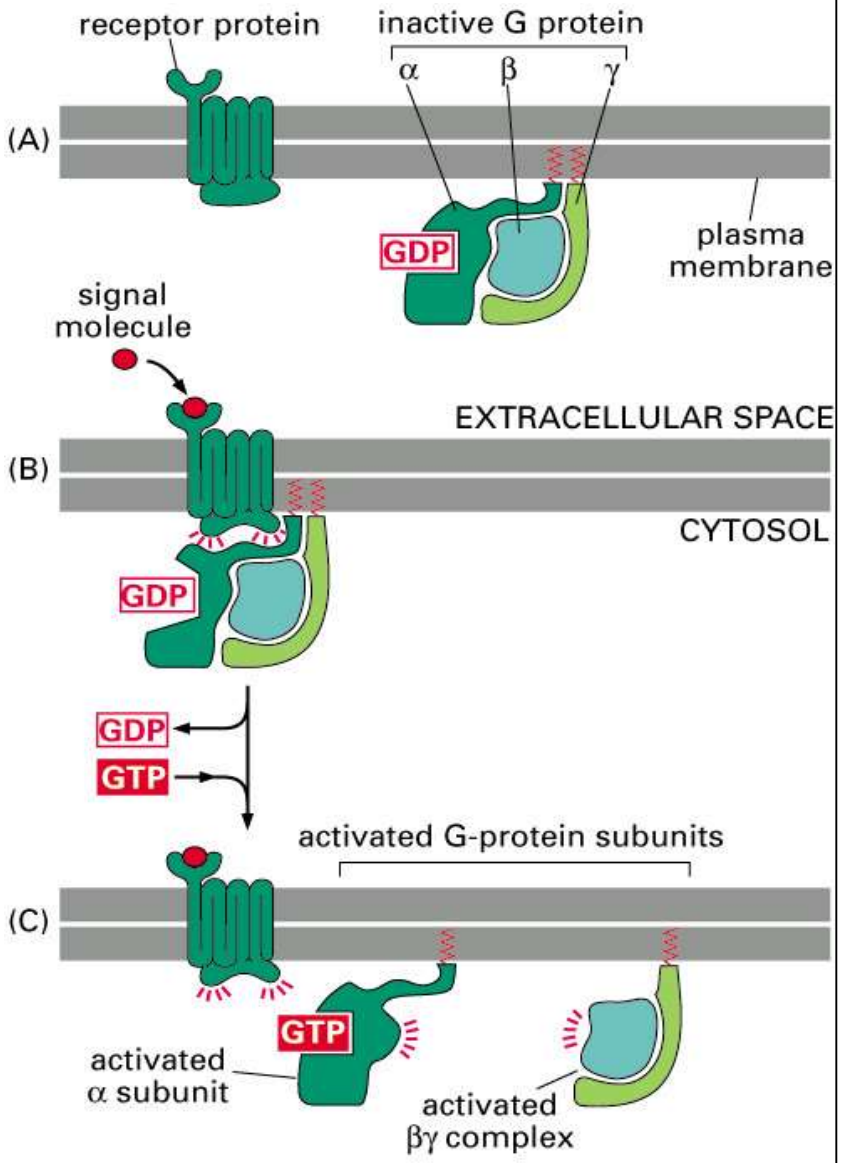


Figure 15–28. Molecular Biology of the Cell, 4th Edition.