Introduction to Endocrinology

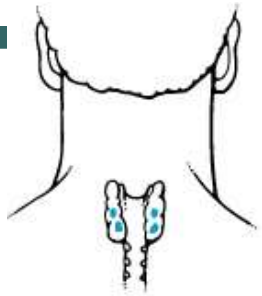
Objectives

- Differentiate endocrine system and nervous system
- Define hormone
- List the types of hormones
- Follow up the mechanism of action of hormones
- Explain hormone regulation mechanism

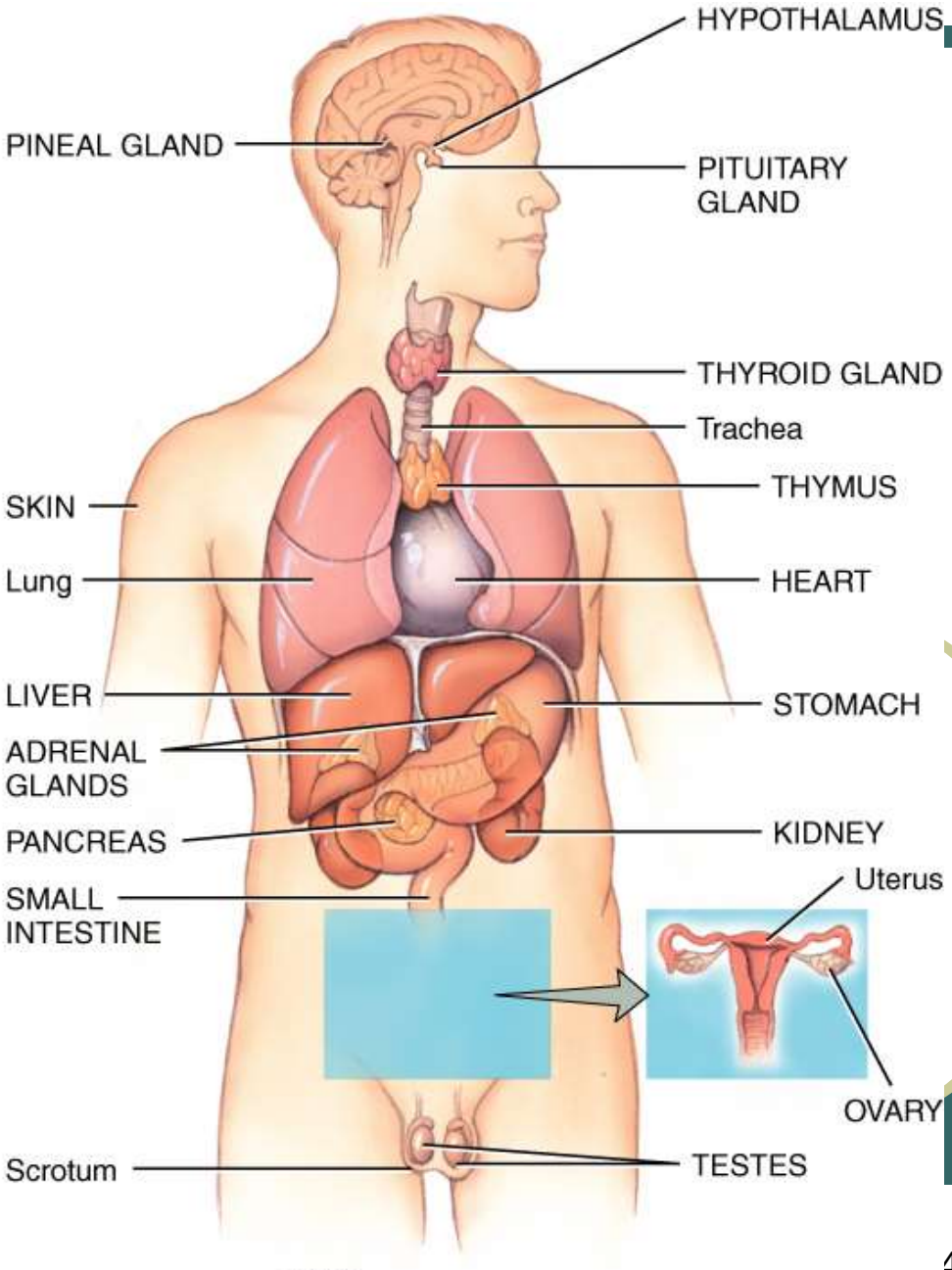
Comparison between Nervous and Endocrine Control System

- Nervous system is fast compared to endocrine
- Nervous system uses Action Potentials compared to chemicals (Hormones) the endocrine system uses
- Nervous system have low gain compared to very high gain for the Endocrine system
- Nervous system affects skeletal muscle and glands, but the endocrine affects growth, metabolism and reproduction

$$Gain = \frac{Correction}{Error}$$



PARATHYROID GLANDS (behind thyroid glands)



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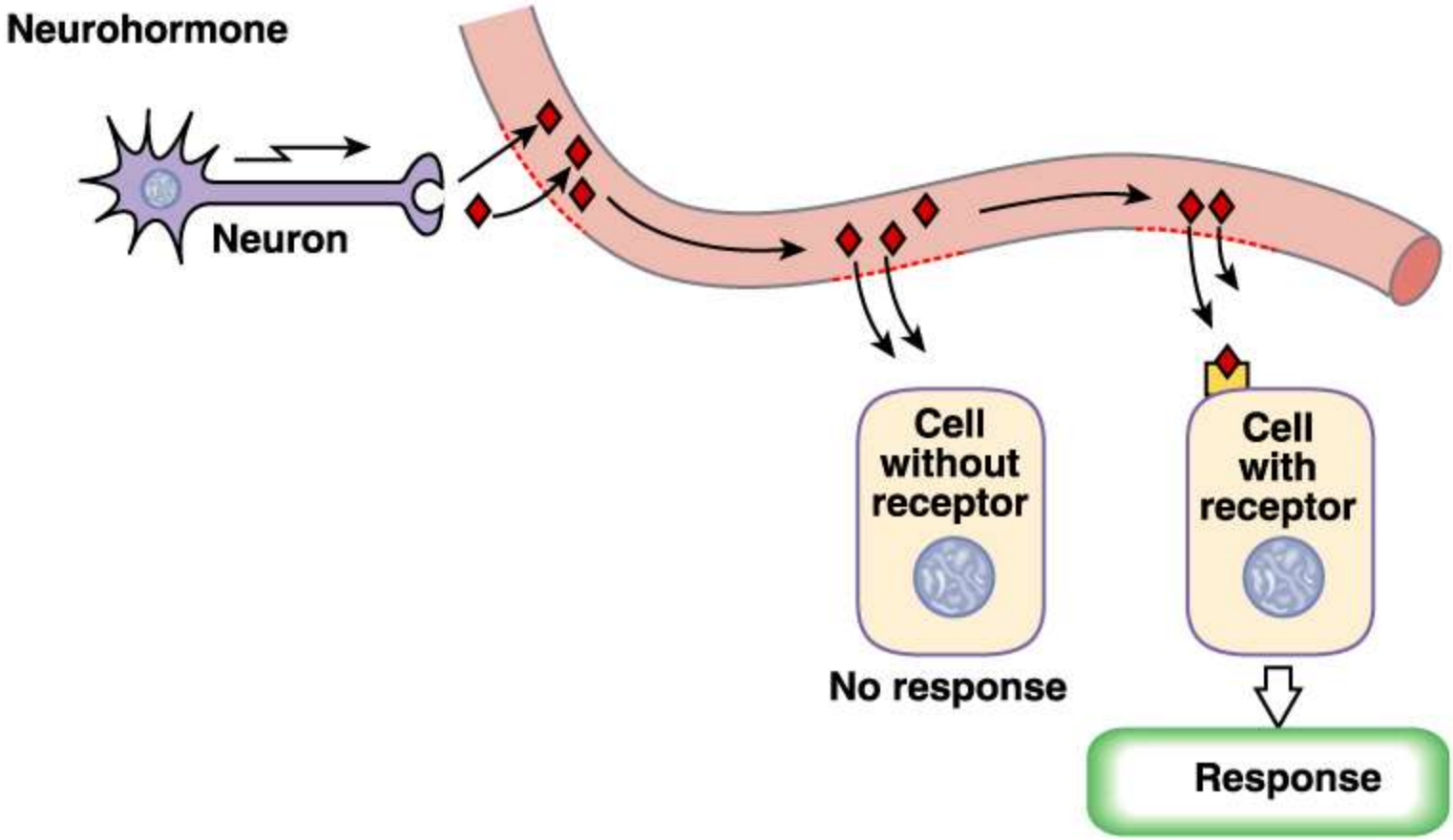
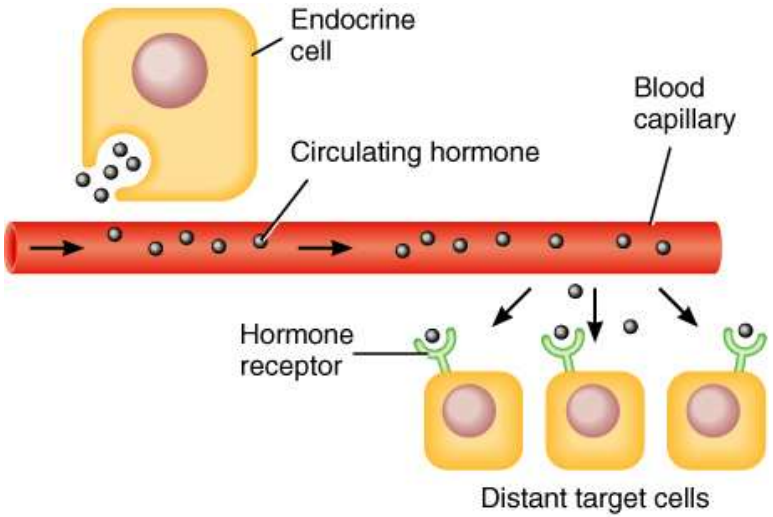
Endocrine Glands and Hormones

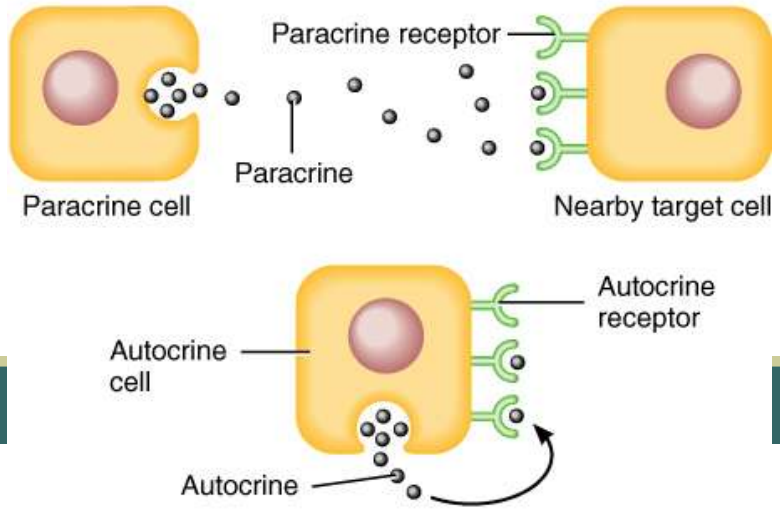
- Neurohormone:
  - Specialized neurons that secrete chemicals into the blood rather than synaptic cleft.
    - Chemical secreted is called neurohormone.
- Hormones:
  - Affect metabolism of target organs.
    - Help regulate total body metabolism, growth, and reproduction.


Neurohormone
Neuron
Cell without receptor
Cell with receptor
No response
Response

- Hormone types
  - Circulating – circulate in blood throughout body- Endocrine
  - Local hormones – act locally
    - Paracrine – act on neighboring cells
    - Autocrine – act on the same cell that secreted them



(a) Circulating hormones



(b) Local hormones (paracrines and autocrines)

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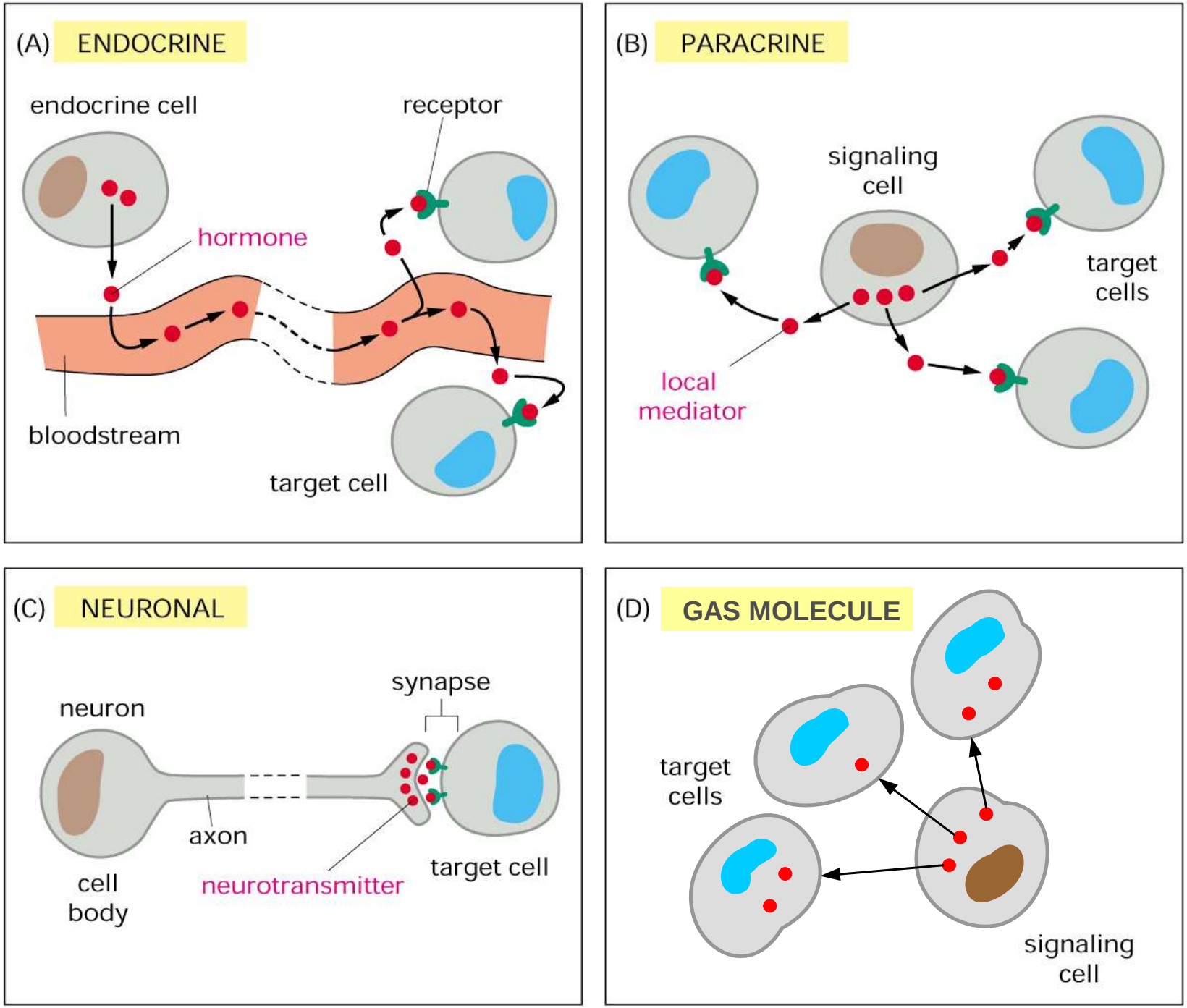
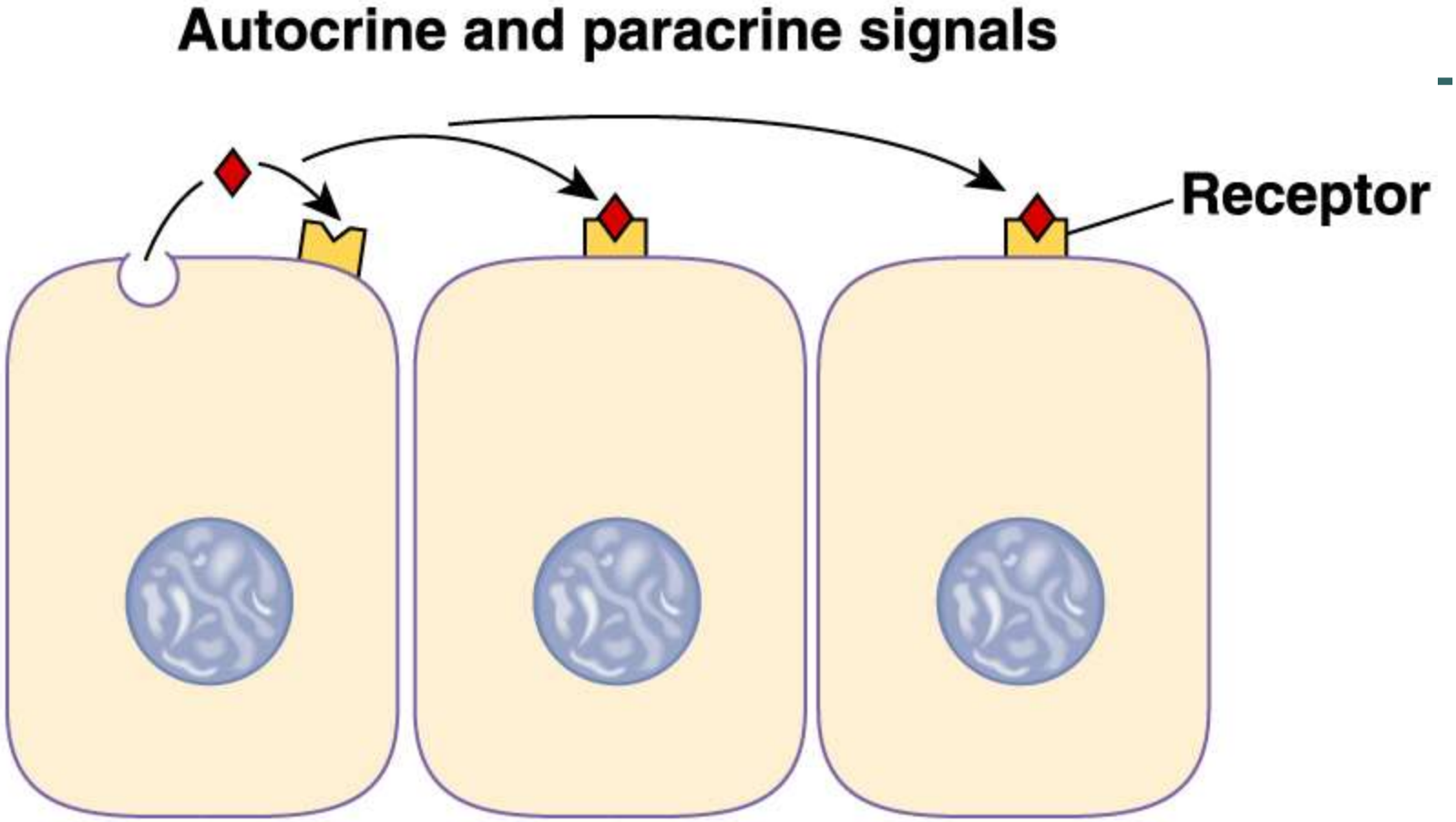
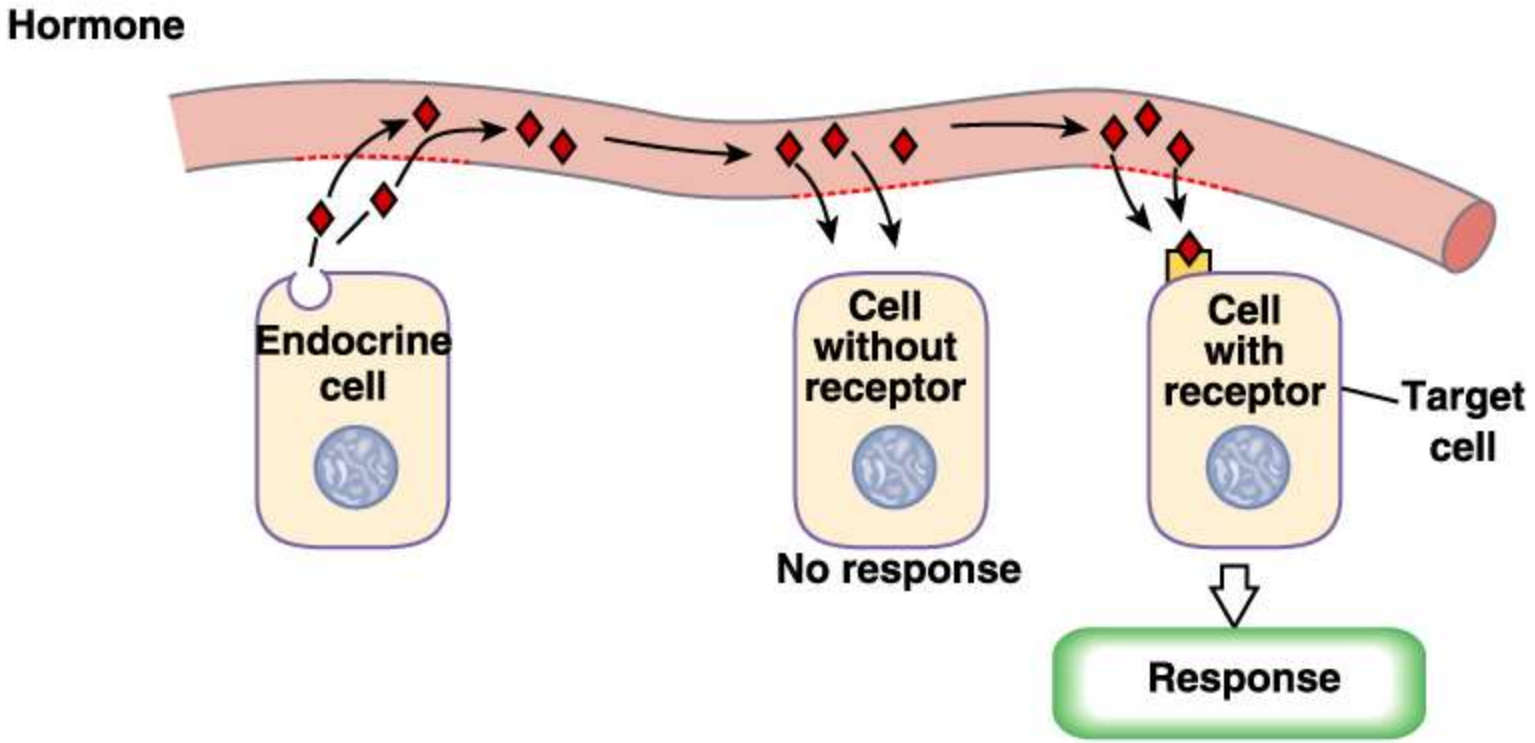

(A) ENDOCRINE
endocrine cell
receptor
hormone
bloodstream
target cell
(B) PARACRINE
signaling cell
target cells
local mediator
(C) NEURONAL
synapse
neuron
axon
cell body
neurotransmitter
target cell
(D) GAS MOLECULE
target cells
signaling cell


Autocrine and paracrine signals
Receptor


Hormone
Endocrine cell
Cell without receptor
No response
Cell with receptor
Target cell
Response

Chemical classes of hormones

- Lipid-soluble – use transport proteins
  - Steroid: Lipids derived from cholesterol.
    - Are lipophilic hormones.
      - Testosterone.
      - Estradiol.
      - Cortisol.
      - Progesterone.
  - Thyroid
  - Nitric oxide (NO)

Chemical classes of hormones…cont

- Water-soluble – circulate in "free" form
  - Amines:
    - Hormones derived from tyrosine and tryptophan.
    - NE, Epi, T_4 –tetraiodothyronine (lipid soluble)
  - Polypeptides and proteins:
    - Polypeptides:
      - Chains of < 100 amino acids in length.
        - ADH.
    - Protein hormones:
      - Polypeptide chains with > 100 amino acids.
      - Growth hormone.
  - Eicosanoid (prostaglandins)

Chemical Classification of Hormones …cont

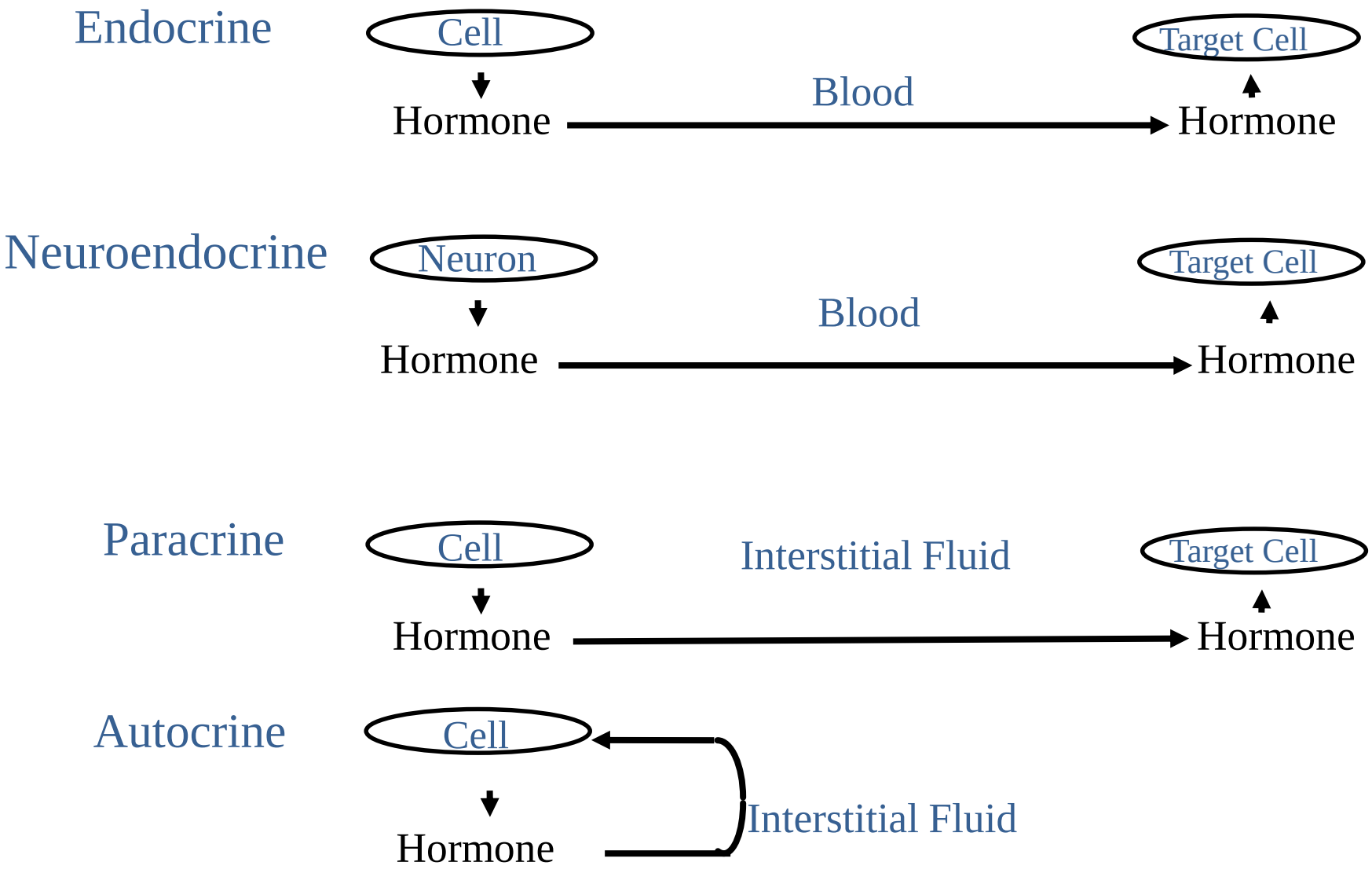
- Glycoproteins:
  - Long polypeptides (>100) bound to 1 or more carbohydrate (CHO) groups.
    - FSH and LH, TSH and hCG (human chorionic gonadotropin)

      They have α and β subunits (α is common and β is specific)
- Hormones can also be divided into:
  - Polar:
    - H_20 soluble.
  - Nonpolar (lipophilic):
    - H_20 insoluble.
      - Can gain entry into target cells.
      - Steroid hormones and T_4.

Prohormones and Prehormones

- Prohormone:
  - Precursor is a longer chained polypeptide that is cut and spliced together to make the hormone.
    - Proinsulin.
- 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.

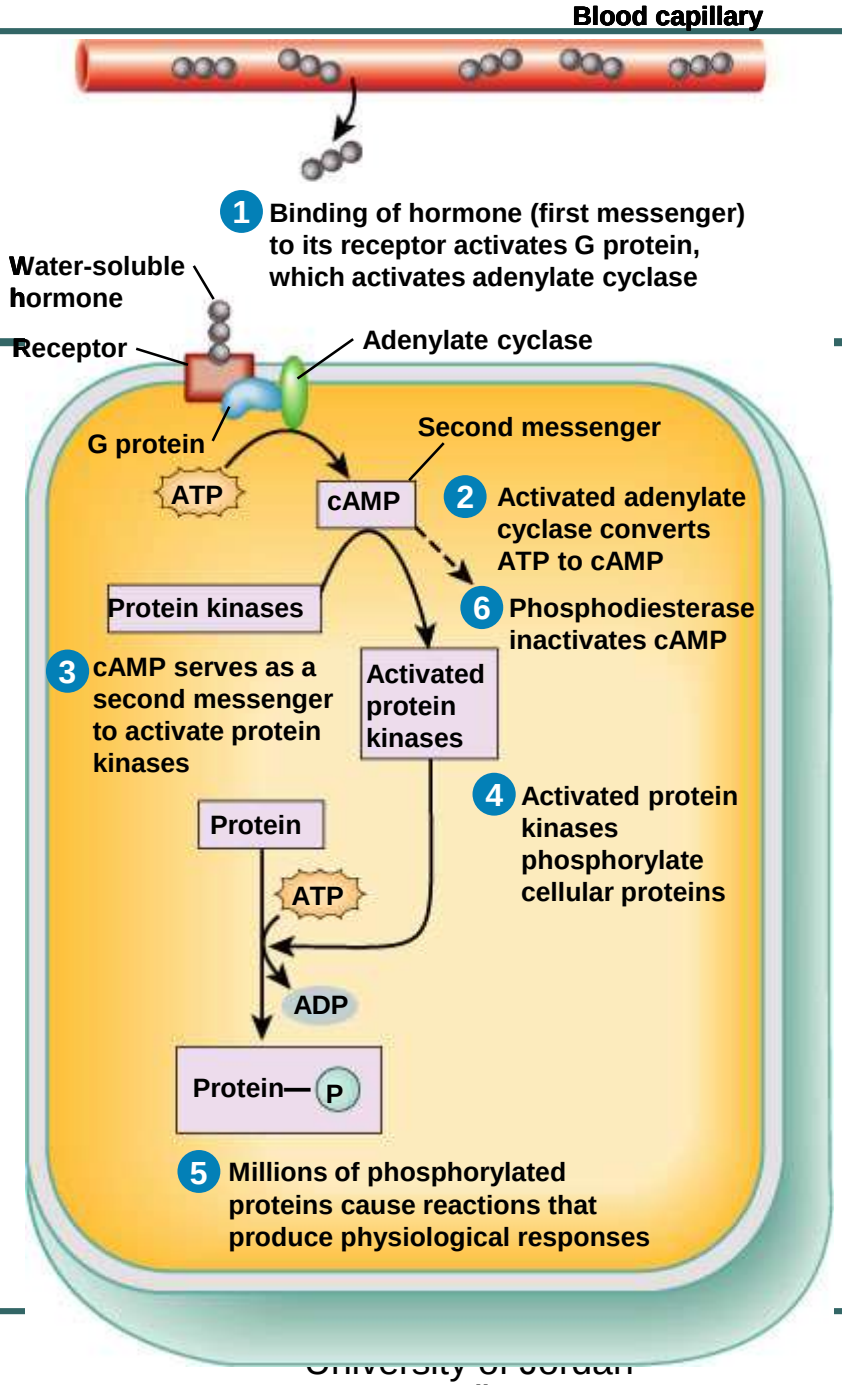
Intercellular Communication

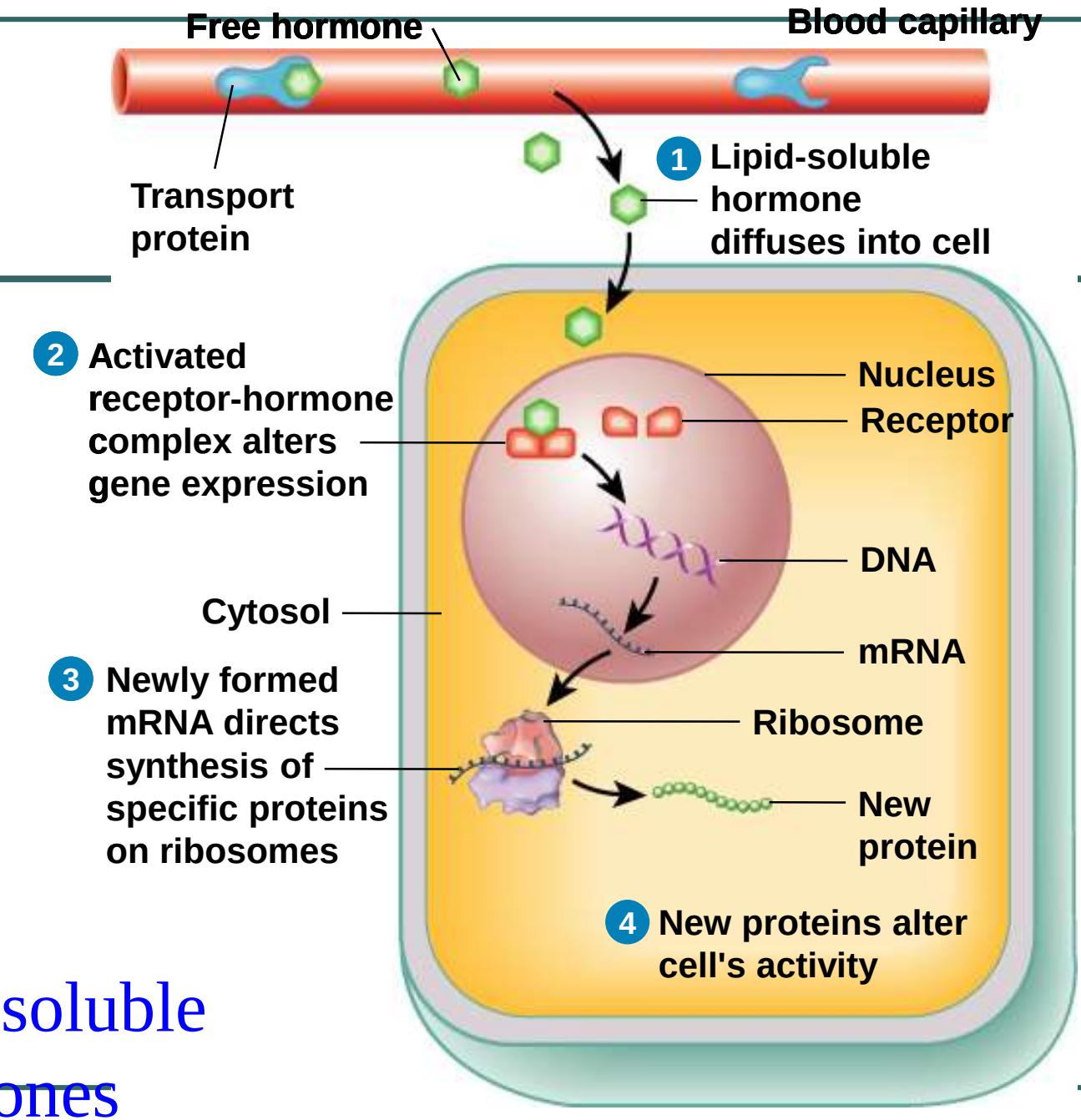


Classes of Hormones

- Peptide & Protein Hormones
- Steroid Hormones
- Amine Hormones
- Gas – Nitric Oxide (NO)

Water-soluble Hormones





Lipid-soluble Hormones

Peptide & Protein Hormones

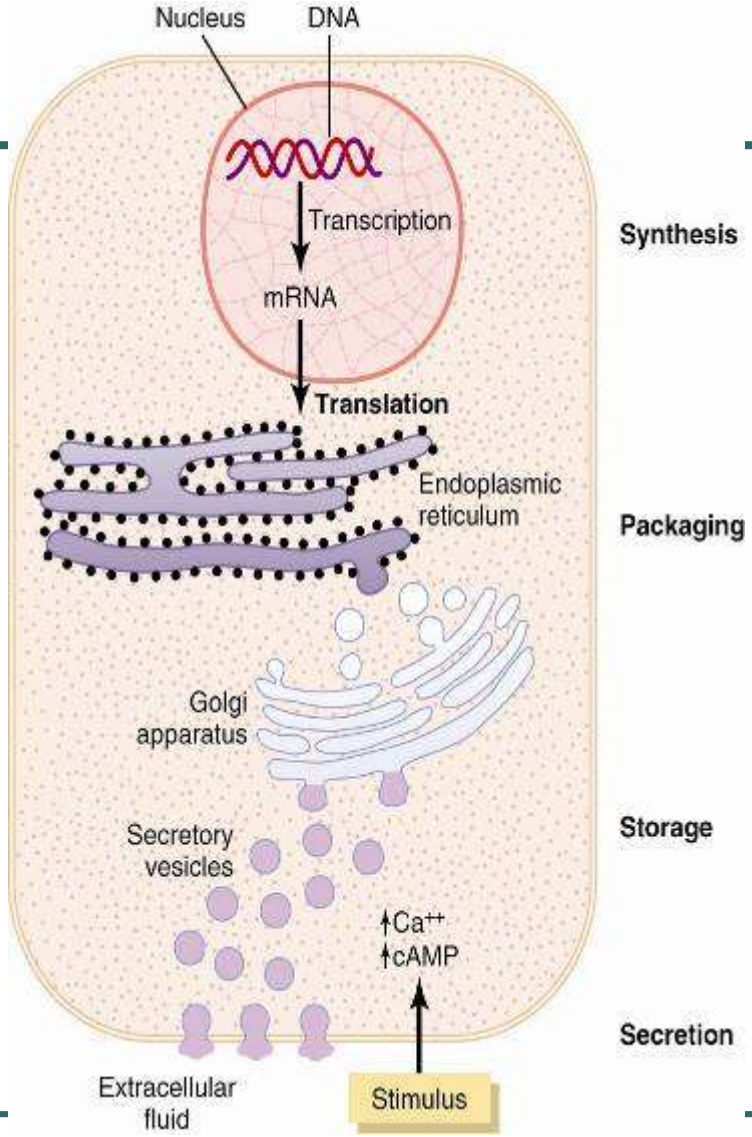
Gland/Tissue	Hormones	Gland/Tissue	Hormones
Hypothalamus	• TRH, GnRH, CRH GHRH, Somatostatin,	Placenta	• HCG, HCS or HPL
Anterior pituitary	• ACTH, TSH, FSH, LH, PRL, GH	Kidney	• Renin
Posterior pituitary	• Oxytocin, ADH	Heart	• ANP
Thyroid	• Calcitonin	G.I. tract	• Gastrin, CCK, Secretin, GIP, Somatostatin, GLP-1
Pancreas	• Insulin,Glucagon, Somatostatin		
Liver	• Somatomedin C (IGF-1)	Adipocyte	• Leptin
Parathyroid	• PTH		

Examples of Peptide Hormone Families

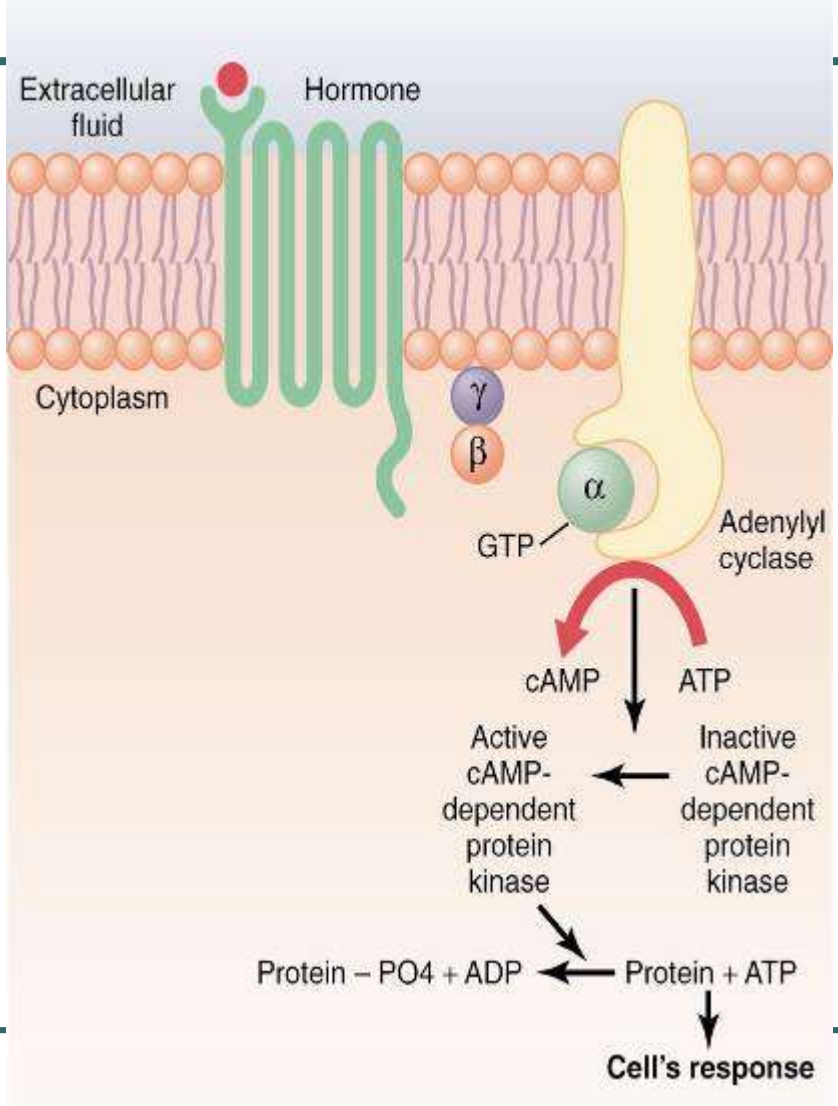
Insulin Family	Glycoprotein Family	POMC Family
Insulin Insulinlike growth factor I (IGF-1, somatomedin C) Insulinlike growth factor II Relaxin	Lutenizing hormone (LH) Follicle-stimulating hormone (FSH) Thyroid-stimulating hormone (TSH) Chorionic gonadotropin (HCG)	Adrenocorticotropic hormone (ACTH) Melanocyte-stimulating hormone (MSH) POMC=Pro-opiomelanocorticotropin

Secretin-Glucagon Family	Growth Hormone Family	Neurohypophyseal Family
Secretin Glucagon Gastrointestinal polypeptide Glicentin Gastric inhibitory polypeptide (GIP) Glucagon-like peptide 1 (GLP-1)	Growth hormone (GH) Prolactin (PRL) Chorionic somatomammotrophin (HCS) or Human placental lactogen (HPL)	Antidiuretic hormone (ADH) Oxytocin

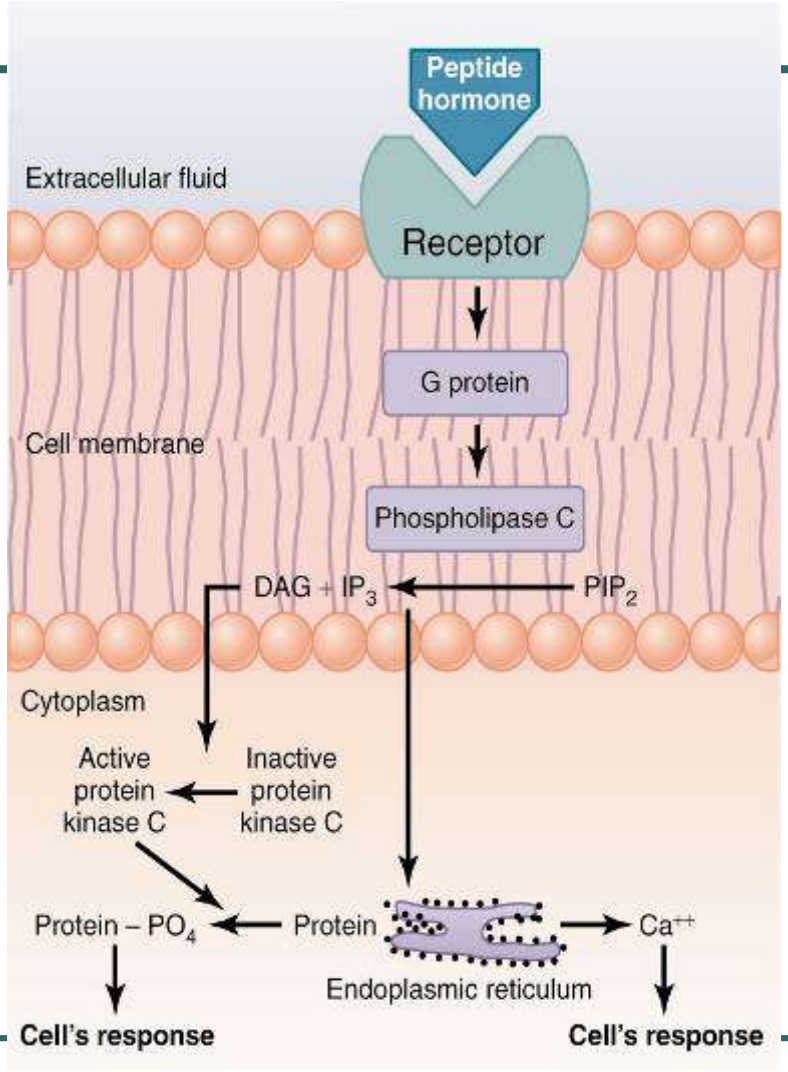
Synthesis & Secretion of Peptide Hormones



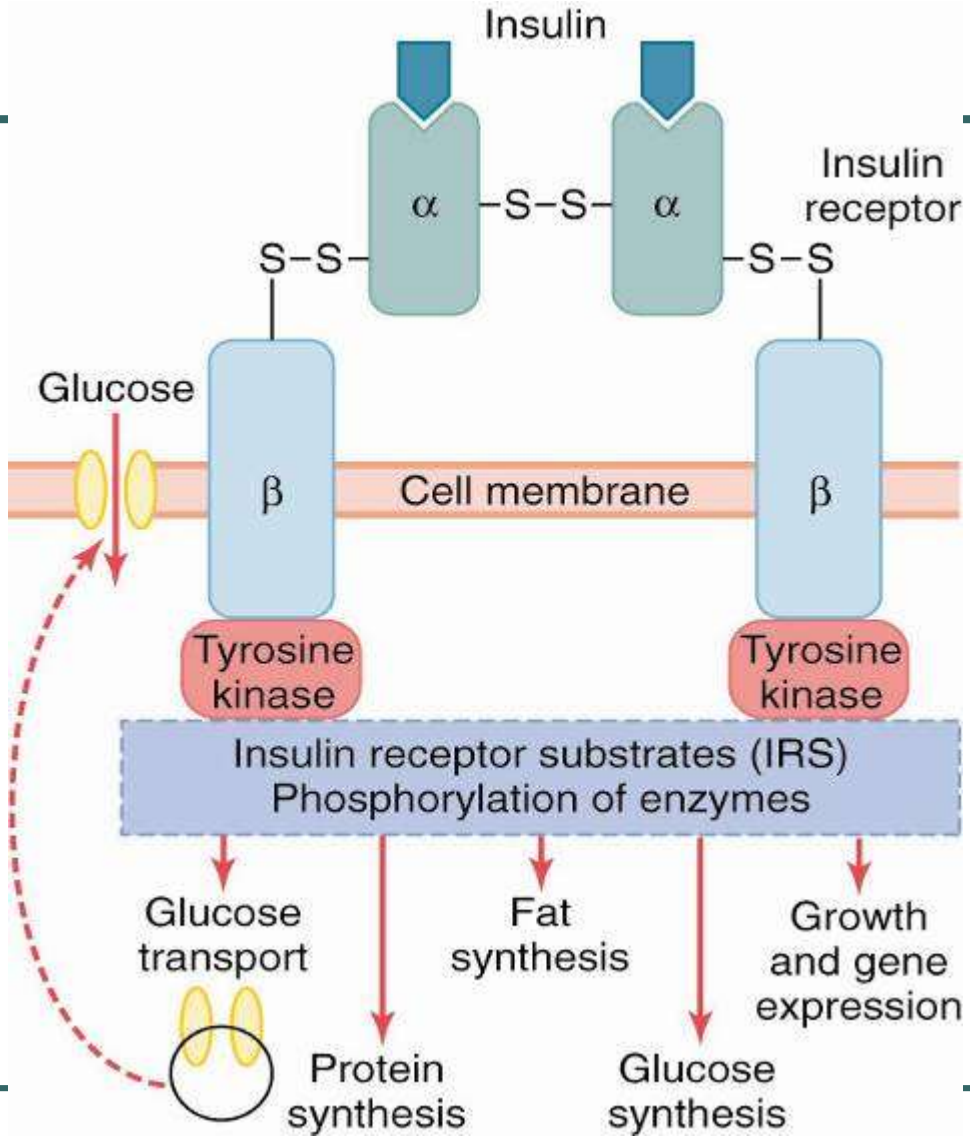
Cyclic Adenosine Monophosphate (cAMP) Second Messenger Mechanism



Cell Membrane Phospholipid Second Messenger System



The Insulin Receptor & Mechanisms of Insulin Action



Protein Hormones - Mechanisms of Action

Adenylyl Cyclase Mechanism	Phospholipid Mechanism	Guanylate Cyclase Mechanism	Tyrosine Kinase/ Cytokine Receptor Mechanism
ACTH	GnRH	ANP	Insulin
LH	TRH		IGF-1
FSH	PTH		GH
TSH	Angiotensin II		Prolactin
GHRH	ADH (V_1 receptor)		
Somatostatin	Oxytocin		
ADH (V_2 receptor)			
HCG			
MSH			
CRH			
Calcitonin			
PTH			
Glucagon			

Correlation of Plasma Half-Life & Metabolic Clearance of Hormones with Degree of Protein Binding

Hormone	Protein binding (%)	Plasma half-life	Metabolic clearance (ml/minute)
Thyroid			
Thyroxine	99.97	6 days	0.7
Triiodothyronine	99.7	1 day	18
Steroids			
Cortisol	94	100 min	140
Testosterone	89	85 min	860
Aldosterone	15	25 min	1100
Proteins			
Thyrotropin	little	50 min	50
Insulin	little	8 min	800
Antidiuretic hormone	little	8 min	600

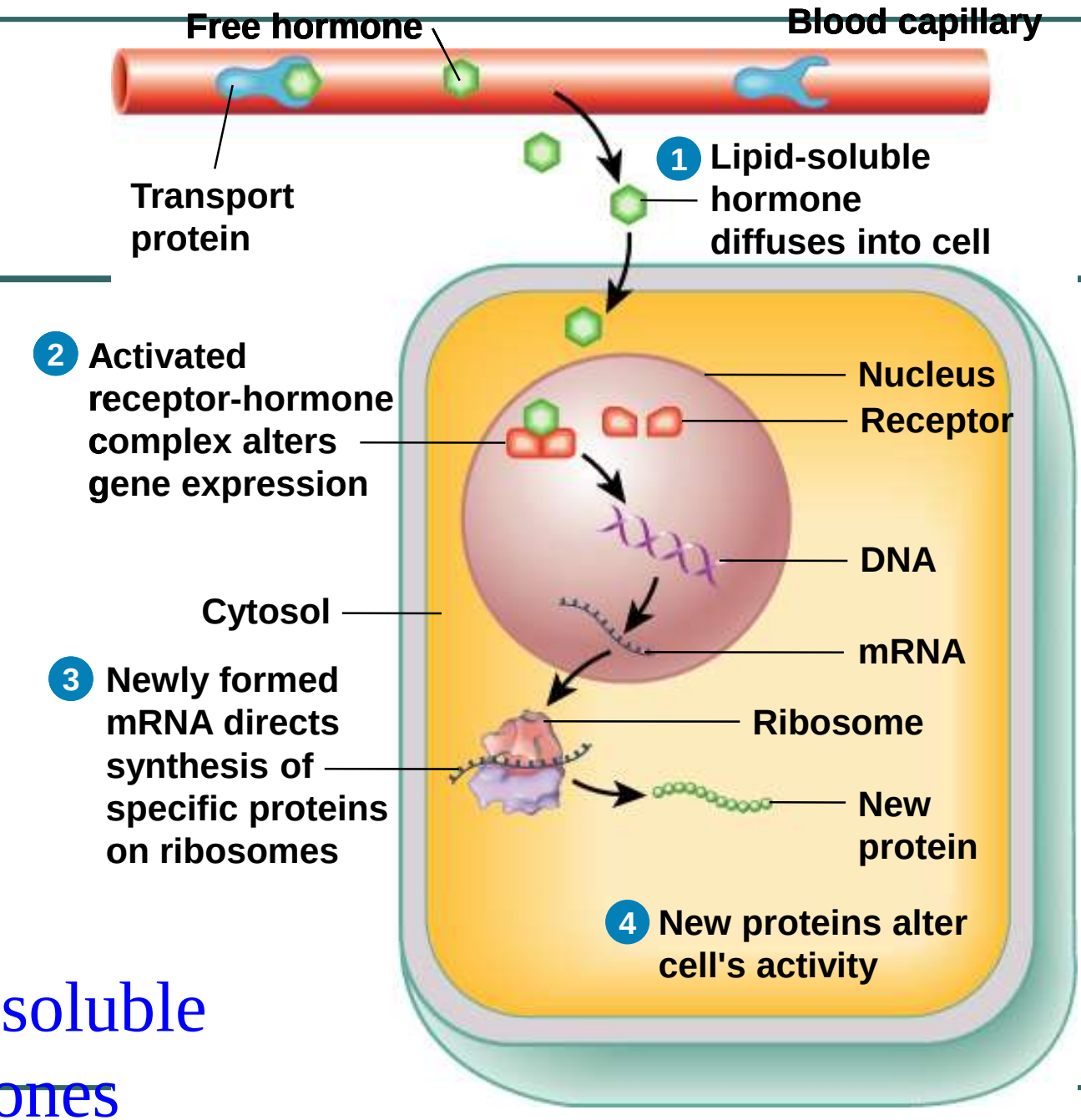
MCR = (mg/minute removed) / (mg/ml of plasma) = ml cleared/minute

Classes of Hormones

- Peptide & Protein Hormones
- Steroid Hormones
- Amine Hormones

Steroid Hormones

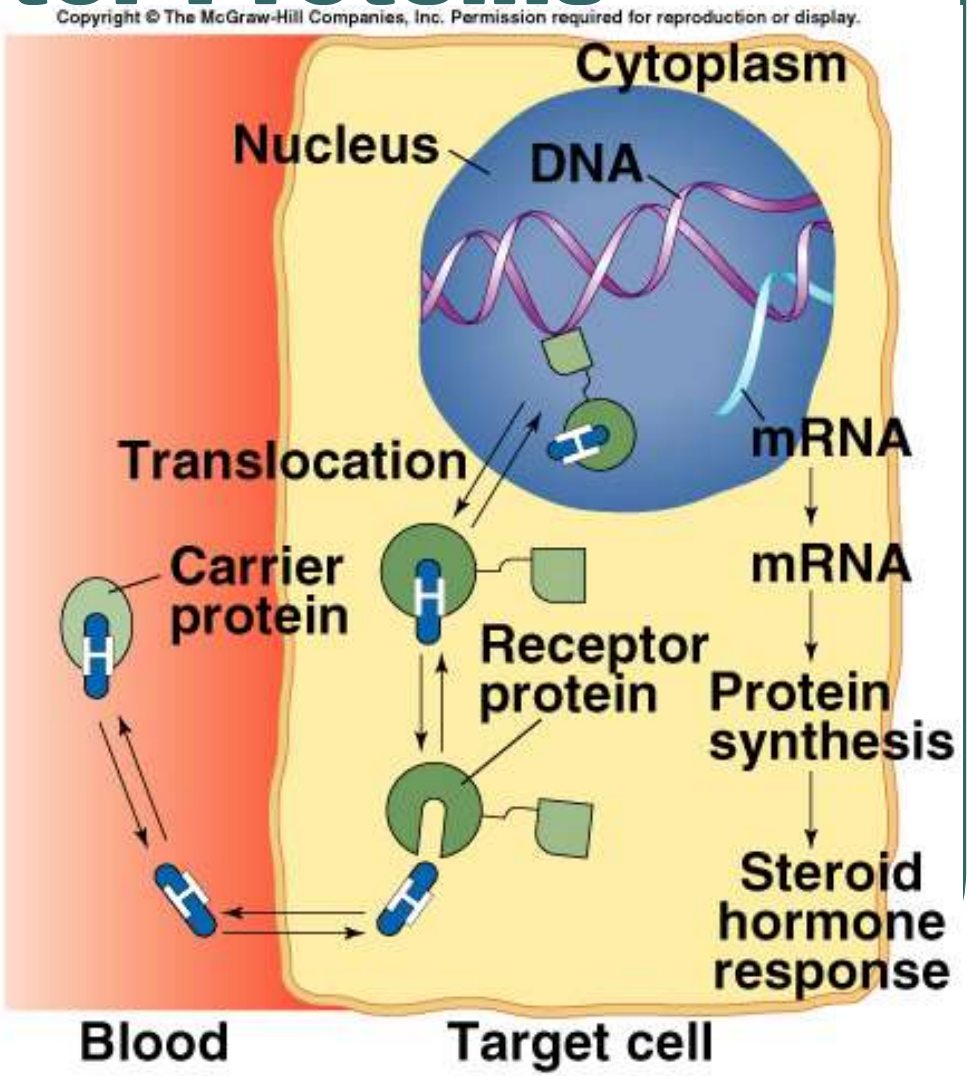
Gland/Tissue	Hormones
Adrenal Cortex	• Cortisol, Aldosterone, Androgens
Testes	• Testosterone
Ovaries	• Estrogens, Progesterone
Corpus Luteum	• Estrogens, Progesterone
Placenta	• Estrogens, Progesterone
Kidney	• 1,25-Dihydroxycholecalciferol



Lipid-soluble Hormones

Hormones That Bind to Nuclear Receptor Proteins

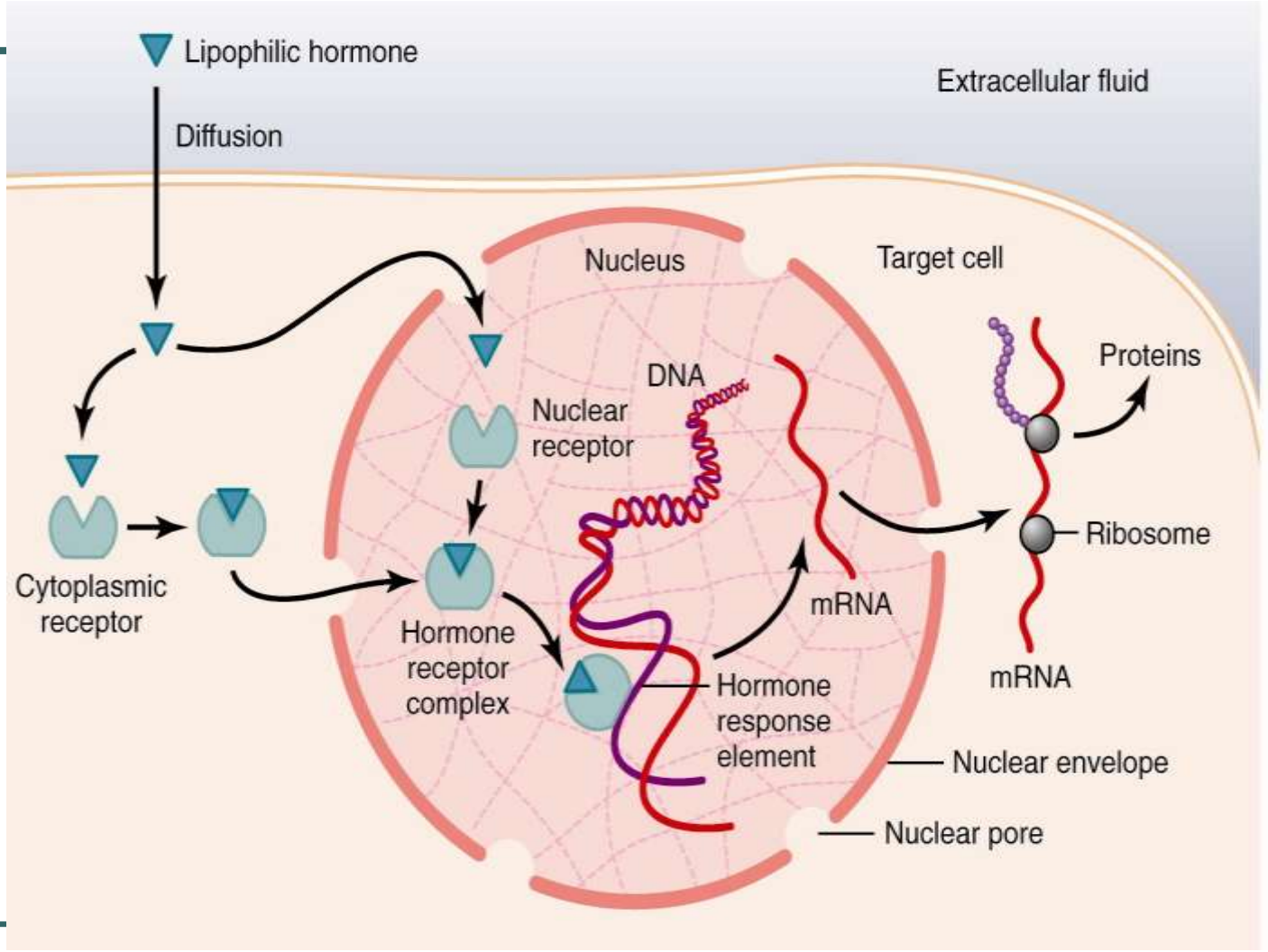
- Lipophilic steroid and thyroid hormones are attached to plasma carrier proteins.
  - Hormones dissociate from carrier proteins to pass through lipid component of the target plasma membrane.
- Receptors for the lipophilic hormones are known as nuclear hormone receptors.



Nuclear Hormone Receptors

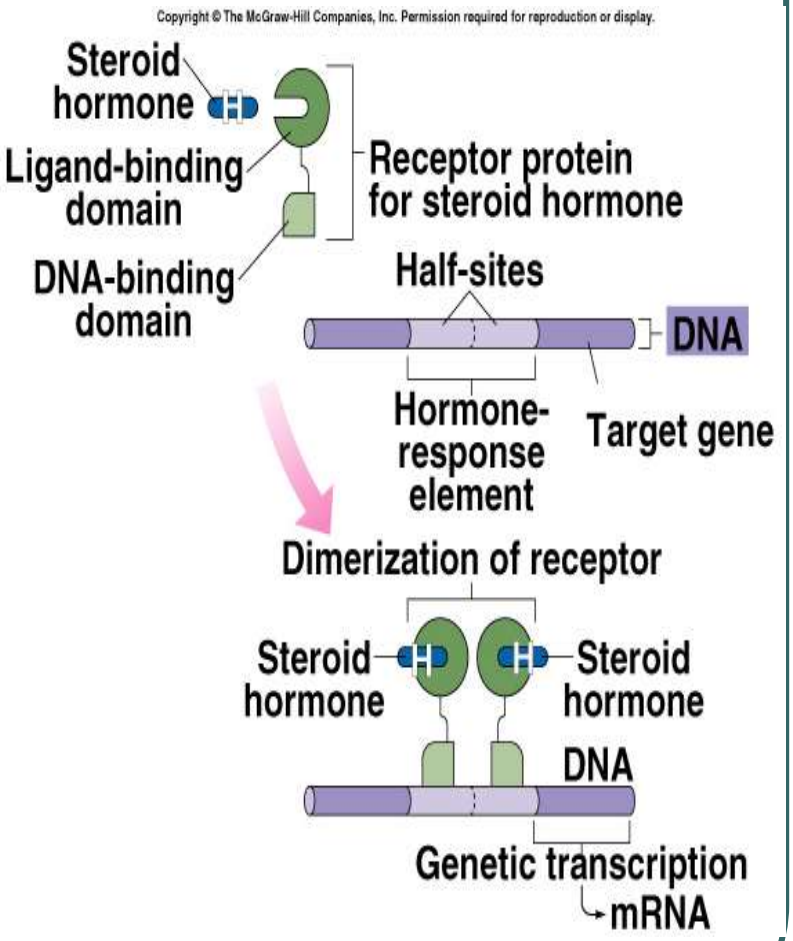
- Steroid receptors are located in cytoplasm and in the nucleus.
- Function within cell to activate genetic transcription.
  - Messenger RNA directs synthesis of specific enzyme proteins that change metabolism.
- Each nuclear hormone receptor has 2 regions:
  - A ligand (hormone)-binding domain.
  - DNA-binding domain.
- Receptor must be activated by binding to hormone before binding to specific region of DNA called HRE (hormone responsive element).
  - Located adjacent to gene that will be transcribed.

Steroid & Thyroid Hormones - Mechanism of Action



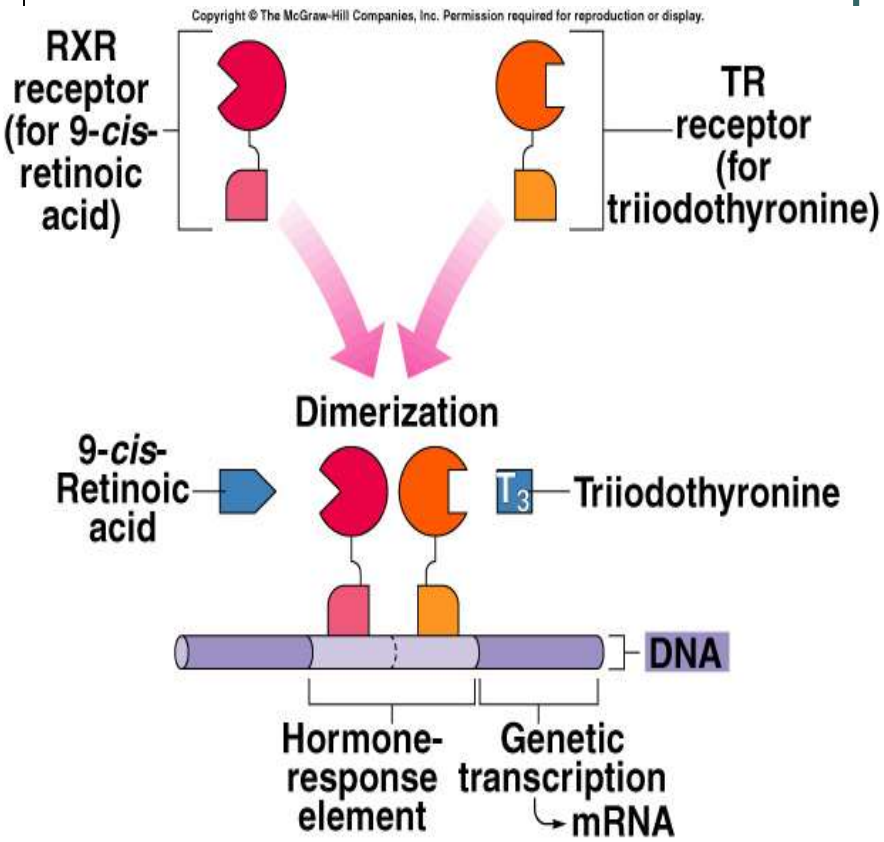
Mechanisms of Steroid Hormone Action

- Cytoplasmic receptor binds to steroid hormone.
- Translocates to nucleus.
- DNA-binding domain binds to specific HRE of the DNA.
- Dimerization occurs.
  - Process of 2 receptor units coming together at the 2 half-sites.
- Stimulates transcription of particular genes.

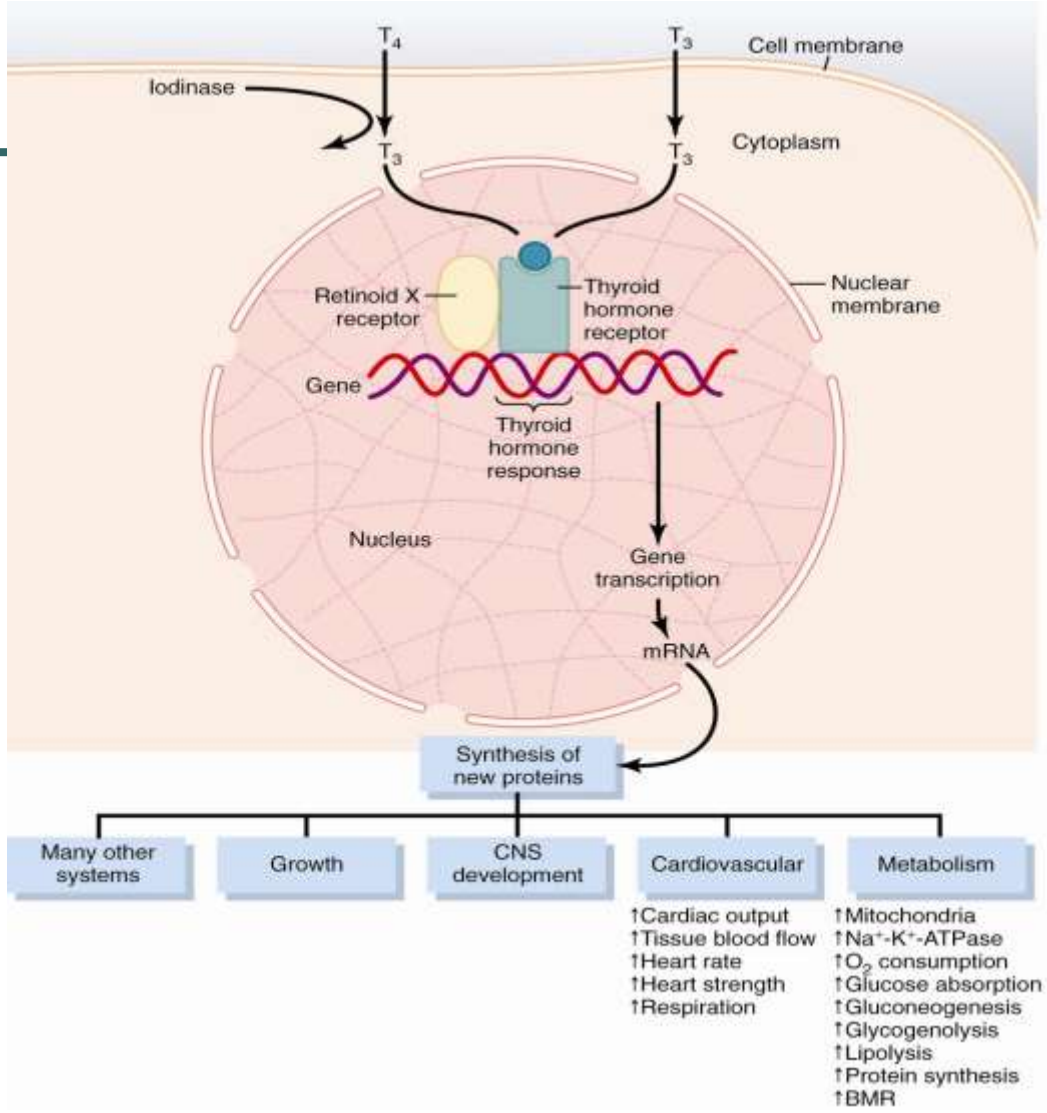


Mechanism of Thyroid Hormone Action

- T_4 passes into cytoplasm and is converted to T_3.
- Receptor proteins located in nucleus.
  - T_3 binds to ligand-binding domain.
  - Other half-site is vitamin A derivative (9-cis-retinoic) acid.
    - DNA-binding domain can then bind to the half-site of the HRE.
  - Two partners can bind to the DNA to activate HRE.
    - Stimulate transcription of genes.



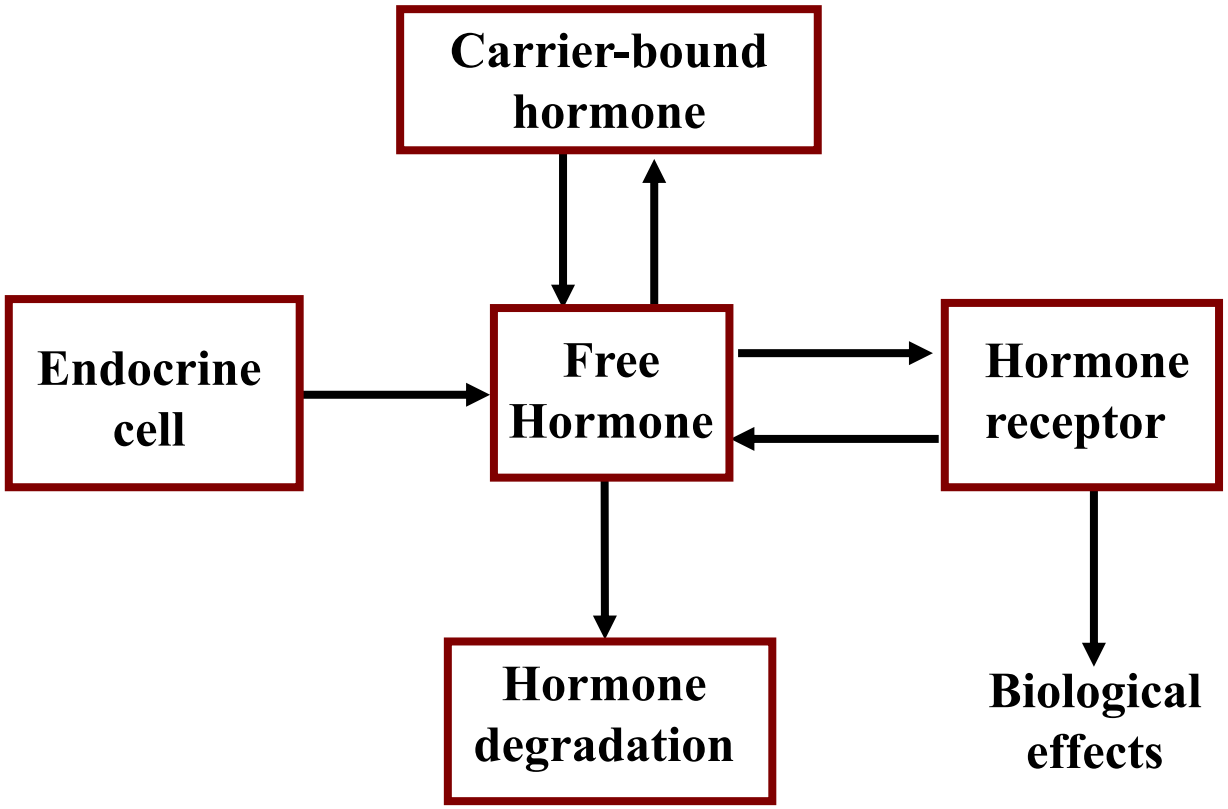
Actions of Thyroid Hormones



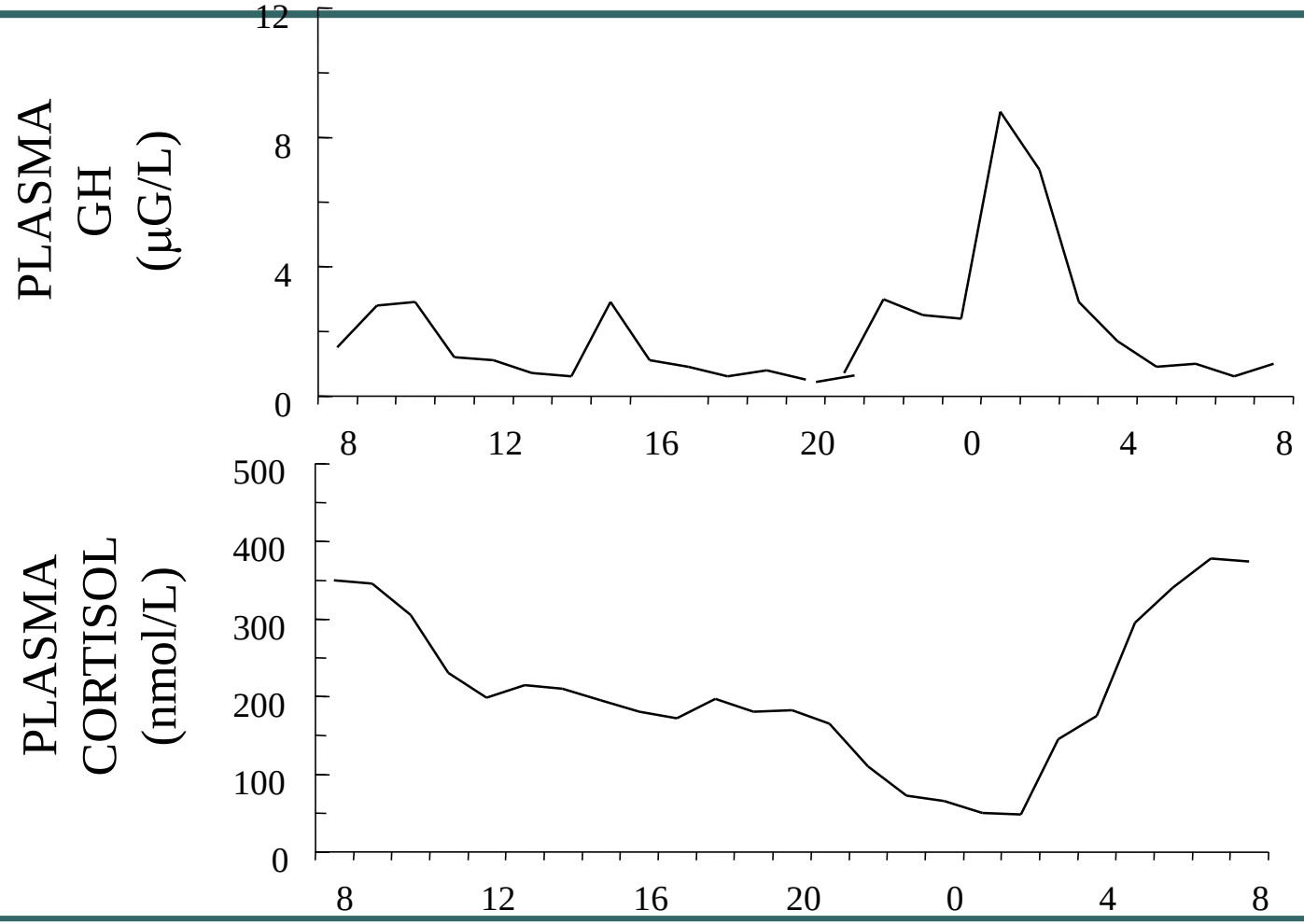
Circulating Transport Proteins

Transport Protein	Principle Hormone Transported
Specific	
Corticosteroid binding globulin (CBG, transcortin)	Cortisol, aldosterone
Thyroxine binding globulin (TBG)	Thyroxine, triiodothyronine
Sex hormone-binding globulin (SHBG)	Testosterone, estrogen
Nonspecific	
Albumin	Most steroids, thyroxine, triiodothyronine
Transthyretin (prealbumin)	Thyroxine, some steroids

Determinants of Free Hormone Receptor Binding

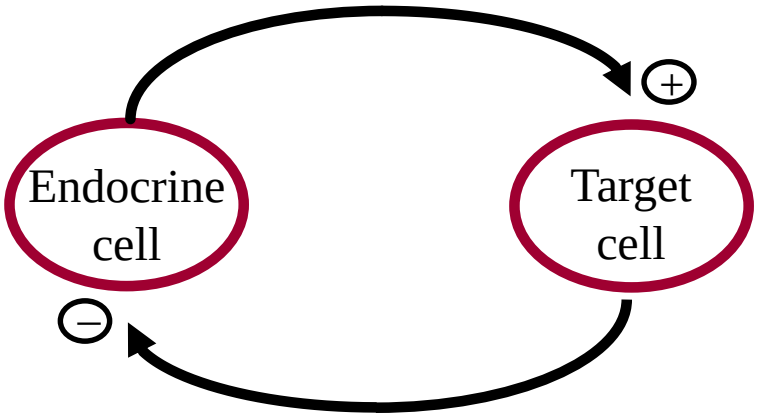


Hormonal Rhythms

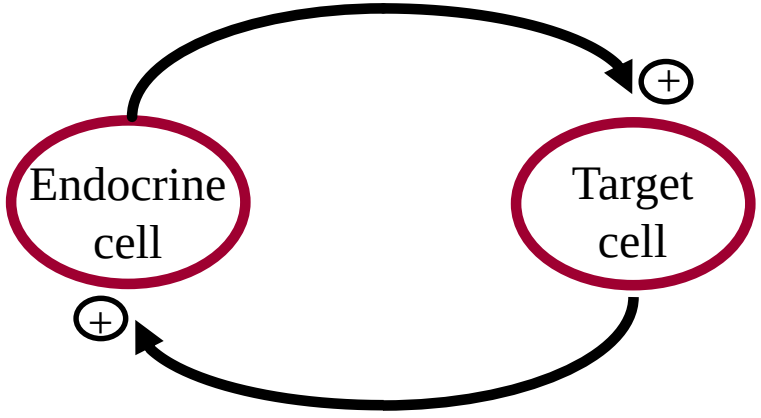


Feedback Mechanisms

Negative Feedback



Positive Feedback



Causes of Endocrine Hyperfunction

- Neoplastic
  - –Benign: pituitary adenomas, hyperparathyroidism, autonomous thyroid or adrenal nodules
  - –Malignant: adrenal and thyroid cancer
  - –Ectopic: ACTH, SIADH
- Autoimmune
  - –Graves' disease
- Iatrogenic
  - –Cushing's syndrome, hypoglycemia
- Infectious/Inflammatory
  - –Subacute thyroiditis
- Activating receptor mutations
  - –TSH

Causes of Decreased Endocrine Function

- Hypofunction

–Autoimmune:	Hashimoto's thyroiditis, type I DM, Addison's disease
–Iatrogenic:	radiation-induced hypopituitarism, hypothyroidism, surgical
–Infectious/Inflammatory:	adrenal insufficiency
–Hormone mutations:	GH, AVP
–Enzyme defects:	21-hydroxylase deficiency
–Nutritional/vitamin deficiency:	vitamin D deficiency, iodine deficiency
–Hemorrhage/infarction:	Sheehan's syndrome, adrenal insufficiency

- Hormone resistance

–Receptor mutations:	GH, AVP
–Postreceptor mutations:	type II DM

Hormone Activity

- Hormones affect only specific target tissues with specific receptors
- Receptors are dynamic and constantly synthesized and broken down
  - Down-regulation
  - Up-regulation

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] 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.
- 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.

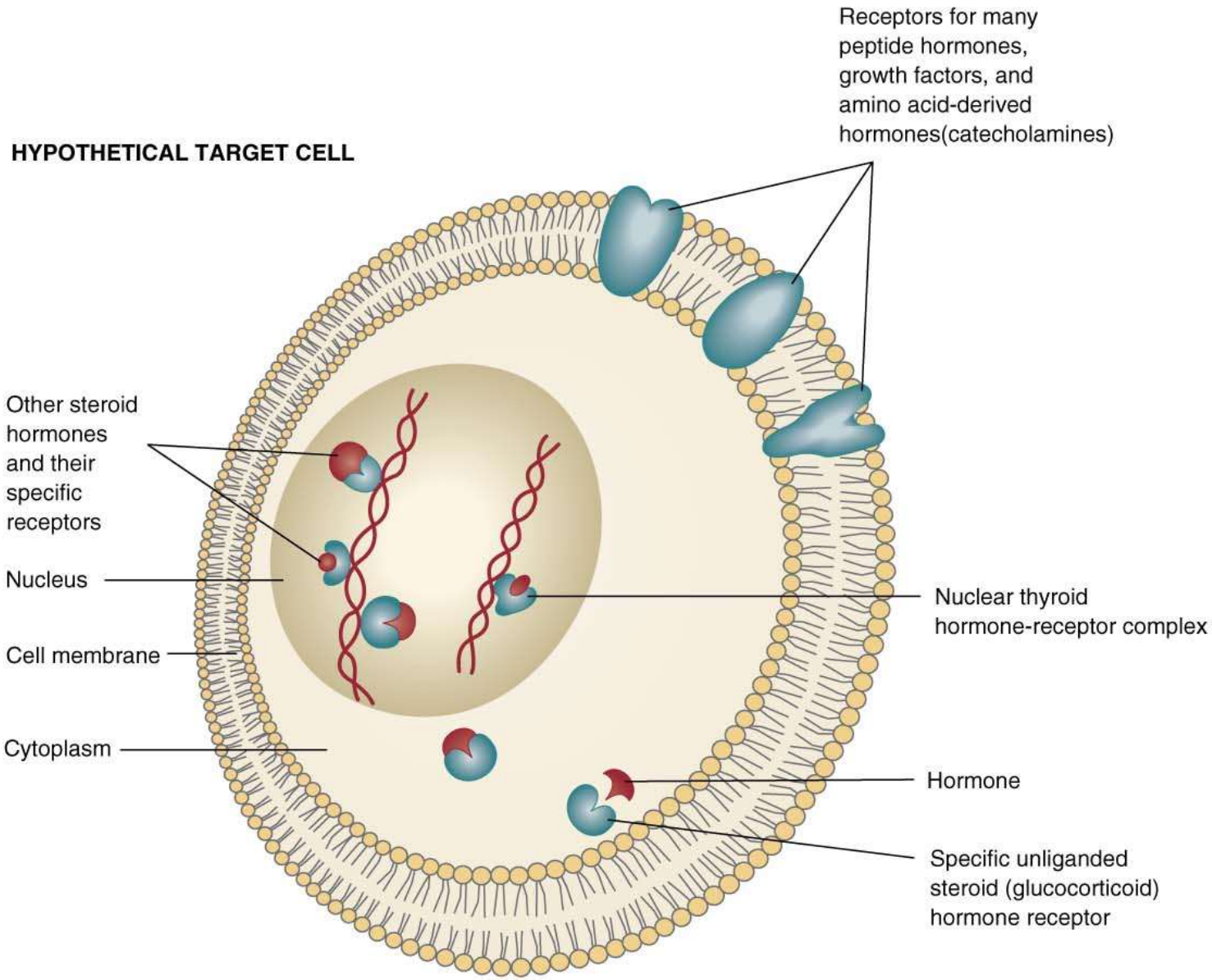
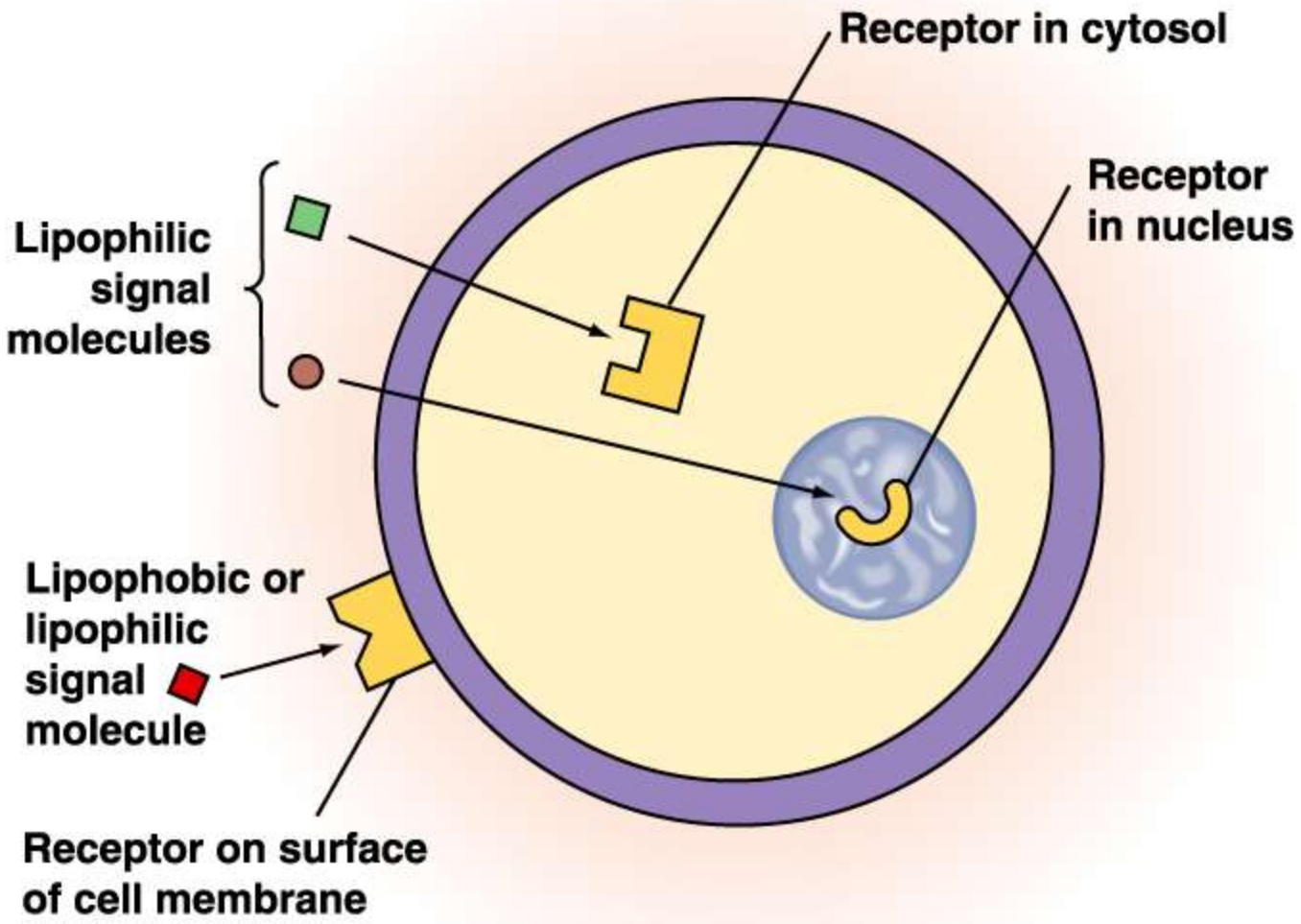


Figure 23.1. Diagram showing the different locations of classes of hormone receptors expressed by a target cell.

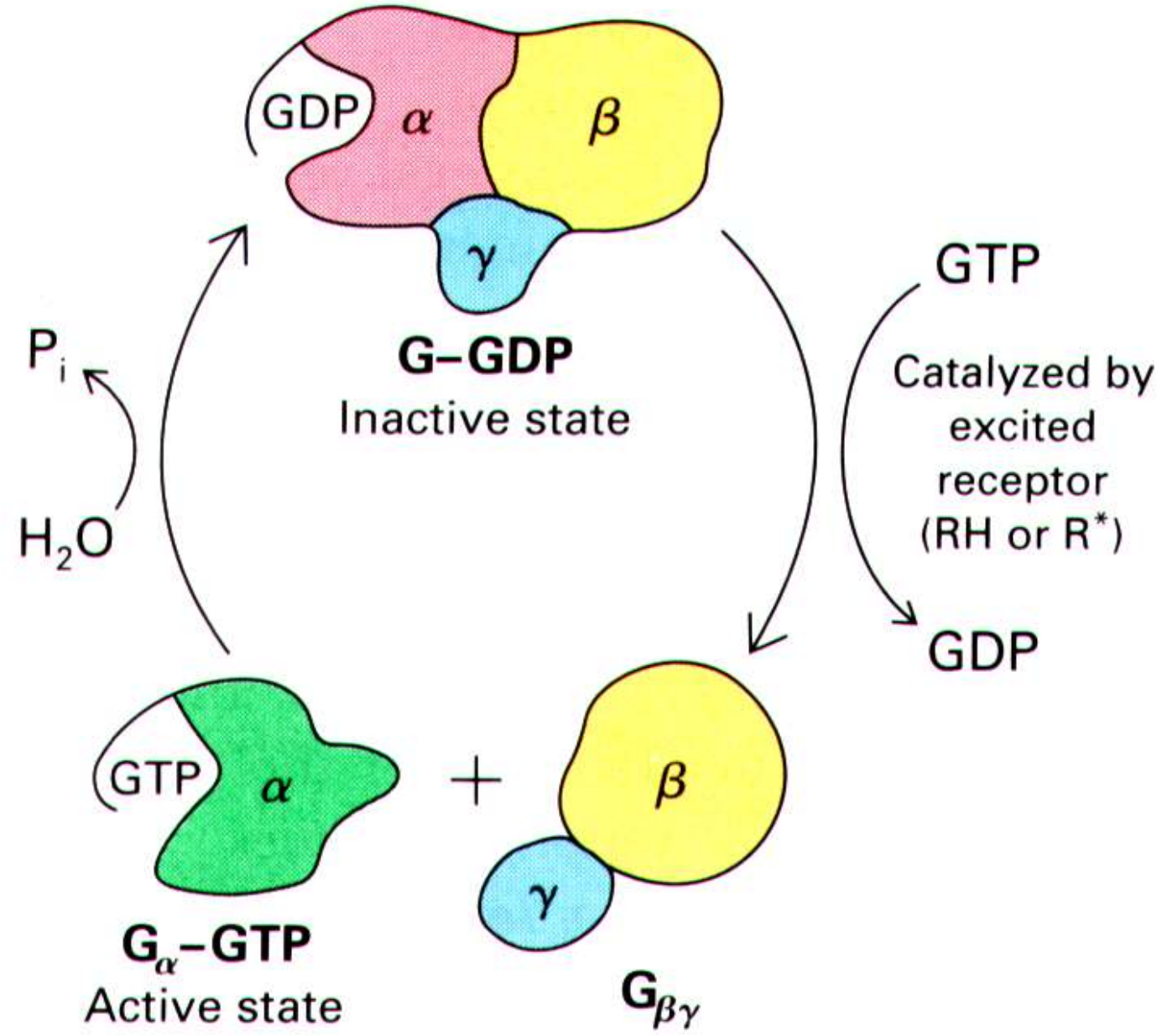

Receptor in cytosol
Receptor in nucleus
Lipophilic signal molecules
Lipophobic or lipophilic signal molecule
Receptor on surface of cell membrane

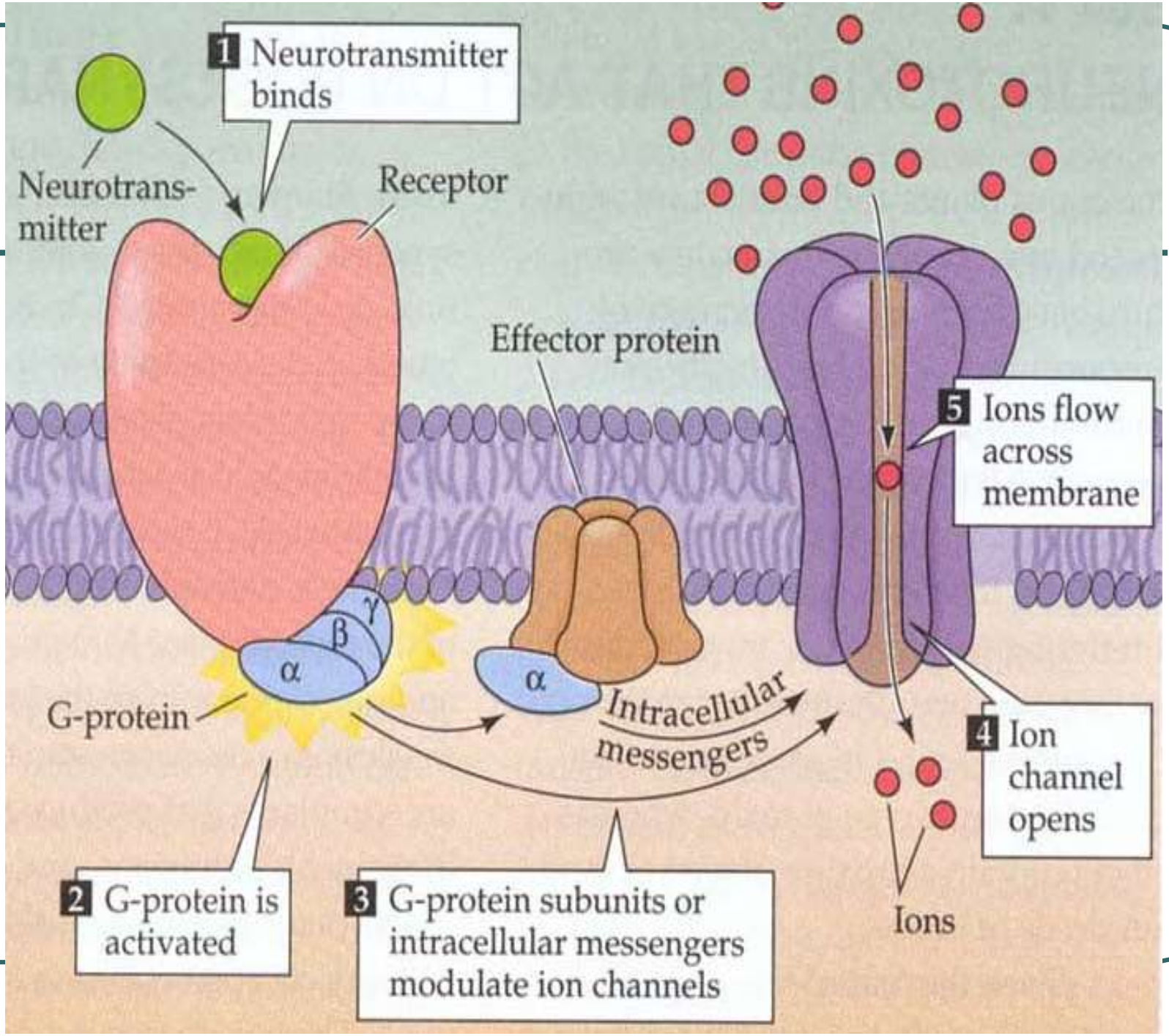
Mechanisms of Hormone Action

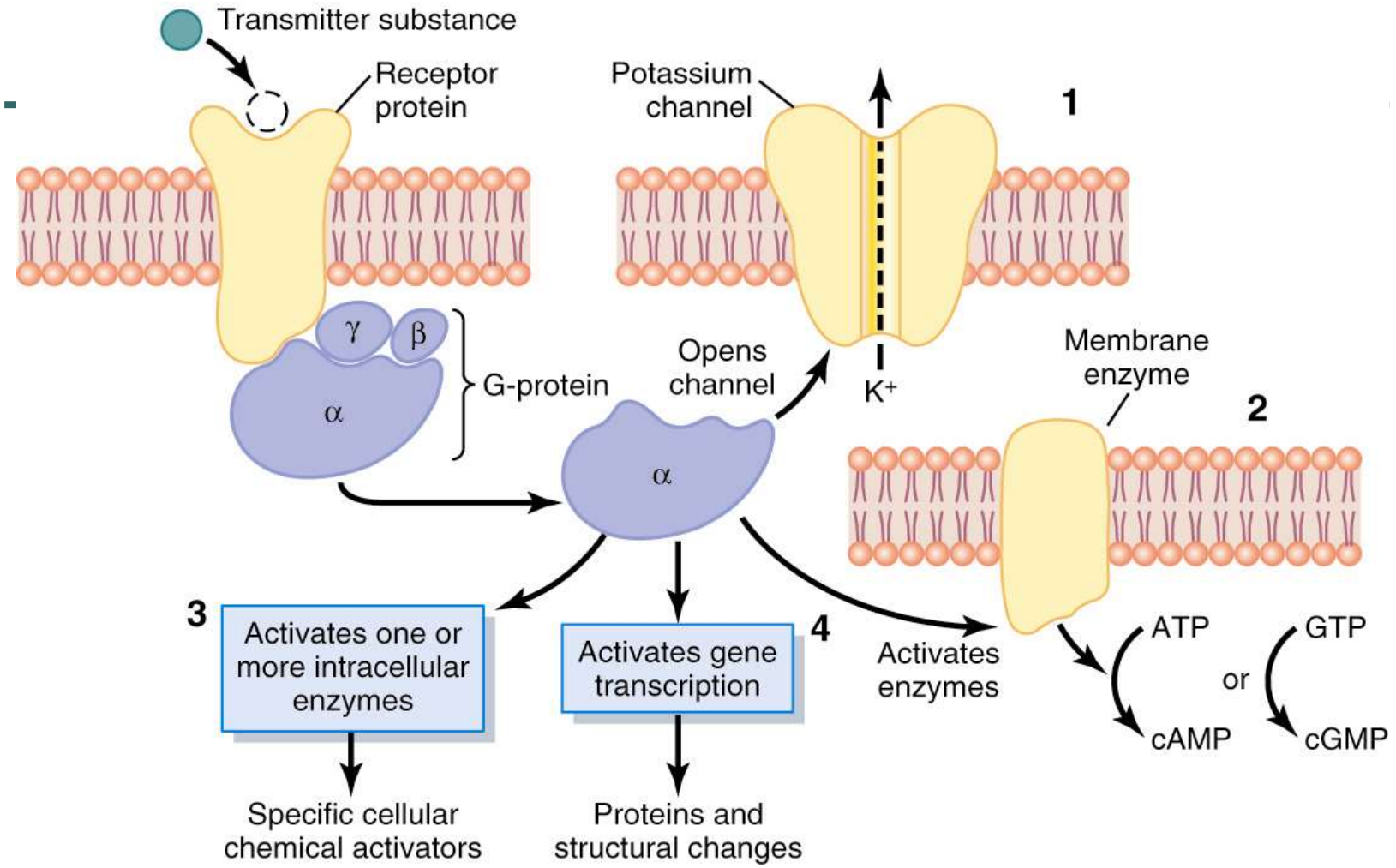
- Hormones of same chemical class have similar mechanisms of action.
  - Similarities include:
    - Location of cellular receptor proteins depends on the chemical nature of the hormone.
    - Events that occur in the target cells.
- To respond to a hormone:
  - Target cell must have specific receptors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

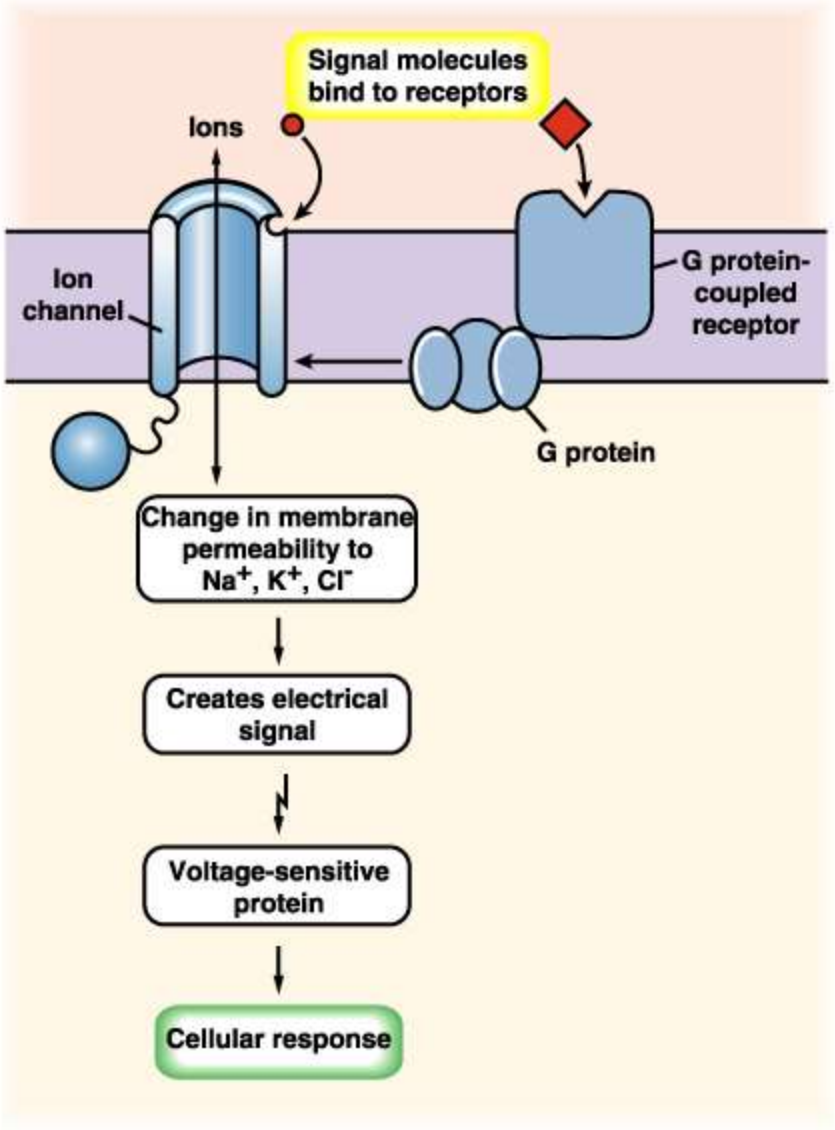
Mechanisms of Hormone Action

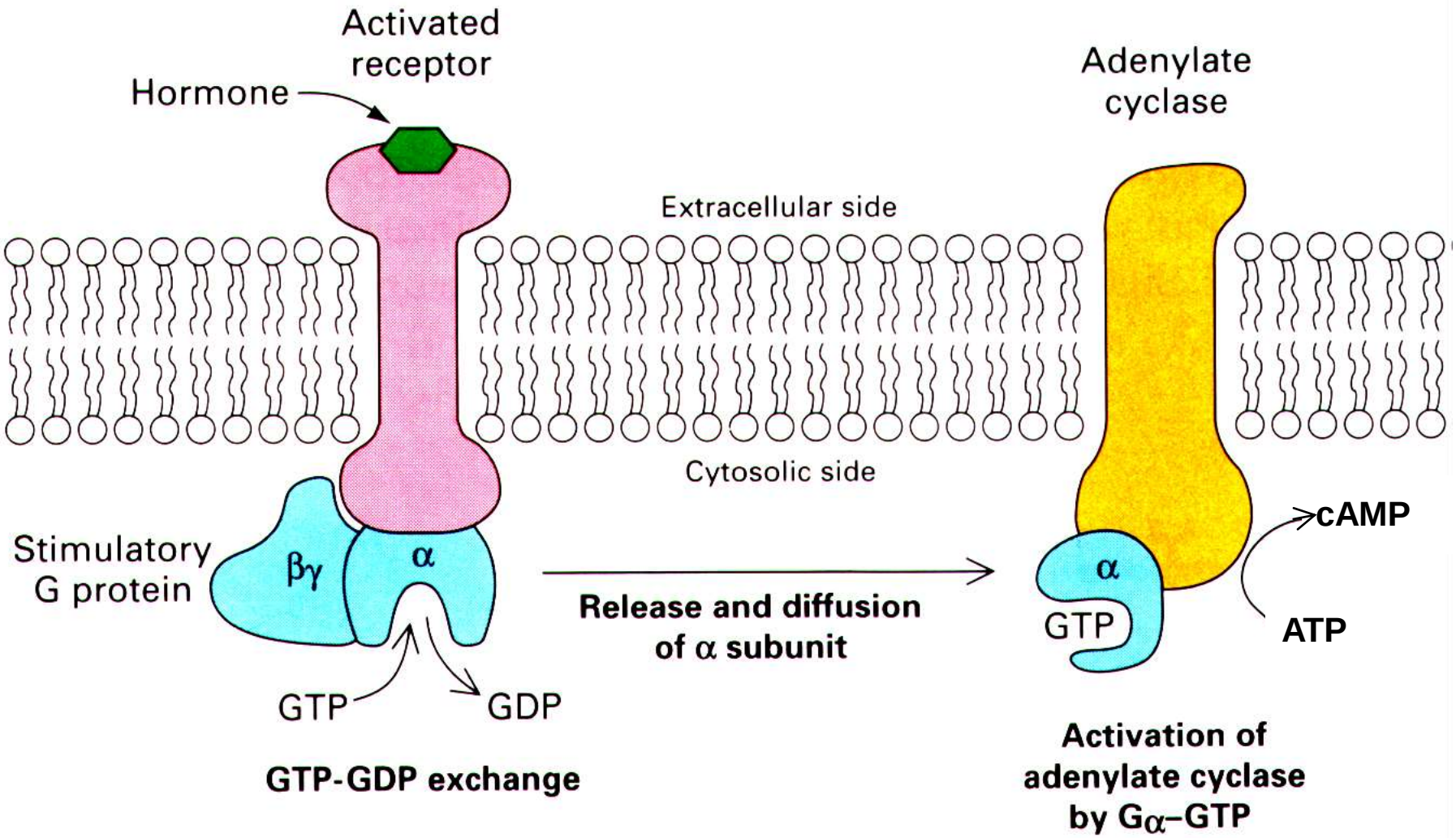
- Response depends on both hormone and target cell
- Lipid-soluble hormones bind to receptors inside target cells
- Water-soluble hormones bind to receptors on the plasma membrane
  - Activates second messenger system
  - Amplification of original small signal
- Responsiveness of target cell depends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


GDP
α
β
γ
G–GDP
Inactive state
GTP
Catalyzed by
excited
receptor
(RH or R*)
GDP
Pi
H2O
GTP
α
β
γ
Gα–GTP
Active state
Gβγ


1 Neurotransmitter binds
Neurotrans-
mitter
Receptor
Effector protein
5 Ions flow across membrane
α
β
γ
α
G-protein
Intracellular messengers
4 Ion channel opens
2 G-protein is activated
3 G-protein subunits or intracellular messengers modulate ion channels
Ions


Transmitter substance
Receptor protein
Potassium channel
1
γ
β
α
G-protein
Opens channel
K+
Membrane enzyme
2
α
3
Activates one or more intracellular enzymes
Specific cellular chemical activators
4
Activates gene transcription
Proteins and structural changes
Activates enzymes
ATP
or
GTP
cAMP
cGMP


Signal molecules bind to receptors
Ions
Ion channel
G protein-coupled receptor
G protein
Change in membrane permeability to Na^+, K^+, Cl^-
Creates electrical signal
Voltage-sensitive protein
Cellular response


Activated receptor
Hormone
Adenylate cyclase
Extracellular side
Cytosolic side
Stimulatory G protein
βγ
α
GTP
GDP
GTP-GDP exchange
Release and diffusion of α subunit
α
GTP
cAMP
ATP
Activation of adenylate cyclase by Gα–GTP

Properties of binding of H and R

- highly specificity
- highly affinity
- saturation
- reversible binding
- special function model

Receptor Types

- Channel-linked receptors
  - Ionotropic
- Enzyme-linked receptors
  - Protein kinases → phosphorylation
  - Neurotrophins
- G-protein-coupled receptors
  - Metabotropic
- Intracellular receptors
  - Activation by cell-permeant signals ~

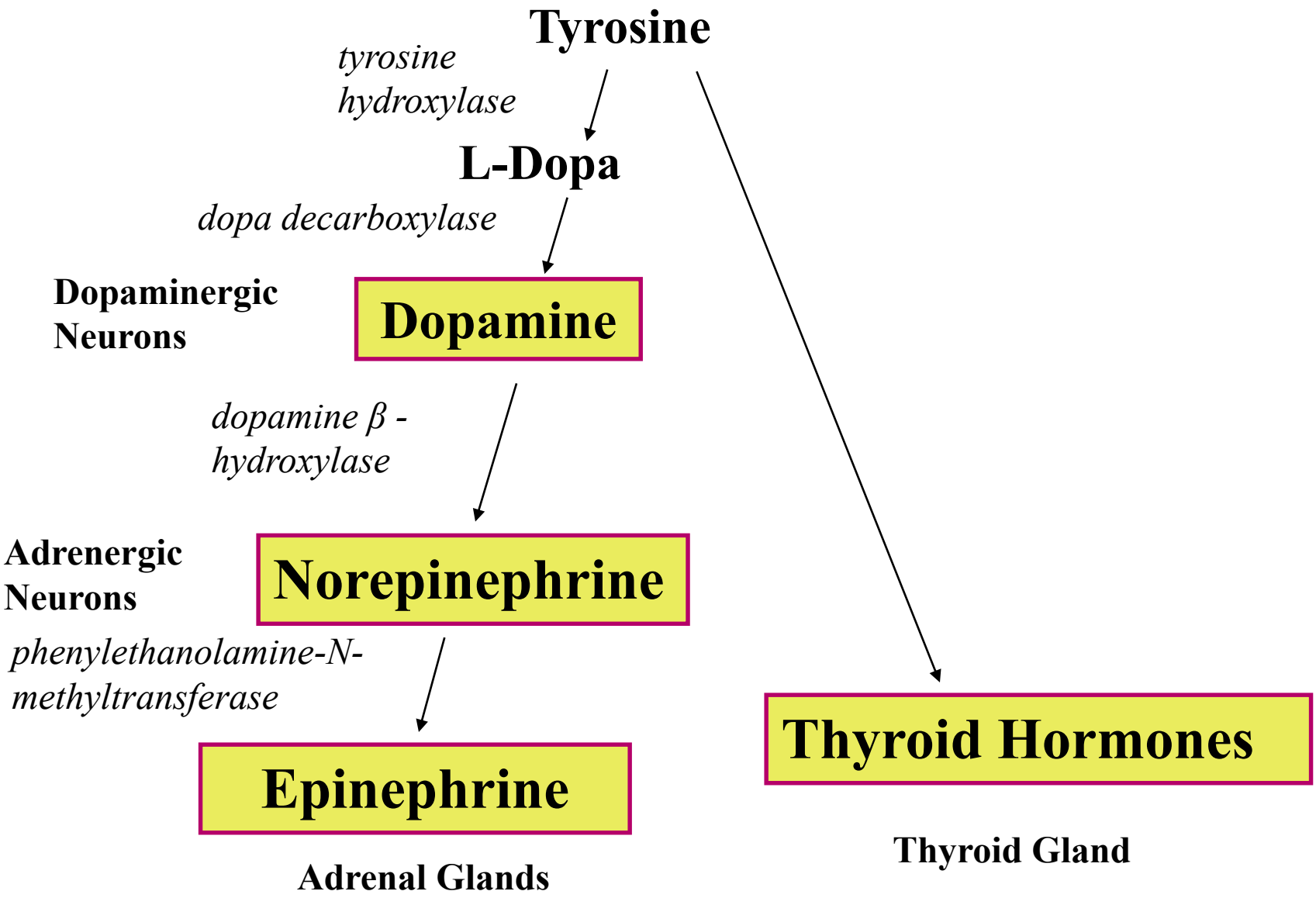
Classes of Hormones

- Peptide & Protein Hormones
- Steroid Hormones
- Amine Hormones

Amine Hormones

Gland/Tissue	Hormones
Hypothalamus	• Dopamine
Thyroid	• T_3, T_4
Adrenal medulla	• NE, EPI

Synthesis of Amine Hormones




THANKYOU